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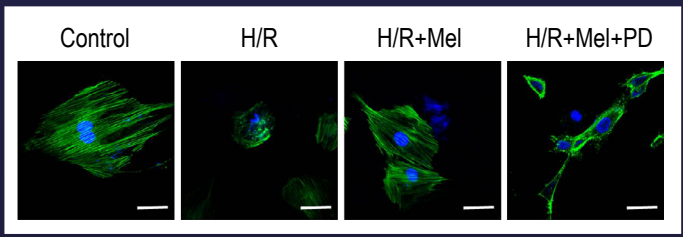

Figure 3 – *Melatonin protects F-actin organization in H9C2 cells against H/R via ERK1 in vitro. Representative confocal microscopy images show H9C2 cells stained with FITC-phalloidin. The results showed that simulated H/R induced more diffuse and irregular actin disposition compared with control group. Melatonin preserved more regular and well-defined actin organization and PD98059 (ERK1 inhibitor) reduced the protection of melatonin. bar = 20μm. (Control: control group; H/R:H/R group; H/R+mel: H/R+ melatonin group; H/R+mel+PD: H/R+ melatonin+PD98059 group). Page 48*

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New Editor-in-Chief, New Challenges

Carlos Eduardo Rochitte

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It was a great honor and privilege to be appointed to serve as the new editor-in-chief of the *Arquivos Brasileiros de Cardiologia* for the 2018-2021 period. In this first editorial, I would like to thank my peers and colleagues, who have manifested sincere and total support to my indication. It is undoubtedly a great challenge to contribute to the most important scientific journal of Cardiology in South America.

Moreover, it is on the shoulders of the previous editors-in-chief that I humbly make myself available to collaborate with this communication channel of the Brazilian Cardiology. The work here developed is monumental and was only possible because of the collaboration of the associate editors and reviewers, who are part of the great family of the *Arquivos Brasileiros de Cardiologia*. And it will go on like this. Thus, I ask for the support of all involved in the task in the coming years.

The constitution of a writing committee for the Brazilian Society of Cardiology journal was proposed by Dante Pazzanese and Luiz V. Décourt, and the first "director" of the *Arquivos Brasileiros de Cardiologia* was Dr. Jairo Ramos, who suggested the journal's name, which has persisted since 1948. The histories of the Brazilian Cardiology, of the Brazilian Society of Cardiology and of the *Arquivos Brasileiros de Cardiologia* have mingled for decades. It is worth noting that the first study published, entirely written in English, was "*The electrocardiographic evidence of local ventricular ischemia*", by Robert H. Bayley and Jolm S. La Due, from Oklahoma City, United States (Figure 1).[1] This clearly shows that the internationalization potential of the *Arquivos Brasileiros de Cardiologia* has always been in its DNA. It is up to us, as a Society of Cardiology, to fully develop it.

I am especially grateful to our former editor-in-chief Dr. Luiz Felipe P. Moreira for its excellent management and for handing on a well-structured and organized journal to me. His editorial from last December revisits the accomplishments of the past eight years, a period when I was associate editor of diagnostic and imaging methods.[2] What I learned during his management, as well as his support, substantiated my decision of applying for editor-in-chief of the *Arquivos Brasileiros de Cardiologia*.

Several actions have been planned to speed up the article review process of our journal and make it more attractive to authors. With the constant progress of science and of its outreach channels, the *Arquivos Brasileiros de Cardiologia* need to be prepared to keep up with such changes and innovations.

In the 2018-2021 period, two master beams will provide the base for that innovation: our journal's internationalization and its impact factor improvement. Those two master beams were chosen because of the stability, in the past years, of our journal's impact factor slightly above 1 and non-adherence to the internationalization issues recommended by Scielo.

The first master beam has been championed by Scielo for a while and will be emphasized in coming the championed years. One aspect of internationalization is the participation of international associate editors. In 2018 we will begin with two new international editors and one international co-editor, thus meeting the Scielo recommendation of having approximately 30% of international associate editors. We aim at getting more international visibility and attracting "good science" for the *Arquivos Brasileiros de Cardiologia* in the form of original articles. Review articles will maintain the tradition of reviewing Cardiology topics and its limits with other specialties, always indicating the future steps in the area, such as the review article of the January issue.[3] We are renewing our associate editors, the international reviewers and our editorial board aiming at both speeding up the publication of articles in the *Arquivos Brasileiros de Cardiologia* and improving their quality.

International collaboration has been a mechanism to enhance the impact factor of some European international journals. I believe we need to refine our performance in that area, having, thus, to adopt internationalization measures for the *Arquivos Brasileiros de Cardiologia*. Our two major objectives are obviously synergistic.

In addition, measures to speed up and modernize the article review process are programmed, in an attempt to rapidly notify the authors about the acceptance or refusal of their articles in the *Arquivos Brasileiros de Cardiologia*. We want to increase the satisfaction of the authors and reviewers during the editorial processes in our journal. The first important step is the adoption of a new electronic system of submission, most likely the *ScholarOne*, which will allow a faster and more practical management of the articles from the viewpoints of all involved: authors, associate editors, editor-in-chief, reviewers and editorial assistants. In addition, we will work close to authors and reviewers to obtain a rapid and effective review, allowing the editors to decide more accurately and efficiently.

Some changes in the formats of the articles are being planned to make them more concise, direct and pragmatic. In a recent visit of Prof. Valentin Fuster, JACC's editor-in-chief, we asked "*How do you do it?*", and the answer was "*Keep it simple!!*". I believe we should listen to that advice and follow it. Thus, mini-editorials for the original articles and a Figure 1 summarizing the article are formal changes to be implemented.

Keywords

Periodicals as topic/history; Periodicals as Topic/trends; Journal Impact Factor; Publishing/trends.

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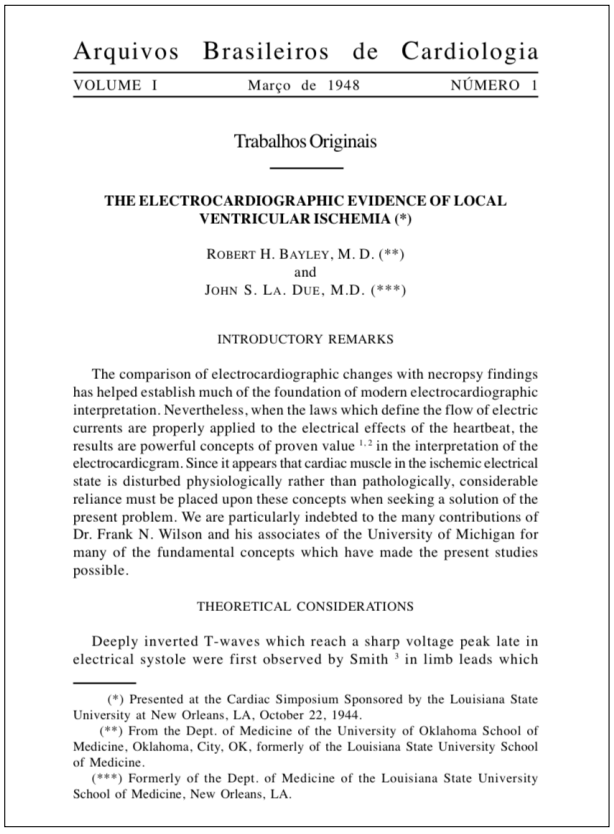
Editorial



Arquivos Brasileiros de Cardiologia

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Trabalhos Originais

THE ELECTROCARDIOGRAPHIC EVIDENCE OF LOCAL VENTRICULAR ISCHEMIA (*)

ROBERT H. BAYLEY, M. D. (**)
and
JOHN S. LA. DUE, M.D. (***)

INTRODUCTORY REMARKS

The comparison of electrocardiographic changes with necropsy findings has helped establish much of the foundation of modern electrocardiographic interpretation. Nevertheless, when the laws which define the flow of electric currents are properly applied to the electrical effects of the heartbeat, the results are powerful concepts of proven value [1,2] in the interpretation of the electrocardiogram. Since it appears that cardiac muscle in the ischemic electrical state is disturbed physiologically rather than pathologically, considerable reliance must be placed upon these concepts when seeking a solution of the present problem. We are particularly indebted to the many contributions of Dr. Frank N. Wilson and his associates of the University of Michigan for many of the fundamental concepts which have made the present studies possible.

THEORETICAL CONSIDERATIONS

Deeply inverted T-waves which reach a sharp voltage peak late in electrical systole were first observed by Smith [3] in limb leads which

(*) Presented at the Cardiac Simposium Sponsored by the Louisiana State University at New Orleans, LA, October 22, 1944.
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(***) Formerly of the Dept. of Medicine of the Louisiana State University School of Medicine, New Orleans, LA.

Figure 1 – *First page of the first article published by the Arquivos Brasileiros de Cardiologia in 1948.*

However, not everything is planned linearly as described above. New challenges will ask for the participation of all players in this scientific process, including our Brazilian Society of Cardiology members. In a recent meeting, Scielo has determined new guidelines to be followed by Latin American journals, some of which with disruptive characteristics and unpredictable final effects. The most important examples are the continuing publication and the concept of "open science". The latter includes the publication in repositories of source data that generated the manuscript's results. Such publication makes data public and available to be used, checked and re-analyzed by groups other than the original authors. Although extremely controversial, that mechanism seems to increase the number of citations of the articles, and, thus, the impact of the articles and of the journal, in addition to adding credibility to them. Would this function in the same way in the Brazilian scientific environment? This response can only be provided by the scientific community, and its adoption by the *Arquivos Brasileiros de Cardiologia* has to undergo a deep and thorough discussion. Likewise, and possibly even more controversial, "open science" proposes accepting the articles in the "preprint" format. Briefly, there are online repositories that accept scientific articles before undergoing peer review. This ensures the authors maintain "property" of the idea and data immediately, allowing them to be cited by other authors, but this can generate the exposure of low-quality articles. However, during exposure, similarly to an Internet forum, comments can be made, and the authors can use them to improve their publication quality. Several journals already accept the submission of articles that had been published as preprint. Should the *Arquivos Brasileiros de Cardiologia* accept that too? Again, this has to be thoroughly discussed, and we have to face a new challenge to adapt to the new digital reality of our virtual world. Scielo seems to strongly support those measures that will soon be mandatory. There is evidence in the literature that the movement towards "open science" increases the impact factor of the journals.[4,5] I believe we have to go along with the change of times.

In addition, we have planned to use more intensively the social media to disseminate the *Arquivos Brasileiros de Cardiologia* content. There is evidence in the literature that the presence of journals in Twitter significantly increases the number of citations of articles and their impact.[6]

However, some things never change, and the "good science" and the relevance of the articles continue to depend on traditional scientific aspects, such as the changes in clinical practice and the generation of new knowledge or ideas on the pathophysiology, natural history or treatment of a disease. Based on the "good science" that has been fostered by the *Arquivos Brasileiros de Cardiologia* over seven decades of existence, and because it represents the science of one of the major societies of Cardiology in the world, I am sure that the future of our *Arquivos Brasileiros de Cardiologia* is brilliant and will continue to merge with the history of the Brazilian Cardiology.

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Cardiovascular Risk Stratification: From Phenotype to Genotype?

Marcio Sommer Bittencourt

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Cardiovascular risk scores, such as the Framingham score, have been strongly recommended by clinical guidelines on the assessment of cardiovascular risk.[1] However, several studies have shown limitations for their use,[2,3] particularly in patients at intermediate risk, young patients with a definite family history, and women. Among different tools aimed at improving risk stratification by complementary methods, the use of genetic information has been proposed to enhance risk prediction.[4]

Although many genetic polymorphisms have been associated with increased cardiovascular risk, the additional value of their use in the clinical practice has not been defined yet. One of the reason for such limitation lies on the fact that atherosclerosis is a multifactorial disease, and the individual role of each polymorphism is limited. Since many polymorphisms associated with atherosclerotic disease have been identified, some authors have investigated combinations of several polymorphisms aiming to develop genetic scores that serve as stronger predictors of cardiovascular risk. Nevertheless, despite great enthusiasm about the role of genetic information on the development of cardiovascular risk, previous data have suggested that even with the combination of more than 50 polymorphisms, the best risk stratification achieved was still poor, and of low clinical value in its current form.[5]

In another attempt to assess the role of genetic scores on atherosclerotic disease, Fisher et al. investigated 116 individuals with metabolic syndrome and recent history of acute coronary syndrome (ACS) to assess the association between several genetic polymorphisms and the extension of coronary artery disease (CAD).[6] While lipoprotein lipase gene polymorphism was associated with atherosclerotic load, polymorphism-derived genetic score was not associated with atherosclerotic load defined by Gensini score in invasive angiography.

These findings may be explained by several reasons. First, the sample size was relatively small for a genetic study. Second, the value of each polymorphism, alone is usually small. In addition, while most studies use gene panels composed of tens of markers, only seven markers were used in this study. Finally, the population studied was different from those of population-based studies. Using recent ACS as an inclusion criterion, the present study included not only patients with clear evidence of atherosclerosis, but also with recent history of plaque instability. The selection of individuals with such different phenotypes may also have affected the development of a genetic score.

Despite these limitations, the study expands the literature on genetic assessment of CAD, demonstrating once again that this association is not simple.

In order to make genetic score part of routine clinical care, improvement of genetic sequencing techniques, development of studies involving larger, representative populations, and the use of modern data modeling methodologies that incorporate nuances beyond the linear association between predictors and outcomes are required.[7]

Keywords

Acute Coronary Syndrome/genetic; Metabolic Syndrome; Risk Factors; Risk Assessment; Polymorphism, Genetic.

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Cardioprotective Effects of Melatonin in Reperfusion Injury

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The possibility of limiting ischemic myocardial injury has been a major focus of cardiovascular research over 4 decades and literally thousands of interventions have been tested in this direction.[1] Unfortunately, this has been a long, unsolved saga, and, apart from reperfusion, most interventions have been largely unsuccessful at the clinical arena.[1] With the advent of clinical forms of reperfusion, the goal of these studies has slightly changed to identify adjuvant therapies that protect the myocardium from reperfusion injury. However, essentially no interventions have yet come to a realistic clinical testing scenario, although cellular therapies and other emerging interventions such as mitochondrial transplantation have concrete possibilities to bring a novel perspective to cardioprotection. The overall worldwide investments in cardioprotection research by funding agencies alone can be estimated to be over US$ 1 billion so far.[1] Thus, it is plausible to ask whether it is reasonable to keep pursuing this type of investigation.[1] To this end, the National Institutes of Health in the USA has created a consortium to perform a rigorous preclinical assessment of cardioprotective therapies (CAESAR).[2] At present, the answer to these questions in the ischemia/reperfusion setting has yet to wait results of ongoing studies.[1,3] Meanwhile, it is likely that understanding the mechanisms whereby specific interventions afford cardioprotection in reperfusion injury can have additional mechanistic implications in other areas. For example, several abnormalities of calcium handling observed in ischemia/reperfusion can be relevant to understand the pathophysiology of heart failure,[4] and signaling pathways associated with hypoxia responses can modulate several aspects of vascular response to injury.[5] Therefore, the investigation of nontoxic affordable interventions that provide cardiomyocyte protection, and in particular the identification of underlying associated mechanisms, can be relevant in diverse aspects.

Keywords

Melatonin / pharmacology; Myocardial Reperfusion / physiopathology, Myocardial Reperfusion / prevention & control, Antioxidants / pharmacology.

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The article by Hu S et al.,[6] in this issue, brings a contribution to this scenario. The authors show that pharmacological concentrations of the pineal hormone melatonin (N-acetyl-5-metoxytriptamine) support cardioprotection. They first used an *in vitro* cardiomyocyte culture model submitted to hypoxia/reperfusion and showed that melatonin pretreatment results in decreased cell death and improved organization of the actin cytoskeleton. The authors interrogated whether these protective mechanisms could be associated with improved calcium handling. Indeed, melatonin incubation promoted decrease in cellular calcium overload and prevented the hypoxia/reperfusion-associated increase in the expression of the inositol trisphosphate receptor, as well the associated decrease in the expression of SERCA (sarcoplasmic reticulum calcium ATPase). The latter two alterations were reproduced in a rat model of ischemia/ reperfusion. Together, they indicate that the handling of calcium by the sarcoplasmic reticulum was improved, allowing the inference of a possible mechanism of cardioprotection. Of additional interest, melatonin incubation increased the phosphorylation of ERK1 (i.e., activation of the extracellular signal-regulated kinase 1) and pharmacological inhibition of ERK1 with the compound PD98059 negated the protective effects of melatonin on cell survival, actin organization and calcium handling. Thus, preservation of ERK1 activation is a likely mechanism of the protective effects of melatonin.

This study adds to other reports indicating a cardioprotective effect of melatonin by an array of antioxidant mechanisms,[7] which include the preservation of mitochondrial integrity.[8] It is likely that such antioxidant effect may have contributed to the improved calcium handling. Altogether, these data suggest that the mechanisms associated with melatonin-dependent cardioprotection deserve further investigation that may lead to the development of affordable non-toxic interventions. These, in turn, might have multiple implications, including showing that cardioprotection is not yet dead.[1]

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Oral Anticoagulation in Atrial Fibrillation: Development and Evaluation of a Mobile Health Application to Support Shared Decision-Making

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Abstract

Background: Atrial fibrillation is responsible for one in four strokes, which may be prevented by oral anticoagulation, an underused therapy around the world. Considering the challenges imposed by this sort of treatment, mobile health support for shared decision-making may improve patients' knowledge and optimize the decisional process.

Objective: To develop and evaluate a mobile application to support shared decision about thromboembolic prophylaxis in atrial fibrillation.

Methods: We developed an application to be used during the clinical visit, including a video about atrial fibrillation, risk calculators, explanatory graphics and information on the drugs available for treatment. In the pilot phase, 30 patients interacted with the application, which was evaluated qualitatively and by a disease knowledge questionnaire and a decisional conflict scale.

Results: The number of correct answers in the questionnaire about the disease was significantly higher after the interaction with the application (from 4.7 ± 1.8 to 7.2 ± 1.0, $p < 0.001$). The decisional conflict scale, administered after selecting the therapy with the app support, resulted in an average of 11 ± 16/100 points, indicating a low decisional conflict.

Conclusions: The use of a mobile application during medical visits on anticoagulation in atrial fibrillation improves disease knowledge, enabling a shared decision with low decisional conflict. Further studies are needed to confirm if this finding can be translated into clinical benefit. (Arq Bras Cardiol. 2018; 110(1):7-15)

Keywords: Anticoagulants / therapeutic use; Atrial Fibrillation; Stroke; Hemorrhage; Medication Adherence; Telemedicine.

Introduction

Atrial fibrillation (AF) affects 33.5 million people in the world[1] and is the cause of 28% of strokes.[2] Prophylaxis with oral anticoagulants (OACs) can reduce the risk of stroke by 60-70%,[3-6] with a variable risk of bleeding.

AF guidelines recommend the use of the CHA_2DS_2-VASc (for stroke) and HAS-BLED (for bleeding) risk scores to recognize those patients who will benefit the most from anticoagulants.[7-10] More recently, the SAMe-TT_2R_2 score[11] was validated to predict a poor anticoagulation control with coumarins, contributing to the selection of the anticoagulant type. Although many scores are available,[12] their use should be done with caution. The current European guideline,[8] for example, recommends the use of bleeding scores to identify modifiable risk factors for major bleeding rather than to contraindicate anticoagulation. Besides, these scores do not take into account patients' worries, objectives and values, and do not evaluate costs, posology, and frequency of visits to physician and exams, which influence adherence to treatment.[13] The complexity of such decision process is reflected in the suboptimal number of patients who receive an OAC prescription, maintain target coagulation and adhere to drug treatment.[13-15]

New approaches for the management of chronic diseases have been patient-centered, in which the patient practices shared treatment decision making, leading to improved outcomes and efficacy of the health system.[16,17] Patients with AF are likely to benefit from these strategies, due to the importance of patient ownership of decisions that require patient action, such as taking the medication and monitoring of treatment.[18]

Mobile health technology, or just mobile health (mHealth) – seems promising in expanding healthcare coverage, facilitating the decision-making process and improving the management of chronic diseases.[17-20] In 2015, more than 3 billion health app downloads were made worldwide.[21] It is important that this new technology includes other specific groups, such as the elderly and low-income adults with limited access to mobile communication.[18,22] In this article, we describe the development of a mHealth application to be used during medical visits, aiming to facilitate the shared decision-making on thromboembolic prophylaxis in AF. The app was tested in low-income patients with low educational attainment by the measurement of disease knowledge before and after its use.

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Methods

Development of the application

The development staff was composed by a cardiologist, an electrophysiologist, a software developer and a designer.

First, the following fundamental aspects were defined: condition/problem to be approached (thromboembolic prophylaxis in AF); target users/population (patients with AF and low socioeconomic and cultural status); initial application targets (increased knowledge about disease and treatment); situation in which the app would be used (during medical visits); device in which the app would be installed (doctor's tablet computer) and programming languages (Android and iOS).

A comprehensive literature review was performed, including the main randomized clinical trials, systematic reviews, meta-analyses, and guidelines on AF and OAC, which provided the main scores to be used and relevant information to be conveyed to the users.

Aiming to translate this information into knowledge to the patient, a simplified navigation through five screens (Figure 1): (1) Knowing the disease – a video about how AF occurs and how it can cause a thromboembolic event; (2) Individualizing the risks – a calculator integrated with the CHA_2DS_2-VASc, HAS-BLED and SAMe-TT2R2[11] scores; (3) Understanding risks and benefits – a screen with pictograms to visualize the percentage of the risk of stroke and bleeding in each treatment option; (4) Knowing the treatment option – a summary of the main characteristics of the drugs available; and (5) Making a choice – the final screen, in which information is saved and the number of patient's cell phone may be registered to receive information via Short Message Service (SMS).

This navigation format emphasized the main points, providing additional access to more detailed information through the links, according to the users' needs. For example, in the area of medications, data of posology, approximate costs, advantages and disadvantages of each drug were informed. Also, the official package insert of the drug provided by the Brazilian National Health Surveillance Agency was accessible through a link. Push technology by SMS is a strategy used to enhance the provision of information without overloading the patient with information in only one meeting. In this technology, the patient periodically receives alerts on the importance of adhering to drug therapy and doing some tests, as well as disease information, which can be saved in message box for further reading by the patient.

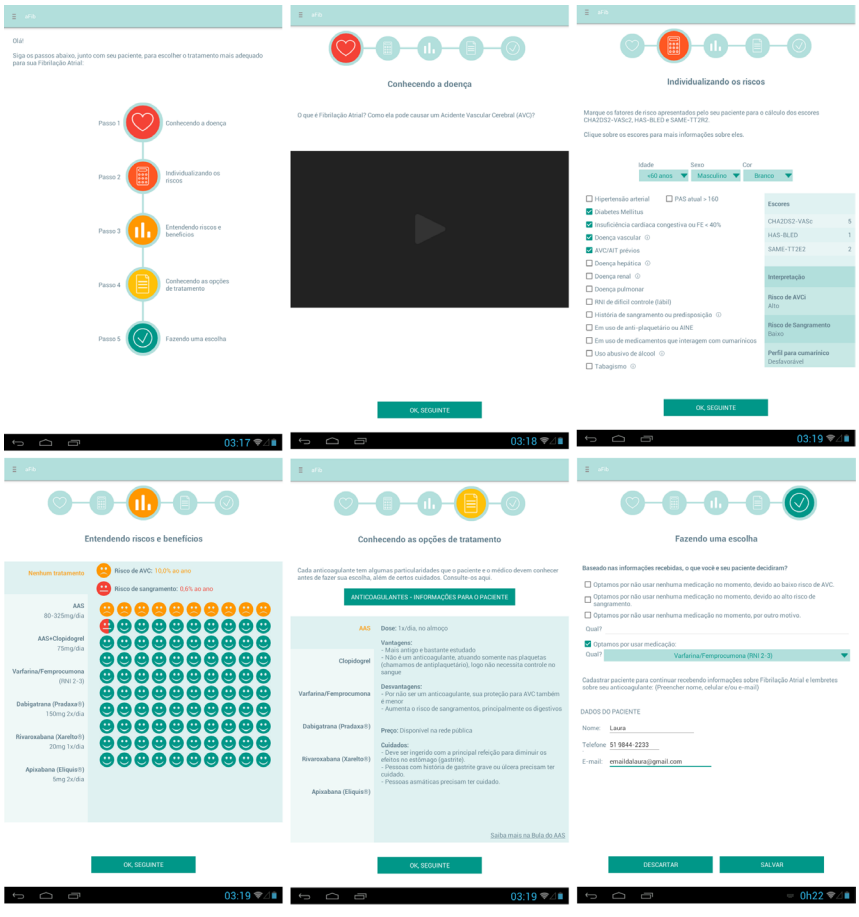

Figure 1 – *Main screens of the aFib app, developed to help in the shared decision about thromboembolic prophylaxis in atrial fibrillation.*

We opted for a clean and clear design, with a color code for the risks and the use of graphical information whenever possible to complement the written information. Terminology was adapted to the target users. Personal health information were protected by unique identification and secured by cryptography. A privacy policy was presented prior to the use.

Study design

Intervention study in patients diagnosed with AF in the anticoagulation outpatient service at Porto Alegre Institute of Cardiology, in April and May 2016.

Population and sample characteristics

The study population comprised patients attending the anticoagulation outpatient service, and the study was carried out during patients' waiting time for the prothrombin time (PT) test. Before starting their treatment at the anticoagulation outpatient service, each patient receives instructions about AF, the use of OAC, as well as appropriate dose adjustment every 1-3 months. In ten random mornings, all AF patients attending the outpatient center for the PT test were invited for the study and all of them agreed to participate. There was no patient with severe visual disorder, hearing loss or cognitive disorder that would impair patient's interaction with the app. Patients with one of these conditions would be excluded from the study.

Pilot study and sample calculation

In the pilot phase, the beta version of the app was used with 10 patients, who gave their feedback to questions about usability, written and visual language, understanding of information, design and adequacy of time for scrolling the screens. Before the appointment, a questionnaire developed by the investigators was administered to measure the mean level of knowledge about AF in this population. This questionnaire sought to evaluate the minimum essential information required for the patient to understand their condition and adhere to the treatment. Patients were asked to answer each of eight statements with "true", "false" or "don't know". All statements were true. Mean number of correct answers was 5.9 ± 1.37 (73% of correct answers). In a previous study conducted at the same service, 64% of patients had adequate knowledge about the therapy.[19] Considering that the number of correct answers was estimated to increase to 8 (100% of correct answers) after the explanatory intervention, 18 patients were required for a 5% alpha error and a beta error of 90%.

Outcome measures

After adjustments made after the feedback of the pilot study patients, the app was tested in a sample of 20 patients.

As the primary outcome, we analyzed the scores obtained by the patients in the AF knowledge questionnaire before and after the interaction with the app.

As secondary outcome, we evaluated patients' scores in the Decisional Conflict Scale in Health (DCSH) by O'Connor,[20] used to evaluate strategies for shared decision-making in health care.[20,21] DCSH was validated in Portuguese in 2013 by Martinho et al.[22] and included questions on uncertainties, knowledge, values and provided support. The total score varied from 0 (no decisional conflict) to 100 (extremely high decisional conflict). Also as a secondary outcome, we analyzed the perceived risk of stroke and bleeding with the use of OAC. Patients were asked if they believed they had a low, moderate, or high risk of each event. This question was repeated after the interaction with the app, and results were compared with the "real" risk, calculated by the CHA_2DS_2-VASc and HAS-BLED scores.

Data analysis

Data were analyzed using the SPSS software version 20.0. Tables of absolute and relative frequencies were used for sample characterization. Normality of data was tested by the Shapiro-Wilk test.

Continuous variables with normal distribution were expressed as mean and standard deviation, and those with non-normal distribution as median and interquartile ranges. Mean knowledge scores about the disease, before and after the intervention, were compared using the paired Student's t-test and risk perception was compared with the Wilcoxon test. The level of significance was set at $p < 0.05$.

Ethical considerations

The study was approved by the Research Ethics Committee of the Institute of Cardiology University Foundation. Privacy, anonymity and confidentiality of data collected were guaranteed, and informed consent form was presented to the patients.

Results

Mean age of the 20 patients studied was 67.7 years; most patients were men (60.0%), white (83.3%) and lived with their relatives (53.3%). Self-reported educational level was some secondary education in 73.3% of patients, and 33.3% studied less than 4 years. Family income was lower than 2 minimum wages in 53.3% of patients. Most patients (66.7%) used anticoagulants for at least one year. Table 1 summarizes the socioeconomic characteristics and clotting time of the study population.

Table 2 shows the prevalence of the main risk factors included in the CHA2DS2-VASc, HAS-BLED and SAMe-TT2R2 scores, and the mean ratings obtained by the patients in these scores. The most prevalent comorbidities were arterial hypertension (80%), diabetes *mellitus* (30%), and heart failure (30%). With respect to other factors that may influence the risk of bleeding and anticoagulation, the most common factors were the use of medications that interact with coumarins (43.3%), and the use of antiplatelet or anti-inflammatory drugs (26.7%). Most patients (86.6%) had a CHA2DS2-VASc score equal to or greater than 2 and 76.6% of patients had a SAMe-TT2R2 score equal to or greater than 2.

The number of correct answers in the disease knowledge questionnaire significantly increased after the interaction with

Table 1 – Socioeconomic characteristics of the population and time in anticoagulation therapy

Characteristics	
Age (years)	67.7 ± 9.4
Male sex (%)	60
White (%)	83.3
Who patients live with	
Alone (%)	16.7
Companion (%)	26.7
Family (%)	53.3
Institutionalized (%)	3.3
Schooling years	
0-4 years (%)	33.3
5-8 years (%)	40
> 8 years (%)	26.7
Family income	
4-10 minimum wages (%)	26.7
2-4 minimum wages (%)	20
< 2 minimum wages (%)	53.3
Time in anticoagulation therapy	
< 1 month (%)	13.3
1 – 11 months (%)	13.3
1-5 years (%)	33.3
> 5 years (%)	33.4
Not in current use	3.3

Table 2 – Prevalence of the variables present in the CHA_2DS_2-VASc, HAS-BLED and SAMe-TT2R2 scores and average scores

Systemic arterial hypertension (%)	80
Systolic blood pressure > 160 mmHg (%)	10
Diabetes Mellitus (%)	30
Congestive heart failure and ejection fraction < 40% (%)	30
Cardiovascular disease (%)	23.3
Stroke or transient ischemic accident (%)	16.7
Liver disease* (%)	0
Kidney disease † (%)	6.7
Pulmonary disease (%)	16.7
Labile or difficult-to-control INR ‡ (%)	23.3
History of or predisposition to major bleeding (%)	16.7
Use of antiplatelet or anti-inflammatory agents (%)	26.7
Use of medications that interact with coumarins (%)	43.3
Abusive use of alcohol (%)	3.3
Smoking (%)	10
CHA_2DS_2-VASc ≥ 2 § (%)	86.6
CHA_2DS_2-VASc per score (%)	
0	3.3
1	10
2	23.4
3	23.4
4	20
5	13.3
7	3.3
8	3.3
Mean CHA_2DS_2-VASc	3 ± 1.8
Mean HAS-BLED	2 ± 1.2
SAMe-TT2R2 ≥ 2 // (%)	76.6

** Chronic liver disease (e.g.: cirrhosis), or biochemical evidence of significant liver dysfunction (bilirubin > 2 - 3 times the upper level, transaminase or alkaline phosphatase > 3 times the upper level); † Chronic hemodialysis, kidney transplant, serum creatinine > 2.2 mg/dl; ‡ in the target range < 60% of times; § A score ≥ 2 indicates the necessity of anticoagulation; // A score ≥ indicates patients who require additional interventions to achieve an acceptable anticoagulation control with coumarins.*

the application, from 4.7 (± 1.8) to 7.2 (± 1.0), $p < 0.001$. Figure 2 depicts the mean number of correct answers before and after the interaction.

DCSH administered to the patients after selecting the therapy with the aid of the app resulted in an average of 11 ± 16/100 points.

Regarding risk perception, before interacting with the app, 20% of patients had an appropriate perception of their risk of stroke, and 75% believed to have a risk lower than the real risk. After the interaction, adequate perception increased to 30%, with a non-significant p-value (0.608). With respect to the risk of bleeding, before using the app, 45% of patients had a correct perception and 35% believed they had a higher risk than the real one. After using the app, there was a non-significant increase (0.218) in the adequate perception for 60% of patients. Figure 3 depicts variations in risk perception.

Discussion

The development of mHealth apps for specific populations and health problems is viable and should be stimulated. This study with low income and low educational level patients demonstrated increased knowledge about AF and anticoagulation after the use of the app, enabling a shared decision-making about anticoagulation, with low decisional conflict. However, the perception of stroke and bleeding risk was not affected by the application use.

Thromboembolic prophylaxis in AF is a global problem. It is generally underused, of difficult management and known to be prone to poor adherence.[23] One of the proposed strategies to optimize the use of OAC is the shared decision-making, which is currently recommended in the guidelines as part of an integrated management of the disease, and a clinical performance indicator.[8,24] Patients' understanding of the therapy and their individual risk-benefit analysis is crucial in this process.[25] Nevertheless, there are significant gaps in this knowledge, even in patients treated for years.[18]

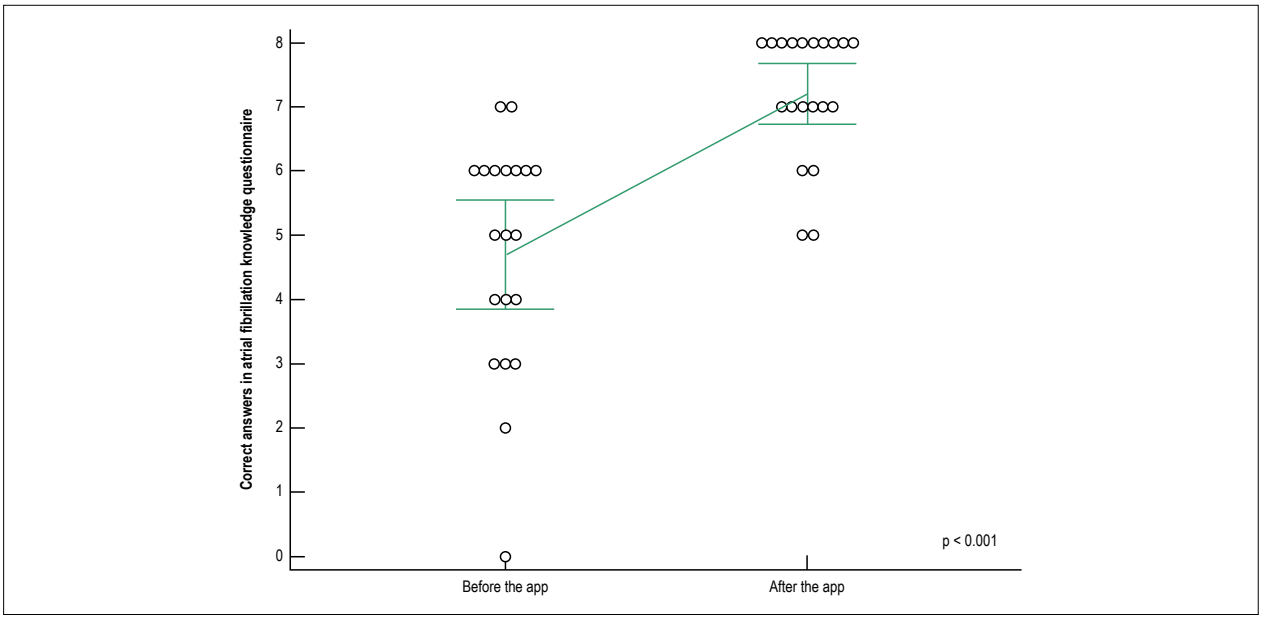

Figure 2 – *Mean number of correct answers in the questionnaire about the disease before (4.7) and after (7.2) the intervention, compared by the paired-sample t test, indicating a significant increase in patients' knowledge after interacting with the application. Error bars indicate standard deviations, and circles represent the score of each patient.*

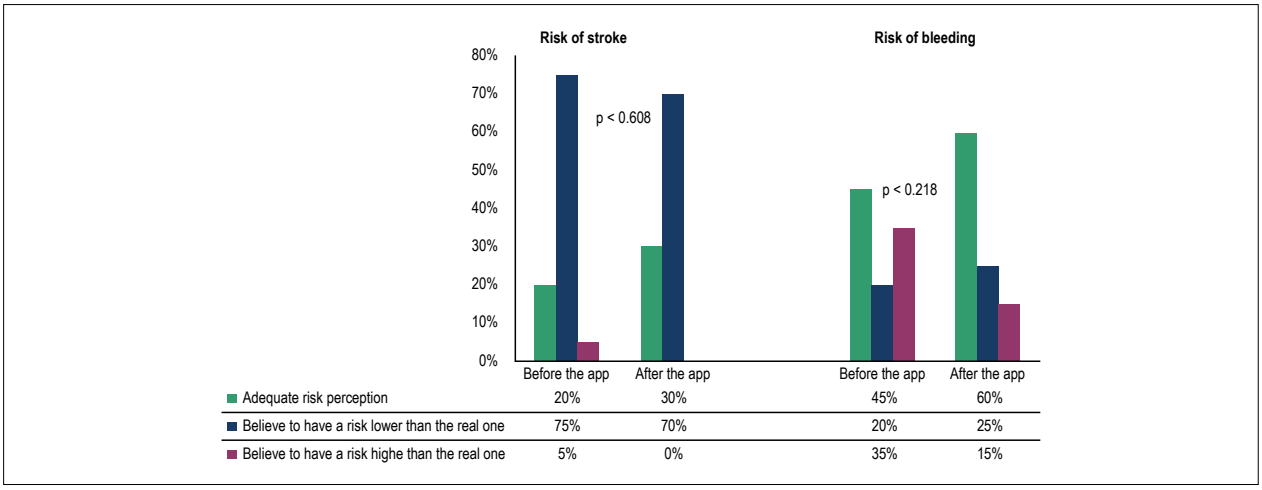

Figure 3 – *Risk perception of stroke and bleeding by the patients before and after interacting with the application compared with the real risk, calculated by the CHA_2DS_2-VASc and HAS-BLED scores, showing a non-significant increase in the adequate perception of the risk. Comparisons were performed by the Wilcoxon test.*

Several studies have mentioned instruments that facilitate shared decision-making strategies of anticoagulation in AF, by means of behavior change and patients' education using leaflets, and interventions using videos and softwares. A Cochrane meta-analysis published in 2013 reviewed these studies, and concluded that there is no sufficient evidence that evaluate the impact of these strategies on the International Normalized Ratio in therapeutic range (TTR, time in therapeutic range).[26] Another recent review concluded that decision-making strategies with patients' participation are powerful tools to improve the management of AF and that these instruments should be developed and tested.[18] Subsequently, the TREAT study, a randomized, controlled study of behavioral intervention in patients who had recently initiated warfarin, showed a significant improvement of TTR in six months, compared with usual care.[27] Another study involving a multidisciplinary intervention for patients with AF, which included a decision support software, and was conducted and supervised by nurses and cardiologists, respectively, demonstrated a significant reduction in the number of cardiovascular deaths and hospitalization (14.3 vs. 20.8%; risk ration of 0.65; 95% CI 0.45–0.93).[28]

These interventions are based on the premise that the healthcare professional is responsible for the provision of essential information to the patient and for stimulating the patient to search for knowledge. In this context, technology shows up as an allied, by improving information access, organization, transmission and retention. In particular, mobile technology introduces a new era of health care, by bringing care closer to the patient and allowing a better doctor-patient interaction.

In this rapidly expanding market, in 2015, there were 45,000 mHealth publishers and more than 3 billion mHealth app downloads.[29] Current evaluations are, in general, favorable. A recent analysis of the American Heart Association on mHealth and cardiovascular disease prevention included 69 apps for weight loss, increase in physical activity, smoking cessation, glycemic control, hypertension and dyslipidemia. Despite heterogeneous, positive results were found for the proposed behavioral changes, and future studies using more rigorous methodology, more diversified samples and a long-term follow-up were suggested to evaluate the duration of the effects.[30]

With respect to the target populations, the literature highlights the necessity of these technologies to encompass other specific populations – older subjects with age-related changes (e.g. reduced vision or mobility), minorities in need of culturally sensitive contents and interventions, and low-income adults with inconsistent access to mobile communication.[30-32]

AF is a largely explored subject in mHealth. Most studies have reported the use of home monitoring devices for heart rate. With regards to patients' education, the American Heart Association and the European Society of Cardiology have high-quality applications and web materials in English that help in the shared decision-making process.[33,34] There are also many risk calculation methods available for the clinical practice. However, neither the development process nor the evaluation of these apps is described in the literature. Also, we have not found any support instrument for shared decision-making in AF, be it in mHealth or in other media.

A strength of our study was the development of the app based on evidence, taking into account many factors mentioned in guidelines of shared decision making and care of anticoagulated patients.[25,35] The level of patients' previous knowledge was analyzed, and the learning style was adequate to their preferences of terminology and navigability. The amount and detail of information was adjusted, and could be increased or reduced, according to each individual's understanding.

Another advantage was the fact that patients' evaluation could be saved for further analyses by other professionals, indicating the role of the instrument as a bridge in the multidisciplinary care. In an integrated outpatient service, for example, the patient could watch the video and have their risk factor evaluated during the screening process and focus on treatment during the medical visit.

In addition, the selected population was appropriate for implementing a shared decision strategy. Most patients had a SAMe-TT2R2 score equal to or greater than two, suggesting a lower probability to maintain anticoagulation at acceptable levels with coumarins and hence a greater necessity for strategies for an adequate control.

Results of the analysis of patients' risk perception showed how this understanding is inappropriate and requires attention. Most patients believed they had a stroke risk lower than the calculated and one third of patients believed they had a bleeding risk with the use of OAC higher than the calculated. Other studies showed similar results on awareness of the risk of stroke.[36,37] Such inadequate understanding may lead to poor treatment adherence, since patients do not perceive themselves to be at risk for thromboembolic events and also believe they have a high risk of bleeding using the medication. After interacting with the app, no significant change in risk perception was observed. In attempt to improve such perception, the following observation was added to the second version of the app, currently under test: "This risk is considered LOW/INTERMEDIATE/HIGH", with a color code to each level of risk (green/yellow/red), together with the percentages exhibited on the screen "Understanding risks and benefits".

Several limitations are inherent to the development of an instrument that utilizes a relatively new technology for our population. Although the screen size, the visual communication methods and the terminology had been carefully considered, they still can be inadequate for some patients. Besides, even though the information provided to the patients had been adapted to the patients, the fact that it had been excessive in some cases and not maintained after some months cannot be ruled out. It is expected that the continuous provision of information by SMS compensate part of this issue. Besides, the interaction with the app may be repeated in other visits whenever necessary.

The small number of patients studied may also be questioned. Nevertheless, in studies evaluating the usability of apps, the number of subjects involved is usually small and shown sufficient.[38] Another current limitation is the necessity of a long-term evaluation of the outcomes, such as the TTR, adherence and occurrence of thromboembolic events and bleeding. This limitation is expected to be eliminated with a randomized intervention study, by using the app in the care of our patients attending the anticoagulation outpatient service and comparing the results with the care currently provided.

Conclusions

The use of the mHealth app during the medical visit about anticoagulation in AF improves disease knowledge and the treatment of low-income patients with low educational level, enabling a shared decision with low decisional conflict. Further studies are needed to confirm whether such improvement can be translated into hard outcomes.

Author contributions

Conception and design of the research, Writing of the manuscript and Critical revision of the manuscript for intellectual content: Stephan LS, Almeida ED, Guimarães RB, Ley AG, Mathias RG, Assis MV, Leiria TLL; Acquisition of data:

Stephan LS, Almeida ED, Guimarães RB, Ley AG; Analysis and interpretation of the data and Statistical analysis: Stephan LS, Almeida ED, Guimarães RB, Ley AG, Leiria TLL; Obtaining financing: Stephan LS, Leiria TLL.

Potential Conflict of Interest

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

Sources of Funding

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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 de Cardiologia / Fundação Universitária de Cardiologia under the protocol number 5043/14. 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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Association of Multiple Genetic Variants with the Extension and Severity of Coronary Artery Disease

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Abstract

Background: **Metabolic syndrome (MS) is a condition that, when associated with ischemic heart disease and cardiovascular events, can be influenced by genetic variants and determine more severe coronary atherosclerosis.**

Objectives: **To examine the contribution of genetic polymorphisms to the extension and severity of coronary disease in subjects with MS and recent acute coronary syndrome (ACS).**

Methods: **Patients (n = 116, 68% males) aged 56 (9) years, with criteria for MS, were prospectively enrolled to the study during the hospitalization period after an ACS. Clinical and laboratory parameters, high-sensitivity C-reactive protein, thiobarbituric acid reactive substances, adiponectin, endothelial function, and the Gensini score were assessed. Polymorphisms of paraoxonase-1 (PON-1), methylenotetrahydrofolate reductase (MTHFR), endothelial nitric oxide synthase (ENOS), angiotensin-converting enzyme (ACE), angiotensin II type 1 receptor (AT1R), apolipoprotein C3 (APOC3), lipoprotein lipase (LPL) were analysed by polymerase chain reaction (PCR) technique, followed by the identification of restriction fragment length polymorphisms (RFLP, and a genetic score was calculated. Parametric and non-parametric tests were used, as appropriate. Significance was set at $p < 0.05$.**

Results: **Polymorphisms of PON-1, MTHFR and ENOS were not in the Hardy-Weinberg equilibrium. The DD genotype of LPL was associated with higher severity and greater extension of coronary lesions. Genetic score tended to be higher in patients with Gensini score < P50 (13.7 ± 1.5 vs. 13.0 ± 1.6, p = 0.066), with an inverse correlation between genetic and Gensini scores (R = –0.194, p = 0.078).**

Conclusions: **The LPL polymorphism contributed to the severity of coronary disease in patients with MS and recent ACS. Combined polymorphisms were associated with the extension of coronary disease, and the lower the genetic score the more severe the disease. (Arq Bras Cardiol. 2018; 110(1):16-23)**

Keywords: **Coronary Artery Disease / genetic; Polymorphism, Genetic; Metabolic Syndrome; Sedentary Lifestyle.**

Introduction

Ischemic heart disease and stroke account for the majority of deaths in the world.[1] With progressive urbanization, adoption of a sedentary lifestyle and better access to packaged food, increasing incidence of obesity and overweight has been observed in the population,[2] accompanied by an increase in metabolic disorders and cardiovascular risks. The concept of metabolic syndrome (MS) was first described by Reaven, as a relationship between insulin resistance, arterial hypertension, lipid abnormalities and visceral obesity.[3,4]

MS has been associated with higher rates of fatal and non-fatal cardiovascular events.[5,6] Its high prevalence in acute coronary syndrome (ACS) has also been associated with greater anatomical obstruction.[7] Our group showed that patients with MS and ACS had lower insulin sensitivity, severe coronary artery disease (CAD) associated with high levels of C-reactive protein (CRP) and low IgG antibody titers to oxidized low-density lipoprotein,[8-10] associated with greater extension of CAD.[11]

Some studies have explored the association of genetic variants with cardiovascular outcomes.[12-16] Large Mendelian randomization studies have allowed the understanding of the effects of some clinical parameters throughout life, such as LDL-c, HDL-c and triglycerides on cardiovascular risk, as well as the protective effect of polymorphisms associated with lower systolic blood pressure.[17-19] Although hypothetical, the effects of polymorphisms have been associated with the extension and severity of CAD.[20-22]

Smaller studies, systematic review and meta-analyses have proposed genetic variants associated with CAD, as well as genetic scores to identify individuals at higher cardiovascular risk,[23-25] since many genetic variants with only modest individual effect may have a larger impact when a greater

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number of genetic polymorphism is evaluated. Therefore, the use of genetic scores that evaluate the additional effect of each of these genetic variants may be relevant in the early identification of individuals at higher cardiovascular risk, who may benefit from differential attention.[23-25]

We chose polymorphisms related to lipid metabolism, lipoprotein oxidation, blood pressure changes and vasoreactivity to determine their possible association with coronary atherosclerosis severity in patients with MS and recent ACS. Studies on genetic polymorphisms in MS patients who developed ACS are poorly described in the literature, which reinforces the importance of the present study. We examined the contribution of combined and isolated genetic polymorphisms of potential importance in cardiovascular disease, by a genetic score, to the extension and severity of coronary obstructive disease in patients at very high cardiovascular risk.[26]

Methods

Subjects

A total of 116 consecutive patients of both sexes, mean age 56 ± 9 years, with 3 or more criteria for MS according to the NCEPIII[4] were prospectively assessed during hospitalization for ACS (acute myocardial or unstable angina).

Inclusion criteria:

1. Men and women aged from 30 to 75 years;
2. Understanding and agreement in giving written consent.
3. Two or more ACS criteria including chest pain, increased enzyme levels and electrocardiographic changes;
4. Three or more MS criteria,[4]
5. LDL-c < 130 mg/dL, HDL-c < 40 mg/dL in the first 24 hours of hospitalization;

Exclusion criteria:

1. Use of hypolipidemic agents in the last 30 days;
2. Uncontrolled hypothyroidism (TSH > 8.0 μU/mL);
3. Infections, inflammatory diseases, active liver or kidney diseases;
4. Pregnant women, patients selected for surgeries, including myocardial revascularization in the next six weeks or patients who underwent surgeries during hospitalization.

Ethical aspects

The study protocol was approved by the Research Ethics Committee and the study was conducted according to the Helsinki Declaration. All patients signed the informed consent form before participating in any study procedure.

Study design

This was a prospective study that included hospitalized patients after ACS. Genetic polymorphisms related to lipid and lipoprotein metabolism, oxidative stress, endothelial function and blood pressure were evaluated.

Clinical evaluation

Clinical evaluation and blood collection for laboratory measurements were performed in the first three days of hospital discharge. Demographic data, risk factors, medical history, clinical examination, anthropometric data (weight, height, waist circumference), systolic and diastolic blood pressure were obtained.[27,28]

Blood collection for laboratory tests

Blood was collected after 12 hours of fasting and laboratory tests were performed at the *Associação Fundo de Apoio à Psicobiologia* (AFIP - Psychobiology Support Fund Association). Genetic tests were carried out at the Molecular Biology Laboratory of the Division of Lipids, Atherosclerosis and Vascular Biology.

Biochemical tests

Lipid profile (total cholesterol, LDL-c, HDL-c, triglycerides) was analyzed by automated method (Ópera, Bayer, Germany); glucose levels were determined by colorimetric reaction (ADVIA 1650 Chemistry System, USA), glycated hemoglobin (HbA1-c) was determined by high performance liquid chromatography (HPLC, Tosoh A1c 2,2 plus, USA). Mean insulin at -15min, -5min and 0min was assessed by direct chemiluminescence method (ADVIA Centaur, USA) with values expressed as μU/mL. Apolipoproteins A1, B and Lp(a) were analyzed by nephelometry (R100 analyzer, Behringer). Adiponectin was determined by ELISA (enzyme-linked immunosorbent assay), using the Humam Adiponectin/Acrp30 Immunoassay kit – Quantiquine, R&D Systems, and the BioTek ELx800 Absorbance Microplate Reader, with values expressed as ng/mL.

Albuminuria was assessed in 12-hour overnight urine samples, and measured by immunoturbidimetric method (ADVIA 1650, Chemistry System, USA), with results expressed as mg/L.

Plasma oxidative stress was analyzed by TBARS (Thiobarbituric acid reactive substances) test, as described by Ohkawa et al.,[29] and measured using a spectrophotometer (Genesys 2, Spectronic); the results were expressed as nanomoles of malondialdehyde (MDA) per milliliter of plasma (ηmoles/mL plasma).

Vasoreactivity

Endothelium-dependent (FMD, flow-mediated dilation) and endothelium-independent (EIR, endothelium-independent relaxation) vasodilation tests were performed in the morning, after a 12-hour fast by an experient ultrasound technician according to the International Brachial Artery Reactivity Task Force guidelines.[30] An ultrasound system (Sonos 5500; Hewlett-Packard-Phillips, Palo Alto, CA) was used, equipped with a vascular software for two-dimensional imaging, color and spectral Doppler, internal electrocardiogram (ECG) monitor and a linear array transducer (with a frequency of 7.5-12.0 MHz). Image acquisition, FMD and EIR measures with isosorbide dinitrate (5mg; sublingual) were performed. Percentage variations in vessel diameter were calculated for

FMD and EIR determination, and expressed as percentage. Intra- and inter-observer variability were < 1% and 2%, respectively.

Gensini score

Gensini score was used to classify CAD severity determined by cineangiography. Gensini score is calculated taking into account the magnitude of the lesions and the myocardium at risk, assigning different ratings to different levels of obstruction in the segments affected. A 25%, 50%, 75%, 90%, 99% and 100% obstruction were given, respectively, the scores 1, 2, 4, 8, 16 and 32. The method also assigned a different score depending on the lesion location - left coronary trunk (5 points), proximal anterior descending artery (2.5 points), middle third of the anterior descending artery (1.5 point), distal anterior descending artery (1 point), second diagonal artery (0.5 point), proximal and distal right coronary artery and posterior descending branch (1 point). Gensini score results from the sum of individual scores given to each lesion, multiplying the stenosis severity by the lesion location; results were expressed as arbitrary units (AU).[11,31]

Genetic study

Polymorphisms of the genes paraoxonase-1 (*PON-1*), methylenotetrahydrofolate reductase (*MTHFR*), endothelial nitric oxide synthase (*ENOS*), angiotensin-converting enzyme (*ACE*), angiotensin II type 1 receptor (*AT1R*), apolipoprotein C3 (*APOC3*), lipoprotein lipase (*LPL*) were analyzed from total blood samples, collected with EDTA (ethylenediaminetetraacetic acid), using the polymerase chain reaction (PCR) technique, followed by the identification of restriction fragment length polymorphisms (RFLP), under conditions described in Table 1. Genetic score was calculated assuming the dominant model of the polymorphisms, which were considered as binary, dichotomous variables.

Statistical analysis

Sample size was estimated for comparisons between proportions, considering the polymorphism dominant model, an α error of 5%, a β power of 80%, a 95% confidence interval, and an expected proportion of 50%. The estimated sample size was of 90 participants. All analyses were performed using the SPSS 22.0 for Mac. Categorical variables were expressed as n (%) and compared between the genotypes using the Pearson's chi-square test or the Fisher's exact test, as appropriate. The chi-square test was used to analyze whether the distribution of observed and expected genotypic frequencies were in the Hardy–Weinberg equilibrium. Numerical variables were expressed as mean ± standard deviation or as median and interquartile range. The Kolmogorov – Smirnov test was used to evaluate whether the variables were normally distributed. For descriptive statistics, in case the variables were not normally distributed, the Student's t test and the Mann Whitney test were used for unrelated samples. Pearson correlation was used to evaluate the correlations between the genetic score and the Gensini score. P-values lower than 0.05 were considered statistically significant.

Results

A total of 116 patients were evaluated. Baseline characteristics of participants are described in Table 2.

Table 3 presents the distribution of allele and genotypic frequencies of the studied polymorphisms. The *PON-1, MTHFR* and *ENOS* genes were not in the Hardy-Weinberg equilibrium in the study population.

Distribution of clinical, demographic and laboratory characteristics

Results were analyzed by genetic polymorphism. The results are presented in details in electronic version in the Supplementary

Table 1 – Conditions for amplification and digestion of the studied polymorphisms

Polymorphism	Starters	Annealing temperature	Cycles	Restriction enzyme
PON-1 Q192R	*Forward*: 5'-TATTGTTGCTGTGGGACCTGAG-3' *Reverse*: 5'-CACGCTAAACCCAAATACATCTC-3'	61°C	35	Alw I
MTHFR C677T	*Forward*: 5'-GAAGCAGGGAGCTTTGAGG-3' *Reverse*: 5'-ACGATGGGGCAAGTGATG-3'	63°C	32	Hinf I
ENOS G894T	*Forward*: 5'-CTGGAGATGAAGGCAGGAGAC-3' *Reverse*: 5'-CTCCATCCCACCCAGTCAATC-3'	56°C	35	Ban II
ACE I/D	*Forward*: 5'-CTGGAGACCACTCCCATCCTTTCT-3' *Reverse*: 5'-GTCTCGATCTCCTGACCTCGTG-3'	55°C*	32	-
AT1R A1166C	*Forward*: 5'-AATGCTTGTAGCCAAAGTCACCT-3' *Reverse*: 5'-GGCTTTGCTTTGTCTTGTTG-3'	59°C	35	Dde I
LPL D9N	*Forward*: 5'-AAAATCAAGCAACCCTCAAG-3' *Reverse*: 5'-TAGGGCAAATTTACTTGCGA-3'	57°C*	35	Taq I
APOC3 SST I	*Forward*: 5'GGTGACCGATGGCTTCAGTT-3' *Reverse*: 5'-CAGAAGTGGATAGAGCGCT-3'	58°C	30	Sst I

** the touchdown PCR protocol was used for the ACE and LPL genes*

Table 2 – Demographic and clinical characteristics of participants

Variable	n = 116
Male (%)	74 (68)
Age (years)	56 ± 9
Hypertension (%)	104 (90)
Smoking (%)	35 (30)
Diabetes mellitus (%)	36 (31)
AMI (%)	55 (47)
Unstable angina (%)	61 (53)
Stroke (%)	9 (8)
PVD (%)	12 (10)
BMI (Kg/m^2)	30.2 ± 4.7
Waist circumference (cm)	104.4 ± 10.8
Systolic arterial pressure (mmHg)	132 ± 24
Diastolic arterial pressure (mmHg)	86 ± 16
Heart rate (bpm)	68 ± 13
Gensini score (au)	21 (0-36)
Gensini ≥ median (%)	42 (51)
FMD (%)	13.7 ± 8.6
EIR (%)	14.9 (7.3-18.8)

Categorical variables expressed as N (%); numerical variables expressed as mean ± standard deviation or median and interquartile ranges. PVD: peripheral vascular disease; FMD: flow-mediated dilation; AMI: acute myocardial infarction; BMI: body mass index, EIR: endothelium-independent relaxation; AU: arbitrary units.

Tables 1-14 (access the link: http://publicacoes.cardiol.br/portal/2017/abc/english/v11001/pdf/i11001005_anexo.pdf). For didactic purposes, data are presented by genotype, considering the R allele of *PON-1*, the T allele of *MTHFR*, the T allele of *ENOS*, the D allele of *ACE*, the C allele of *AT1R*, the S1 allele of *APOC3* and the N allele of *LPL* as risk alleles.

Summary of findings

For the *PON-1* gene, hs-CRP (mg/dL) values were higher in the QQ genotype as compared with the QR/RR genotype [(12.8 (6.7-24.1) vs. 7.0 (4.8-16.5), p = 0.029] (Supplementary Tables 1 and 2), (access the link: http://publicacoes.cardiol.br/portal/2017/abc/english/v11001/pdf/i11001005_anexo.pdf). For the *MTHFR* gene, HbA1-c (%) and adiponectin (ng/mL) levels were higher in the CT/TT genotype as compared with the CC genotype [6.0 (5.5-7.3) vs. 5.7 (5.2-6.6); p = 0.031 and 6.996 ± 5.032 vs. 4.990 ± 3.165; p = 0.015] (Supplementary Tables 3 and 4), access the link: http://publicacoes.cardiol.br/portal/2017/abc/english/v11001/pdf/i11001005_anexo.pdf. In addition, fasting glucose (mg/dL), HbA1c (%) and adiponectin levels (ng/mL) were higher in GT/TT vs. GG genotypes [(127 ± 48 vs. 106 ± 12, p = 0,001; 6,6 ± 1,9 vs. 5,9 ± 0,6, p = 0,028; 5010 (2688-10139) vs. 2148 (1912-3435), p = 0,011] (Supplementary Tables 5 and 6), (access the link: http://publicacoes.cardiol.br/portal/2017/abc/english/v11001/pdf/i11001005_anexo.pdf). For the ACE gene, heart rate (bpm) was higher in the ID/DD genotype compared with the II genotype (71 ± 13 vs. 65 ± 11, p = 0.042 (Supplementary Tables 7 and 8), (access the link: http://publicacoes.cardiol.br/portal/2017/abc/english/v11001/pdf/i11001005_anexo.pdf). Polymorphisms in the *AT1R* gene

Table 3 – Distribution of allele and genotypic frequencies for the polimorphisms of PON-1, MTHFR, ENOS, ECA, AT1R, APOC3 and LPL genes

Gene	Allele frequency		Genotypic frequency (%)			p-value (Hardy Weinberg)
PON-1	Q	R	QQ	QR	RR	
	0.63	0.37	36 (31)	76 (65)	4 (4)	0.0004
MTHFR	C	T	CC	CT	TT	
	0.61	0.39	35 (30)	72 (62)	9 (8)	0.0131
ENOS	G	T	GG	GT	TT	
	0.43	0.57	10 (9)	80 (69)	26 (22)	0.0006
ACE	I	D	II	ID	DD	
	0.33	0.67	17 (15)	42 (36)	57 (49)	0.1955
AT1R	A	C	AA	AC	CC	
	0.75	0.25	70 (60)	35 (30)	11 (10)	0.2351
APOC3	S1	S2	S1S1	S1S2	S2S2	
	0.16	0.84	2 (2)	33 (28)	81 (70)	0.8310
LPL	D	N	DD	DN	NN	
	0.34	0.66	17 (15)	45 (39)	54 (46)	0.3095

PON-1: paraoxonase-1; MTHFR: methylenotetrahydrofolate reductase; ENOS: endothelial nitric oxide synthase; ACE: angiotensin-converting enzyme; AT1R: angiotensin II type 1 receptor; APOC3: apolipoprotein C3; LPL: lipoprotein lipase. p < 0.05, chi-square test. Expected vs. observed genotypic frequencies were not in the Hardy-Weinberg equilibrium in the studied population

had no effect on clinical or laboratory variables (Supplementary Tables 9 and 10), (access the link: http://publicacoes.cardiol.br/portal/2017/abc/english/v11001/pdf/i11001005_anexo.pdf).

For the APOC3 gene, FMD (%) was higher among S2S2 patients than in S1S1/S1S2 patients (14.7 ± 9.6 vs. 11.5 ± 5.2, p = 0.026) (Supplementary Tables 11 and 12), (access the link: http://publicacoes.cardiol.br/portal/2017/abc/english/v11001/pdf/i11001005_anexo.pdf), and for the LPL gene, diastolic arterial pressure (mmHg) was lower in the DD genotype as compared with DN/NN (79 ± 15 vs. 87 ± 16, p = 0.043). In addition, a more severe degree of coronary atherosclerosis, evaluated by the Gensini score > median (%) value was found in patients with DD genotype compared with DN/NN (77% vs. 46%, p = 0.039) (Supplementary Tables 13 and 14) (access the link: http://publicacoes.cardiol.br/portal/2017/abc/english/v11001/pdf/i11001005_anexo.pdf).

Associations of genotypes with CAD extension and severity

A dominant model was assumed, as well as the score from 1 to 3 for the isolated genotypes – 1 for absence of risk allele; 2 for the presence of one risk allele; and 3 for the presence of 2 risk alleles in the same gene. Then, score 1 was assigned to the genotypes QQ of *PON-1*, CC of *MTHFR*, GG of *ENOS*, II of *ACE*, AA of *AT1R*, S2S2 of *APOC3* and DD of *LPL*. The score 2 was assigned to the genotypes QR of *PON-1*, CT of *MTHFR*, GT of *ENOS*, ID of *ACE*, AC of *AT1R*, S1S2 of *APOC3* and DN of *LPL*. The score 3 was assigned to the genotypes RR of *PON-1*, TT of *MTHFR*, TT of *ENOS*, DD of *ACE*, CC of *AT1R*, S1S1 of *APOC3* and NN of *LPL*.

The sum of the values assigned to each gene (7-21) yielded a genetic score, which was evaluated in absolute values and also in relation with the median (above or below) value. Correlations between genetic and Gensini scores were performed in absolute values and in relation to the median. Results are described in Table 4 and Supplementary Table 15 (access the link: http://publicacoes.cardiol.br/portal/2017/abc/english/v11001/pdf/i11001005_anexo.pdf). Both genetic and Gensini scores had a normal distribution.

Table 4 – Distribution of genetic score considering all polymorphisms of the PON-1, MTHFR, ENOS, ACE, AT1R), APOC3 and LPL genes

Genetic score	
N	116
Mean	13.3
Median	13.5
Standard deviation	1.58
Minimum	10
Maximum	17
Asymmetry	-0.263
Kurtosis	-0.146
P25	12.0
P75	14.0

PON-1: paraoxonase-1; MTHFR: methylenotetrahydrofolate reductase; ENOS: endothelial nitric oxide synthase; ACE: angiotensin-converting enzyme; AT1R: angiotensin II type 1 receptor; APOC3: apolipoprotein C3; LPL: lipoprotein lipase.

Genetic score tended to be higher in patients with a Gensini score < 50th percentile (13.7 ± 1.5 vs. 13.0 ± 1.6; p = 0.066, Student's t test for independent samples).

Gensini score was not different between genetic scores above and below the median (p50) [26 (0.00-44.00) vs. 18 (0.25-33.70), P=0.329]. In this population of patients with recent ACS and MS, a weak, inverse correlation was observed between the genetic and the Gensini scores (R = –0.194, p = 0.078, Pearson correlation coefficient).

Discussion

The present study demonstrated that the genetic polymorphisms analyzed in patients with MS and recent ACS had a modest association with the severity of obstructive coronary disease. Only the DD genotype of D9N polymorphism of LPL was associated with higher prevalence of more severe coronary lesions. Analysis of the genetic score revealed that the combinations of the studied polymorphisms showed a trend of negative correlation with the anatomical extension of the coronary disease. This finding suggests that in these MS patients, coronary disease may be primarily associated with other mechanisms, with a strong environmental influence.

Many of the studied polymorphisms were associated with clinical and laboratory variables, such as heart frequency, diastolic arterial pressure, CRP, HbA1c and adiponectin.

A study involving six polymorphisms of LPL, including the D9N, showed that the severity of obstructive lesions, analyzed by the Gensini score, was associated with LPL haplotypes.[32] Corsetti et al.[33] showed an interaction of D9N polymorphism with Taq1B of CETP, which was a predictor of cardiovascular disease risk in women. In addition, *LPL* polymorphisms have been associated with increased concentrations of triglycerides;[34] in our study, a trend towards higher values was found for the DD genotype as compared with the DN/NN genotype (p = 0.07), possibly due to the high prevalence of overweight/obesity and changes in glucose metabolism in these MS patients.

APOC3 polymorphism has an important role in the metabolism of triglyceride-rich lipoproteins and an influence on the development of CAD, particularly in MS and diabetes, with an association of haplotypes in the AI-C3-AIV gene cluster with coronary disease.[35]

Renin-angiotensin system genetic polymorphisms (I/D of *ACE* and *AT1R*) were not associated with CAD severity in our study. However, the ACE gene was previously associated with higher ACE levels in D/D patients with CAD,[36] which was not confirmed in a larger sample.

In our study, the 192R allele of *PON-1* was associated with higher CRP levels, which is a biomarker of cardiovascular outcomes. In a large, three-year follow-up study (n = 3668), arylesterase activity, but not paraoxonase levels or PON-1 polymorphism, was associated with cardiovascular outcomes.[37]

For the *MTHFR* C677T polymorphism, a meta-analysis (n = 6912) demonstrated its association with early CAD,[38] with higher homocysteine levels in the presence of T allele.[39] In our study, CT/TT individuals had higher HbA1c and adiponectin levels as compared with CC individuals.

ENOS polymorphisms are involved in endothelial dysfunction. The T allele of the G894T polymorphism

showed lower levels of nitric oxide and an association with CAD.[40] The variant allele -786T (promoter region) was associated with CAD in a meta-analysis.[41]

Genetic score was inversely associated with greater extension and higher severity of CAD. In this population with MS, environmental factors may have an impact on the modulation of the expression of genes related to lipid metabolism, lipoprotein oxidation, endothelial function and blood pressure, and hence on atherogenesis.

Conclusion

The studied polymorphisms had a small contribution to the extension of CAD. Only *LPL* D9N polymorphism was associated with CAD extension in patients with MS and recent ACS. Analysis of combined genetic polymorphisms showed a weak association with CAD extension, and an inverse relationship of genetic score with CAD extension and severity.

Study limitations

The small sample size and the cross-sectional design may be considered limitations of our study. However, the exploratory aim of the study was to identify genetic polymorphisms that may be used in the identification of more severe atherosclerotic disease in this population of patients with MS and recent ACS. Its results contribute to the selection of genetic polymorphisms to be tested in prospective studies involving larger samples.

Author contributions

Conception and design of the research: Fischer SCPM, Fonseca FAH, Izar MCO;Acquisition of data: Fischer SCPM, Pinto SP, Lins LCAS, Monteiro CMC, Pinheiro LFM, Izar MCO; Analysis and interpretation of the data and Critical revision of the manuscript for intellectual content: Fischer SCPM, Pinto SP, Lins LCAS, Bianco HT, Monteiro CMC, Pinheiro LFM, Fonseca FAH, Izar MCO; Statistical analysis: Bianco HT, Monteiro CMC, Pinheiro LFM, Fonseca FAH, Izar MCO; Obtaining financing: Izar MCO; Writing of the manuscript: Fischer SCPM, Fonseca FAH, Izar MCO.

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 Universidade Federal de São Paulo (CEP UNIFESP) under the protocol number CEP 0283/11. 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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Prognostic Accuracy of the GRACE Score in Octogenarians and Nonagenarians with Acute Coronary Syndromes

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Abstract

Background: **The GRACE Score was derived and validated from a cohort in which octogenarians and nonagenarians were poorly represented.**

Objective: **To test the accuracy of the GRACE score in predicting in-hospital mortality of very elderly individuals with acute coronary syndromes (ACS).**

Methods: **Prospective observational study conducted in the intensive coronary care unit of a tertiary center from September 2011 to August 2016. Patients consecutively admitted due to ACS were selected, and the very elderly group was defined by age ≥ 80 years. The GRACE Score was based on admission data and its accuracy was tested regarding prediction of in-hospital death. Statistical significance was defined by p value < 0,05.**

Results: **A total of 994 individuals was studied, 57% male, 77% with non-ST elevation myocardial infarction and 173 (17%) very elderly patients. The mean age of the sample was 65 ± 13 years, and the mean age of very elderly patients subgroup was 85 ± 3.7 years. The C-statistics of the GRACE Score in very elderly patients was 0.86 (95% CI = 0.78 – 0.93), with no difference when compared to the value for younger individuals 0.83 (95% CI = 0.75 – 0.91), with p = 0.69. The calibration of the score in very elderly patients was described by χ^2 test of Hosmer-Lemeshow = 2.2 (p = 0.98), while the remaining patients presented χ^2 = 9.0 (p = 0.35). Logistic regression analysis for death prediction did not show interaction between GRACE Score and variable of very elderly patients (p = 0.25).**

Conclusion: **The GRACE Score in very elderly patients is accurate in predicting in-hospital ACS mortality, similarly to younger patients. (Arq Bras Cardiol. 2018; 110(1):24-29)**

Keywords: **Acute Coronary Syndrome / mortality; Aged 80 years and over; Prognosis; Risk Assessment; Data Reliability.**

Introduction

Acute coronary syndromes (ACS) are an important cause of in-hospital death in the Western world.[1,2] Due to the great heterogeneity of clinical and prognostic presentation of ACS, risk stratification is essential so that more aggressive actions can be adopted toward patients at higher risk. In this context, the GRACE Score is the most accurate predictor of hospital death in ACS.[3-6]

However, the derivation and validation of the GRACE Score were conducted in a low representative cohort of octogenarians or nonagenarians.[3,4] Provided that old age is an important risk indicator, which accumulates aspects of constitutional fragility and higher prevalence of comorbidities, there are reasons to question whether the GRACE Score has modified accuracy in very elderly people.

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The present study aimed to test the hypothesis that the GRACE Score has a satisfactory accuracy in predicting in-hospital death when applied to octogenarian and nonagenarian individuals with ACS. The cohort of Prospective Registry of Acute Coronary Syndromes was used in order to answer this question, comparing the discriminatory capacity and calibration of GRACE among individuals aged ≥ 80 years old *versus* < 80 years old.

Methods

Sample selection

Patients consecutively admitted to the coronary unit of the tertiary hospital between September 2011 and August 2016, due to suspected ACS (unstable angina and myocardial infarction) were screened for the study. The inclusion criteria were precordial discomfort within 48 hours prior to admission associated with at least one of the following criteria:

1. Positive myocardial necrosis marker, defined by troponin T ≥ 0.01 ug/L or troponin I > 0.034 g/L, which corresponds to values above 99 percent;[7]

2. Ischemic electrocardiographic alteration, consisting of inversion of the T wave (≥ 0.1 mV) or alterations of the ST segment (≥ 0.05 mV); and
3. Previously documented coronary artery disease, defined by a history of myocardial infarction with Q wave or previous angiography demonstrating coronary obstruction ≥ 70%.

The protocol is in compliance with the Declaration of Helsinki, released by the Research Ethic Committee of the institution and all patients evaluated signed the Informed Consent.

GRACE Score

The clinical data of each patient's admission in the emergency unit, electrocardiograms performed within the first 6 hours of treatment, troponin T and troponin I dosage in the first 12 hours of treatment and the value of the first plasma creatinine were used to calculate the GRACE Score. The increased myocardial necrosis marker as a component of the scores was defined as troponin over 99 percent. The GRACE Score consists of eight variables: five semi-quantitative ones, *i.e.*, different weight for each age range (systolic blood pressure, heart rate, plasma creatinine and Killip class); and three dichotomic ones (ST segment depression, elevation of myocardial necrosis marker and cardiac arrest at the moment of admission). The final score can range from 0 to 372.[4]

Data analysis

The accuracy of the GRACE Score was evaluated by discrimination and calibration analyses, which were compared between two groups: one referred to as "very elderly" and the other as "not very elderly"; the first one defined by individuals ≥ 80 years old. The GRACE Score has its performance evaluated by the ability to predict death by any given cause during the hospitalization period.

Statistical analysis

Numerical variables were expressed as mean and standard deviation when presenting normal distribution or a small deviation from normality, whilst median and interquartile interval were preferable in the presence of at least a moderate deviation from normality. The analysis of normality was performed through combined visualization of the histogram and Q-Q plots, description of *skewness* and *kurtosis* with confidence intervals, and normality tests (Shapiro-Wilk and Kolmogorov-Smirnov). Continuous variables were compared by the Student's t-test or Wilcoxon test when they presented normal and non-normal distribution, respectively. Categorical variables were expressed in proportion and compared through the χ^2 test.

The discriminatory capacity of the GRACE Score for mortality was evaluated by the area below the curve of receiver operator characteristics – ROC (statistic-C), which was compared between the two groups by the unpaired Hanley-McNeil test.[8] The calibration of the scores had a hypothesis test carried out by the Hosmer-Lemeshow technique and was described by the comparison between mortality predicted by GRACE and the one observed in each prediction quartile. The influence of age in the performance of GRACE was tested by the p-value of the interaction by logistic regression analysis.

The SPSS software, version 21, was used. The statistical significance was defined by two-tailed p-value lower than 0.05.

Results

Characteristics of the sample

A total of 994 individuals were studied, of which 57% were male and 77% had non-ST elevation ACS. The mean age of the sample was 65 ± 13 years old, of which 173 (17%) were classified as very elderly for being 80 years old or older. The mean age of the very elderly was 85 ± 3.7 years old, compared to 61 ± 11 years of age in the rest of the sample ($p < 0.001$). The GRACE Score for very elderly patients was 162 ± 34, significantly higher than the one of other patients (115 ± 35; $p < 0.001$). This higher score in GRACE for very elderly people is due to the difference not only in age, but also in the variables troponin, non-ST elevation, Killip and blood pressure. Percutaneous revascularization during hospitalization was similar in both groups, while surgical revascularization was less frequent in the group of the very elderly. During hospitalization, in-hospital mortality was 5.8% of the total sample, being significantly higher in the group of very elderly people in relation to patients with less than 80 years of age (16% *versus* 3.7%; $p < 0.001$) (Table 1).

Discriminatory ability of the GRACE Score

In the total sample, the GRACE Score had statistic-C of 0.87 (95% CI = 0.82 – 0.92) in predicting hospital death. GRACE's statistic-C among the very elderly was 0.86 (95% CI = 0.78 – 0.93), without difference in relation to the value found in patients aged less than 80 years old (statistic-C = 0.83; 95% CI = 0.75 – 0.91), with $p = 0.69$ in the comparison of both curves (Figure 1). In the logistic regression in which GRACE and very elderly people were simultaneously inserted in the prediction model, there was no interaction between these two variables ($p = 0.25$). In addition, GRACE remained an independent predictor of age ($p < 0.001$).

According to the ROC curve, the cutoff score in GRACE with best performance in the group of not very elderly was 134, with sensitivity of 83% and specificity of 76%. Among the very elderly, the cutoff point is displaced upward, with a value of 184, corresponding to the sensitivity of 77% and specificity of 87%.

Calibration of the GRACE Score

In the prediction of the incidence of death during hospitalization, the Hosmer-Lemeshow test showed satisfactory calibration in both groups, very elderly ($\chi^2 = 2.2$; $p = 0.98$) and not very elderly ($\chi^2 = 9.0$; $p = 0.35$). Figure 2 presents the stratified analysis per quartile of the probability predicted by GRACE for hospital death, comparing the predicted and the observed within both age groups. Only the fourth quartile had an underestimated predicted mortality compared to the one observed, in both groups.

Table 1 – Comparison of clinical characteristics, laboratory characteristics, GRACE Score and mortality between very elderly versus not very elderly

	Age ≥ 80	Age < 80	p-value
Sample size	173 (17%)	821 (83%)	–
Age (years)	85 ± 3.7	61 ± 11	< 0.001‡
Male	82 (47.0%)	487 (59.0%)	0.004§
Non-ST elevation ACS	23 (13.0%)	205 (25.0%)	0.001§
Diabetes	60 (35.0%)	300 (37.0%)	0.613§
Non-ST elevation	55 (32.0%)	308 (37.5%)	0.155§
Positive troponin	123 (71.0%)	557 (68.0%)	0.403§
Classification of Killip			**< 0.001**
Killip I	127 (73.0%)	724 (88.0%)	
Killip II	21 (12.0%)	49 (6.0%)	
Killip III	23 (13.0%)	41 (5.0%)	
Killip IV	2 (1.2%)	7 (0.9%)	
Systolic pressure (mmHg)	151 ± 32	155 ± 30	0.098‡
Heart rate	80 ± 17	80 ± 18	0.519‡
Serum Creatinine (mg/dl)	1.1 ± 0.5	1.1 ± 0.9	0.669‡
Hemoglobin at admission	13 ± 1.8	14 ± 1.9	< 0.001‡
Triarterial or LMD*	38 (30.0%)	126 (18.0%)	< 0.001§
Percutaneous Coronary Intervention†	66 (39.0%)	368 (45.0%)	0.129§
Revascularization surgery†	4 (2.0%)	92 (11.0%)	< 0.001§
GRACE Score	162 ± 34	115 ± 35	< 0.001‡
In-hospital death	28 (16.0%)	30 (4.0%)	< 0.001§

*ACS: acute coronary syndrome; *Coronariography performed during hospitalization; LMD: left main disease; †Myocardial revascularization treatments during hospitalization; ‡Compared through Student's t-test; §Compared through χ^2 test.*

Discussion

The present study demonstrates that the GRACE Score presents satisfactory accuracy in predicting hospital death of very elderly individuals with ACS (octogenarian and nonagenarian ones). The comparison with individuals aged less than 80 years old did not show loss of discriminatory capacity or GRACE's calibration as the age progressed. Statistic-C values above 0.80 with narrow confidence intervals, in addition to linear growth of mortality observed in the different quartiles of mortality predicted by GRACE, are clear evidence of maintenance of the performance of this score in very elderly. Although the fourth quartile of predicted mortality has underestimated the risk in relation to what was observed, this difference did not compromise the categorization of the fourth larger groups of risk, once that both the observed and the predicted were in mortality ranges considered high for ACS.[4] There was no interaction between the adequacy of GRACE's model and the age range group defined by the cutoff point of 80 years of age, confirming GRACE's accuracy among elderly.

Age is the marker of greater influence on the probability of hospital death in patients hospitalized with ACS, with exponential risk growth as the value of this variable increases.[6,9,10] The uncertainty of GRACE's accuracy among very elderly individuals comes from the possibility that there could be less variability of important predicting values within a very advanced age range. For instance, the uniformity of advanced age in this sample may deprive this variable of its discriminatory power, which would not depict great contrast among the individuals. The inclination of this risk function may be lower when there are only very elderly patients. The same may occur with other variables which may be systematically altered in a very elderly sample. Also, the calibration of the score in estimating the numerical risk of death may be different for these patients, once the alpha constant (intercept) tends to be greater in samples with the highest risk. This could explain the need for recalibration of the score.

This uncertainty becomes greater when realized that octogenarian patients were not well represented by the sample which derived and validated the GRACE Score as a hospital death predictor.[4,11,12] The median age of that sample was 66 years old, with upper limit of 75 years of age for the interquartile interval, indicating that 3/4 of patients were less than 75 years old, with no description as to who were the octogenarian or the nonagenarian ones. Due to the

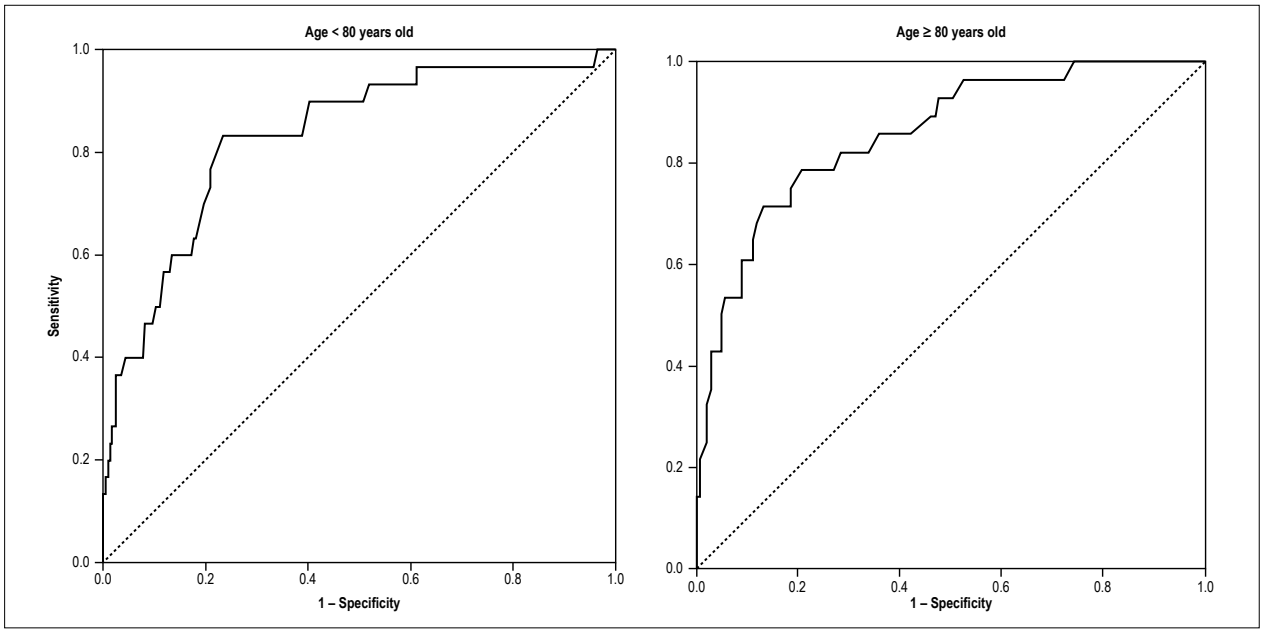

Figure 1 – *ROC curves of the GRACE Score for the prediction of in-hospital mortality in patients aged ≥ 80 years old versus < 80 years old with acute coronary syndromes. Area below the curve in very elderly was 0.86 (95% CI = 0.78 – 0.93), with no difference in relation to the value found in patients aged < 80 years old (statistic-C = 0.83; 95% CI = 0.75 – 0.91), with p = 0.69 in the comparison between both curves.*

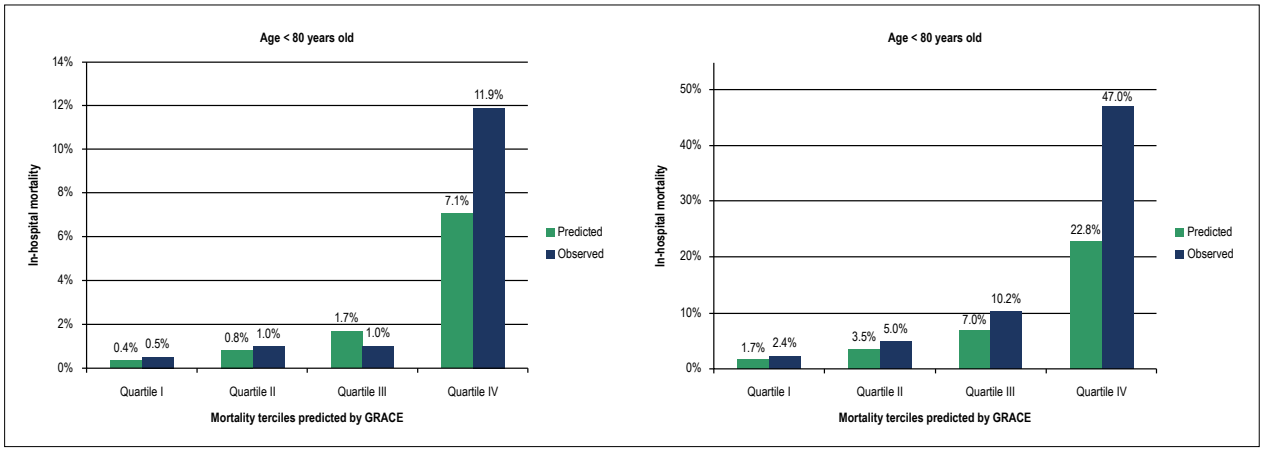

Figure 2 – *Calibration of the GRACE Score in the prediction of in-hospital mortality in patients aged ≥ 80 years old versus < 80 years old with acute coronary syndromes. The graphics represent the comparison between predicted and observed mortality, in quartiles of probability predicted by the GRACE Score.*

uncertainty of this age range, "very elderly" was defined in our method as people from 80 years of age on, when the occurrence of fragility and comorbidities become more prevalent. Our findings are in agreement with preliminary studies which evaluated the GRACE Score in very elderly, respectively, two European works (Portugal and Spain), and two Chinese ones.[12-15] Therefore, our results support the literature, being the first to compare the sample of very elderly with individuals aged less than 80 years old. That is, not only do we present an accurate score, but also the suggestion that there is no loss of accuracy.

A risk-treatment paradox depending on age has been described in ACS,[11,12,16-19] that is, individuals with higher risk being treated in a more conservative way due to the fear of complications, while lower-risk and young individuals receive more aggressive treatment. The use of risk scores in elderly will potentially prevent this paradox, once it allows estimating greater magnitude of the benefit when more aggressive strategies are applied in patients with higher absolute risk derived from GRACE.

On the other hand, it should be recognized that provided the mortality is an outcome resulting from cardiovascular

protection *versus* complications in procedures, the greatest benefit in very elderly may be antagonized by greater incidence of complications. Therefore, we emphasize this age range needs validation of the GRACE Score as for the prediction of benefits of more aggressive therapeutic strategies. This is a gap to be filled by future studies.

Conclusion

In conclusion, the present study represents a favorable evidence to the accurate use of the GRACE Score in the prediction of in-hospital death among octogenarian and nonagenarian patients hospitalized with ACS.

Author contributions

Conception and design of the research: Cerqueira Junior AMS, Pereira LGS, Souza TMB, Correia VCA, Alexandre FKB, Suerdieck JG, Ferreira F, Rabelo MMN, Correia LCL; Acquisition of data: Cerqueira Junior AMS, Pereira LGS, Souza TMB, Correia VCA, Sodré GA, Suerdieck JG, Ferreira F, Correia LCL; Analysis and interpretation of the data: Cerqueira Junior AMS, Pereira LGS, Souza TMB, Correia VCA, Sodré GA, Suerdieck JG, Ferreira F, Rabelo MMN, Correia LCL; Statistical analysis and Writing of the manuscript: Cerqueira Junior AMS, Pereira LGS, Souza TMB, Correia VCA, Alexandre FKB, Sodré GA, Suerdieck JG, Ferreira F, Rabelo MMN, Correia LCL; Obtaining financing: Rabelo MMN, Correia LCL; Critical revision of the manuscript for intellectual content: Cerqueira Junior AMS, Souza TMB, Correia VCA, Alexandre FKB, Sodré GA, Suerdieck JG, Ferreira F, Rabelo MMN, Correia LCL.

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 35/11. 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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Prevalence of Dyslipidemias in Three Regions in Venezuela: The VEMSOLS Study Results

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Abstract

Background: The prevalence of dyslipidemia in multiple regions of Venezuela is unknown. The Venezuelan Metabolic Syndrome, Obesity and Lifestyle Study (VEMSOLS) was undertaken to evaluate cardiometabolic risk factors in Venezuela.

Objective: To determine the prevalence of dyslipidemia in five populations from three regions of Venezuela.

Methods: During the years 2006 to 2010, 1320 subjects aged 20 years or older were selected by multistage stratified random sampling from all households in five municipalities from 3 regions of Venezuela: Lara State (Western region), Merida State (Andean region), and Capital District (Capital region). Anthropometric measurements and biochemical analysis were obtained from each participant. Dyslipidemia was defined according to the NCEP/ATPIII definitions.

Results: Mean age was 44.8 ± 0.39 years and 68.5% were females. The prevalence of lipids abnormalities related to the metabolic syndrome (low HDL-c [58.6%; 95% CI 54.9 – 62.1] and elevated triglycerides [39.7%; 36.1 – 43.2]) were the most prevalent lipid alterations, followed by atherogenic dyslipidemia (25.9%; 22.7 – 29.1), elevated LDL-c (23.3%; 20.2 – 26.4), hypercholesterolemia (22.2%; 19.2 – 25.2), and mix dyslipidemia (8.9%; 6.8 – 11.0). Dyslipidemia was more prevalent with increasing body mass index.

Conclusion: Dyslipidemias are prevalent cardiometabolic risk factors in Venezuela. Among these, a higher prevalence of low HDL is a condition also consistently reported in Latin America. (Arq Bras Cardiol. 2018; 110(1):30-35)

Keywords: Dyslipidemias / epidemiology; Cardiovascular Diseases; Risk Factors; Stroke / mortality; Obesity; Metabolic Syndrome.

Introduction

In Venezuela, cardiovascular disease (CVD), represented by ischemic heart disease (16.3%) and stroke (7.7%), was the major cause of death in 2012.[1] Both are strongly related with modifiable risk factors. According to the INTERHEART[2] and the INTERSTROKE[3] studies, dyslipidemias, assessed as increased levels of apolipoprotein (ApoB/ApoA1 ratio), represented the 49.2% and the 25.9% of the attributable risk for acute myocardial infarction and stroke, respectively. Randomized controlled clinical trials have consistently demonstrated that a reduction in low-density lipoprotein cholesterol (LDL-C) with statin therapy reduces the incidence of heart attack and ischemic stroke. For every 38.6 mg/dL LDL-c reduction, the annual rate of major vascular events decreases to one-fifth.[4]

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Studies evaluating the prevalence of dyslipidemias in Venezuela have been compiled.[5] However, most of them have small samples, and only two are representative of a city or a state. In 1,848 adults from the city of Barquisimeto, in the western region of the country, the Cardiovascular Risk Factor Multiple Evaluation in Latin America (CARMELA) study[6] reported the lowest prevalence of hypercholesterolemia (cholesterol ≥ 240 mg/dL) observed in Latin America (5.7%).[6] In 3,108 adults from the state of Zulia, Florez et al.[7] documented the prevalence of atherogenic dyslipidemia (high triglycerides and low levels of high- density lipoprotein of cholesterol [HDL-c]) in 24.1%. This number was higher in men than women, and increased with age. No study in Venezuela has included more than one region, prompting the design of the Venezuelan Metabolic Syndrome, Obesity and Lifestyle Study (VEMSOLS). This paper presents the results of VEMSOLS, specifically the prevalence of dyslipidemia in five populations of three regions in Venezuela.

Methods

Design and Subjects

An observational, cross-sectional study was designed to determine the prevalence of cardiometabolic risk factors in

a sub-national sample of Venezuela. Five municipalities from three regions were evaluated: Palavecino, in Lara State (urban), from the Western region; Ejido (Merida city), in Merida State (urban), and Rangel (Páramo area), in Merida State (rural), both from the Andes region; Catia La Mar, in Vargas state (urban), and Sucre, in the Capital District (urban), both from the Capital region. From 2006 to 2010, a total of 1,320 subjects aged 20 years or more, who had lived in their houses for at least six months, were selected by a two-stage random sampling. Three different geographic regions of the country – Andes, mountains at the south; Western, llanos in the middle; and the Capital District, coast at the north – were assessed. Each region was stratified by municipalities and one was randomly selected. A map and a census of each location were required to delimit the streets or blocks, and to select the households to visit in each municipality. After selecting the sector to be surveyed in each location, the visits to households started from number 1 onwards, skipping every two houses. Pregnant women and participants unable to stand up and/or communicate verbally were excluded. All participants signed the informed consent form for participation.

The sample size was calculated to detect the prevalence of hypercholesterolemia (the lowest prevalent condition reported in Venezuela) in 5.7%[6], with standard deviation of 1.55%, which allows to calculate the 95% confidence interval (95% CI). The minimal estimated number of subjects to be evaluated was 830. Overall, 1,320 subjects were evaluated (89.4% from the urban and 10.6% from the rural area).

Clinical and biochemical data

All subjects were evaluated in their households or in a nearby health center by a trained health team according to a standardized protocol. Each home was visited twice. In the first visit, the participants received information about the study and signed the written informed consent form. Demographic and clinical information was obtained using a standardized questionnaire. Weight was measured with as few clothes as possible, without shoes, using a calibrated scale. Height was measured using a metric tape on the wall. Waist circumference was measured with a metric tape at the iliac crest at the end of the expiration. Body mass index was calculated (BMI: weight[kg]/height[m]^2).

In the second visit, blood samples were drawn after 12 hours of overnight fasting. Then, they were centrifuged for 15 minutes at 3000 rpm, within 30-40 minutes after collection, and transported with dry ice to the central laboratory, where they were properly stored at -40°C until analysis. Data from participants who were absent during the first visit were collected. Total cholesterol,[8] triglycerides,[9] LDL-c, and HDL-c[10] were determined by standard enzymatic colorimetric methods.

Categorization of variables

Dyslipidemia was defined according the National Cholesterol Education Program /Adult Treatment Panel III (NCEP/ATPIII)[11], being categorized in 6 types. Of these, four were isolated dyslipidemias: Low HDL-c (hyperalphalipoproteinemia) < 40 mg/dL in men and < 50 mg/dL in women; high triglycerides: ≥ 150 mg/dL; hypercholesterolemia (≥ 240 mg/dL of total cholesterol); high LDL-c ≥ 160 mg/dL; and two were combined dyslipidemias: atherogenic dyslipidemia (triglycerides ≥ 150 mg/dL + low HDL-c) and mixed dyslipidemia (triglycerides ≥ 150 mg/dL + total cholesterol ≥ 240 mg/dL). Additionally, individuals were classified according to BMI as normal weight (BMI < 25 kg/m^2), overweight (BMI ≥ 25 kg/m^2 and < 30 kg/m^2), or obese (BMI ≥ 30 kg/m^2).[12] Abdominal obesity was established by waist circumference ≥ 94 cm in men and ≥ 90 cm in women.[13]

Statistical analysis

All calculations were performed using the SPSS 20 software (IBM corp. Released 2011. Armonk, NY: USA). It was verified that all variables had normal distribution using a normality test (Kolmogorov-Smirnov). All variables were continuous and data were presented as mean ± standard deviation (SD). Differences between mean values were assessed with the t-test. Proportions of subjects with dyslipidemia were presented as prevalence rates and 95% confidence intervals (CI). A Chi-square test was applied to compare different frequencies by gender, nutritional status and abdominal obesity. P-value of < 0.05 was considered statistically significant.

Results

Characteristics of the subjects

Two thirds of the study subjects were female. Men had higher triglycerides, waist circumference and lower HDL-c than women (Table 1). Age, BMI, total cholesterol and LDL-c were similar.

Prevalence of dyslipidemia

Low HDL-c was the most prevalent lipid change present in nearly seven of ten women, and in about four of ten men ($p < 0.01$), followed by high triglycerides that were present in half of the men and in one third of women ($p < 0.01$). Their combination, atherogenic dyslipidemia, was observed in 25.9% of subjects, followed in frequency by increasing LDL-c and total cholesterol levels (Table 2). Mixed dyslipidemia was observed in only 8.9% of the subjects, and was higher among men than in women. An increasing prevalence of all types of dyslipidemias was found when individuals were classified according to BMI and at the presence of abdominal obesity (Figure 1 and Figure 2). The prevalence of hypercholesterolemia, high LDL-c and mixed dyslipidemia were similar in overweight and obese subjects, but higher than those found in the normal weight group.

Discussion

The present study reports that the most prevalent lipid abnormality in our sub-national sample of adults in Venezuela is the low HDL-c (58.6%), followed by high triglycerides (38.7%), whereas the prevalence of hypercholesterolemia (22%) and its combination with hypertriglyceridemia (8.9%) were lower. Similar findings have been reported in earlier studies, both in Venezuela (Zulia state, Low HDL-c 65.3%, high triglycerides 32.3%),[7] and Mexico (Low-HDL

Table 1 – Subject Characteristics

	Men	Women	Total	Significance
Participants (n, %)	412 (31.2)	908 (68.8)	1320 (100)	
Age (years)	45.8 ± 14.8	44.4 ± 14.0	44.8 ± 14.3	NS
Body mass index (kg/m^2)	27.7 ± 5.0	27.6 ± 5.3	27.6 ± 5.2	NS
Waist circumference (cm)	96.6 ± 13.2	89.8 ± 12.3	91.9 ± 13.0	< 0.0001
High density lipoprotein (HDL-c) (mg/dL) *	43.2 ± 10.4	47.2 ± 10.9	45.9 ± 10.9	NS
Triglycerides (mg/dL)	175.3 ± 154.7	140.0 ± 87.3	151.0 ± 114.3	< 0.0001
Total cholesterol (mg/dL)	207.7 ± 46.5	206.3 ± 47.6	206.7 ± 47.2	NS
Low density lipoprotein (LDL-c) (mg/dL)	131.0 ± 43.4	131.4 ± 43.8	131.3 ± 43.7	NS

Data are mean ± SD. Gender differences according t-test.

Table 2 – Prevalence of Dyslipidemias by Gender

	Men	Women	Total	Significance
	412	908	1320	
Low HDL-c (< 40 mg/dL in men and < 50 mg/dL in women)	42.2 (38.6 – 45.8)	66.0 (62.5 – 69.4)	58.6 (54.9 – 62.1)	< 0.0001
Elevated triglycerides (≥ 150 mg/dL)	49.5 (45.8 – 53.1)	35.2 (31.7 – 38.7)	39.7 (36.1 – 43.2)	< 0.0001
Hypercholesterolemia (≥ 240 mg/dL)	23.8 (20.7 – 26.8)	21.5 (18.5 – 24.5)	22.2 (19.2 – 25.2)	NS
Elevated LDL-c (≥ 160 mg/dL)	22.8 (19.8 – 25.9)	23.5 (20.5 – 26.6)	23.3 (20.2 – 26.4)	NS
Atherogenic dyslipidemia (triglycerides ≥ 150 mg/dL + low HDL-c)	25.2 (22.1 28.0)	26.2 (23.0 – 29.4)	25.9 (22.7 – 29.1)	NS
Mixed dyslipidemia (triglycerides ≥ 150 + cholesterol ≥ 240 mg/dL)	12.4 (9.9 – 14.7)	7.4 (5.5 – 9.3)	8.9 (6.8 – 11.0)	0.002

Data are showed in percentage (95% CI). Gender differences according to the Chi-square test.

48.4% and high triglycerides 42.3%).[14] Using a cut-off point similar to that in our study, an extremely high prevalence of hypoalphalipoproteinemia has been also observed in Valencia city (90%)[15] and the Junquito municipality (81.1%),[16] both in the central region of Venezuela. Similarly to the observed in men in our study (49.5%), the aforementioned studies in Valencia and Junquito also reported high prevalence of elevated triglycerides (51%).[15,16] Most of these results are consistent with previous findings in the Latin America region. In a systematic review of metabolic syndrome in Latin America, the most frequent change was low HDL-c in 62.9% of the subjects.[17]

Although hypercholesterolemia (22.2%) is significantly less common compared with the aforementioned alterations, it was higher than the CARMELA study (5.7%) in Barquisimeto,[6] and similar to that observed in Valencia (19.0%).[15] Therefore, hypercholesterolemia remains as a cardiovascular risk factor to be considered when implementing public health measures in the Venezuelan population. Other of our findings are consistent with previous studies reporting that the prevalence of dyslipidemia increases with adiposity, and subjects with overweight/obesity[14,18] and abdominal obesity[18] show worse lipid profiles than subjects of normal weight. As in our study, higher figures of elevated triglycerides in male,[14,18] and no differences between overweight and obese subjects when grouped according to BMI,[14] have been reported.

Dyslipidemias can be caused by both genetic and environmental factors (obesity, smoking, low physical activity). In our study, the prevalence of low HDL-c without other lipid abnormalities was 29.2% (male 15%, female 35.7%). Of these, those with low HDL-c and normal weight (total 10.6%, male 5.3%, female 13.0%) could suggest the proportion of cases of hypoalphalipoproteinemia that could be associated with genetic factors. Also, part of the prevalence of low HDL-c in this population can be explained by metabolic factors (i.e., insulin resistance), a condition that produces modifications in more than one lipid sub-fraction. In fact, the prevalence of atherogenic dyslipidemia (25.9%) in our study was significant and remarkably similar to that reported by Florez et al.[7] in the Zulia region (24.1%). Atherogenic dyslipidemia is the pattern most frequently observed in subjects with metabolic syndrome and insulin resistance, and both abnormalities are components of the metabolic syndrome definition. Besides genetic or metabolic factors, environmental adverse conditions are also important in Venezuela. The factors involving nutritional transition promoted inappropriate eating and lifestyle patterns in Venezuela and other Latin American countries, clearly contributing with the incidence of non-communicable diseases, especially those related to obesity and diabetes.[19] A follow-up survey of food consumption, based on the food purchase, reported that caloric intake and the selection of foods with lower quality have increased in Venezuela.[20] A high rate of physical inactivity (68%) has also been reported in Venezuela in two studies involving 3,422 adults.[5]

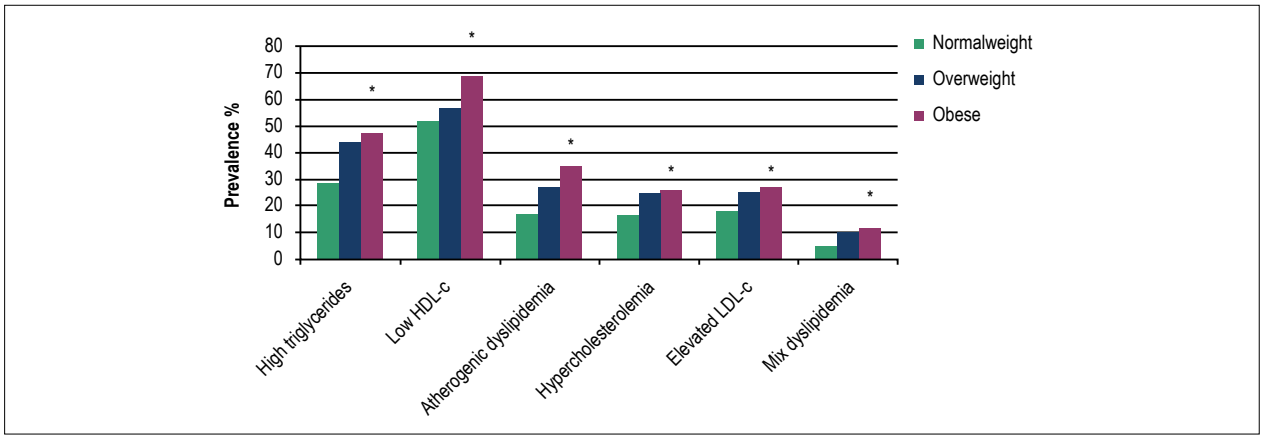

Figure 1 – *Prevalence of dyslipidemia by nutritional status.*
**Difference in the prevalence of dyslipidemia according to nutritional status using Chi-square (p < 0.01). High triglycerides: 150 mg/dL; low HDL-c: < 40 mg/dL in men and < 50 mg/dL in women; atherogenic dyslipidemia: triglycerides = 150 mg/dL + low HDL-c; hypercholesterolemia: total cholesterol = 240 mg/dL; elevated LDL-c: = 160 mg/dL; mixed dyslipidemia: triglycerides = 150 + total cholesterol = 240 mg/dL.*

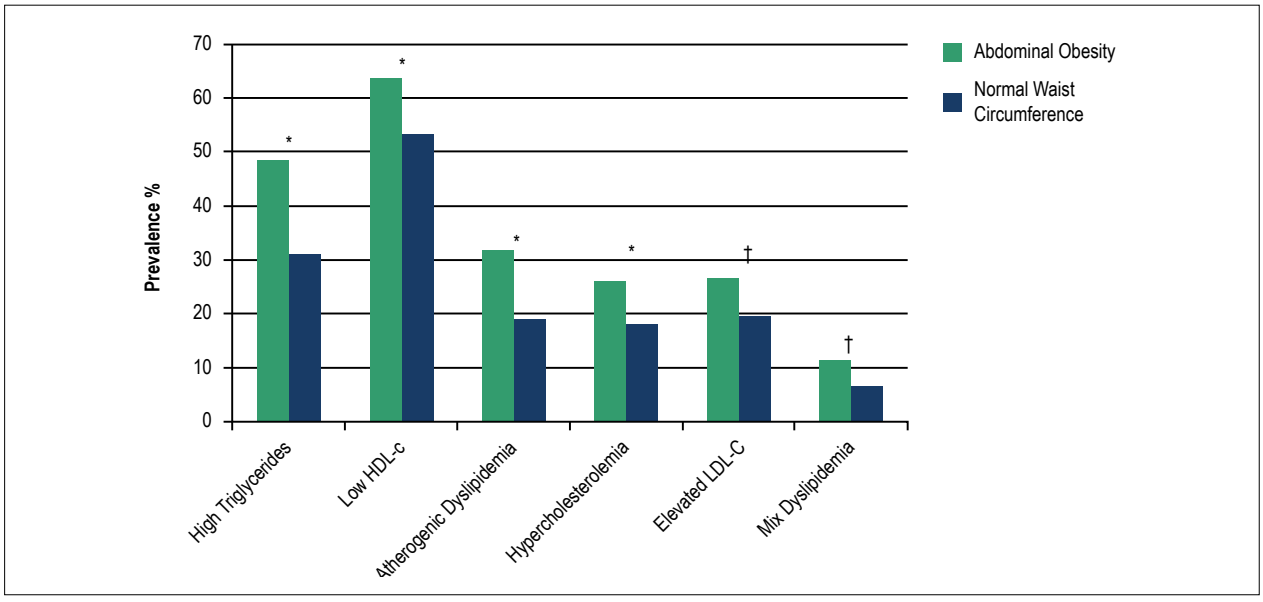

Figure 2 – *Prevalence of dyslipidemias by abdominal obesity (waist circumference = 94 cm in men and = 90 cm in women).*
*Significant difference of the prevalence of dyslipidemia between abdominal obesity or normal waist circumference *(p < 0.001) †(p = 0.002). High triglycerides = 150 mg/dL; Low HDL-c < 40 mg/dL in men and < 50 mg/dL in women; Atherogenic dyslipidemia triglycerides =150 mg/dL + low HDL-c; Hypercholesterolemia =240 mg/dL; Elevated LDL-c = 160 mg/dL; Mix dyslipidemia triglycerides = 150 + cholesterol = 240 mg/dL.*

Successful dietary strategies to reduce dyslipidemias and other metabolic syndrome components should include energy restriction and weight loss, manipulation of dietary macronutrients, and adherence to dietary and lifestyle patterns, such as the Mediterranean diet and diet/exercise.[21] After the evaluation of the typical food-based eating and physical activity pattern in the Venezuelan population, culturally-sensitive adaptations of the Mediterranean diet with local foods and physical activity recommendations have been proposed.[5,22] Specific recommendations for patients with dyslipidemia have been also included in local clinical practice guidelines.[23]

Some limitations can be observed in the present study. The sample did not represent the entire population of the country; only three of the eight regions of Venezuela were included. Additionally, in the VEMSOLS, eating pattern and physical activity were not investigated. The cut-off point for low HDL and triglycerides used was established for the metabolic syndrome definition, which can limit the comparison with other studies using a level below 35[14] or 40[18] mg/dL to define hypoalphalipoproteinemia. However, despite these limitations, this study is the first report of dyslipidemias in more than one region of Venezuela. A national survey in Venezuela in ongoing (Estudio Venezolano de Salud Cardiometabólica, EVESCAM study). Data collection will be completed in 2017.

Conclusions

This is the first report presenting the prevalence of dyslipidemia in more than one region of Venezuela. The results observed are consistent with other Latin American studies, reporting low HDL-c as the most frequent lipid alteration in the region. Additionally, high levels hypercholesterolemia were observed. Both conditions could be related with CVD, which represent a major public health problem in the region. A suggestion resulting from our findings is to monitor a complete lipid profile during medical check-ups, because in some Latin-American countries it is common to check only total cholesterol. The triggers of these changes need to be determined in future studies. The implementation of strategies focused in proper nutrition, more physical activity and avoiding weight gain is imperative.

Author contributions

Conception and design of the research and Acquisition of data: González-Rivas JP, Nieto-Martínez R, Brajkovich I, Rísquez A; Analysis and interpretation of the data: González-Rivas JP, Nieto-Martínez R, Ugel E; Statistical analysis: González-Rivas JP, Ugel E; Obtaining financing: Nieto-Martínez R; Writing of the manuscript: González-Rivas JP, Nieto-Martínez R; Critical revision of the manuscript for intellectual content: González-Rivas JP, Nieto-Martínez R, Brajkovich I, Ugel E, Rísquez A.

Potential Conflict of Interest

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

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Study Association

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

Ethics approval and consent to participate

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

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Leisure-Time Physical Activity, but not Commuting Physical Activity, is Associated with Cardiovascular Risk among ELSA-Brasil Participants

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Abstract

Background: Despite reports in the literature that both leisure-time physical activity (LTPA) and commuting physical activity (CPA) can promote health benefits, the literature lacks studies comparing the associations of these domains of physical activity with cardiovascular risk scores.

Objective: To investigate the association between LTPA and CPA with different cardiovascular risk scores in the cohort of the Longitudinal Study of Adult Health ELSA-Brasil.

Methods: Cross-sectional study with data from 13,721 participants of both genders, aged 35-74 years, free of cardiovascular disease, from ELSA Brazil. Physical activity was measured using the International Physical Activity Questionnaire (IPAQ). Five cardiovascular risk scores were used: Framingham score — coronary heart disease (cholesterol); Framingham score — coronary heart disease (LDL-C); Framingham score — cardiovascular disease (cholesterol); Framingham score — cardiovascular disease (body mass index, BMI); and pooled cohort equations for atherosclerotic cardiovascular disease (ASCVD). Associations adjusted for confounding variables between physical activity and different cardiovascular risk scores were analyzed by logistic regression. Confidence interval of 95% (95%CI) was considered.

Results: LTPA is inversely associated with almost all cardiovascular risk scores analyzed, while CPA shows no statistically significant association with any of them. Dose-response effect in association between LTPA and cardiovascular risk scores was also found, especially in men.

Conclusions: LTPA was shown to be associated with the cardiovascular risk scores analyzed, but CPA not. The amount of physical activity (duration and intensity) was more significantly associated, especially in men, with cardiovascular risk scores in ELSA-Brasil. (Arq Bras Cardiol. 2018; 110(1):36-43)

Keywords: Exercise; Exercise Movement Techniques; Risk Factors; Cardiovascular Diseases / prevention & control; Epidemiology.

Introduction

Physical activity (PA) is inversely associated with all-cause mortality, especially with cardiovascular mortality.[1,2] Several studies have shown that PA, especially when considered in leisure-time domain, has a protective effect against chronic diseases and cardiovascular risk factors, including diabetes, dyslipidemia, hypertension and inflammatory markers.[3-7]

Cardiovascular risk scores are algorithms that have been proposed to stratify coronary and/or cardiovascular risks in order to estimate the probability of developing such diseases in ten years from the calculation in a given population. The first to be developed was presented by Wilson et al.[8], focusing on coronary artery disease risk and based on the Framingham score. Afterwards, D'Agostino et al.[9] developed an assessment tool that would allow the identification of patients at high risk for all and any initial atherosclerotic event in ten years from the test application (coronary artery disease, cerebrovascular diseases, peripheral vascular disease, and heart failure) by means of measures readily available in clinical practice. More recently, the American College of Cardiology (ACC) and the American Heart Association (AHA)[10] suggested new pooled equations to assess the risk of atherosclerotic cardiovascular diseases (within ten years), defined as the first occurrence of nonfatal myocardial infarction, death from coronary artery disease, and fatal/nonfatal stroke.

Despite reports in the literature that both leisure-time physical activity (LTPA)[11,12] and commuting physical activity (CPA)[13] can benefit health, there is a lack of studies analyzing and comparing the association of both PA domains with cardiovascular risk scores.[14] The main explanations for associations found between PA and cardiovascular risk scores are related to the favorable changes caused that PA causes in blood pressure, lipid profile, and glycemic levels.[15-17]

Establishing a quantitative relation between LTPA and/or CPA with cardiovascular risk scores can help public health authorities in best spreading messages that encourage the society to practice physical activities.

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The purpose of this paper was to verify the association between LTPA and/or CPA with different cardiovascular risk scores in the cohort from Longitudinal Study of Adult Health (ELSA-Brasil).

Methods

Population and sample

ELSA-Brasil is a cohort study of 15,105 economically active or retired people of both genders, aged 35-74, from six teaching and research institutions in the cities of Salvador, Vitória, Belo Horizonte, Rio de Janeiro, São Paulo, and Porto Alegre, whose methodological details have been previously described.[18,19] For the present study, all baseline participants (2008-2010) who answered the questionnaires about PA were selected, as long as they had the information required to calculate cardiovascular risk scores. After excluding participants who reported previous myocardial infarction, stroke, peripheral vascular disease, and heart failure, the sample was formed with 13,721 participants (45.3% males, 54.7% females).

ELSA-Brasil was approved by the National Commission for Research Ethics (CONEP) and by all Ethics Committees of the research centers involved. All participants signed the informed consent form, assuring secrecy and confidentiality to data.

Data production

Data were collected by a team of interviewers and trained evaluators, all of them certified by a quality control committee[19] and able to carry out the study protocol at the ELSA-Brasil Research Center. Face-to-face interviews were conducted with standardized and previously validated questionnaires.

Evaluation of physical activity

The International Physical Activity Questionnaire (IPAQ) was applied to identify and quantify PA, consisting of questions about the frequency and duration of physical activities at work (moderate and vigorous walking), while commuting, in domestic activities, and in leisure time.[20] ELSA-Brasil only addressed leisure time and commuting activities. PA was measured in minutes per week by multiplying weekly frequency by each event's duration of each.

For the purpose of this study, participants were classified as to leisure-time activities as follows:

- sedentary (< 10 min/week, any PA);
- (≥ 10 min to < 150 min/week of walking, moderate PA and/or 10 min to < 60 min/week of vigorous PA and/or 10 min to < 150 min/week of any combination of walking, moderate and vigorous PA);
- physically active (≥ 150 min/week of walking, moderate PA and/or ≥ 60 min/week of vigorous PA and/or ≥ 150 min/week of any combination of walking, moderate and vigorous PA);
- very active (≥ 150 min/week of vigorous PA, or ≥ 60 min/week of vigorous PA plus 150 min/week of any combination of walking and moderate PA).

For dichotomized analyzes, participants sorted as sedentary and not very active were considered insufficiently active, and active participants were those sorted as physically active and very active.

Commuting PA was categorized as insufficiently active (< 150 min/week of walking and/or cycling) and physically active (150 min/week of walking and/or cycling).

Evaluation of cardiovascular risk

Five cardiovascular risk scores were used. Two of them were proposed by Wilson et al.[8] and aimed to estimate the risk of coronary artery disease. Variables used were: age, systolic and diastolic blood pressure (BP), high-density lipoprotein (HDL-C), diabetes, smoking, and total cholesterol in the first; and age, systolic and diastolic BP, HDL-C, diabetes, smoking and low-density lipoprotein (LDL-C) in the second. The third and fourth scores, proposed by D'Agostino et al.,[9] aimed to identify patients at high risk for any initial atherosclerotic event (coronary heart disease, cerebrovascular diseases, peripheral vascular disease, and heart failure), using following variables: age, treated and untreated systolic and diastolic BP, HDL-C, body mass index (BMI), diabetes, smoking, and total cholesterol in the third; and age, treated and untreated systolic and diastolic BP, HDL-C, diabetes, smoking, and BMI in the fourth. The fifth score, indicated by ACC and AHA,[10] aimed at estimating the risk for atherosclerotic diseases. The variables used were: age, treated and non-treated systolic BP, total cholesterol, HDL-C, smoking, and diabetes. All cardiovascular risk scores were calculated for ELSA-Brasil participants, with detailed scoring scheme previously reported.[8-10] Participants with scores ≥ 20% were considered at high risk for future cardiovascular events.[21]

Evaluation of covariables

BP was obtained with a validated oscillometric device (Omron HEM-705CPINT) after a five-minute rest, with the subject sitting in a quiet and temperature-controlled room (20-24°C). Three measurements were taken at 1-min intervals each. The mean of the last two BP measurements was calculated and used in our analysis.

Definition of diabetes was based on self-reported information and laboratory exams. Patients were considered to have been diagnosed if they had been previously informed by a physician that they had diabetes or if they had used medication for diabetes in the last two weeks. Patients not previously diagnosed with diabetes were classified as having diabetes when fasting plasma glucose level was ≥ 7.0 mmol/L, two-hour post-load glucose was ≥ 11.1 mmol/L, or glycated hemoglobin (HbA1c) was ≥ 6.5%.[22,23] Participants were sorted as hypertensive if systolic blood pressure (SBP) was ≥ 140 mmHg, diastolic blood pressure (DBP) was ≥ 90 mmHg or if they had taken any medication to treat hypertension in the last two weeks.

Total cholesterol and HDL-C were determined by the enzymatic colorimetric method. LDL-C was calculated by the Friedewald equation.

Obesity was identified by BMI, being applied the equation BMI = weight(kg)/height(m)^2 and adopted the following cutoff point: obesity = 0 if BMI <30.0 and obesity = 1 if BMI ≥ 30.0.

Data analysis procedures

Descriptive measures (proportions) were calculated for all categorized variables. Analyzes were stratified by gender at first. The differences between men and women as to variables were identified by the chi-square test. Associations between dependent (different cardiovascular risk scores) and independent variables (LTPA and CPA) were analyzed by logistic regression. The following were considered as potential confounding variables: age, obesity, family income, educational level, and functional status. Variables presenting simultaneous evaluation (tetrameric matrix) of correlation coefficient rho < 0.60 and p ≤ 0.05 upon bivariate analysis were selected as model.

Analysis of confounding variables was made by comparing Odds Ratio (OR) of the crude association and adjusted association for possible confounders. The parameter used to identify the difference between associations was 10%. Then logistic regression analysis was performed, starting with the complete model and then removing each of the possible confounding variables that resulted in alteration equal to or greater than 10% in the association between LTPA/CPA and cardiovascular risk scores.[24] The modeling process did not identify effect-modifying variables, and variables age, obesity and educational level were considered confounders for men, while only age and education were identified as confounders for women. Therefore, the best model to analyze the association between LTPA/CPA with cardiovascular risk scores was adjusted for age, obesity, and educational level for males and for age and educational level for females.

Dose-response effect was also assessed for the association between LTPA and cardiovascular risk scores. Dummy variables were created for comparison between the reference group (sedentary) and each strata of the PA variable (not very active, active, very active). The Mantel Haenszel test was used to evaluate homogeneity of OR values between variables' strata, with a significance level set at 0.05. The confidence interval was set at 95% (95%CI), and the statistical software Stata version 12.0 was used.

Results

A total of 6,222 men (45.3%) and 7,499 women (54.7%) were included in the study. Sample characteristics are shown in Table 1. The former were reported as higher family income, more active in free time and while commuting, with higher values for cardiovascular risk scores analyzed, while the latter were found to be more educated and more frequently obese. There was a higher percentage of retired women and no statistically significant differences between men and women as to age.

The association between LTPA/CPA and cardiovascular risk scores in males and females are presented in Tables 2 and 3. LTPA is inversely associated with almost all cardiovascular risk scores analyzed, while CPA is not significantly associated with none of them. Tables 4 and 5 show us the existence of a dose-response effect in association between LTPA and cardiovascular risk scores, especially among men.

Discussion

This study analyzed the association between LTPA/CPA with different cardiovascular risk scores. LTPA was shown to be inversely associate with risk scores analyzed, while CPA was not. These results, especially regarding LTPA, were similar to those found among 41,053 male and female Finns when moderate or high LTPA levels among both men and women, and daily walking or cycling for work only among women were found to be associated with reduced risk for coronary events.[14]

Another study which analyzed healthy behaviors, including PA measured by accelerometry, and showed an inverse dose-response association between healthy positive behaviors and risk for atherosclerotic diseases.[25] In our study, we also found a dose-response effect in the association between LTPA and cardiovascular risk scores, mainly for males. That is, the higher the level of PA, the lower the risk of cardiovascular events.

The dose-response effect we found in this study has been reported for a long time. Kohl,[5] has shown, in a vast literature review, the inverse dose-response association between PA and cardiovascular events, especially coronary heart disease, in different longitudinal studies. Important to note that the classification adopted in this study had the amount of LTPA calculated based on both its duration and intensity. In other studies conducted by our research group,[11,12] in which PA was classified by intensity alone, only moderate PA was shown to hold relation with absence of hypertension and diabetes. Thus, one can assume that increasing physical activity levels to achieve greater health benefits should be suggested, bearing in mind both their intensity and duration.

Results found in the association between LTPA and cardiovascular risk scores are expected, considering that the main variables composing scores are separately associated with LTPA. Studies have pointed out that LTPA is inversely associated with high BP levels,[7,12] diabetes,[11,26] lipid changes,[27] and risk of coronary heart disease.[28] According to our results, the associations reported in previous studies are more consistent among men than among women.[28,29]

Regarding CPA, we could not demonstrate associations with cardiovascular risk scores, although previous studies have found a relationship between this type of activity and diabetes and cardiovascular mortality in individuals with type 2 diabetes. Important to note that these associations, when it comes to mortality by cardiovascular disease, have lost significance after additional adjustments for LTPA and CPA.[30,31] These findings most probably show that the instrument used in our study to assess PA (IPAQ) does not distinguish CPA intensity—walking or cycling, for example. Thus, if subjects' displacement is done slowly, health benefits may not be significant.

In this sense, a recent publication with data from ELSA-Brasil reported that the association between CPA and arterial hypertension was positive in women, but not statistically significant in men, while the association between LTPA and arterial hypertension was inverse

Table 1 – Baseline sample characteristics: Longitudinal Study of Adult Health (ELSA-Brasil), 2008–2010

	Males (n = 6,222)	Females (n = 7,499)	p
Age (years)			
34–50	3,112 (49.3%)	3,675 (48.3%)	
51–60	1,941 (30.7%)	2,437 (32.0%)	
> 60	1,261 (20.0%)	1,500 (19.7%)	0.27
Family income (Minimum wages)			
Up to 2	72 (1.1%)	101 (1.3%)	
2 to 8	2,496 (39.7%)	2,968 (39.2%)	
8 to 18	2,100 (33.4%)	2,927 (38.6%)	
Above 18	1,619 (25.8%)	1,582 (20.9%)	0.00
Education			
Incomplete elementary school	489 (7.7%)	265 (3.5%)	
Complete elementary school	515 (8.2%)	388 (5.1%)	
Complete high school	2,116 (33.5%)	2,723 (35.7%)	
Complete higher education/post-graduation	3,194 (50.6%)	4,236 (55.7%)	0.00
Work situation			
Retired	879 (13.9%)	1,615 (21.2%)	
Active	5,431 (86.1%)	5,991 (78.8%)	0.00
Obesity			
BMI < 30 kg/m^2	4,985 (78.9%)	5,755 (75.6%)	
BMI ≥ 30 kg/m^2	1,329 (21.1%)	1,857 (24.4%)	0.00
Commuting physical activity			
Insufficiently active	3,955 (63.6%)	5,081 (67.7%)	
Active	2,267 (36.4%)	2,418 (32.3%)	0.00
Leisure-time physical activity			
Sedentary	2,308 (37.1%)	3,572 (47.6%)	
Insufficiently active	1,166 (18.7%)	1,366 (18.2%)	
Active	1,562 (25.1%)	1,690 (22.6%)	
Very active	1,186 (19.1%)	871 (11.6%)	0.00
Cardiovascular risk scores			
Framingham score — coronary heart disease (Cholesterol)			
Score < 20%	5,481 (86.8%)	7,484 (98.3%)	
Score ≥ 20%	833 (13.2%)	128 (1.7%)	0.00
Framingham score — coronary heart disease (LDL-C)			
Score < 20%	5,792 (91.7%)	7,435 (97.7%)	
Score ≥ 20%	522 (8.3%)	177 (2.3%)	0.00
Framingham score — cardiovascular disease (cholesterol)			
Score < 20%	4,742 (75.3%)	7,194 (94.6%)	
Score ≥ 20%	1,554 (24.7%)	408 (5.4%)	0.00
Framingham score — cardiovascular disease (BMI)			
Score < 20%	4,355 (69.2%)	6,997 (92.1%)	
Score ≥ 20%	1,938 (30.8%)	603 (7.9%)	0.00
Pooled cohort equations for atherosclerotic cardiovascular disease risk			
Score < 20%	5,480 (88.3%)	7,304 (97.1%)	
Score ≥ 20%	728 (11.7%)	219 (2.9%)	0.00

BMI: body mass index; LDL-C: low-density lipoprotein. Values for both males and females were compared with chi-square test.

Table 2 – Association between leisure-time or commuting physical activity and cardiovascular risk scores for males: Longitudinal Study of Adult Health (ELSA-Brasil), 2008–2010

Cardiovascular risk score	Leisure-time physical activity (n = 6,222)	Commuting physical activity (n = 6,222)
Framingham score — coronary heart disease (cholesterol)*	0.72 (0.60–0.85)	0.99 (0.84–1.19)
Framingham score — coronary heart disease (LDL-C) *	0.72 (0.58–0.88)	1.04 (0.84–1.28)
Framingham score — cardiovascular disease (cholesterol)*	0.76 (0.65–0.88)	0.97 (0.83–1.17)
Framingham score — cardiovascular disease (BMI)#	0.68 (0.59–0.79)	0.96 (0.83–1.11)
Pooled cohort equations for atherosclerotic cardiovascular disease risk*	0.78 (0.65–0.95)	0.95 (0.79–1.15)

*BMI: body mass index; LDL-C: low-density lipoprotein. *Adjusted for age, obesity, and educational level; #Adjusted for age and educational level.*

Table 3 – Association between leisure-time or commuting physical activity and cardiovascular risk scores for females: Longitudinal Study of Adult Health (ELSA-Brasil), 2008–2010

Cardiovascular risk score	Leisure-time physical activity (n = 7,499)	Commuting physical activity (n = 7,499)
Framingham score — coronary heart disease (cholesterol)*	0.64 (0.42–0.97)	1.26 (0.87–1.82)
Framingham score — coronary heart disease (LDL-C)*	0.60 (0.42–0.86)	1.14 (0.83–1.58)
Framingham score — cardiovascular disease (cholesterol)*	0.63 (0.50–0.81)	1.13 (0.90–1.41)
Framingham score — cardiovascular disease (BMI)*	0.78 (0.64–0.96)	1.02 (0.84–1.24)
Pooled cohort equations for atherosclerotic cardiovascular disease risk*	0.85 (0.63–1.16)	0.98 (0.73–1.32)

*BMI: body mass index; LDL-C: low-density lipoprotein. * Adjusted for age and educational level.*

Table 4 – Dose-response effect in association between leisure-time physical activity and cardiovascular risk scores for females: Longitudinal Study of Adult Health (ELSA-Brasil), 2008–2010

Leisure-time physical activity*	Framingham score — coronary heart disease (cholesterol)*	Framingham score — coronary heart disease (LDL-C)*	Framingham score — cardiovascular disease (cholesterol)*	Framingham score — cardiovascular disease (BMI)#	Pooled cohort equations for atherosclerotic cardiovascular disease risk*
Sedentary	1.00	1.00	1.00	1.00	1.00
Not very active	0.86 (0.68–1.08)	1.02 (0.78–1.34)	1.08 (0.87–1.33)	0.99 (0.81–1.20)	1.03 (0.80–1.32)
Active	0.81 (0.65–0.99)	0.79 (0.61–1.03)	0.91 (0.75–1.10)	0.85 (0.71–1.02)	0.87 (0.68–1.10)
Very active	0.43 (0.32–0.58)	0.52 (0.37–0.74)	0.55 (0.43–0.69)	0.47 (0.38–0.59)	0.62 (0.46–0.84)

*BMI: body mass index; LDL-C: low-density lipoprotein. *Adjusted for age, obesity, and educational level; #Adjusted for age and educational level.*

Table 5 – Dose-response effect in association between leisure-time physical activity and cardiovascular risk scores for females: Longitudinal Study of Adult Health (ELSA-Brasil), 2008–2010

Leisure-time physical activity*	Framingham score — coronary heart disease (cholesterol)	Framingham score — coronary heart disease (LDL-C)	Framingham score — cardiovascular disease (cholesterol)	Framingham score — cardiovascular disease (BMI)	Pooled cohort equations for atherosclerotic cardiovascular disease risk
Sedentary	1.00	1.00	1.00	1.00	1.00
Not very active	1.20 (0.76–1.91)	1.04 (0.69–1.56)	1.07 (0.80–1.43)	0.92 (0.71–1.19)	1.17 (0.80–1.72)
Active	0.71 (0.43–1.16)	0.61 (0.40–0.94)	0.70 (0.52–0.93)	0.88 (0.64–1.03)	1.01 (0.72–1.44)
Very active	0.63 (0.29–1.37)	0.64 (0.34–1.20)	0.52 (0.32–0.83)	0.67 (0.46–0.95)	0.66 (0.37–1.23)

*BMI: body mass index; LDL-C: low-density lipoprotein. *Adjusted for age and educational level.*

for both gender.[32] Data from ELSA-Brasil which are unpublished yet suggest that active commuting, more common in less privileged social strata, is more likely to reflect inequalities in urban mobility across Brazilian cities than a healthy habit.

The mechanisms by which PA reduces BP, blood glucose, and lipid profile remain speculative. Recent studies have emphasized the need for further research to better understand the cellular and molecular aspects involved in the main health benefits induced by PA.[33] Relevant evidence for PA, according to the American College of Sports Medicine (ACSM),[15] is: a) decrease in insulin levels with consequent reduction of renal sodium retention and basal sympathetic tone; b) reduction of catecholamine release levels; c) release of vasodilator substances in circulation by skeletal muscles.

As to lipid profile, there is little information about the mechanisms responsible for the reduction of LDL-C levels and very low-density lipoprotein (VLDL-C) dosage. However, the main reason for evaluating HDL-C is the greater action of lipoprotein lipase (LPL) in response to exercise: LPL accelerates VLDL-C decomposition, thus moving triglycerides from bloodstream to muscles; This causes cholesterol and other substances to be transferred to HDL-C, thereby increasing its concentration.[16] PA also seems to play an important role in reducing blood glucose levels because it promotes proliferation of capillaries, increasing LPL activity in the muscles — which in turn increases insulin sensitivity. In addition, higher levels of PA may increase oxidative muscle fibers, which are more sensitive to insulin and can reduce glycemia.[17]

A highlight of the study is that the sample was a cohort of volunteers consisting of public servants; although they do not represent the general population, there was a significant number of participants from six Brazilian capitals. Calculation of different cardiovascular risk scores is another strong point, for it allowed us to analyze the association between them and both LTPA and CPA.

A possible limitation of the study (memory bias) can be attributed to information about PA obtained through questionnaires, even though this is an instrument widely used in national and international studies. It is important to mention that ELSA-Brasil was a longitudinal study, therefore it is expected to incorporate a more objective measure — the accelerometry — which may increase the validity of information about PA.

Conclusions

LTPA was shown to be associated with the cardiovascular risk scores analyzed, but CPA was not. The amount of physical activity (duration and intensity) was more significantly associated with cardiovascular risk scores in ELSA Brazil.

Our results can bring important contributions to public health, since the management of public policies that promote PA can be influenced by the knowledge about type of PA that bring more health benefits. Knowing that LTPA is associated with cardiovascular risk decrease while CPA is not should be taken to public health authorities so that actions encouraging exercises in leisure and free time can be implemented.

Important to note that, although association between CPA and cardiovascular risk was not established, active commuting — such as walking and cycling — should be encouraged in certain population groups, especially when displacement to work is made at moderate intensities. Furthermore, considering dose-response effects found, especially in men, the population should be encouraged to practice more PA to maximize health benefits.

Author contributions

Conception and design of the research: Alvim S, Almeida MC, Aquino EML; Acquisition of data and Obtaining financing: Alvim S, Almeida MC, Barreto SM, Aquino EML; Analysis and interpretation of the data: Pitanga FJG, Alvim S, Almeida MC, Aquino EML; Statistical analysis: Pitanga FJG, Almeida MC; Writing of the manuscript: Pitanga FJG; Critical revision of the manuscript for intellectual content: Pitanga FJG, Alvim S, Almeida MC, Barreto SM, Aquino EML.

Potential Conflict of Interest

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

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Study Association

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

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Instituto de Saúde Coletiva da UFBA under the protocol number 027.06/CEP-ISC. 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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Melatonin-Induced Protective Effects on Cardiomyocytes Against Reperfusion Injury Partly Through Modulation of IP3R and SERCA2a Via Activation of ERK1

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Resumo

Background: **Melatonin is a neuroendocrine hormone synthesized primarily by the pineal gland that is indicated to effectively prevent myocardial reperfusion injury. It is unclear whether melatonin protects cardiac function from reperfusion injury by modulating intracellular calcium homeostasis.**

Objective: **Demonstrate that melatonin protect against myocardial reperfusion injury through modulating IP3R and SERCA2a to maintain calcium homeostasis via activation of ERK1 in cardiomyocytes.**

Methods: **In vitro experiments were performed using H9C2 cells undergoing simulative hypoxia/reoxygenation (H/R) induction. Expression level of ERK1, IP3R and SERCA2a were assessed by Western Blots. Cardiomyocytes apoptosis was detected by TUNEL. Phalloidin-staining was used to assess alteration of actin filament organization of cardiomyocytes. Fura-2 /AM was used to measure intracellular Ca^{2+} concentration. Performing in vivo experiments, myocardial expression of IP3R and SERCA2a were detected by immunofluorescence staining using myocardial ischemia/ reperfusion (I/R) model in rats.**

Results: **In vitro results showed that melatonin induces ERK1 activation in cardiomyocytes against H/R which was inhibited by PD98059 (ERK1 inhibitor). The results showed melatonin inhibit apoptosis of cardiomyocytes and improve actin filament organization in cardiomyocytes against H/R, because both could be reversed by PD98059. Melatonin was showed to reduce calcium overload, further to inhibit IP3R expression and promote SERCA2a expression via ERK1 pathway in cardiomyocytes against H/R. Melatonin induced lower IP3R and higher SERCA2a expression in myocardium that were reversed by PD98059.**

Conclusion: **melatonin-induced cardioprotection against reperfusion injury is at least partly through modulation of IP3R and SERCA2a to maintain intracellular calcium homeostasis via activation of ERK1. (Arq Bras Cardiol. 2018; 110(1):44-51)**

Keywords: **Melatonin; Myocardial Reperfusion; Cardiac Myocytes; Myocardial Infarction; Heart Failure.**

Introduction

Myocardial ischemia-reperfusion injury typically arises in patients presenting with acute ST-segment elevation myocardial infarction (STEMI), in whom the most effective therapeutic intervention for reducing acute myocardial ischemic injury and limiting the size of myocardial infarction (MI) is timely and effective myocardial reperfusion therapy.[1] However, the process of myocardial reperfusion can itself induce further myocardial reperfusion injury.[1-4] Myocardial reperfusion injury weakens the benefit of reperfusion therapy and brings to patients larger MI size, more severe heart failure and worse prognosis. Restoration of cardiac circulation is accompanied by cell damages and death (lethal reperfusion injury), reperfusion arrhythmias, myocardial stunning, and no-reflow phenomenon. Lethal reperfusion injury (cardiomyocyte death induced by reperfusion) is a key therapeutic target with anticipated significant impact on the patient's prognosis.[1-6] Melatonin (N-acetyl-5-methoxytryptamine) is a neuroendocrine hormone, which is synthesized primarily by the pineal gland.[7,8] Melatonin presents profound protective effects against myocardial ischemia-reperfusion injury through antioxidant actions.[9-18] Ca^{2+} overload is the primary stimulator to ischemia/reperfusion injury and induce cardiomyocytes apoptosis in ischemia/reperfusion condition. It is unclear whether melatonin protects cardiac function from reperfusion injury by modulating intracellular calcium homeostasis. Yeung et al.[19] suggested that melatonin is cardioprotective against chronic hypoxia-induced myocardial injury because it improves calcium handling in the sarcoplasmic reticulum (SR) of cardiomyocytes via an antioxidant mechanism.

However, the evidence about melatonin's effect and underlying mechanism on Ca^{2+} overload under acute ischemia/reperfusion is rare. The cardiac inositol 1,4,5-trisphosphate receptors (IP3R) and sarcoplasmic reticulum Ca^{2+}-ATPase (SERCA2a) are key mediators for intracellular calcium handling, contractility and

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death in cardiac cells.[20-23] So in the present study we hypothesized melatonin has protective effects on cardiomyocyte against reperfusion injury through modulating IP3R and SERCA2a to maintain intracellular calcium homeostasis. Ischemia-reperfusion has been shown to activate the anti-apoptotic pro-survival kinase signalling cascades including p42/p44 extra-cellular signal-regulated kinases (ERK 1/2) which have been implicated in cellular survival.[24,25] It is not clear if ERK1 plays important role during modulation of melatonin on calcium homeostasis in cardiomyocytes. The present study aimed to elucidate whether melatonin protects cardiomyocytes against reperfusion injury through modulating IP3R and SERCA2a to reduce calcium overload via ERK1 pathway.

Methods

Ethics statement

The present study was performed in accordance with the guidelines of the Ethic Committee of Chinese PLA (People's Liberation Army) General Hospital, Beijing, China.

H9C2 Cells culture

H9C2 cells (derived from the rat embryonic cardiomyoblast) were obtained from Chinese Academy of Medical Sciences (Shanghai, China) were cultured in Dulbecco's Modified Eagle Medium: Nutrient Mixture F-12 (DMEM/F12, Thermo Fisher Biochemical Products, Beijing, China) supplemented with 10% fetal bovine serum (FBS, Invitrogen Life Technologies, Carlsbad, CA, USA) and 100 mg/mL penicillin/streptomycin (Beyotime Institute of Biotechnology, China).

H/R injury induction in vitro and melatonin or plus with PD98059 treatment

Hypoxic conditions were produced using fresh Hanks solution with 95% N_2 and 5 % CO_2. The pH was adjusted to 6.8 with lactate to mimic ischemic conditions. The dishes were put into a hypoxic incubator (Invivo2-400, Ruskinn) that was equilibrated with 95% N_2 and 5% $CO_2$and the actual oxygen concentration was zero. Ambient O_2 levels in the hypoxia incubator were monitored by an O_2 analyzer (series-2000, Alpha Omega Instruments). After hypoxic treatment, the culture medium was rapidly replaced with fresh DMEM with 1% FBS to initiate reoxygenation. Hypoxia/reoxygenation procedure was achieved by 4 h of hypoxia treatment (anoxia) and 4 h of reoxygenation treatment. For melatonin treatment, cultured cells were pre-incubated with melatonin (5 uM) 12 h before hypoxia, or plus with PD98059 with concentration of 10 uM prior to melatonin treatment. The dose of melatonin was chosen according to previous studies.[18,26]

In vitro TUNEL apoptosis assay of cardiomyocytes by confocal microscopy

The apoptosis of H9C2 cells was examined by TUNEL assay. Briefly, cultured cardiomyocytes were fixed with 4% paraformaldehyde (PFA) (Millipore, USA) and permeabilized with 1% Triton X-100 (Sigma Aldrich, USA) in phosphate-buffered saline (PBS) (Invitrogen, USA) for 30 minutes, followed by 3 times (3×10 mins) wash with fresh PBS. Then, an Apo-BrdU in Situ DNA Fragmentation Assay Kit (BioVision, USA) was applied for 1 hour, followed by incubating the treated plates with 5 μl anti-BrdUFITC antibody. Fifteen minutes of DAPI immunostaining were performed to identify the nuclei of cardiomyocytes. Then, the images were taken with an inverted Leica TCS-SP2 AOBS confocal laser-scanning microscope (Leica, Germany). Apoptosis was quantified as the percentage of cultured cardiomyocytes.

F-actin study with fluorescent phalloidin and confocal microscopy

F-actin detection with phalloidin was done according to manufacturer's instructions. Briefly, H9C2 were fixed on polylysine-treated glass with 3.7% paraformaldehyde and later washed with 0.1% Triton X-100-PBS. Thereafter they were stained with 0.8unit/ml fluorescent FITC-phalloidin conjugate solution (KeyGen Bio TECH Corp,China) for 10 min at room temperature. Finally, they were washed three times with PBS. Mounted samples were analyzed using confocal microscopy.

Detection of intracellular Ca^{2+} concentration

Intracellular Ca^{2+} was measured using the calcium-dependent fluorescent dye Fura-2 according to the manufacturer's instructions. Briefly, H9C2 cultures were transferred to 1 mL fresh DMEM containing 5 μL Fura-2-acetoxy-methylester (AM; 10 μM; Life Technologies, Carlsbad, CA, USA) and incubated in a CO_2 incubator at 37°C for 1 h. Fura-2-loaded cells were then placed on the stage of a confocal microscopy (Olympus) and viewed using a 60× oil immersion objective.

Western blots

Following the appropriate treatments, cultured cells were lysed with RIPA lysis buffer (Beyotime,China) for 30 min and centrifuged at 14,000xg for 30 min. Equal amounts of protein were separated by 10% sodium dodecyl sulfate-polyacrylamide gel electrophoresis and transferred to a polyvinylidene difluoride membrane (Millipore). After being blocked with 5% milk in Tris buffered saline containing 0.05% Tween20 (TBST) at room temperature for 1h, the membrane was incubated at 4°C overnight with the following primary antibodies: t-ERK1(1:2000, Abcam), p-ERK1(1:1000, Abcam), IP3R (1:1000,Abcam), and SERCA2a (1:1000,Ab-cam). After being washed with TBST and further incubated with the appropriate secondary antibody at 37°C for 60 min, the blots were visualized with an enhanced chemiluminescence (ECL) reagent.

Myocardial ischemia/reperfusion (I/R) model and melatonin treatment

Male Sprague–Dawley (SD) rats (250 ± 10 g) were purchased from the Experimental Animal Center, Chinese PLA General Hospital. All procedures were approved by the Institutional Animal Care and Use Committee of the Chinese PLA General Hospital. Rats were divided into the following groups (n = 5 in each group): (1) Control group, (2) I/R group, (3) I/R+Melatonin group, (4) I/R+Melatonin+PD98059. Rats were intraperitoneally anaesthetized with sodium pentobarbital

(50 mg/kg). The animals were then incubated and ventilated by a volume- regulated respirator during surgery. After a left lateral thoracotomy and pericardectomy, the left coronary artery was identified and gently ligated with a 6.0 prolene suture. Successful AMI was confirmed by the typical ST segment elevation in electrocardiography. Myocardial ischemia lasted for 30 mins and reperfusion for 2 hours. Freshly prepared melatonin (Sigma-Aldrich, St. Louis, MO, USA) was administered intraperitoneally at a dose of 20 mg/kg 12 hours prior to MI. PD98059 (ERK1 inhibitor, Sigma,USA) was administered with intraperitoneal injection at a dose of 5 mg/kg 4 hours prior to melatonin treatment. At the end of the reperfusion period, the hearts were excised for the preparation of sections (4 μm thickness) to detect the expression of SERCA2a and IP3R by immunofluorescence staining.

Detection of myocardial SERCA2a and IP3R expression by immunofluorescence staining

After being treated as above, the heart sections were fixed with 4% paraformaldehyde in PBS for 15 min at room temperature, permeabilized with 0.1% Triton X-100 for 10 min, and then blocked with 5% BSA for 1 h. Then, samples were incubated overnight at 4°C with monoclonal mouse anti-rat SERCA2a antibody (1:100;Abcam, Cambridge, USA). After being washed with PBS for three times, samples were incubated with goat anti-mouse polyclonal IgG (1:400; Abcam,Cambridge, USA) at room temperature in the dark for 2 h. For nuclear counterstaining, samples were incubated with 4′, 6-diamidino-2-phenylidone (DAPI; Sigma, USA) for 5 min. Finally, the immunofluorescence images were obtained by inverted fluorescence microscope (Olympus, Tokyo, Japan).

Statistical analysis

Data were described as the mean ± SD of at least three independent analyzed experiments. The differences among more than 2 groups were evaluated through 1-way ANOVA (all data met the variances homogeneity and normal distribution),and LSD method was used to compare the statistical difference in the post-hoc analysis. A value of $P < 0.05$ was considered statistically significant. All of the statistical analyses were performed with SPSS for Windows version 16.0 (SPSS Inc., Chicago, IL).

Results

Melatonin promoted activation of ERK1 in cardiomyocytes against H/R

At 4h after reoxygenation, we investigated the effect of melatonin on phosphorylation of ERK1 (p-ERK1) using Western blot. The expression level of p-ERK1 did not show significant difference between control and H/R group. Melatonin significantly promoted the expression of p-ERK1 in cardiomyocytes which was reversed by PD98059 (ERK1 inhibitor) (Figure 1).

Melatonin prevents H/R-induced apoptosis of cardiomyocytes via ERK1 pathyway in vitro

The apoptosis of H9C2 cells was detected at 4h after reoxygenation by TUNEL staining. The results demonstrated H/R induce apoptosis of H9C2 cells in vitro. Pretreament with melatonin decreased H/R-induced apoptosis of H9C2. The results showed percentage of apoptotic cells was obviously higher in H/R group compared to control group, however, which was significantly lower in melatonin group than H/R group. PD98059 (ERK1 inhibitor) reduced the effect of melatonin on preventing cardiomyocytes apoptosis against H/R (Figure 2).

Melatonin protects F-actin organization in H9C2 cells against H/R via ERK1 pathway

We investigated F-actin organization in H9C2 cells at 4h after reoxygenation by fluorescent FITC-phalloidin staining. Control cardiomyocytes showed regular and well-defined actin organization, while cardiomyocytes in H/R group showed a more diffuse and irregular F-actin disposition.

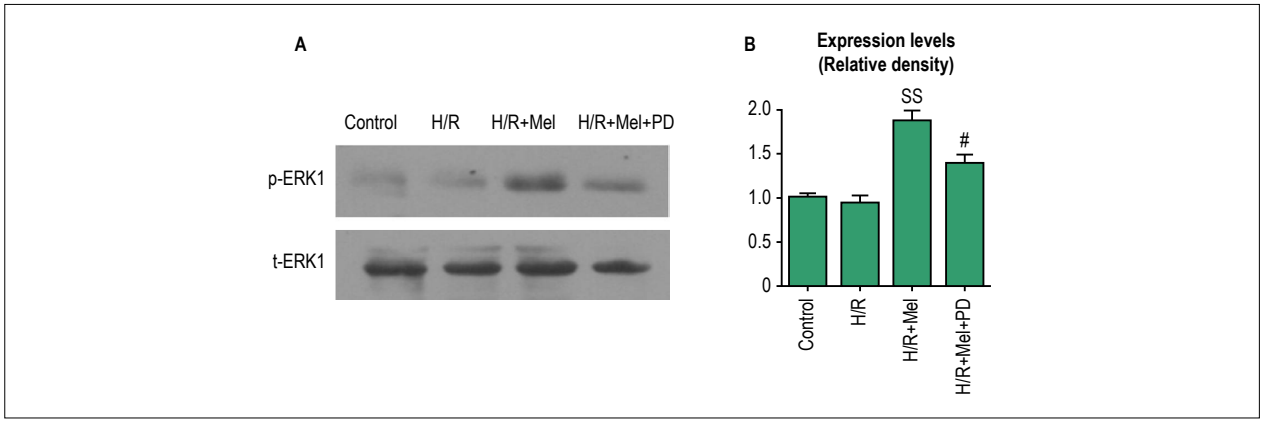

Figure 1 – *Melatonin promoted activation of ERK1 in H9C2 cells against H/R. H9C2 cells incubated in normal condition or in simulated H/R condition, in simulated H/R condition plus pretreatment with melatonin, or in simulated H/R condition plus pretreatment with melatonin and PD98059 (ERK1 inhibitor).The expression levels of phosphorylated ERK1 (p-ERK1) were evaluated by Western blotting (A) and were quantitatively analyzed (B). All values are presented as the mean±SD. n = 3. SSp < 0.01 vs. H/R group; #p < 0.05 vs. H/R+Mel group.(Control: control group; H/R:H/R group; H/R+mel: H/R+ melatonin group; H/R+mel+PD: H/R+ melatonin+PD98059 group)*

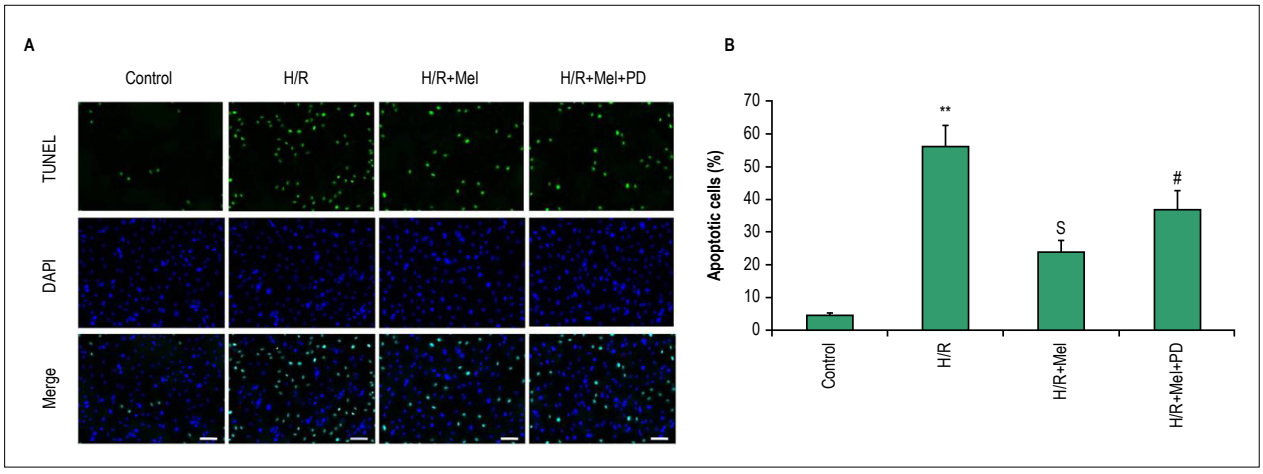

Figure 2 – *Melatonin prevents H9C2 cells apoptosis against H/R via ERK1 in vitro. Apoptosis was assessed by fluorescence TUNEL. Representative TUNEL staining images (A) and quantitative analysis in H9C2 cells(B). bar = 50 μm. All values are presented as the mean±SD. n = 3.**p < 0.01 vs. control group; Sp < 0.05 vs. H/R group; #p < 0.05 vs. H/R+Mel group. (Control: control group; H/R:H/R group; H/R+mel: H/R+ melatonin group; H/R+mel+PD: H/R+ melatonin+PD98059 group)*

The differences can be visualized in the representative cardiomyocytes. Pretreatment of melatonin improved F-actin organization in cardiomyocytes compared with H/R group, but PD98059 damaged F-actin organization by inhibiting melatonin's effect (Figure 3).

Melatonin reduces Ca^{2+} overload in cardiomyocytes against H/R via ERK1

At 4h after reoxygenation, we investigated effect of melatonin on H/R-induced Ca^{2+} overload in cardiomyocytes using the calcium-dependent fluorescent dye Fura-2. The results showed the fluorescence was stronger in H/R group than in control group, meanwhile the fluorescence was decreased in melatonin group compared with H/R group, which indicated that H/R caused a marked increase of cytosolic Ca^{2+} concentration and that melatonin pretreatment significantly inhibited H/R-induced increase of cytosolic Ca^{2+} concentration which was reduced by PD98059 (Figure 4).

Melatonin modulated expression of IP3R and SERCA2a in cardiomyocytes against H/R via ERK1

At 4h after reoxygenation, we investigated the effect of melatonin on expression of IP3R and SERCA2a in H9C2 by Western blot. The results indicated H/R increase expression of IP3R and reduce expression of SERCA, respectively. Pretreatment of melatonin inhibited expression of IP3R and induced expression of SERCA, which were reversed by PD98059. (Figure 5).

Melatonin modulated expression of IP3R and SERCA2a via ERK1 pathway in reperfused rat hearts

In vivo, we investigated the effect of melatonin on expression of IP3R and SERCA2a in reperfused rat hearts. IP3R expression was higher in I/R group compared with control group, and melatonin reversed the change. The results demonstrated expression of SERCA2a was lower in I/R group compared with control group, but expression of SERCA2a was higher in melatonin group than I/R group. The pretreament of PD98059 reduced the effect of melatonin on expression of IP3R and SERCA2a in rat hearts against I/R (Figure 6).

Discussion

Reperfusion-induced death of cardiomyocytes that were viable at the end of the ischemic event is defined as lethal myocardial reperfusion injury (reperfusion infarction).[1,3,27] The existence of lethal myocardial reperfusion injury has been inferred in both experimental MI models and in patients with STEMI(1). The major contributory factors for reperfusion-induced death of cardiomyocytes include oxidative stress, calcium overload, mitochondrial permeability transition pore (mPTP) opening, and hypercontracture.[28,29] Ca^{2+} overload is one of the main actors of this lethal reperfusion injury,[30] which results in part from excessive sarco/endoplasmic reticulum (SR/ER) Ca^{2+} release and Ca^{2+} influx through the plasma membrane.[31] Although ryanodine receptors (RyRs) are the major cardiac SR/ER Ca^{2+}-release channels involved in excitation–contraction coupling and ischemia–reperfusion injury,[32,33] some studies reported an increasing role for inositol 1,4,5-trisphosphate receptors (IP3R) Ca^{2+}-release channels in the modulation of excitation–contraction coupling and cell death.[22,23] Gomez et al[34] indicated that inhibition of IP3R Ca^{2+} channeling complex limited SR/ER Ca^{2+} release and reduced both cytosolic and mitochondrial Ca^{2+} overload and inhibited subsequent PTP opening. Meantime, the cardiac SERCA2a is a key pump responsible for intracellular calcium handling and contractility in cardiac cells. Impaired calcium reuptake resulting from decreased expression and activity of SERCA2a is a hallmark of HF.[20] IP3R and SERCA2a have been confirmed to play important roles in maintaining intracellular calcium homeostasis in cardiomyocytes.[20,22,23,35]

Melatonin as one type of neuroendocrine hormone, is synthesized primarily by the pineal gland.[7,8] Previous studies showed melatonin confers important protective effects against myocardial

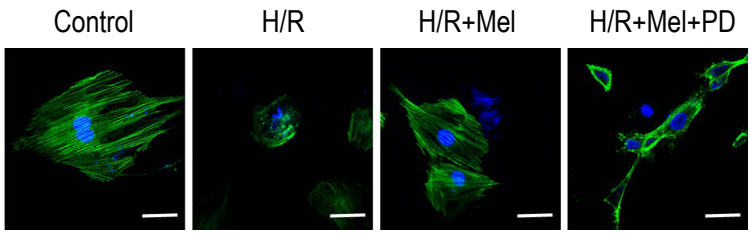

Figure 3 – *Melatonin protects F-actin organization in H9C2 cells against H/R via ERK1 in vitro. Representative confocal microscopy images show H9C2 cells stained with FITC-phalloidin. The results showed that simulated H/R induced more diffuse and irregular actin disposition compared with control group. Melatonin preserved more regular and well-defined actin organization and PD98059 (ERK1 inhibitor) reduced the protection of melatonin. bar = 20μm. (Control: control group; H/R:H/R group; H/R+mel: H/R+ melatonin group; H/R+mel+PD: H/R+ melatonin+PD98059 group)*

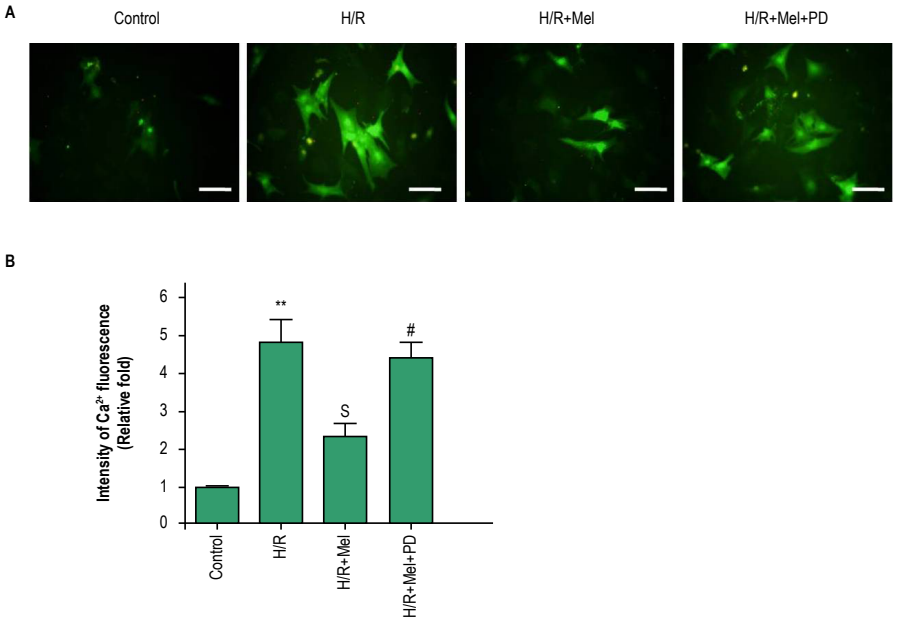

Figure 4 – *Melatonin reduces Ca^{2+} overload in H9C2 cells against H/R via ERK1 in vitro. Ca^{2+} content was assessed using Fura-2/AM in H9C2 cells incubated in normal condition or in simulated H/R condition, in simulated H/R condition plus pretreatment with melatonin, or in simulated H/R condition plus pretreatment with melatonin and PD98059 (ERK1 inhibitor). The green fluorescence intensity by Fura-2 was obviously stronger in H/R group, and melatonin pretreatment reversed the change which was inhibited by ERK1 inhibitor.bar = 30 μm. All values are presented as the mean ± SD. n = 3.**p < 0.01 vs. control group; Sp < 0.05 vs. H/R group; #p < 0.05 vs. H/R+Mel group. (Control: control group; H/R:H/R group; H/R+mel: H/R+ melatonin group; H/R+mel+PD: H/R+ melatonin+PD98059 group)*

ischemia-reperfusion injury.[9-14] Melatonin administration showed to contribute to the rehabilitation of contractile function on isolated heart during reperfusion and to reduce the sensitivity of mPTP opening to Ca^{2+}.[36]

Melatonin has also demonstrated to play a role in the mitochondrial adaptive changes.[37] Melatonin and its metabolites efficiently interact with various ROS and reactive nitrogen species, and additionally they up regulate antioxidant enzymes and downregulate pro-oxidant enzymes.[9,15,16] Previous studies confirmed that melatonin pretreatment attenuated IR injury by reducing oxidative damage and inhibiting mPTP opening. However, the evidence about melatonin's effect and underlying mechanism on Ca^{2+} overload under acute ischemia/reperfusion is rare. The present study demonstrated that melatonin performs cardioprotection through modulation of IP3R and SERCA2a to maintain calcium homeostasis via ERK1 pathway in cardiomyocytes. ERK1 pathway has been shown to have anti-apoptotic effect during the process of reperfusion injury.[24,25] It is not clear if melatonin maintains calcium homeostasis through modulating IP3R and SERCA2a via ERK1.

In the present study, the results showed that melatonin promote phosphorylation of ERK1 in cardiomyocytes against H/R, and pretreatment of PD98059 (ERK1 inhibitor) reduced phosphorylation of ERK1. In vitro results indicated melatonin prevents cardiomyocytes apoptosis against H/R. Meantime, melatonin can preserve structure of cardiomyocytes against reperfusion injury. Moreover, calcium overload induced by H/R is significantly reversed by melatonin. Moreover, the pretreatment of PD98059 inhibited the effect of melatonin

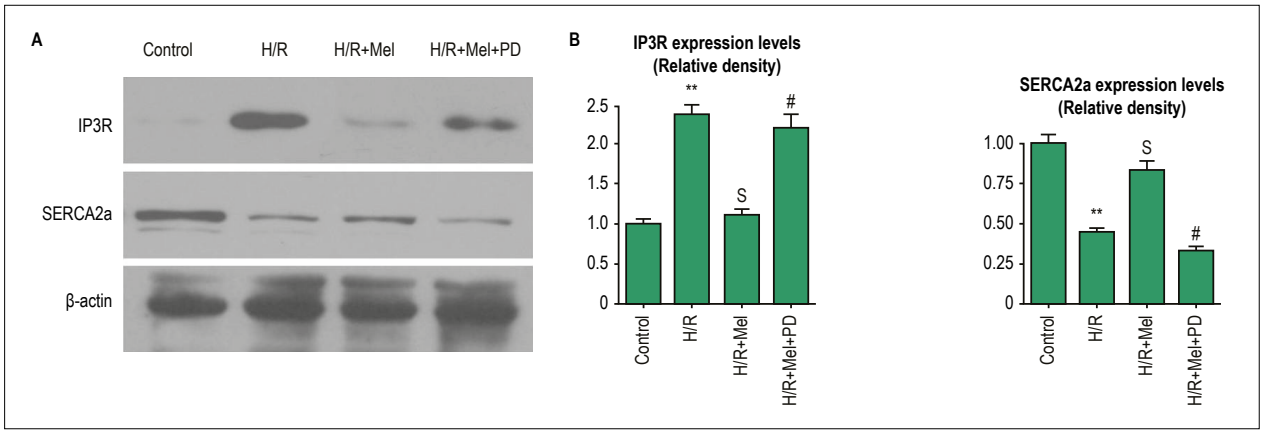

Figure 5 – *Melatonin modulated expression of SERCA2a and IP3R in H9C2 cells against H/R via ERK1 pathway in vitro. The results indicated melatonin inhibited expression of IP3R and promoted expression of SERCA2a which was reduced by PD98059. Representative Western blot images (A) and quantitative analysis (B-C) showed melatonin's effect on expression of IP3R and SERCA2a via ERK1 pathway in H9C2 cells against H/R.bar = 30 μm. **p < 0.01 vs. control group; Sp < 0.05 vs. H/R group; #p < 0.05 vs. H/R+Mel group. (Control: control group; H/R:H/R group; H/R+mel: H/R+ melatonin group; H/R+mel+PD: H/R+ melatonin+PD98059 group)*

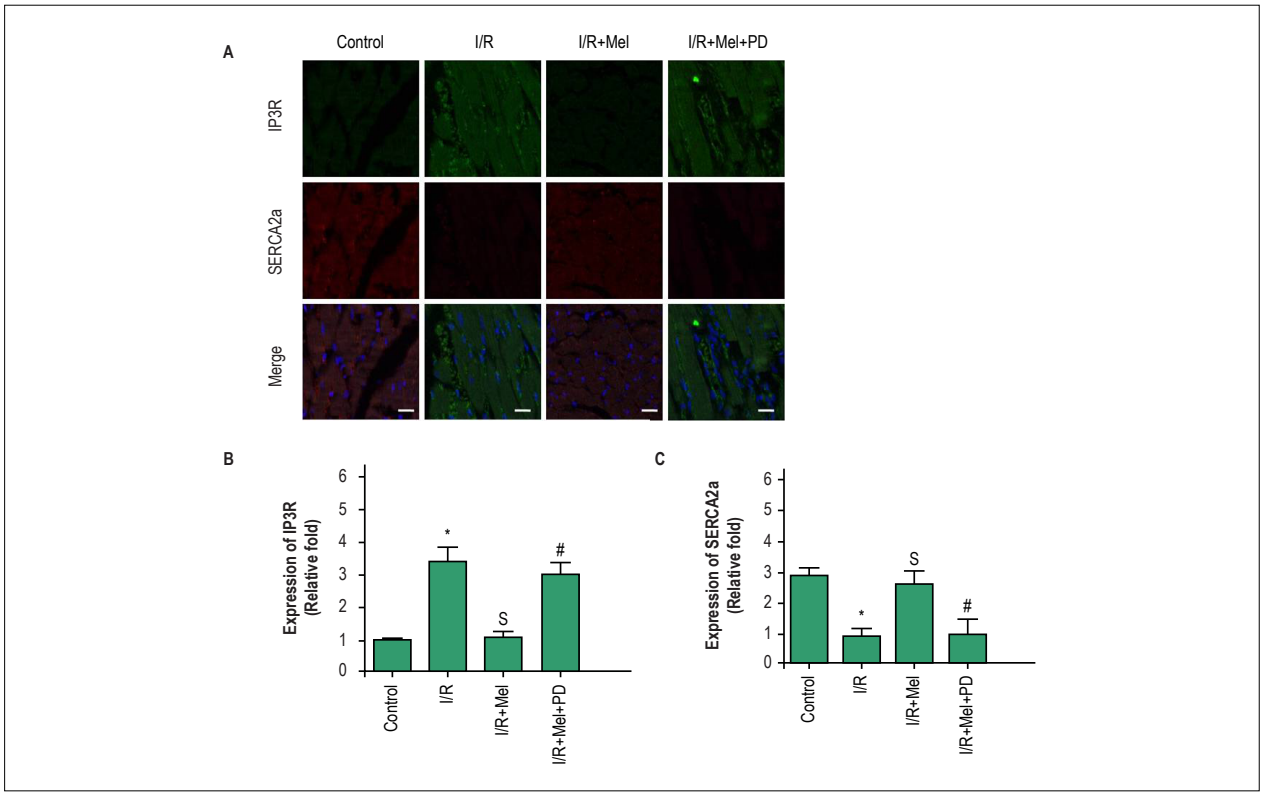

Figure.6 – *Melatonin modulated expression of IP3R and SERCA2a via ERK1 pathway in reperfused rat hearts. In reperfused myocardium, expression of IP3R and SERCA2a were assessed by immunofluorescence staining (A) and quantitative analysis (B-C). The results showed that fluorescence intensity of IP3R was increased in I/R group more than in control group, but was lower in melatonin group compared with I/R group. On the contrary, melatonin increased expression of SERCA2a in reperfused myocardium. Both of the effects of melatonin on expression of IP3R and SERCA2a were inhibited by PD98059 (ERK1 inhibitor). bar = 30 μm. All values are presented as the mean ± SD. n = 5.*p < 0.05 vs. control group; Sp < 0.05 vs. I/R group; #p < 0.05 vs. I/R+Mel group. (Control: control group; I/R:I/R group; I/R+mel: I/R+ melatonin group; I/R+mel+PD: I/R+ melatonin+PD98059 group).*

on apoptosis, F-actin organization and calcium overload in cardiomyocytes against H/R. To further elucidate the underlying mechanism for protective effect of melatonin cardiomyocytes against H/R, we observed the effects of melatonin on expression of IP3R and SERCA2a. The results showed SERCA2a expression is decreased in H/R group compared with control group, but melatonin promoted SERCA2a expression in cardiomyocytes. Contrarily, H/R induces IP3R expression, and melatonin inhibits

the expression of IP3R. Pretreatment of PD98059 reversed the effect of melatonin on expression of IP3R and SERCA2a. In vivo, myocardial IP3R level is reduced and SERCA2a expression is increased by pretreatment of melatonin, however, PD98059 reversed the effect of melatonin on expression of IP3R and SERCA2a. Melatonin in the dose used in the study did not show obvious side effects compared with other groups. In vivo results further confirmed that melatonin regulates the expression of IP3R and SERCA2a via ERK1. From the above results, it is reasonable to infer that melatonin could protect cardiomyocytes against reperfusion injury through affecting IP3R and SERCA2a expression to inhibit calcium overload via ERK1 pathway.

Conclusion

Melatonin can protect cardiomyocytes against reperfusion injury through modulation of IP3R and SERCA2a attenuating calcium overload via ERK1 pathway. Improved calcium homeostasis followed by preserved function and structure of cardiomyocytes can decrease cardiomyocytes apoptosis and improve heart function. The present study provide more evidence for the use of melatonin to protect cardiac function in patients with STEMI undergoing myocardial reperfusion therapy.

Author contributions

Conception and design of the research: Hu S, Zhu P, Zhou H, Zhang Y, Chen Y; Acquisition of data: Hu S, Zhu P, Zhou H, Zhang Y; Analysis and interpretation of the data, Statistical analysis and Critical revision of the manuscript for intellectual content: Hu S, Zhou H; Obtaining financing and Writing of the manuscript: Hu S.

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 on Animal Experiments of the Chinese PLA General Hospital.

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Correlation of Electrocardiographic Changes with Cardiac Magnetic Resonance Findings in Patients with Hypertrophic Cardiomyopathy

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Abstract

Background: Electrocardiogram is the initial test in the investigation of heart disease. Electrocardiographic changes in hypertrophic cardiomyopathy have no set pattern, and correlates poorly with echocardiographic findings. Cardiac magnetic resonance imaging has been gaining momentum for better assessment of hypertrophy, as well as the detection of myocardial fibrosis.

Objectives: To correlate the electrocardiographic changes with the location of hypertrophy in hypertrophic cardiomyopathy by cardiac magnetic resonance.

Methods: This descriptive cross-sectional study evaluated 68 patients with confirmed diagnosis of hypertrophic cardiomyopathy by cardiac magnetic resonance. The patients' electrocardiogram was compared with the location of the greatest myocardial hypertrophy by cardiac magnetic resonance. Statistical significance level of 5% and 95% confidence interval were adopted.

Results: Of 68 patients, 69% had septal hypertrophy, 21% concentric and 10% apical hypertrophies. Concentric hypertrophy showed the greatest myocardial fibrosis mass ($p < 0.001$) and the greatest R wave size in D1 ($p = 0.0280$). The amplitudes of R waves in V5 and V6 ($p = 0.0391$, $p = 0.0148$) were higher in apical hypertrophy, with statistical significance. Apical hypertrophy was also associated with higher T wave negativity in D1, V5 and V6 ($p < 0.001$). Strain pattern was found in 100% of the patients with apical hypertrophy ($p < 0.001$).

Conclusion: The location of myocardial hypertrophy by cardiac magnetic resonance can be correlated with electrocardiographic changes, especially for apical hypertrophy. (Arq Bras Cardiol. 2018; 110(1):52-59)

Keywords: Hypertrophic cardiomyopathy / genetic; Electrocardiography; Magnetic Resonance Spectroscopy.

Introduction

Hypertrophic cardiomyopathy (HCM) is an autosomal dominant disease, characterized by myocardial hypertrophy in the absence of cardiac or systemic diseases.[1] In adults, the diagnosis is defined by a diastolic thickness of any ventricular wall ≥ 15 mm measured on any imaging test.[2]

Electrocardiogram (ECG) is the initial test to be performed when investigating heart diseases. In HCM, the ECG has not a defined pattern, and can show signs of left ventricular overload, presence of q waves, changes in the ST segment, abnormal T waves, or be even normal in 6% of the patients.[3]

Some specific electrocardiographic findings may suggest the location of hypertrophy, as well as the presence of fibrosis. Giant inverted T waves (> 10 mm) in the precordial or inferolateral leads suggest apical involvement. Deep q waves in the inferolateral leads with positive T waves are associated with the asymmetric distribution of the HCM, and q waves lasting more than 40 ms relate to fibrosis. The ST-segment elevation in the lateral wall can correlate to small apical aneurysms, which are associated with fibrosis.[2] Electrocardiographic patterns similar to that of myocardial infarction in young individuals can precede the echocardiographic evidence of myocardial hypertrophy.[4]

The electrocardiographic changes can lead to the suspicion of HCM, and together with the clinical history and other imaging tests can establish the diagnosis.

Traditionally, echocardiography is the imaging test of choice to diagnose HCM, because of its wide availability and lower cost. However, the relationship between the electrocardiographic changes and the morphology and severity of myocardial thickness has not been well established when assessed on the echocardiogram.[5,6]

Cardiac magnetic resonance imaging has gained importance in the HCM assessment, because of its superiority in measuring the thickness of ventricular walls, mainly in regions difficult

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to visualize on echocardiography, in addition to providing ventricular morphology and function assessment. Detection of delayed contrast-enhancement has prognostic value.[2]

This study was aimed at correlating electrocardiographic variables with the location of myocardial hypertrophy assessed on cardiac magnetic resonance imaging.

Methods

This is a descriptive cross-sectional study that assessed patients diagnosed with HCM and followed up at the Cardiomyopathy Sector of the Instituto Dante Pazzanese de Cardiologia (IDPC), who underwent cardiac magnetic resonance imaging from January 2012 to September 2015.

The patients' inclusion criteria were: age over 18 years and diagnosis of HCM confirmed on interpretable ECG and magnetic resonance imaging performed at the Imaging Sector of the IDPC. The exclusion criteria were: age < 18 years; ejection fraction lower than 50% on cardiac magnetic resonance imaging; resistant arterial hypertension; presence of coronary artery disease, characterized by a coronary lesion greater than 50% on angiography; presence of Chagas disease; previous diagnosis of amyloidosis; endomyocardial fibrosis; Fabry disease; presence of definitive pacemaker; and septal myectomy or alcoholization prior to cardiac magnetic resonance imaging.

The HCM database of the Cardiomyopathy Sector of the IDPC was analyzed, and the medical records of 112 patients meeting this study inclusion criteria, which were stored at the Sector of Medical File and Statistics (SAME) of the IDPC, were assessed. After reviewing the medical files, 44 patients were excluded from the study.

The ECGs previously performed for the outpatient clinic visit at the Cardiomyopathy Sector were reviewed by the chief of the Tele-Electrocardiography Sector of the IDPC, in accordance with the 2016 Brazilian Guidelines on ECG Analysis and Report.[7] The ECG report comprised the following variables: rhythm, heart's QRS axis, ventricular and atrial overloads, intraventricular blocks, presence of strain, R wave size (millimeters) in leads DI, V1, V5 and V6, and T wave size (millimeters) in leads D1, V5 and V6.

Cardiac magnetic resonance imaging was assessed by the Radiology Team of the IDPC regarding the location of myocardial hypertrophy, based on the segmentation proposed by the American Heart Association,[8] and the presence of delayed enhancement, as well as quantification of the fibrosis mass in grams. The 17 segments were grouped into five regions: anterior, inferior, lateral, septal and apical. (Figure 1)

Patients with hypertrophy > 15 mm in at least three of those regions were considered to have concentric hypertrophy. (Figure 2)

Statistical analysis

The electrocardiographic variables previously described were compared with the region of hypertrophy, the presence of delayed enhancement and the amount of fibrosis identified on cardiac magnetic resonance imaging.

Normality of the data was assessed by use of Kolmogorov-Smirnov test, and nonparametric tests were used to compare between the groups. The summary measures median and 25th and 75th percentiles were calculated for the continuous variables, and nonparametric Kruskal-Wallis test was used to check the statistical significance between the groups, followed by two-by-two comparisons (Dunn's multiple comparison test).

For attribute variables, the results were presented as percentages and frequency. Fisher-Freeman-Halton exact test was used to assess the statistical significance between the groups. Statistical significance level of 5% and 95% confidence interval were adopted.

The findings were recorded in an electronic spreadsheet of Microsoft Office Excel, version 2013e, and the Statistical Package for the Social Sciences (SPSS), version 21.0 for Windows®, was used for analysis.

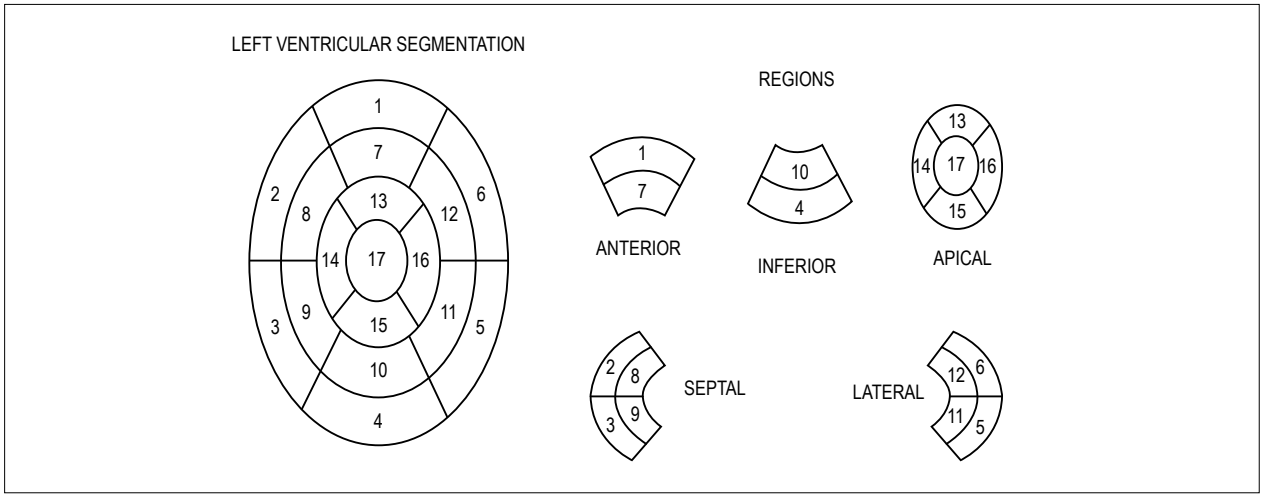

Figure 1 – *Left ventricular segmentation proposed by the American Heart Association.*

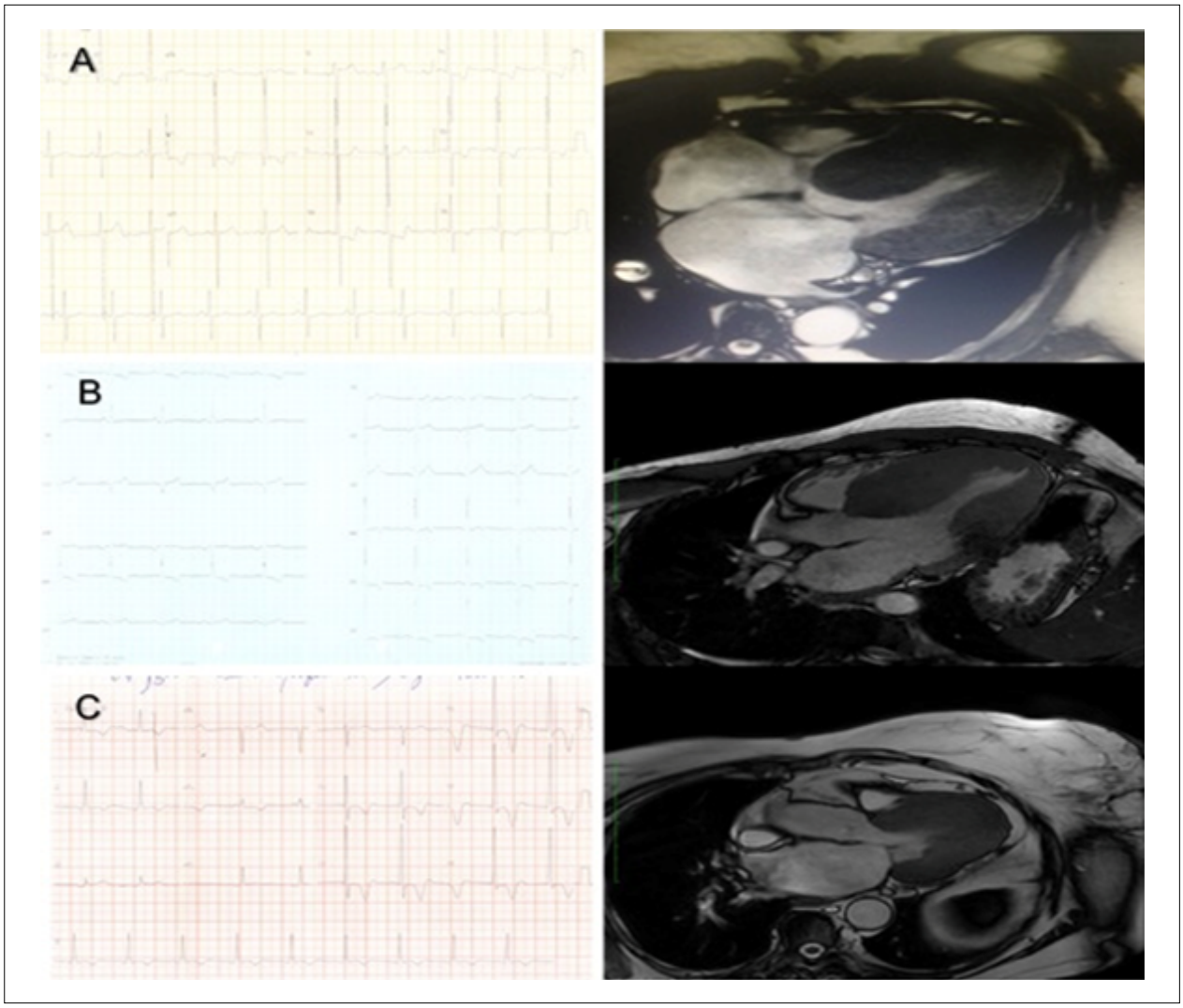

Figure 2 – *A) E.D.S., male sex, 35 years. ECG: R wave in D1 of 35 mm, and R wave in V5 of 29 mm. Magnetic resonance imaging compatible with concentric hypertrophy. Fibrosis mass of 128 g (greatest fibrosis mass found of all patients analyzed). B) M.L.S.F., female sex, 60 years. ECG: R wave in D1 of 23 mm, and R wave in V5 of 22 mm. Magnetic resonance imaging compatible with septal hypertrophy. C) P.M., male sex, 77 years. ECG: R wave of 35 mm in V5, and negative T wave of 12 mm with strain pattern. Magnetic resonance imaging compatible with apical hypertrophy.*

Results

This study assessed 70 patients, 55.9% of the female sex, with a mean age of 51.3 years (ranging from 20 to 81 years). Of the six location patterns of hypertrophy, only three were found: apical (10%), concentric (21%) and septal (69%). (Figure 3)

Most patients (81.4%) showed delayed enhancement on magnetic resonance imaging, and all patients with concentric hypertrophy had fibrosis. In quantifying the mass of fibrosis according to the location of hypertrophy, the highest mean (57.1 g) was observed in concentric hypertrophy as compared to the other locations ($p = 0.001$). (Table 1, Figure 4)

The concomitant presence of right ventricular hypertrophy on magnetic resonance imaging was found in 35.7% of the patients with concentric hypertrophy, showing statistical significance ($p = 0.0447$) as compared to septal and apical hypertrophies.

Patients with apical hypertrophy more frequently had atrial fibrillation (14.3%), preserved heart axis being identified in 100% of the cases. Such findings, however, had no statistical significance ($p = 0.7964$, $p = 0.6730$, respectively).

Regarding ventricular overloads, there was higher prevalence of both left and right ventricular overloads (71.4% and 21.4%, respectively) in concentric hypertrophy, with no statistical significance ($p = 0.1883$, $p = 0.2117$, respectively).

The strain pattern showed statistical significance between the types of hypertrophy ($p < 0.0001$), being present in 100% of the apical hypertrophy cases and in 71.4% of the concentric hypertrophy cases.

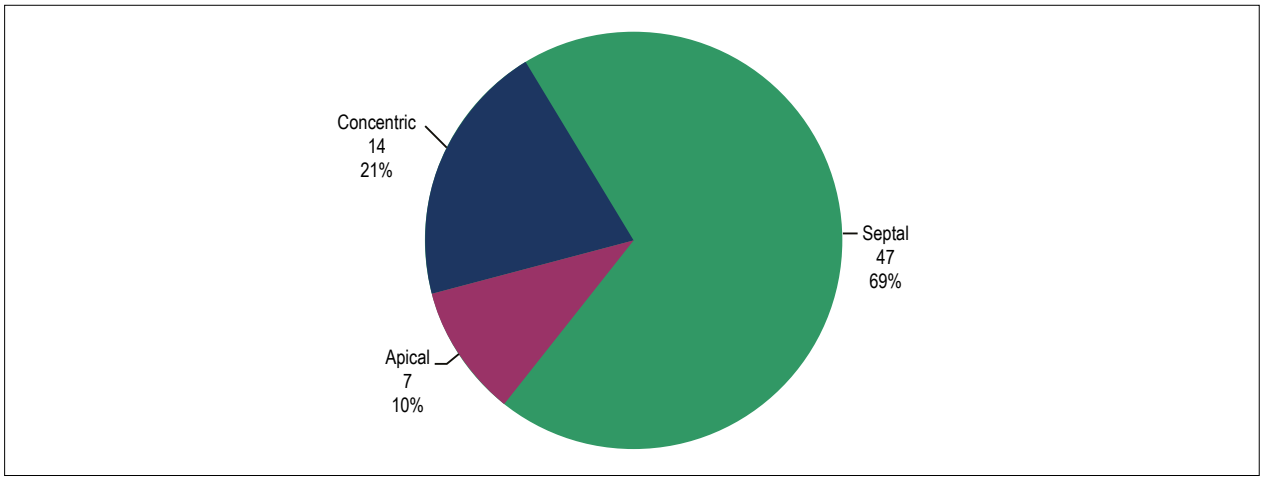

Figure 3 – *Distribution of the patients according to the hypertrophy pattern.*

Table 1 – Median and percentiles for mass and percentage of myocardial fibrosis on cardiac magnetic resonance imaging, according to the location of myocardial hypertrophy

Variables		Apical	Concentric	Septal	p-value			
					K-W	AxC	AxS	CxS
Fibrosis mass (grams)	Median (P25; P75)	0 (2; 27)	7 (40; 83.5)	0 (3.5; 15)	<.0001	0.0210	0.9974	< 0.0001
% Fibrosis	Median (P25; P75)	0 (2; 20)	4 (20; 31.75)	0 (3; 13)	0.0014	0.1160	0.9998	0.0010

P25: 25th Percentile; P75: 75th Percentile. P-values: K-W: Kruskal-Wallis test; multiple comparisons between the groups: AxC: Apical x Concentric; AxS: Apical x Septal; CxA: Concentric x Apical (Dunn's multiple comparison test).

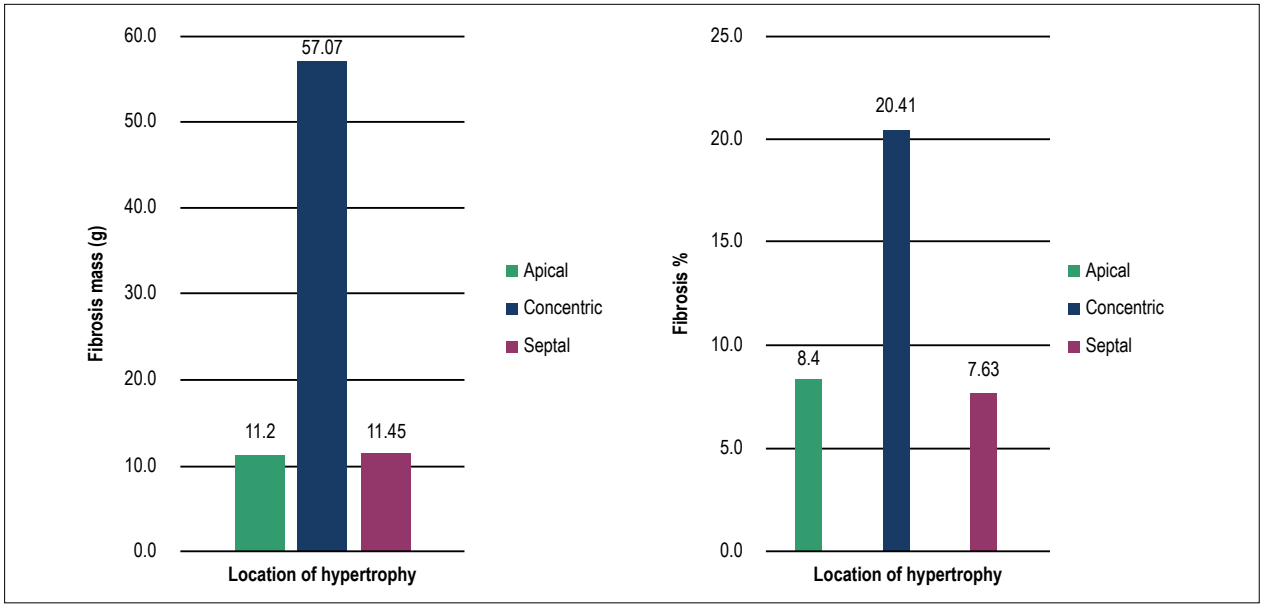

Figure 4 – *Means of the mass and percentage of myocardial fibrosis on cardiac magnetic resonance imaging according to the location of myocardial hypertrophy.*

Left atrial overload was more frequent in apical hypertrophy (42.9%), with no statistical significance (p = 0.4082). However, right atrial overload was rare, being identified in only two patients with septal hypertrophy.

Intraventricular blocks, such as left bundle-branch block, right bundle-branch block and left anterior hemiblock, were infrequent in the three types of hypertrophy, with no statistical difference between the groups. (Table 2, Figure 5)

Table 2 – Frequency and percentages for the attribute variables according to the location of myocardial hypertrophy

Variables	Group	Apical	Concentric	Septal	p-value
Right ventricular hypertrophy	Absent	7 (100.0%)	9 (64.3%)	44 (89.8%)	0.0447
	Present	0 (0.0%)	5 (35.7%)	5 (10.2%)	
Rhythm	AF	1 (14.3%)	1 (7.1%)	4 (8.2%)	0.7964
	Sinus	6 (85.7%)	13 (92.9%)	45 (91.8%)	
Heart axis	Deviated to left	0 (0.0%)	2 (14.3%)	9 (18.4%)	0.6730
	Normal	7 (100.0%)	12 (85.7%)	40 (81.6%)	
LVO	Absent	4 (57.1%)	4 (28.6%)	28 (57.1%)	0.1903
	Present	3 (42.9%)	10 (71.4%)	21 (42.9%)	
Strain	Absent	0 (0.0%)	4 (28.6%)	35 (71.4%)	< 0.0001
	Present	7 (100.0%)	10 (71.4%)	14 (28.6%)	
RVO	Absent	7 (100.0%)	11 (78.6%)	45 (93.8%)	0.1990
	Present	0 (0.0%)	3 (21.4%)	3 (6.3%)	
LBBB	Absent	7 (100.0%)	14 (100.0%)	47 (95.9%)	1.0000
	Present	0 (0.0%)	0 (0.0%)	2 (4.1%)	
LAHB	Absent	7 (100.0%)	12 (85.7%)	43 (87.8%)	0.8548
	Present	0 (0.0%)	2 (14.3%)	6 (12.2%)	
RBBB	Absent	7 (100.0%)	13 (92.9%)	47 (95.9%)	0.6634
	Present	0 (0.0%)	1 (7.1%)	2 (4.1%)	
LAO	Absent	4 (57.1%)	10 (71.4%)	38 (77.6%)	0.4615
	Present	3 (42.9%)	4 (28.6%)	11 (22.4%)	
RAO	Absent	7 (100.0%)	14 (100.0%)	47 (95.9%)	1.0000
	Present	0 (0.0%)	0 (0.0%)	2 (4.1%)	

AF: atrial fibrillation; LVO: left ventricular overload; RVO: right ventricular overload; LBBB: left bundle-branch block; LAHB: left anterior hemiblock; RBBB: right bundle-branch block; LAO: left atrial overload; RAO: right atrial overload. P-value for the Fisher-Freeman-Halton test.

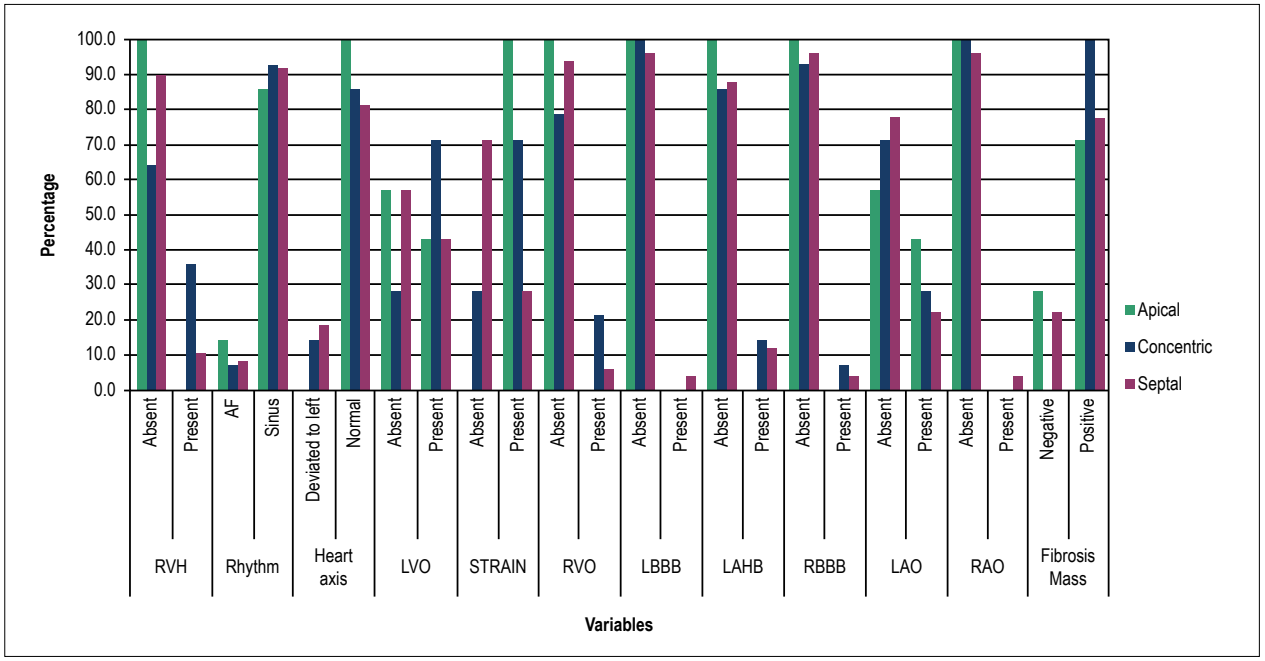

Figure 5 – *Percentages of the attribute variables according to location of myocardial hypertrophy. RVH: right ventricular hypertrophy; AF: atrial fibrillation; LVO: left ventricular overload; RVO: right ventricular overload; LBBB: left bundle-branch block; LAHB: left anterior hemiblock; RBBB: right bundle-branch block; LAO: left atrial overload; RAO: right atrial overload.*

Table 3 – Median and percentiles of the continuous variables according to location of myocardial hypertrophy

Variables	Group	Apical	Concentric	Septal	p-value			
					K-W	AxC	AxS	CxS
R D1 (mm)	Median (P25, P75)	9 (11; 13)	9 (14; 19.5)	5.75 (8.5; 13)	0.0280	0.6870	0.2717	0.0444
R V1 (mm)	Median Median (P25, P75)	0 (1.5; 6)	0.88 (1.5; 4.13)	0 .88 (1.75; 3.25)	0.9563			
R V5 (mm)	Median (P25, P75)	20 (22; 35)	12 (21.5; 27)	9 (15; 22.25)	0.0391	0.5481	0.0440	0.3785
R V6 (mm)	Median (P25, P75)	20 (25; 31)	9.75 (19; 21.75)	8.25 (13; 22)	0.0148	0.1577	0.0125	0.5619
T D1 (mm)	Median (P25, P75)	-4 (-3.5; -2)	-5.13 (-2.75; -1.88)	-2 (0; 2)	< 0.0001	0.9725	0.0032	0.0010
T V5 (mm)	Median (P25, P75)	-12 (-8; -6)	-6.63 (-4.5; -2)	-2.5 (2; 3.5)	< 0.0001	0.0487	0.0009	0.0040
T V6 (mm)	Median (P25, P75)	-9 (-7; -4)	-6 (-3; -2.5)	-3 (1; 2.5)	< 0.0001	0.0685	0.0016	0.0072

P25: 25th Percentile; P75: 75th Percentile. P-values: K-W: Kruskal-Wallis test; multiple comparisons between the groups: AxC: Apical x Concentric; AxS: Apical x Septal; CxA: Concentric x Apical (Dunn's multiple comparison test).

The analysis of the size of the R wave in lead DI showed higher mean (15.6 mm) in concentric hypertrophy, and lower mean in septal hypertrophy (10 mm), with a significant difference between the three groups ($p = 0.0280$). In lead V1, the R wave showed no difference in its size ($p = 0.9563$).

As compared to septal and concentric hypertrophies, apical hypertrophy showed greater R wave amplitude in leads V5 and V6 (means of 26.9 mm and 26 mm, respectively), with statistical significance ($p = 0.0391$, $p = 0.0148$, respectively).

Regarding ventricular repolarization, apical hypertrophy correlated with the highest T wave negativity in DI (-3.8 mm), V5 (-10.2 mm) and V6 (-7.9 mm), with statistical significance in the three leads ($p < 0.001$). (Table 3)

Discussion

Analysis of the patients with HCM showed a mild predominance of the female sex (55.9%), which differs from that reported in other studies.[2]

The distribution of myocardial hypertrophy found in this study by use of magnetic resonance imaging showed predominance of the septal location of hypertrophy (69% of the cases), followed by the concentric (21%) and apical (10%) locations, similar to that reported in the literature.[9] Mid-ventricular and lateral involvements, not identified in this study, are rare, with reported prevalence of 1% to 2% of the cases.[10]

The presence of delayed enhancement on cardiac magnetic resonance worsens the prognosis of patients with HCM. Moon JC et al.,[11] in a prospective study with 53 patients with HCM undergoing magnetic resonance imaging with gadolinium, have concluded that the presence of fibrosis relates to the occurrence of ventricular arrhythmias, ventricular dilatation and sudden death. Concentric hypertrophy showed a bigger mass of fibrosis as compared to that of the other hypertrophy locations. The R wave amplitude in DI was higher in concentric hypertrophy, showing a possible electrocardiographic pattern correlated with that location.

However, in leads V5 and V6, the R wave amplitude measured in millimeters showed a significant correlation with apical hypertrophy, in accordance with the findings of other studies.[12] The mean R wave amplitude in V5 and V6 in the apical region was 26 mm, which is similar to that described by Yamaguchi et al. in patients with apical hypertrophy confirmed on the echocardiogram.[12] The analysis of the R wave in V1 failed to show a good correlation with the anatomic pattern of hypertrophy.

In addition, apical hypertrophy was related to higher T wave negativity in the leads DI, V5 and V6 (means of -3.8 mm, -10.2 mm, and -7.9 mm, respectively). Chen X et al.,[13] assessing 118 patients with HCM, have observed that negative T waves associated with apical hypertrophy ($p = 0.009$), corroborating the present study. Giant T waves, described as inversion ≥ 10 mm in any anterior lead, were also associated with apical hypertrophy, being found in the patients of that study in leads V5 and V6.[14,15] The same relationship has been reported by Song et al.,[15] studying 70 patients, who have evidenced a correlation of a deep negative T wave with apical hypertrophy on magnetic resonance imaging ($p = 0.018$).

Regarding the analysis of the strain pattern on ECG (change in the ST segment and T wave), that electrocardiographic finding showed a 100% correlation with the anatomic location of apical hypertrophy of the left ventricle. In patients with concentric hypertrophy, that pattern of ventricular repolarization change was found in 71% of the cases, while in the septal pattern, only in 28% of the cases, with statistical significance. Sung-Hwan Kim et al.,[16] analyzing 864 patients with HCM, have found that same correlation of the strain pattern with apical hypertrophy; however, that was assessed by use of echocardiography ($p < 0.001$). The specific analysis of that electrocardiographic finding and its correlation with magnetic resonance imaging findings in HCM have not been found in the literature.

Electrocardiographic left ventricular overload was more frequently found in patients with the concentric pattern of hypertrophy (71%) than in the others (42%), but there was no statistical significance in those correlations. Previous studies have only assessed the presence or absence of electrocardiographic criteria of left ventricular overload, without comparing that finding with the location of hypertrophy.[6,17]

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Conclusion

The importance of the ECG as an initial tool to assess patients with HCM is confirmed in this study, which evidenced electrocardiographic patterns that correlate with the location of hypertrophy on magnetic resonance imaging.

The greater amplitude of the R wave in the leads V5 and V6, and the inversion of the T wave in the leads DI, V5 and V6, already reported in previous studies, were significantly related to apical hypertrophy. The presence of the strain pattern on ECG, when HCM is suspected, suggests apical hypertrophy on magnetic resonance imaging.

Concentric hypertrophy was associated with wide R waves in DI and a greater mass of fibrosis on magnetic resonance imaging assessment.

Author contributions

Conception and design of the research: Paixão GMM, Veronesi HE, Silva HAGP, Alencar Neto JN, Maldi CP, Correia EB; Acquisition of data: Paixão GMM, Veronesi HE, Silva HAGP, Alencar Neto JN, Maldi CP, Aguiar Filho LF, França FFAC; Analysis and interpretation of the data: Paixão GMM, Veronesi HE, Silva HAGP, Alencar Neto JN, Aguiar Filho LF, França FFAC; Critical revision of the manuscript for intellectual content: Paixão GMM, Aguiar Filho LF, Pinto IMF, França FFAC, Correia EB.

Potential Conflict of Interest

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

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

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Development and Psychometric Validation of HIPER-Q to Assess Knowledge of Hypertensive Patients in Cardiac Rehabilitation

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Abstract

Background: The absence of instruments capable of measuring the level of knowledge of hypertensive patients in cardiac rehabilitation programs about their disease reflects the lack of specific recommendations for these patients.

Objective: To develop and validate a questionnaire to evaluate the knowledge of hypertensive patients in cardiac rehabilitation programs about their disease.

Methods: A total of 184 hypertensive patients (mean age 60.5 ± 10 years, 66.8% men) were evaluated. Reproducibility was assessed by calculation of the intraclass correlation coefficient using the test-retest method. Internal consistency was assessed by the Cronbach's alpha and the construct validity by the exploratory factorial analysis.

Results: The final version of the instrument had 17 questions organized in areas considered important for patient education. The instrument proposed showed a clarity index of 8.7 (0.25). The intraclass correlation coefficient was 0.804 and the Cronbach's correlation coefficient was 0.648. Factor analysis revealed five factors associated with knowledge areas. Regarding the criterion validity, patients with higher education level and higher family income showed greater knowledge about hypertension.

Conclusion: The instrument has a satisfactory clarity index and adequate validity, and can be used to evaluate the knowledge of hypertensive participants in cardiac rehabilitation programs. (Arq Bras Cardiol. 2018; 110(1):60-67)

Keywords: Hypertension / prevention & control; Rehabilitation; Health Education; Validation Studies as Topic.

Introduction

Cardiovascular diseases are the leading cause of mortality in the world, as a consequence of population aging and disease-related epidemiological changes,[1] imposing high costs to health.[2] Among these conditions, systemic arterial hypertension (SAH) stands out as a multifactorial clinical condition associated to functional, structural and metabolic changes, with consequent increase in the risk of fatal and nonfatal cardiovascular events.[3]

SAH is a serious public health problem, affecting nearly one billion people.[4] In an important study,[5] SAH emerges as the main risk factor in the world, and is associated with 9.4 million global deaths a year.[5] In Brazil, the prevalence of SAH is estimated to be from 22 to 42% of adult population.[6]

Cardiac rehabilitation (CR) is one of the recommended treatments for cardiovascular diseases, consisting of a multidisciplinary approach for secondary prevention,[7] that reduces the recurrence of cardiovascular events and mortality.[8] The benefits of CR are mostly due to habit changes and, in this regard, patient education has been considered one of the most important approaches.[9-12]

In this context, an efficient SAH management depends on patient's understanding about his condition and treatment.[13] Therefore, patients that participate in education programs are more able to successfully control over their own health care. Thus, hypertensive patient's knowledge about his condition is part of the therapeutic success, who becomes co-responsible for the treatment.[9,14,15]

Nevertheless, there are few validated tools able to provide accurate information about education of hypertensive patients. While some instruments does not focus CR,[16-19] others include only questions deemed as relevant by the authors, without undergoing a psychometric validation.[13-15,20-23]

This gap in the knowledge opens the possibility of investigation, since assessment tools are important instruments in educational programs. These instruments enable the identification of patients'[9] educational needs and of specific conditions involving paradigms of health and disease, which are likely to change.[10] Thus, the aim of this study was to develop and psychometrically validate an instrument to assess the knowledge about the disease of patients enrolled in CR programs (HIPER-Q).

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Methods

Conception and procedures

This study was approved by the research ethics committee of Santa Catarina State University (UDESC) (approval number 159.213/2012). The study had a cross-sectional, observational design.

In the first stage of the study, a literature review was performed to identify the pieces of knowledge about SAH considered relevant to hypertensive individuals.[3,24] The bibliographic search was performed in Pubmed database from January 2010 to September 2016.

The questionnaire was constructed and revised by a commission composed of 17 health specialists, with experience in CR. These specialists carried out an analysis of content and clarity of the instruments, to verify its adequacy to hypertensive patients participating in CR programs.

The second stage was a pilot study to evaluate both applicability and reproducibility of the instrument, as well as patients' understanding of the items (clarity). A convenience sample of hypertensive patients, who participated in CR programs, was studied, and the results were used for refinement of the HIPER-Q instrument. Patients of the pilot study did not participate in the psychometric validation.

The third step was the psychometric validation. The refined tool was used in a larger convenience sample, composed of hypertensive patients participating in CR programs at the Clinic of Cardiology and Cardiopulmonary and Metabolic Rehabilitation (Cardiosport), the Center of Cardiology and Sports Medicine (*Núcleo de Cardiologia e Medicina do Esporte,* NCME) of the clinic, and the Santa Catarina Institute of Cardiology (ICSC). Data were collected between November 2015 and May 2016.

Participants

Patients of the pilot study and patients of the psychometric validation group were recruited from the CR programs mentioned above if they met the following inclusion criteria: clinical diagnosis of SAH, age ≥ 18 years, participation in a CR program for a period longer than one month, and agreement to participate in the study by signature of the informed consent form, according to the CNS 466/12 resolution. Patients with cognitive dysfunctions that could make the completion of the questionnaire difficult, *i.e.*, who did not demonstrate a minimal understanding of socio-demographic questions were excluded, at the investigator's discretion.

Measurements

To assess the clarity of the instrument, participants of the study pilot were asked to classify each item of the questionnaire in a 1 (not clear) to 10 (very clear) scale.[25] Also, these patients answered the HIPER-Q at two different occasions with a 14-day interval for analysis of the reproducibility of the instrument. Patients who participated in the psychometric validation were characterized by sex, age, educational attainment, comorbidities, time in CR, cardiac risk factors and clinical history. These characteristics were self-reported.

Statistical analysis

Sample calculation for the psychometric analysis was performed according to Hair & Anderson's[26] who recommend a minimal sample size of 10 subjects per item and/or a minimum of 100 participants. Since the questionnaire was composed of 17 items, a sample of 170 hypertensive subjects was considered sufficient.

Test-retest reproducibility of the instrument was validated in the pilot study group using the intraclass correlation coefficient (ICC). The items should meet the minimal recommended standard – ICC > 0.7.[27,28]

Psychometric properties of the new tool were assessed by analysis of internal consistency, criterion validity and factorial structure. First, internal consistency was analyzed in the psychometric validation group by Cronbach's alpha, reflecting the internal correlation between items and factors.[26] Values greater than 0.60 are generally considered acceptable.[29] Second, criterion validity was analyzed by relating the HIPER-Q scores to patients' educational attainment and family income, using the Spearman correlation. Third, the dimensional structure (as well as the construct validity) was evaluated by exploratory factor analysis. A component method for factor extraction was performed, considering only those factors with characteristic values > 1.0. When necessary, items with low factor loading (< 0.35) were excluded.

Once the factors were selected, a correlation matrix was generated, in which the associations between items and factors were identified by factorial loadings greater than 0.30 in only one factor. The promax method was used for matrix interpretation,[30] and the Spearman correlation was used for analysis of criterion validity.

Finally, a descriptive analysis of HIPER-Q was performed using mean values and standard deviations of normally distributed variables, and median and interquartile ranges for variables with non-normal distribution. Data normality was evaluated by the Kolmogorov-Smirnov test. Due to non-normality of data, we used the chi-square test to evaluate the association between the HIPER-Q scores based on patients' sociodemographic and clinical characteristics. Patients' total knowledge was represented by the median of total score.

Statistical analyses were performed using the *Statistical Package for Social Sciences (*SPSS) version 20 (IBM Inc. 2011, NYC), and the level of significance was set at 5% for all tests.

Results

Participants

For content validation, 17 health professionals with experience in CR were consulted: 6 (35.5%) physicians, 6 physiotherapists (35.3%), 2 nurses (11.8%), 2 physical educators (11.8%) and 1 dietitian (5.9%). For the pilot test, 30 hypertensive patients participating in CR programs were recruited by convenience to answer the questionnaire; 11 (22%) of them were women, with mean age of 62 ± 8 years.

For psychometric validation, 184 hypertensive patients with mean age of 60.5 ±10 years and median time of diagnosis of 8 years (interquartile range 18 years) completed the HIPER-Q.

Of these patients, 101 (54.9%) were retired. Participants' characteristics are described in Table 1.

Development of HIPER-Q

The literature review on health education for hypertensive patients in CR programs revealed consistent findings between the articles. The first version of the HIPER-Q was developed based on literature data. Nineteen items were constructed encompassing seven important domains in patient education: self-care, treatment, diagnosis, physical exercise, concept and pathophysiology, signs and symptoms and risk factors. Similar to other educational instruments,[12,31] for each item, one answer is considered the "most correct" one and receives score 3, and another answer is considered "partially corrected" and receives score 1. The other two answer options – the incorrect option and the "don't know" option receives no score (zero). According to the classification described in Table 2, the sum of the scores represents mean total knowledge, where the maximum score of 51 points corresponds to 'perfect' knowledge.

Clarity validation

The construction rules of the item sources and of the theoretical analysis of the items, content and semantics were considered 'clear' by 79% of the specialists, with a median clarity score of 8.5 (0.75). However, most of the items received comments on their semantic contexts. Each item was widely discussed by the authors, and all changes suggested by the specialists were accepted. This version of the questionnaire was analyzed by the same professionals, and the final version was then provided, with 96% of agreement between the items and median clarity score of 9.54 (0.30).

Pilot study

The average time for completion of the questionnaire by the participants (n = 30) was 15.4 ± 2.2 minutes. The median clarity score was 8.7 (0.25), and no item had a clarity score lower than 7.0, indicating that the questionnaire was well understood by the target population.

Test-retest reproducibility

Total ICC of the instrument was 0.804, obtained by the final test-retest scores.[27] The items "Also with respect to systemic arterial hypertension, we can affirm that" and "What is the best diet for patients with systemic arterial hypertension?" had a ICC lower than 0.7 (0.43 and 0.58, respectively) and were excluded from the final version,[27] which was then composed of 17 questions. The ICC of each question is presented in Table 3.

Psychometric validation

The HIPER-Q was administered to participants of CR programs, and the mean scores of the questionnaire items are shown in Table 3. Overall, the HIPER-Q showed a moderate internal consistency (Cronbach's alpha = 0.648).

With respect to criterion validity, a relationship of HIPER-Q total score was found with educational attainment and family income. Weak positive correlations were found of knowledge level with educational attainment (rho = 0.346; $p < 0.01$) and family income (rho = 0.176; $p = 0.017$).

Dimensional structure was evaluated by exploratory factor analysis. The Kaiser-Meyer-Olkin (KMO = 0.669) test and the Bartlett's sphericity test (X^2 2066.56; $p < 0.001$) indicated adequacy of data for factor analysis. Five factors were extracted and, together, they accounted for 51.1% of the total variance of the items, whose characteristic values were > 1.1. Table 4 displays the factor loadings of the items. Factor "1" reflects "General Conditions", and is responsible for 18.8% of total variance, whereas the other factors had a lower influence of the variance. Factor "2" reflects "Treatment"; factor "4" reflects "Physical Exercise"; factor 4 reflects "risk factors" and factor 5 reflects "self-care'.

Descriptive analysis

The instrument had a median total score of 26 (10). In patients' classification, a high prevalence (44.6%) of "acceptable knowledge" was observed. Patients showed greater knowledge about the items: "If a health professional says that your blood pressure is altered, you should", "On the basis of your knowledge about systemic arterial hypertension, answer the following:" and "Which of the risk factor groups below has the greatest influence on the development of systemic arterial hypertension?". The lowest level of knowledge was seen for the items: "With respect to self-measurement of blood pressure, it is correct to say that", "About the *white coat syndrome*, it is correct to say that" and "Which among the items listed below are the most accurate in the diagnosis of systemic arterial hypertension?". Regarding the knowledge domains, patients showed higher level of knowledge in the areas – "disease" and "concept and pathophysiology". On the other hand, the lowest level of knowledge was shown for the "diagnostic" and "signs and symptoms" domains.

As shown in Table 1, greater knowledge about SAH was associated with coronary artery disease ($p < 0.001$), dyslipidemias ($p = 0.006$), myocardial infarction ($p < 0.001$) and peripheral obstructive arterial disease ($p = 0.004$). In addition, previous angioplasty ($p < 0.001$) or cardiac surgery ($p = 0.002$) was associated with greater knowledge about the disease.

Discussion

Patient's education is one of the central components of CR, and is crucial for promoting the understanding about secondary prevention strategies and adherence to treatment.[9,28,31] In the present study, a new tool for the assessment of knowledge in hypertensive patients enrolled in CR programs was developed and psychometrically validated by a rigorous process. In general, clarity, internal consistency, reliability, dimensional structure and criterion validity were established, indicating the validity and usefulness of the HIPER-Q in the assessment of hypertensive patients' knowledge about the disease.

The first data to be considered is the clarity index, generated by professionals and patients, demonstrating that the instrument proposed can be easily understood

Table 1 – Socioeconomic and clinical characteristics of hypertensive patients (n = 184) and HIPER-Q ratings (median and interquartile range) according to these characteristics

Variable	Category	n(%)	HIPER-Q score Median (IR)	p†
Sex	Male	123(66.8)	25 (10)	0.033*
	Female	61(33.2)	27 (8.5)	
Comorbidities	CAD	149(81)	25 (8.5)	0.033*
	Dyslipidemias	149(81)	25 (8.5)	0.127
	Myocardial infarction	127(69)	24 (8)	0.003*
	Diabetes Mellitus	52(28.3)	25 (10)	0.493
	POAD	24(13)	27 (10)	0.805
	Stroke	23(12.5)	26 (11)	0.928
	Smoking	03(1.6)	26 (0.0)	0.998
	COPD	02(1.1)	35 (0.)	0.539
Cardiologic procedures	Angioplasty	116(63)	24 (7.5)	0.019*
	Cardiac surgery	53(28.8)	23 (8)	0.275
Classes of antihypertensive drugs	ACEI	65(35.3)	28 (10.5)	0.768
	α and β adrenergic blockers	56(30.4)	28 (10.75)	0.186
	Angiotensin II receptor antagonists	52(28.3)	25 (9)	0.669
	Diuretics	21(11.4)	27 (14)	0.820
	Calcium channel blockers	05(2.7)	29 (17)	0.195
	Unknown	15(8.2)	22 (7.75)	0.755
Number of anti-hypertensive drugs	0	37(20.1)	22 (7)	0.993
	1	108(58.7)	26 (10)	
	2	36(19.6)	28 (9.75)	
	3	2(1.1)	23 (0.0)	
Type of rehabilitation	Public	162(88)	25 (9)	0.274
	Private	22(12)	32.5 (10.25)	
Time of rehabilitation	From 01 to 06 months	105(47.3)	26 (9)	0.317
	From 06 to 12 months	10(4.5)	22 (14.25)	
	From 12 to 24 months	17(7.7)	27 (10)	
	Over 24 months	51(23)	27 (10)	
Family income (salary)	< 01	09 (4.9)	22 (8.5)	0.023*
	01 - 05	94(51.1)	25.5 (9)	
	05 - 10	42(22.8)	26 (8)	
	10 - 20	32(17.4)	31 (14.5)	
	> 20	07(3.8)	35 (11)	
Educational level	Never went to school	08(4.3)	20 (8.75)	0.002*
	Some primary education	59(32.1)	25 (7)	
	Completed primary	20(10.9)	27 (6.5)	
	Some high school	16(8.7)	22.5 (4.75)	
	Completed high school	35(19)	27 (11)	
	Some college	13(7.1)	31 (14)	
	Completed college	30(16.3)	31.5 (14.25)	
	Graduate degree	3(1.6)	36 (0.0)	

*IR: interquartile range; CAD: coronary artery disease; POAD: peripheral obstructive arterial disease; COPD: chronic obstructive pulmonary disease; ACEI: angiotensin converting enzyme inhibitors † chi-square; * p < 0.05.*

Table 2 – Classification of patient's knowledge by HIPER-Q score

Sum of the scores	Percentage	Classification of knowledge
From 46 – 51 points	90 – 100%	Excellent
From 36 – 45 points	70 – 89%	Good
From 25 – 35 points	50 – 69%	Acceptable
From 15 – 24 points	30 – 49%	Poor
< 15 points	< 30%	Insufficient

Table 3 – Score of the HIPER-Q items (n = 184) (median and interquartile range), and intra-class correlation coefficient of each item (n = 30)

Domain	Questions	HIPER-Q score in median (interquartile range)	ICC
Self-care	9.If a health professional finds that your blood pressure is altered, you should	3 (0)	0.72
	15. With respect to self-measurement of blood pressure, it is correct to say that	0 (1)	0.96
	17. With respect to systemic arterial hypertension patient's self-care, it is correct to say that:	1 (3)	0.79
Treatment	6. What is the ideal treatment to reduce blood pressure levels?	1 (2)	0.75
	14. Which of these drugs aim to reduce blood pressure levels?	3 (2)	0.80
Diagnosis	5. Which among the items listed below are the most accurate in the diagnosis of systemic arterial hypertension?	1 (1)	0.82
	16. About the "white coat syndrome", it is correct to say that	0 (3)	0.85
Physical exercise	4. Physical exercise for systemic arterial hypertension patients should:	1 (3)	0.81
	8. The practice of physical exercises is contraindicated when the patient:	1 (3)	0.76
	10. On the basis of your knowledge about systemic arterial hypertension, answer the following:	3 (0)	0.81
	11. What favorable changes are systemic arterial hypertension patients able to obtain with the regular practice of physical exercises?	1 (3)	0.82
Concept and pathophysiology	1. Systemic arterial hypertension is:	1 (3)	0.80
	13. What are the main consequences of untreated systemic arterial hypertension?	3 (2)	0.76
Signs and symptoms	3. With respect to systemic arterial hypertension symptoms, check the correct answer	1 (3)	0.81
Risk factors	2. Which of the risk factor groups below has the greatest influence on the development of systemic arterial hypertension?	3 (2)	0.81
	7. Which systolic arterial pressure and diastolic arterial pressure values, respectively, are recommended for systemic arterial hypertension patients?	1 (3)	0.75
	12. With respect to stress, we can say that:	1 (3)	0.78

ICC: intra-class correlation coefficient.

by the study population.[31,32] Second, comparisons of the factorial analysis reported in similar studies[12,31,33] revealed that the HIPER-Q showed similar arrangement of factors and items; in each of the five factors, those items with similar knowledge domains were predominant in the instruments. The factors were clustered by stability, interpretation of the areas and basic principles of construction rules, in order to establish a reliable, consistent construct. In each domain, the factors included different amounts of terms that were correlated with each other, which may be explained by the fact that SAH is characterized as a systemic, multifactorial disease.[3,24]

Results of internal consistency (Cronbach's alpha = 0.648) were consistent with those reported in previous studies involving instruments of assessment of hypertensive patients' knowledge about their conditions,[19,34-36] and in studies with similar structure.[12,33] This indicates an adequate correlation between the items of the questionnaire. Nevertheless, the HIPER-Q was validated in public and private CR programs with different characteristics, which may have affected the alpha value (not as high as those of similar studies).

Regarding the criterion validity, both educational attainment and family income were related to the knowledge

Table 4 – Classification of the HIPER-Q factorial structure by loadings

Item	Domain	Factors				
		1	2	3	4	5
17	Self-care	0.825				
6	Treatment	0.792				
5	Diagnosis	0.745				
11	Physical exercise	0.664				
1	Concept and pathophysiology	0.477				
14	Treatment		0.646			
13	Concept and pathophysiology		0.631			
3	Signs and symptoms		0.525			
16	Diagnostic			0.734		
4	Physical exercise			0.63		
8	Physical exercise				0.635	
7	Risk factors				0.534	
12	Risk factors				0.470	
2	Risk factors				0.328	
10	Physical exercise					0.684
9	Self-care					0.580
15	Self-care					0.426

about SAH. These findings suggest that socioeconomical factors are determinants of knowledge about health, as previously demonstrated.[12,22,31,33]

The current study also evaluated the level of knowledge of the sample patients, who showed an overall knowledge classified as "acceptable". Our findings, supported by other authors,[13,18-21] reflect the importance of evaluating the knowledge about health and formulating hypothesis that elucidate the determining factors of the information gaps. Therefore, patient education is an important component of CR programs[9,28] and is associated with a successful self-management of disease and patient's behavior changes.[33]

We did not find in the literature, longitudinal studies demonstrating the effects of a higher level of knowledge about SAH on outcomes, such as worse prognosis or mortality. Thus, one may expect that the HIPER-Q can be used in this regard in future studies. In this context, studies on other chronic diseases have shown promising results, suggesting that disease-related education may be determinant in the control of risk factors, such as sedentary lifestyle, smoking and continuity of treatment, which may lead to reductions in comorbidities, health costs and even mortality.[34,35]

In this scenario, there is a lack of instruments to measure the knowledge about the disease in participants of CR.[31] Most of the studies reviewed have only developed SAH questions deemed as relevant by the authors,[13,14,20-23] without conducting a psychometric validation as performed in the present study.[25,36] In addition, other validated studies have not specifically evaluated the knowledge of hypertensive patients in CR.[16-19,37-39] Therefore, our study aimed to develop an instrument to healthcare professionals, capable of establishing educational strategies directed to patients' needs,[12,31] and that would help in the evaluation and planning of the educational process of hypertensive subjects in CR programs.

Caution is needed in interpreting these findings. First, the results cannot be generalized, due to the facts that the sample was selected by convenience, and only three CR programs were included, which affects the achievement of the outcomes. Second, the development of the instrument proposed was based on consensus and guidelines, which encompass numerous SAH-related issues not necessarily covered by CR programs. Third, although all patients included were participants of CR programs, the programs were different (of public and private nature), with different approaches, which may have influenced the results. Fourth, the instrument was not developed using plain language techniques, or "simple" language, which may have created difficulties in the interpretation of the items, and consequently affected the results.[36] Fifth, the current study did not achieve the sample size recommended by the test-retest procedure.[36] Sixth, participants were not asked about their occupations, which may also have influenced the results, since patients graduated in medicine and/or other health-related areas, for example, may have had greater chance of giving correct answers. Further studies are needed to evaluate whether the HIPER-Q is sensitive to longitudinal changes by assessing patients' knowledge before and after their participation in CR programs.

Conclusion

The present study demonstrated that the HIPER-Q showed sufficient reliability, consistency and validity, corroborating its use in future studies to evaluate the knowledge of SAH patients in CR programs. This instrument is expected to support the assessment of the educational component of CR programs and to identify the knowledge that is compatible with patients' need for information.

Author contributions

Conception and design of the research: Santos RZ, Ghisi GLM, Benetti M; Acquisition of data: Santos RZ, Bonin CDB; Analysis and interpretation of the data: Santos RZ, Bonin CDB, Martins ETC, Ghisi GLM, Macedo KRP; Statistical analysis: Santos RZ, Pereira Junior M; Writing of the manuscript: Santos RZ, Bonin CDB, Martins ETC, Pereira Junior M; Critical revision of the manuscript for intellectual content: Santos RZ, Ghisi GLM, Macedo KRP, Benetti M.

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 Universidade do Estado de Santa Catarina (UDESC) under the protocol number 159.213/2012. 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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Sensitive Troponin I Assay in Patients with Chest Pain – Association with Significant Coronary Lesions with or Without Renal Failure

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Abstract

Introduction: Despite having higher sensitivity as compared to conventional troponins, sensitive troponins have lower specificity, mainly in patients with renal failure.

Objective: Study aimed at assessing the sensitive troponin I levels in patients with chest pain, and relating them to the existence of significant coronary lesions.

Methods: Retrospective, single-center, observational. This study included 991 patients divided into two groups: with (N = 681) and without (N = 310) significant coronary lesion. For posterior analysis, the patients were divided into two other groups: with (N = 184) and without (N = 807) chronic renal failure. The commercial ADVIA Centaur® TnI-Ultra assay (Siemens Healthcare Diagnostics) was used. The ROC curve analysis was performed to identify the sensitivity and specificity of the best cutoff point of troponin as a discriminator of the probability of significant coronary lesion. The associations were considered significant when $p < 0.05$.

Results: The median age was 63 years, and 52% of the patients were of the male sex. The area under the ROC curve between the troponin levels and significant coronary lesions was 0.685 (95% CI: 0.65 – 0.72). In patients with or without renal failure, the areas under the ROC curve were 0.703 (95% CI: 0.66 – 0.74) and 0.608 (95% CI: 0.52 – 0.70), respectively. The best cutoff points to discriminate the presence of significant coronary lesion were: in the general population, 0.605 ng/dL (sensitivity, 63.4%; specificity, 67%); in patients without renal failure, 0.605 ng/dL (sensitivity, 62.7%; specificity, 71%); and in patients with chronic renal failure, 0.515 ng/dL (sensitivity, 80.6%; specificity, 42%).

Conclusion: In patients with chest pain, sensitive troponin I showed a good correlation with significant coronary lesions when its level was greater than 0.605 ng/dL. In patients with chronic renal failure, a significant decrease in specificity was observed in the correlation of troponin levels and severe coronary lesions. (Arq Bras Cardiol. 2018; 110(1):68-73)

Keywords: Troponin I; Chest Pain; Coronary Artery Disease; Renal Insufficiency, Chronic; Biomarkers.

Introduction

In recent years, cardiology has witnessed the constant development of several biomarkers, of which, current sensitive troponins and high-sensitivity troponins, widespread in Brazil and Europe, stand out.[1]

However, despite the huge gain in sensitivity, allowing early detection of a minimum threshold of myocardial lesion in patients presenting to the emergency department with chest pain, there was a reduction in specificity, which resulted in several patients with non-cardiological or non-coronary problems undergoing unnecessary and even harmful antithrombotic therapy and invasive coronary stratification.[2-5] The adequate troponin level to be considered for the correct interpretation of clinical findings depends on the patient's characteristics and on the troponin assay used, and should be ideally individualized for each service.[2-4,6]

Thus, this study was aimed at assessing the current sensitive troponin I levels for patients with chest pain, in addition to relating them to the existence of significant coronary lesions both in the presence and absence of chronic renal failure in the sample selected.

Methods

Study population

This is a retrospective, single-center, observational study, including 991 patients with chest pain admitted to the emergency department of a high-complexity tertiary cardiology center, between May 2013 and May 2015.

All patients with chest pain undergoing coronary angiography for suspected unstable angina or non-ST-elevation

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acute myocardial infarction were included. Presence of ST-segment elevation was the only exclusion criterion. The coronary lesion was considered significant when ≥ 70% on coronary angiography. Chronic renal failure was defined as a creatinine level > 1.5 mg/dL.

The patients were divided into two groups: with (N = 681) and without (N = 310) significant coronary lesion. For Receiver Operating Characteristic (ROC) curve analysis, the patients were divided into two other groups: with (N = 184) and without (N = 807) chronic renal failure.

The commercial ADVIA Centaur® TnI-Ultra assay (Siemens Healthcare Diagnostics, Tarrytown, NY, USA) was used for current sensitive troponin with a 99th percentile value of 0.04 ng/mL. The flowchart of the management of all patients with chest pain met the criteria established by the last American Heart Association guideline.[7-9] Non-ST-elevation acute coronary syndrome was defined as presence of chest pain associated with electrocardiographic changes or troponin elevation/drop on admission or, in the lack thereof, clinical findings and risk factors compatible with unstable angina (chest pain at rest or on minimal exertion, of severe intensity or occurring in a *crescendo* pattern). The highest troponin level during hospitalization before coronary angiography was considered for analysis, following the every 6-hour marker collection protocol of the institution.

The following data were obtained: age, sex, presence of diabetes mellitus, systemic arterial hypertension, smoking habit, dyslipidemia, family history of early coronary artery disease, chronic coronary artery disease, previous acute myocardial infarction, creatinine, ST-segment depression or T-wave inversion on the electrocardiogram.

This study was submitted to the Ethics Committee in Research and approved by it. All patients provided written informed consent.

Statistical analysis

The ROC curve analysis was performed to identify the sensitivity and specificity of the best cutoff point of troponin as a discriminator of the probability of significant coronary lesion, and 95% confidence interval (CI) was used. That analysis was performed for the general population and separately for patients with and without chronic renal failure.

Descriptive analysis of the categorical variables was performed by use of percentages. Continuous variables with non-normal distribution were expressed as medians and interquartile intervals, and those with normal distribution, as means and standard deviations. The comparison between groups was performed by use of the chi-square test for categorical variables. The continuous variables, when the Kolmogorov-Smirnov test showed normal distribution, were assessed by using the unpaired T test, and when the distribution was not normal, the Mann-Whitney U test was used. Both troponin cutoff points analyzed (the 99th percentile of the method and the best cutoff point found in this study) were entered into the univariate analysis. Comparison between patients with *versus* without significant coronary lesion was performed.

Multivariate analysis was performed with logistic regression, $p < 0.05$ being the significance level adopted. All baseline characteristics listed in Table 1 that reached statistical significance on univariate analysis were considered as variables in the analysis. Multivariate analysis was performed separately for each troponin cutoff point assessed (the 99th percentile of the method and the best cutoff point found in this study).

The calculations were performed with the SPSS software, version 10.0.

Results

The median age was 63 years, and 52% of the patients were of the male sex. The area under the ROC curve between the troponin levels and significant coronary lesions was 0.685 (95% CI: 0.65 – 0.72). In patients with or without renal failure, the areas under the ROC curve were 0.703 (95% CI: 0.66 – 0.74) and 0.608 (95% CI: 0.52 – 0.70), respectively. The best cutoff points to discriminate the presence of significant coronary lesion were: in the general population, 0.605 ng/dL (sensitivity, 63.4%; specificity, 67%; positive predictive value, 65.9%; negative predictive value, 64.7%; accuracy, 65.3%; and likelihood ratio, 1.9); in patients without renal failure, 0.605 ng/dL (sensitivity, 62.7%; specificity, 71%; accuracy, 66.9%; and likelihood ratio, 2.2); and in patients with chronic renal failure, 0.515 ng/dL (sensitivity, 80.6%; specificity, 42%; accuracy, 61.3%; and likelihood ratio, 1.4) (Figure 1). In the general population, the level of 0.05 ng/dL (immediately above the 99th percentile) showed sensitivity of 93.7% and specificity of 23%. For patients with chronic renal failure to reach a specificity of 67% (as in the general population), an elevation in the troponin level to 1.58 ng/dL was necessary.

Troponin was negative in 143 patients, and, in 40.6% of them, significant lesions were observed on coronary angiography. In addition, 10.5% of those patients with negative troponin showed ST-segment depression/T-wave inversion on electrocardiogram. Using the gold-standard procedure of cardiac catheterization, the acute coronary syndrome diagnosis was confirmed in 68.7% of the patients admitted due to chest pain. In 9.1% of those without significant coronary lesion on coronary angiography and with positive troponin, the acute coronary syndrome diagnosis was confirmed by cardiac magnetic resonance. The baseline characteristics of the population studied and the univariate analysis between the groups are shown in Table 1.

In multivariate analysis, considering the 99th percentile of the method, there were significant differences between the groups with and without coronary lesion regarding smoking habit (OR = 1.58, $p = 0.002$), ST-segment depression/T-wave inversion (OR = 2.05, $p < 0.0001$) and troponin positivity (OR = 3.39, $p < 0.0001$), respectively. However, when considering the best troponin cutoff point found in this study, there were significant differences between the groups with and without coronary lesion regarding the male sex (OR = 1.35, $p = 0.039$), smoking habit (OR = 1.64, $p = 0.001$), ST-segment depression/T-wave inversion (OR = 2.22, $p < 0.0001$) and troponin positivity (OR = 3.39, $p < 0.0001$), respectively. The multivariate analysis results are shown in Table 2.

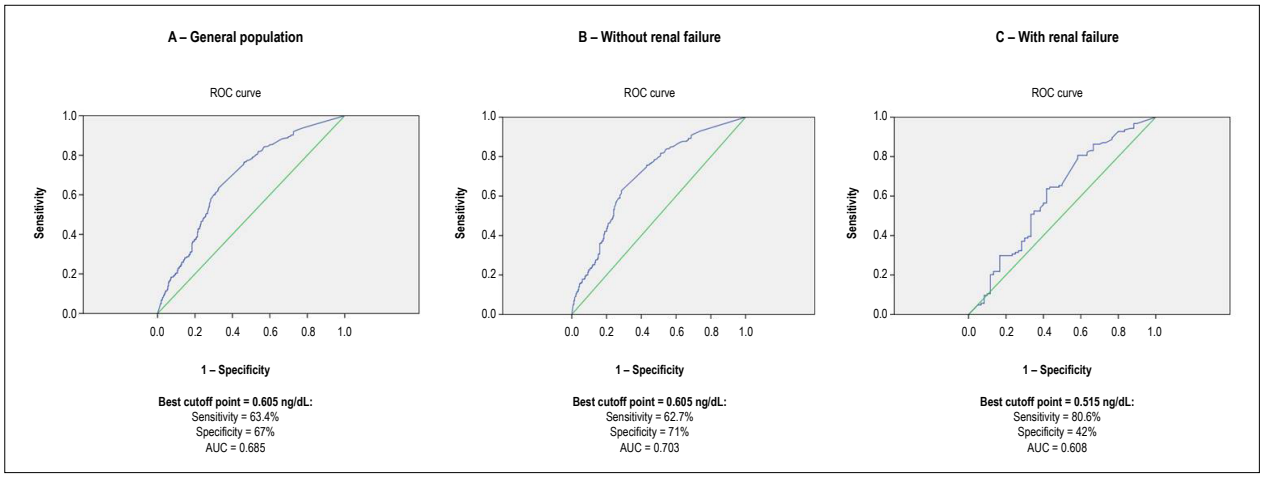

Figure 1 – *ROC curve identifying the sensitivity and the specificity of the best cutoff point of troponin as a discriminator of the probability of significant coronary lesion. AUC: area under the curve.*

Table 1 – Baseline characteristics and univariate analysis comparing patients with versus without significant coronary lesion

	Coronary lesions ≥ 70%		p
	Present (N = 681)	Absent (N = 310)	
Male sex (%)	72.10%	65.10%	0.018#
Age (median)	62.9 ± 11.30	63.9 ± 13.23	0.202π
Diabetes mellitus (%)	38.82%	40%	0.725#
Arterial hypertension (%)	79.30%	84.80%	0.038#
Chronic coronary disease (%)	13.70%	14.50%	0.724#
Dyslipidemia (%)	51.00%	50.00%	0.797#
FH of early CAD (%)	12.50%	10.60%	0.404#
Previous AMI (%)	39.70%	36.10%	0.284#
Smoking (%)	43.50%	31.30%	< 0.0001#
Creatinine (mg/dL) (mean)	1.31 ± 1.20	1.32 ± 1.25	0.896*
ST depression/T-wave inversion	36.30%	18.70%	< 0.0001#
Troponin + / 99th percentile	91.50%	72.60%	< 0.0001#
Troponin + / Best cutoff point	63.40%	32.60%	< 0.0001#

*FH: family history; CAD: coronary artery disease; AMI: acute myocardial infarction; #: chi-square test; *: unpaired T test; π: Mann-Whitney U test.*

Discussion

The results of this study in the Brazilian population are in accordance with those of recently published literature. Troponin positivity without association with coronary angiographic findings was observed in 31.3% of the patients. In addition, better specificity values were only achieved with a troponin cutoff point of 0.605 ng/dL, approximately 15 times the 99th percentile of the method. When assessing the subgroup with renal failure, that level is even higher, hindering its correct interpretation.

In a study published in 2012 derived from the Scottish Heart Health Extended Cohort, blood samples were collected and high-sensitivity troponin I levels were measured. The results showed that, in a population of 15340 individuals, 31.7% of the men and 18.1% of the women had high high-sensitivity troponin with no clinical manifestation at the time of blood collection, highlighting the problem of the specificity of the method. Positivity and worse prognosis were correlated in the long run ($p < 0.0001$), as reported in other studies.[4,10-12] That prevalence of troponin positivity not related to acute coronary artery disease is similar to that found in our study, although we assessed specifically patients with chest pain.

Likewise, a prospective cohort study of 6304 patients with chest pain presenting to the emergency department has reported positive high-sensitivity troponin T in 39% of the cases diagnosed as non-coronary.[13]

Table 2 – Multivariate analysis comparing patients with *versus* without significant coronary lesion: A. Using the 99th percentile of the troponin assay; B. using the best cutoff point for troponin found in the study

A			
	OR	95% CI	p
Male sex (%)	1.32	0.99 - 1.76	0.052
Arterial hypertension (%)	0.81	0.55 - 1.18	0.272
Smoking (%)	1.58	1.18 - 2.14	0.002
ST depression/T-wave inversion	2.05	1.47 - 2.88	< 0.0001
Troponin + / 99th percentile	3.39	2.32 - 4.94	< 0.0001

B			
	OR	95% CI	p
Male sex (%)	1.35	1.02 - 0.180	0.039
Arterial hypertension (%)	0.89	0.60 - 1.31	0.548
Smoking (%)	1.64	1.21 - 2.22	0.001
ST depression/T-wave inversion	2.22	1.58 - 3.12	< 0.0001
Troponin + / Best cutoff point	3.39	2.53 - 4.54	< 0.0001

OR: odds ratio; CI: confidence interval.

Irfan et al.[14] have conducted an observational multicenter study with 1181 patients hospitalized because of non-cardiac causes, 15% of whom had positive high-sensitivity troponin T. Of the major factors related to that unexpected elevation, the presence of kidney dysfunction was identified as a significantly influencing factor. In addition, once again, patients with elevated troponin were at higher risk for death (HR = 3.0; p = 0.02).[14]

In individuals older than 75 years, high-sensitivity troponin T was assessed in the context of chest pain, being measured at baseline and 3-4 hours. Approximately 27% of the patients were classified as having acute coronary syndrome. The sensitivity and specificity found in that population were 88% and 38%, respectively. The greater the initial level or the increase (mainly absolute) in the subsequent measures, the higher the specificity found.[15] That specificity value can be greater than ours found in the general population, probably because of the inclusion of more patients with other heart diseases, because we belong to a referral tertiary cardiology center.

The concept of variation in the levels of sensitive troponin and high-sensitivity troponin in different measurements has been studied, and establishing a correlation between the amplitude of variability and the probability of coronary artery disease has been consecutively attempted. In addition, amplitude can be relative (expressed as percentages) or absolute, with possible implications and distinct interpretations.[1]

A retrospective study published in 2014, including 1054 patients with chest pain, assessed the variability related to high-sensitivity troponin T. Approximately 40% of the patients showed alteration in at least one measurement. Even with a variation greater than 20% as compared to the initial level, the specificity did not exceed 70%.[16]

Assessing specifically the same current sensitive troponin assay used in this study, in 2013 Bonaca et al.[17] published a study comparing current sensitive troponin I *versus* high-sensitivity troponin I in 381 patients with chest pain at the emergency department. Those authors found sensitivity values for the two assays of 94% and 97%, and negative predictive values of 98% and 99%, respectively, with no significant difference.[17] Another similar study of 1807 patients with non-ST-segment elevation acute coronary syndrome has shown no significant difference regarding prognosis when comparing the positivity of current sensitive troponin I *versus* high-sensitivity troponin I.[18] Differently from the findings of those studies and using the same assay, ours showed lower sensitivity and specificity of 23% when using the 99th percentile of the method. That shows the importance of assessing each center's population, respecting their specific individualities.

In alignment with that, the meta-analysis published in 2014 with 17 studies and 8644 patients with chest pain compared the use of high-sensitivity troponin with that of conventional troponin. There were differences regarding sensitivity (88.4% vs. 74.9%; p < 0.001) and specificity (81.6% vs. 93.8%; p < 0.001), respectively. Despite that increase in sensitivity with high-sensitivity troponin, the number of patients with the final diagnosis of myocardial infarction and the need for additional tests for ischemia did not differ between the groups, showing no additional clinical advantage with the use of high-sensitivity troponin.[2]

Finally, some studies have validated the new troponin assays.[1,19,20] The study conducted in 2015 compared seven assays of current sensitive troponins and high-sensitivity troponin in 2813 patients with chest pain, and with (16%) or without kidney dysfunction. Of the patients with nephropathy, in only 45-80% of those with positive troponin, the final diagnosis was myocardial infarction. The optimal cutoff point varied from 1.9 to 3.4 times that of the general population to detect acute coronary artery disease. Assessing only the same current sensitive troponin assay used in this study, in 27% of those with positive troponin, the final diagnosis of myocardial infarction was ruled out. The area under the curve of accuracy of that assay decreased from 0.92 to 0.87 ($p = 0.013$), comparing the general population with the patients with kidney dysfunction.[19] That cutoff point elevation is in accordance with our findings, showing a clear specificity reduction in the group of patients with nephropathy.

Limitations

Despite the large case series, this is a retrospective (hindering the blinded analysis) single-center study, with a much higher number of patients without chronic renal failure than with it. In addition, we used only one troponin assay, and most patients were of the male sex.

Conclusion

In the study population of patients with chest pain, sensitive troponin I showed a good correlation with significant coronary lesions when its level was greater than 0.605 ng/dL. In patients with chronic renal failure, a significant decrease in specificity was observed in the correlation of troponin levels and severe coronary lesions.

Author contributions

Conception and design of the research: Soeiro AM, Gualandro DM, Biselli B, Soeiro MCFA, Leal TCAT; Acquisition of data: Soeiro AM, Bossa AS, Zullino CN, Biselli B, Soeiro MCFA, Leal TCAT; Analysis and interpretation of the data: Soeiro AM, Gualandro DM; Statistical analysis: Soeiro AM, Gualandro DM, Soeiro MCFA; Obtaining financing: Soeiro AM; Writing of the manuscript: Soeiro AM, Leal TCAT; Critical revision of the manuscript for intellectual content: Soeiro AM, Serrano Jr. CV, Oliveira Junior MT.

Potential Conflict of Interest

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

Sources of Funding

There were no external funding sources for this study.

Study Association

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

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo under the protocol number CAAE 38511114.7.0000.0068. 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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Cardiac and Musculoskeletal Responses to the Effects of Passive and Active Tilt Test in Healthy Subjects

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Abstract

Background: Maintenance of orthostatism requires the interaction of autonomic and muscle responses for an efficient postural control, to minimize body motion and facilitate venous return in a common type of syncope called neurocardiogenic syncope (NCS). Muscle activity in standing position may be registered by surface electromyography, and body sway confirmed by displacement of the center of pressure (COP) on a force platform. These peripheral variables reflect the role of muscles in the maintenance of orthostatism during the active tilt test, which, compared with muscle activity during the passive test (head-up tilt test), enables the analyses of electromyographic activity of these muscles that may anticipate the clinical effects of CNS during these tests.

Objective: to evaluate and compare the effects of a standardized protocol of active and passive tests for CNS diagnosis associated with the effects of Valsalva maneuver (VM).

Methods: twenty-thee clinically stable female volunteers were recruited to undergo both tests. EMG electrodes were placed on muscles involved in postural maintenance. During the active test, subjects stood on a force platform. In addition to electromyography and the platform, heart rate was recorded during all tests. Three VMs were performed during the tests.

Results: progressive peripheral changes were observed along both tests, more evidently during the active test.

Conclusion: the active test detected changes in muscle and cardiovascular responses, which were exacerbated by the VM. (Arq Bras Cardiol. 2018; 110(1):74-83)

Keywords: Syncope, Vasovagal; Heart Rate; Postural Balance; Tilt Table Test.

Introduction

Maintenance of balance on orthostatic position is associated with small, constant oscillations of the body that cause changes in plantar pressure areas and contribute to adequate venous return.[1] These oscillations may be confirmed by displacement of the center of pressure (COP) on a force platform. Some individuals cannot stay in an upright position for prolonged period of time and have transient loss of consciousness combined with loss of postural tone and spontaneous recovery, the so called neurocardiogenic syncope (NCS).[2-4] NCS is more common among women due to attenuated responsiveness to orthostasis in women than in men.[5,6] Predisposing factors for NCS include an impaired reflex vasoconstriction.[7]

NCS can be assessed by two non-invasive tests based on the force of gravity – the Head-Up Tilt test (HUT) or passive tilt test [3,8-11], and the Active Standing Test (AS) or active tilt test.[11] In the HUT, the change from supine to orthostatic position of the body is performed passively using a special bed (tilt-table). The subject stays in orthostatic position for 45 minutes.[3] In the AS, NCS is assessed by active change to the vertical position, with no consensus on the test duration.[11,12] Positive HUT and AS tests were defined as loss of consciousness. The combined use of forced expiratory maneuvers, such as the Valsalva maneuver (VM), increases the applicability of these tests in the clinical practice.

Orthostatic stress causes changes in heart rate (HR) and blood pressure,[13] and these cardiovascular responses affect peripheral muscle groups. Investigation of this muscle response to orthostatism may contribute to the understanding of the systemic physiological stress in attempt to predict cardiovascular reactions and interrupt stop the test before syncope occurs. The aim of the study was to evaluate HUT and AS combined with VM on HR and electromyographic (EMG) activity of muscles involved in postural maintenance, and the relationship of active orthostatic stress with changes in COP displacement on a force platform, in order to better understand the effects of prolonged orthostatism.

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Methods

Sample

The study protocol was approved by the Ethics Committee of the General Hospital of Ribeirao Preto Medical School, University of Sao Paulo. All subjects signed the informed consent form before participating in the study.

A convenience sample of 23 healthy female volunteers aged from 18 to 30 years (mean of 23.4 years), mean height 1.62m and mean weight 56.2 Kg, with no history of syncope was selected. Recruitment was performed by the same cardiologist and all subjects underwent clinical examination and electrocardiography to rule out the possibility of cardiovascular changes. Then, functional assessment of the lower limbs was carried out by a physiotherapist to exclude musculoskeletal disorders that could affect the results.

All volunteers underwent both AS and HUT, and the order of the tests was randomized by drawing (cross-over design): HUT was first conducted in 13 patients (HUT-AS, n = 13), and the AS was first conducted in 10 patients (AS-HUT, n = 10). All volunteers were instructed to refrain from consuming caffeine or other stimulating agents on the day before the test, and not to undergo the tests in fasting conditions.

Data collection

HUT test

For HR and EMG activity analyses during the HUT, each volunteer was positioned supine on the tilt table for 15 minutes at rest. On the fifteenth minute, the volunteer was tilted to 70 degrees for 15 minutes or until the initial signs and symptoms of syncope or orthostatic intolerance. Participants were monitored by electrocardiography and muscle activity was recorded using the Myosystem Br-1P84 (DATA-HOMINIS-BR) EMG system with electrodes placed bilaterally over the medial gastrocnemius (MG), the tibialis anterior (TA), the rectus abdominis (RA) and the erector spinae (ES) muscles. Positioning of the electrodes followed the SENIAM (Surface ElectroMyoGraphy for the Non-Invasive Assessment of Muscles - www.seniam.org) guidelines and recorded using the Myosystem I software, version 3.5 (DATA-HOMINIS-BR) for further calculation of the root mean square (RMS) and amplitude of the EMG signal (mV). The mean RMS for each minute of the test was recorded. The EMG data were normalized to the maximal isometric effort of each volunteer.

AS test

For analyses of HR, EMG activity and postural oscillation on the force platform during the AS test, each volunteer was positioned supine for 15 minutes on the tilt table strategically placed beside the force platform (Figure 1). The subject was then instructed to stand up from the supine position and stay in standing position on the center of the platform, with legs 20 cm apart, for another 15 minutes. Data of postural oscillation on the force platform (AMTI - OR6-7-1000, MA - USA) were analyzed using the ByoDinamics software in the LabVIEW environment (DATA-HOMINIS, MG - Brazil). Total displacement (TD) and total mean velocity (TMV) of the COP per minute of the orthostatic test (CP) were analyzed. TD and TMV values in each minute of the AS test were compared with the values of the minute before.

After the fifth minute in standing position in both HUT and AS, patients were instructed to perform three VMs every three minutes (on the 6th, 9th and 12th minute), and the test was finished on the 15th minute. The aneroid manometer was connected to a mouthpiece by a 1.5 m connector. The mouthpiece used for application of the expiratory effort was held by a stand and placed in front of the patient, who did not need to touch it. The same procedure was performed for the VMs during the HUT.

Statistical analysis

Continuous variables with normal distribution was analyzed by within-test (minute-by-minute) and between-test analyzes. Also, these variables were grouped into three periods – pre-VM, during the VM and post-VM and presented as mean and standard deviation. Continuous variables with non-normal distribution were presented as median and interquartile range. Analyses of HR response to the tests and EMG data were performed by linear mixed-effects models (random and fixed effects). These data analysis models are used in case the responses of the same individual are grouped and the assumption of independence between observations within the same group is not adequate. EMG signal was analyzed in time domain by RMS. Normality of the signal amplitude was tested using the by Kolmogorov-Smirnov test and according to the results obtained, non-parametric statistics was used for the analysis.

In the mixed model used for data analysis, subjects were considered as random effect and the orthostatic tests and time points as well as the interaction between them were considered as fixed effects.

The analysis of variance (ANOVA) was used for analyses of the data obtained during the active postural maneuver on the force platform. This analysis was performed using the PROC GLM in the SAS® 9.2 software. Orthogonal contrasts based on t distribution for ANOVA with repeated measures were used for comparisons. Statistical significance was set at 5%. Data were normalized to the maximum values of each variable.

Results

Significant differences in the minute-by-minute HR between AS and HUT were observed during the first VM (minute 6), minute 7 and minute 8, with higher values during the AS than the HUT (Figure 1).

TMV and TD on the force platform during the AS

Mean values of TMV over time are depicted in Figure 2, with statistically relevant values during the first VM (minute 6) and second VM (minute 9) as compared with minute 1. This was also observed during the second VM in comparison with minutes 2-8, and the values measured from minute 10 to 14 in relation to the second VM.

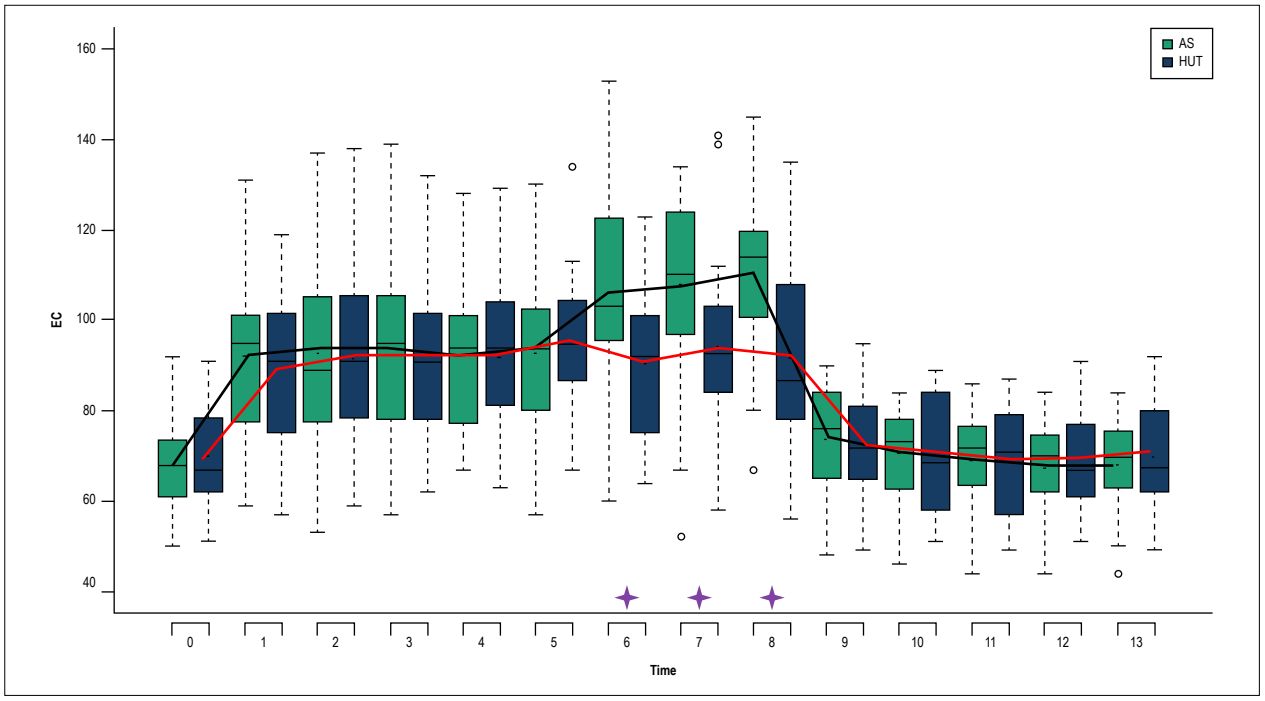

Figure 1 – *Heart rate behavior during the Active Standing Test (AS) and the Head-Up Tilt Test (HUT). ——: Mean variation of heart rate during AS. ——: Mean variation of heart rate during AS. ✦: Significant difference between AS and HUT, p < 0.05. Heart rate in beats per minute (bpm).*

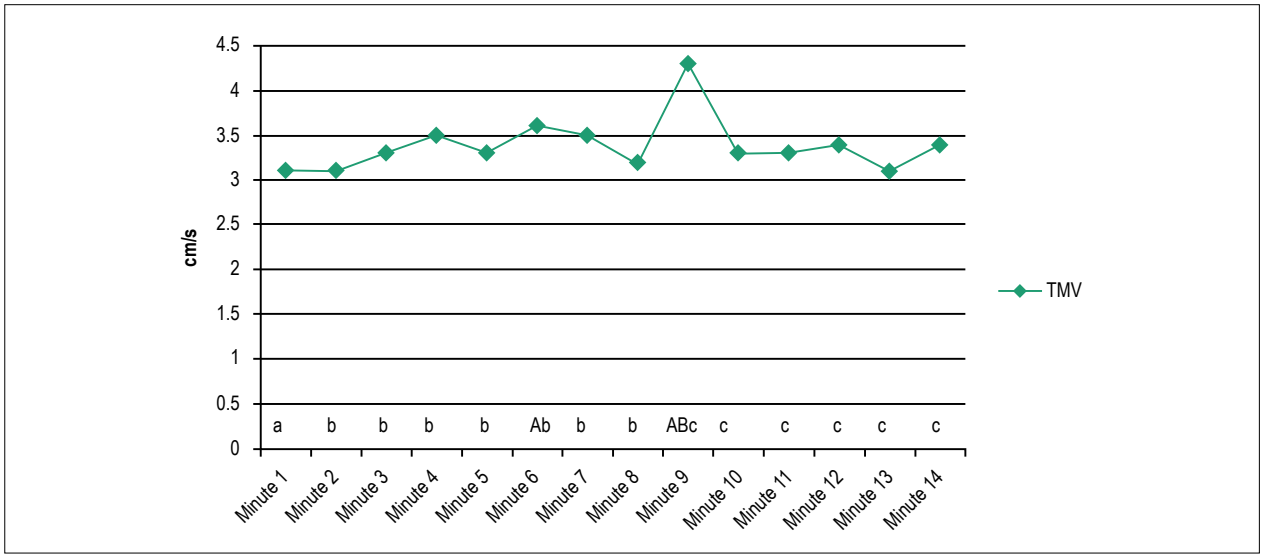

Figure 2 – *Total mean velocity on the force platform during the Active Stand Test. A, B, C: significant difference with their corresponding minutes (a, b, c); p < 0,05.*

With respect to TD, significant differences were detected in minutes 3, 6 (second VM), 7, 9 (second VM), 12 (third VM) and 14 in comparison with minute 1 during the AS. Significant differences were also found in minutes 7, 9 (second VM) and 14 in comparison with minute 2, and during the second VM (minute 6) in comparison with minutes 3, 4, 5, 7 and 8. Finally, from minute 10 to 13, significant values were found as compared with minute 9 (Figure 3).

When the total time of the test was divided into three parts (pre-VM, VM and post-VM), significant differences were found in TD and TMV between VM and pre-VM, and in TMV between VM and post-VM.

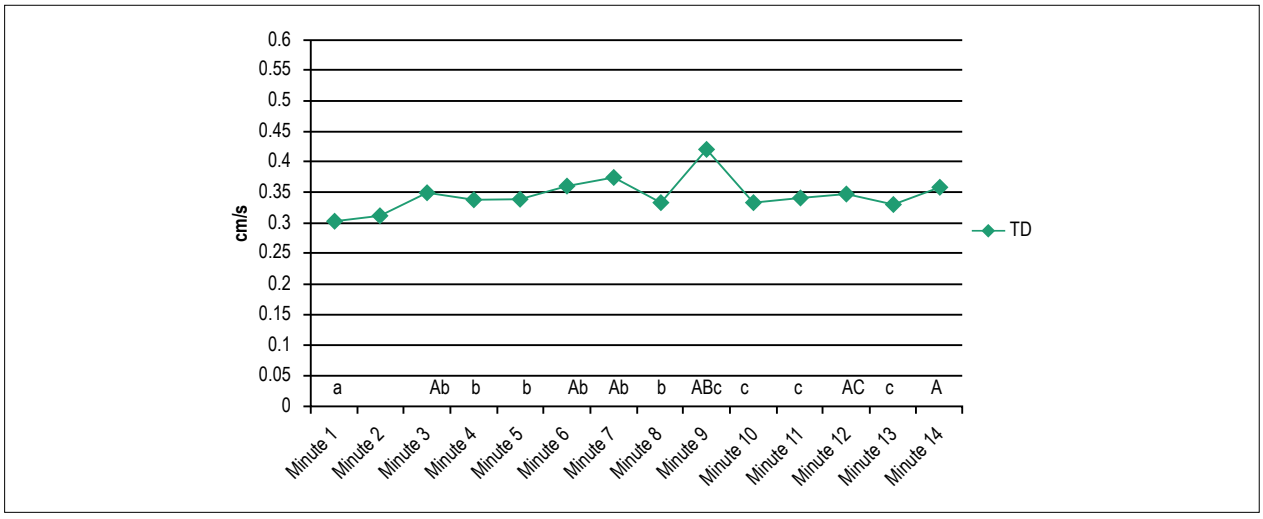

Figure 3 – *Total displacement on the force platform during the Active Standing Test. A, B, C: significant difference with their corresponding minutes (a,b,c); p < 0.05. TD: Total displacement.*

Surface electromyography during AS and HUT divided into three parts – pre-VM, VM and post-VM

EMG analysis of the muscle groups revealed statistically significant differences in all muscle groups during the AS – right (rES) and left ES (lES), right (rMG) and left GM (lMG), left (lRA) and left RA (lRA) and right (rTA) and left TA (lTA) – except for the right RA (rRA). In addition, statistical relevance was found for rES, lES, rMG, lMG, lRA, and rTA between post-VM and pre-VM. Finally, during the AS, statistically significant differences were found for the rMG, lMG, lRA, rTA and lTA muscle groups between post-VM and VM (Figure 6).

During the HUT, statistical relevance was observed for the rES, lES, lMG, rRA, lRA, rTA and lTA muscle groups between VM and pre-VM. Significant difference was found for the rES, lES, lMG, rRA, lRA, rTA and lTA muscle groups between post-VM and pre-VM. Finally, in the comparison between the post-VM and VM periods, statistically relevant differences were found for the rES, lES, rRA, lRA and rTA muscle groups (Figure 7).

Comparison of the periods pre-VM, VM and post-VM between HUT and AS reveled statistical relevance for the VM period for all muscle groups, with higher values during the AS than HUT, except for the rES and lES, whose EMG activity was significantly higher during the HUT than AS (Figure 8).

Discussion

The present study explores an alternative method for the classical HUT used for the diagnosis of NCS. In addition to its long duration, the HUT requires considerable effort and cooperation by the patient,[3] which may contribute for prolonged scheduling period. Our proposal was to better know the effects of prolonged orthostatism on blood pressure, level of consciousness, etc. in healthy individuals. In this sense, AS is faster and, although, in theory, it may be used at patients' bedside, the test should be better performed under controlled conditions, especially in patients very sensitive to NCS.

The comparison between HUT and AS is little discussed in the literature. A previous study showed that the cardio-accelerator effect of AS is more evident than in HUT.[11] However, this study was conducted with children and adolescents only, and different protocols were used for AS and HUT, which make comparisons difficult. In order to define a realistic and optimized study design, we first performed the AS with nine volunteers to establish the optimal duration of the tests for the experimental protocol to detect cardiovascular changes. Three of these volunteers had syncope in minute 15 (mean) and one volunteer syncope prodrome in minute 12, which helped us to define that paired comparisons of the responses between AS and HUT should be performed at minute 15 of the test.

VM has been reported to be able to identify orthostatism intolerance.[10] Prakash e Pravitan[14] observed that a series of 3 VMs performed at predetermined intervals during the AS would yield results similar to the use of vasodepressor drugs.

This finding motivated us to plan a very conservative protocol, i.e., with no use of any drugs or invasive procedure. In line with Matsushima et al.,[11] who proposed the comparison of two active and passive tests, we decided not only to compare these two orthostatic tests, with or without a tilt table, but also to evaluate test the effects of these three VMs.

Liu et al.[15] observed that during the passive tilt test, syncope generally occurred after the 10th minute, whereas during the passive tilt test combined with the use of sublingual nitroglycerin, syncope occurred between 5 and 15 minutes.

Our data showed an increase in HR for AS and HUT when compared with resting conditions, which was incremented by the VM during the AS. Such increase in HR with orthostatic change may be a predictor factor for syncope in susceptible patients,[16] as an exacerbated response to hypovolemia caused by postural change. Besides, the combination of VM to these tests can contribute to the cardio-acceleration in response to changes in blood pressure.[17] These postural changes and subsequent hemodynamic changes lead to

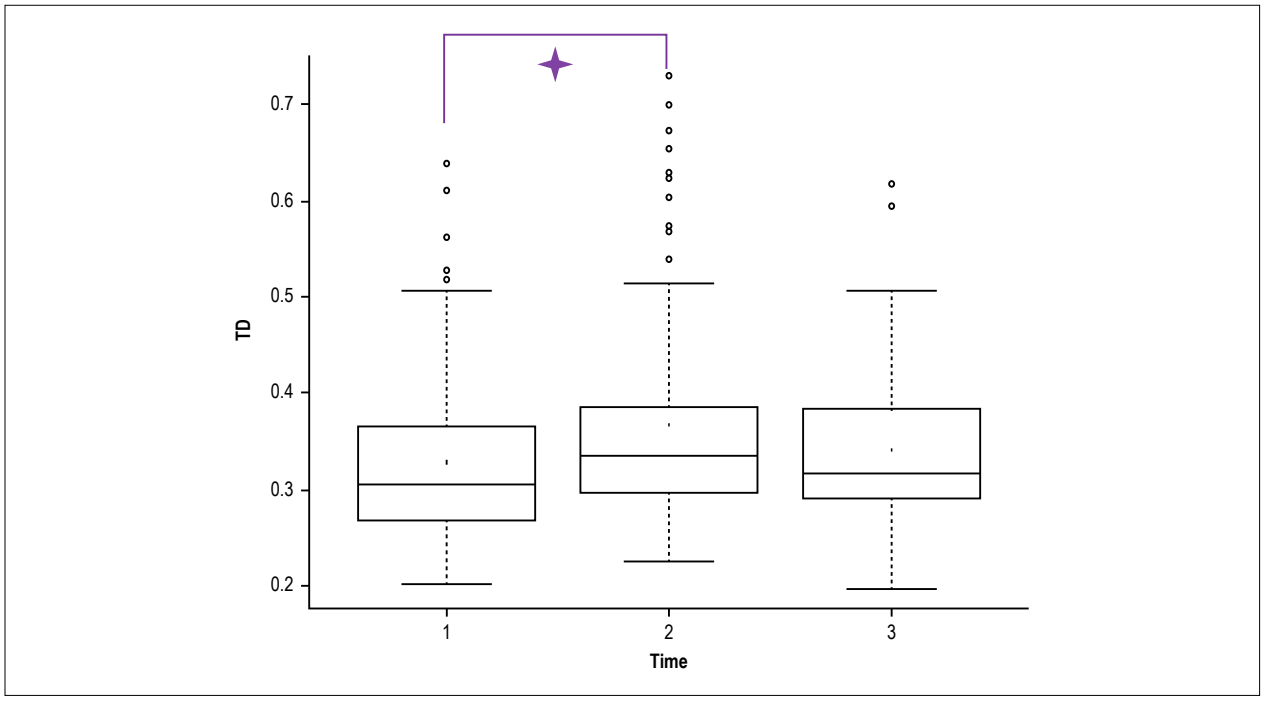

Figure 4 – *Total displacement variation during the pre-Valsalva maneuver (VM) (1), VM (2) and post-VM (3) periods. Significant values between VM and pre-VM; p < 0.05.*

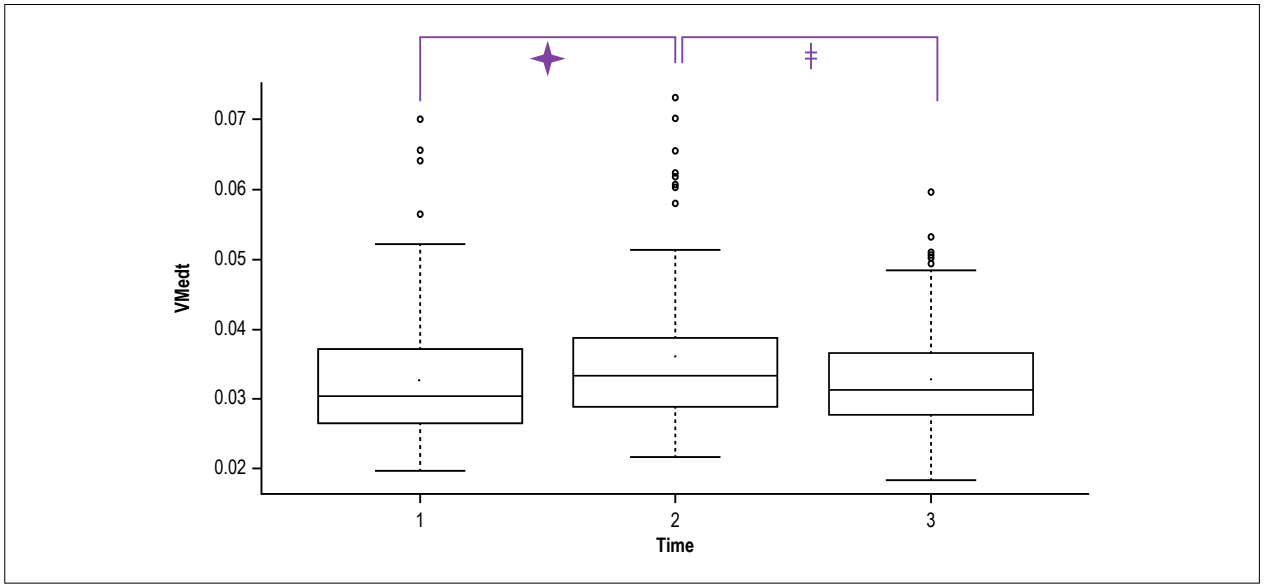

Figure 5 – *Total mean velocity variation during the pre-Valsalva maneuver (VM) (1), VM (2) and post-VM (3) periods. ✦: Significant values between VM and pre-VM; p < 0.05; ǂ: significant values between post-VM and VM; p < 0.05.*

increased sympathetic activity and peripheral resistance. Loss of consciousness in CNS patients may be a response to impaired venous return.[17]

Despite the assumption that the body may be represented by an inverted pendulum during standing, as proposed in kinematic, kinetic and EMG studies,[18,19] slight displacement of joints that maintain the standing posture, such as the ankle and the hip, have an important role in orthostatism that cannot be ignored.[20-22]

Aware of the role of the musculoskeletal system as the venous return protagonist by means of muscle contraction below the heart, we decided to register the activity of some muscles involved in the ankle strategy for maintenance of standing position – the AT and the gastrocnemius – as well as muscles involved in the maintenance of upper hemibody posture – the RA muscle and the ES – and compare it between the two tests. For seven of the eight muscles studied, there was a progression of changes, especially until

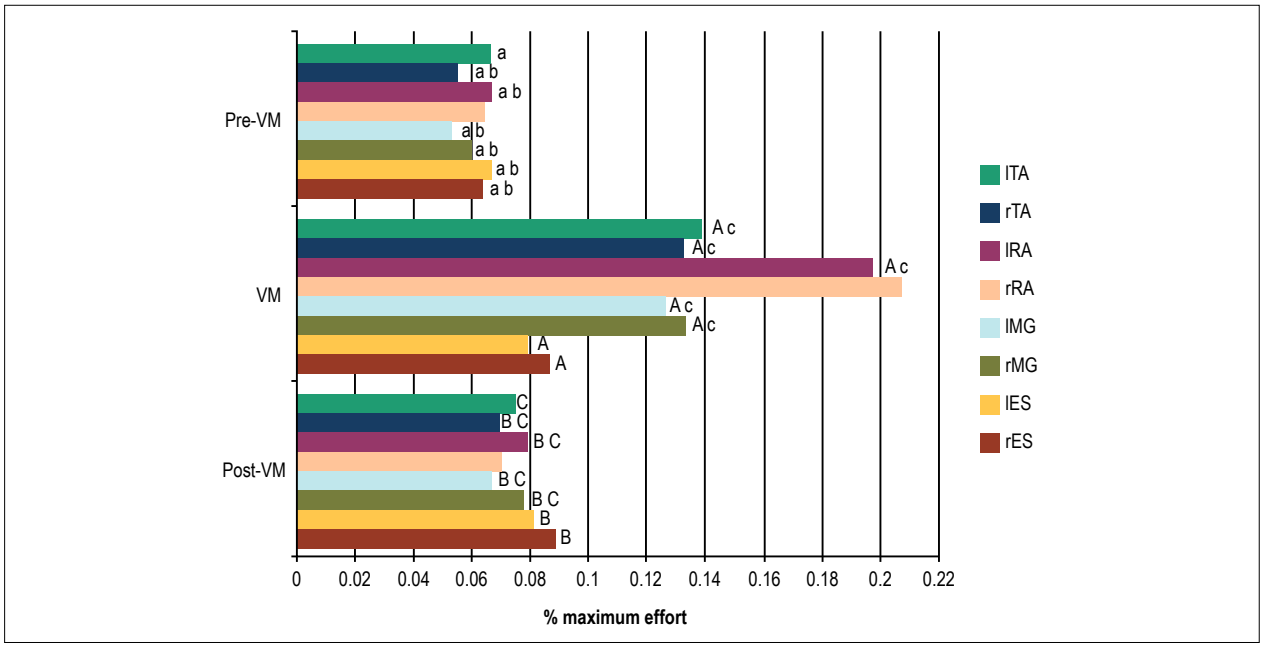

Figure 6 – *Percentage of maximum effort in relation to the electromyographic activity recorded during the test divided into three stages: pre-Valsalva maneuver (VM), during the VM and post-VM during the Active Standing Test. A, B, C: significant difference with their corresponding muscles (a,b,c): p < 0.05.*

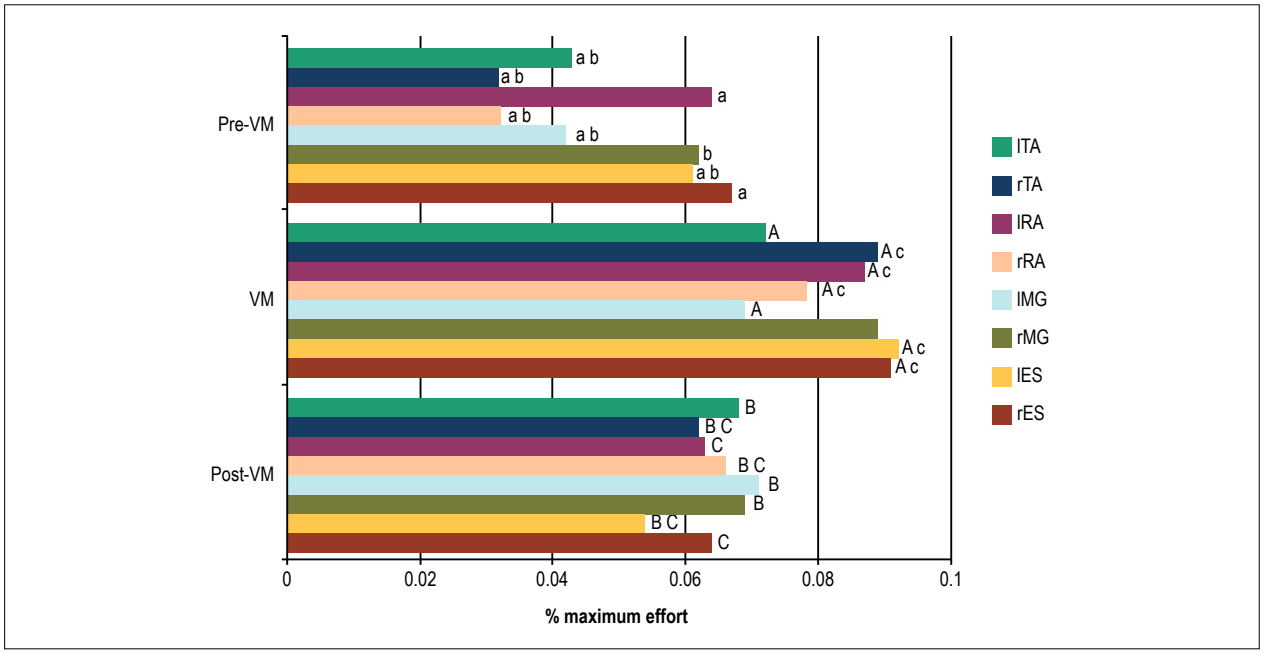

Figure 7 – *Percentage of maximum effort in relation to the electromyographic activity recorded during the test divided into three stages: pre-Valsalva maneuver (VM), during the VM and post-VM during the Head-Up Tilt Test Test. A, B, C: significant difference with their corresponding muscles (a,b,c): p < 0.05.*

the end of the VMs. However, for rRA during the AS and for rMG during HUT had no statistical relevance in the changes observed during the VMs as compared with the pre-VM during orthostatism. If we compare the electrical activity between AS and HUT, we find a higher EMG activity during AS than HUT, except for the rES and lES, whose activity was higher in the HUT than AS.

These data corroborate our hypothesis that the role of muscles would be different in each test. AS allows the use of muscle strategies for postural maintenance by contraction of the muscles, as the patient feels the necessity to correct eventual body sways that may make him fall. On the other hand, during the HUT, such strategies are compromised and the patient can bend forwards only, since the patient is kept

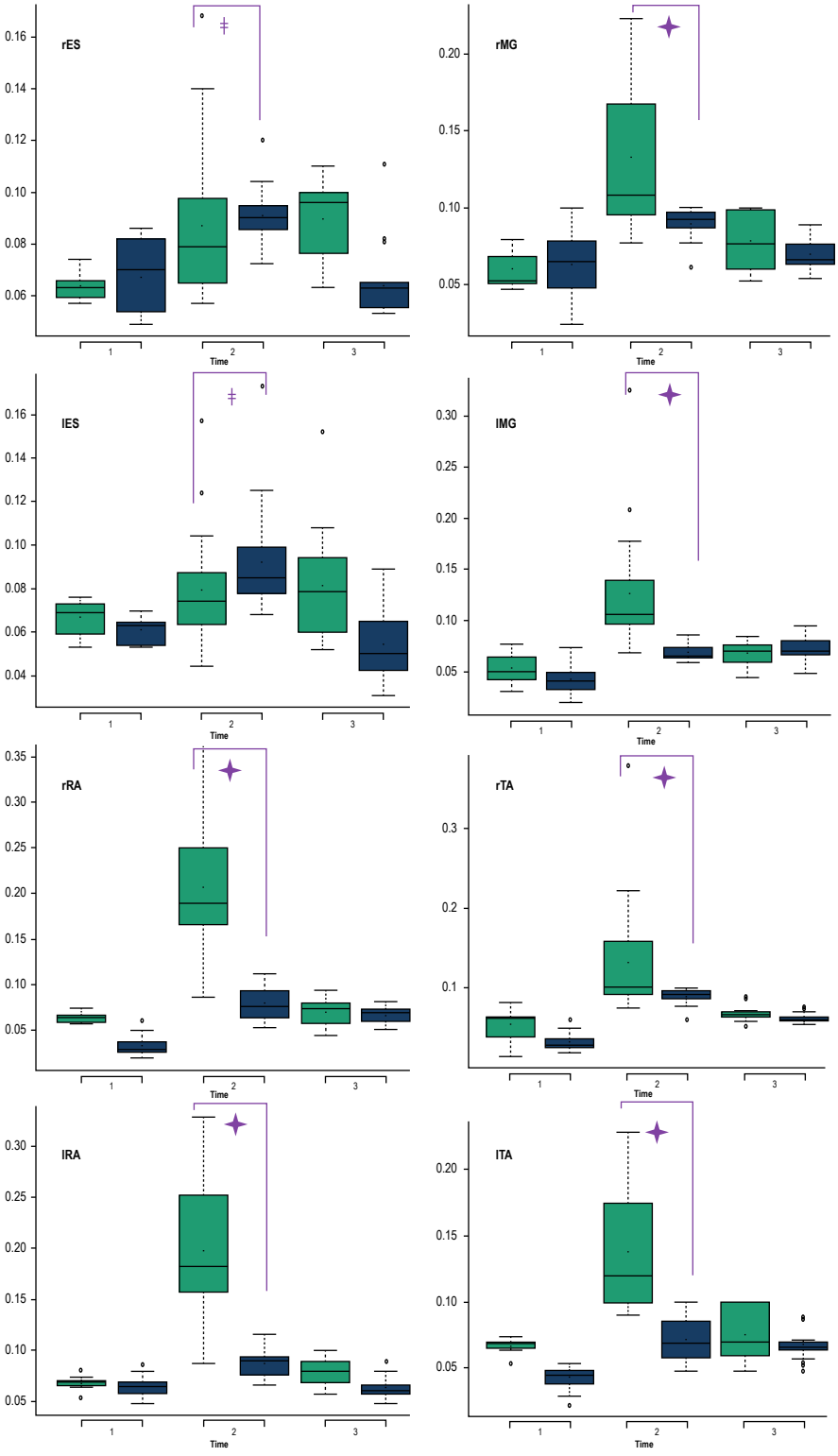

Figure 8 – *Comparison of electromyographic activity of all muscles between the Active Standing Test (white) and the Head-Up Tilt Test (grey) during the Pre- Valsalva maneuver (VM) (1), VM (2) and post-VM (3). ✦: p < 0.05.*

attached to the tilt table, which acts as a support for the whole back of the body. Therefore, during the HUT, what we find is a greater EMG activity for the ESs than during the AS, possibly due to what was discussed above.

In light of the role of muscles in postural control and venous return, we found it reasonable to analyze the COP sway by means of a force platform in attempt to understand when cardiovascular changes and the muscle action in response to these hemodynamic changes would affect oscillations of the body. It is worth pointing out the statistical relevance of TD and TMV at around the second VM, in which oscillation had higher displacement and velocity values as compared with previous time points.

By dividing the total time the patient stayed on the force platform during the AS into three parts – pre-VM, VM and post-VM – considering VM as the period in which the three VMs were performed, we found that TD of COP on the platform and TMV were significantly higher in the VM as compared with the pre-VM. In addition, TMV significantly decreased in the post-VM period. Gatev et al.[23] reported that activity of the lateral gastrocnemius muscle was positively related to the COP displacement. Also, the authors found that this oscillation, especially the anteroposterior motions of the gastrocnemius is in accordance with the "climbing hill" theory for balance maintenance, that states that muscle contracts when tensioned and decreases its activity when it loses its tension.[24] Thus, in case of the ankle, the activity of anterior and posterior muscles increases as the COP displacement increases over time.

In our context, MG showed a concomitant increase in EMG activity with the increase in TD and mean velocity of TD. This also occurred for the TA, which suggests that, although we did not analyze the displacement direction, both MG and TA may follow the same trend as reported by Gatev et al.[23]

The fact that cardiovascular changes were more relevant during the period when the VMs were performed suggests that the VM exerts not only a hemodynamic stress, but its effects also affect body motion, which can result in increased muscle activity to maintain orthostatic and hemodynamic balance. This, in individuals with syncope, who may have impaired venous return by the muscle pump system, this oscillation may be even greater until presyncope symptoms or even syncope *per se* occurs.

Claydon & Hainsworth[25] observed that cardiovascular changes affect orthostatic tolerance that alters the movement of lower limbs for compensation. The authors reported that patients with postural syncope have impaired muscle response to compensate for their smaller reflex responses, which may contribute to the episodes of fainting. These findings are in agreement with our concept of the role of muscles on the COP displacement.

Conclusions

Results of the present study obtained under the experimental conditions corroborate with our initial hypotheses, as we showed that, during the active postural maneuver, postural oscillation and the electrical activity of muscles associated with postural maintenance revealed a progressive change in the response pattern of biomechanical variables and cardiac variables, augmented by repeated VMs. For the passive postural maneuver, muscle activity was qualitatively and quantitatively different.

Study limitations

The study has some limitations that should be considered. The number of participants may have been a limiting factor for the magnitude of the changes reported. This may be caused by the relatively complex design of the study, in which each volunteer underwent two test sessions with approximately 2-hour duration on different days. In addition, we selected patients with no history of syncope, which makes the inclusion of a larger number of patients to the study protocol difficult, since a considerable part of the population has experienced syncope. However, aiming to achieve homogenized responses to the tests and higher consistency of the results, we decided to select only volunteers with no history of syncope.

Changes in systemic arterial pressure were monitored by manual sphygmomanometer. Continuous measurement of blood pressure using the Finapres monitor (Ohmeda, Denver, Colorado) would be interesting, since this instrument allows that both blood pressure and heart rate be measured continuously. Nevertheless, for technical reasons, our Finapres device could not be used during the pilot data collection and, since we used less accurate devices, blood pressure data were not included in this study.

Clinical implications and future studies

The present study seeks to consolidate the proposal of NCS diagnostic tests that would require a shorter period of patient exposure, thereby increasing the number of patients examined per session, and to analyze a test that does not require a tilt table, which is not available in all cardiology clinics. Studies comparing active and passive protocols in NCS subjects are the next step to clarify whether the changes observed in healthy individuals in the present study cause syncope. This is essential before we can present the protocols analyzed in this study as an alternative for the study of NCS by the professional community of interest.

Author contributions

Conception and design of the research: Liporaci RF, Saad MC, Credência JC, Marques F, Bevilaqua-Grossi D, Gallo-Júnior L; Acquisition of data: Liporaci RF, Saad MC, Credência JC; Analysis and interpretation of the data: Liporaci RF, Saad MC; Writing of the manuscript: Liporaci RF; Critical revision of the manuscript for intellectual content: Liporaci RF, Marques F, Bevilaqua-Grossi D, Gallo-Júnior L.

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 article is part of the thesis of master submitted by Rogerio Ferreira Liporaci, from Universidade de São Paulo.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Hospital das Clínicas da Faculdade de Medicina de Ribeirão Preto da Universidade de São Paulo under the protocol number 13626/2008. 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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Genetic Syndromes Associated with Congenital Cardiac Defects and Ophthalmologic Changes – Systematization for Diagnosis in the Clinical Practice

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Abstract

Background: **Numerous genetic syndromes associated with heart disease and ocular manifestations have been described. However, a compilation and a summarization of these syndromes for better consultation and comparison have not been performed yet.**

Objective: **The objective of this work is to systematize available evidence in the literature on different syndromes that may cause congenital heart diseases associated with ocular changes, focusing on the types of anatomical and functional changes.**

Method: **A systematic search was performed on Medline electronic databases (PubMed, Embase, Cochrane, Lilacs) of articles published until January 2016. Eligibility criteria were case reports or review articles that evaluated the association of ophthalmic and cardiac abnormalities in genetic syndrome patients younger than 18 years.**

Results: **The most frequent genetic syndromes were: Down Syndrome, Velo-cardio-facial / DiGeorge Syndrome, Charge Syndrome and Noonan Syndrome. The most associated cardiac malformations with ocular findings were interatrial communication (77.4%), interventricular communication (51.6%), patent ductus arteriosus (35.4%), pulmonary artery stenosis (25.8%) and tetralogy of Fallot (22.5%).**

Conclusion: **Due to their clinical variability, congenital cardiac malformations may progress asymptomatically to heart defects associated with high morbidity and mortality. For this reason, the identification of extra-cardiac characteristics that may somehow contribute to the diagnosis of the disease or reveal its severity is of great relevance. (Arq Bras Cardiol. 2018; 110(1):84-90)**

Keywords: **Heart Defects, Congenital/genetic; Eye Diseases; Diagnostic Tevhniques, Ophtalmologic; Heart Septal Defects, Atrial; Tetralogy of Fallot.**

Introduction

Congenital heart disease (CHD) is any severe structural abnormality of the heart or intrathoracic vessels that is present at birth. CHDs are considered the most common congenital malformation, significantly contributing to child mortality and morbidity, with an incidence of 4-50 cases per 1,000 births in the world.

The etiology of CHDs is still little known, and approximately 15%-20% of the cases have an unknown cause. Chromosomal abnormalities are one of the main known causes of CHDs, affecting 3-18% of the cases.[2] Extracardiac malformations are common in patients with CHDs; defects in intra-abdominal organs and/or defects associated with genetic syndromes are observed in 7-50% of patients,[3] increasing even more the risk of morbidity, mortality as well as of cardiac surgery. Besides, these changes may require treatment, including surgery, regardless of the cardiac problem. Among these, ophthalmological abnormalities are among the main extracardiac malformations.

Although a large number of genetic syndromes with heart disease combined with ocular manifestations have been described in the literature,[4-38] they have not been compiled and summarized for consultation and comparison. A systematic understanding of these conditions may provide important clinical implications, contributing to the investigation and detection of abnormalities. Their diagnosis with identification of all associated conditions is crucial not only for the pediatric cardiologist seeing a patient with CHD and who should suspect ophthalmologic abnormalities, but also for the ophthalmologist who may suspect heart injury according to patients' clinical conditions.

The aim of this study was to systematize available evidence in the literature on different syndromes that may cause CHDs associated with ocular changes, focusing on the types of anatomical and functional changes.

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Methods

A systematic review was performed on the Medline database (Pubmed, Embase, Cochrane, Lilacs). The search strategy is found in Appendix I (access the link: http://publicacoes.cardiol.br/portal/2017/abc/english/v11001/pdf/i11001014_anexo.pdf). Case reports and review studies on the association of ophthalmologic and cardiologic changes in genetic syndrome patients younger than 18 years, published until January 2016 were considered eligible. The search was performed by two independent investigators, who made a systematic analysis of titles and abstracts, and extraction of methodological characteristics, number of patients and results of all articles retrieved using the search strategy. Articles describing changes in patients older than 18 years, and articles on patients without a genetic syndrome with cardiologic and ophthalmologic changes were not considered for analysis.

This study was approved by the Research Ethics Committee of Rio Grande do Sul University Foundation of Cardiology (approval number 101593/2013-9).

Results

A total of 1,685 articles were identified, and 83 of them, related to genetic syndromes associated with CHDs and ophthalmologic disturbances, were included in the review. Most studies were case reports (Figure 1). Tables 1 and 2 describe cardiologic changes by syndrome and ophthalmologic findings by eye segment; the most and the least common genetic syndromes can be found in Table 1 and Table 2, respectively.

The most frequently described genetic syndromes associated with CHD-related ocular changes were Down syndrome, velo-cardio-facial/DiGeorge syndrome, CHARGE syndrome and Noonan syndrome. The most common cardiac malformations (with different etiologies) were interatrial communication (77.4%), interventricular communication (51.6%), patent ductus arteriosus (35.4%), pulmonary artery stenosis (25.8%), and tetralogy of Fallot (22.5%). The highest number of possible cardiac repercussions was found in CHARGE (8), Cat eye (5), velo-cardio-facial (4), and Down (4) syndromes, with a mean of 2.9 cardiologic findings/syndrome.

Regarding the occurrence of concomitant ocular findings, a mean of 4.6 findings were found among the most prevalent CHDs, especially in the velo-cardio-facial, Turner, cat eye, CHARGE and Goldenhar syndrome, and of 3.5 findings among the least common diseases (Table 2), especially the Peters, Phace, Bloch and Leber syndromes. External ocular disorders are the most common manifestations, with a mean of 2.4 findings/syndrome (among the most common syndromes), particularly Down syndrome, CHARGE syndrome, cat eye syndrome and velo-cardio-facial syndrome (Table 1), and a mean of 1.38 findings among the least common syndromes, with emphasis to Bloch, Duane, Mowat-Wilson, oculofaciocardiodental, Peters and Phace syndromes (Table 2).

Refractive error was reported in Down, Turner, cat eye, velo-cardio and Noonan syndromes, as well as in eight rare syndromes (Table 2). Anterior segment of the eye was more frequently affected in the velo-cardio-facial, Down, Peters and

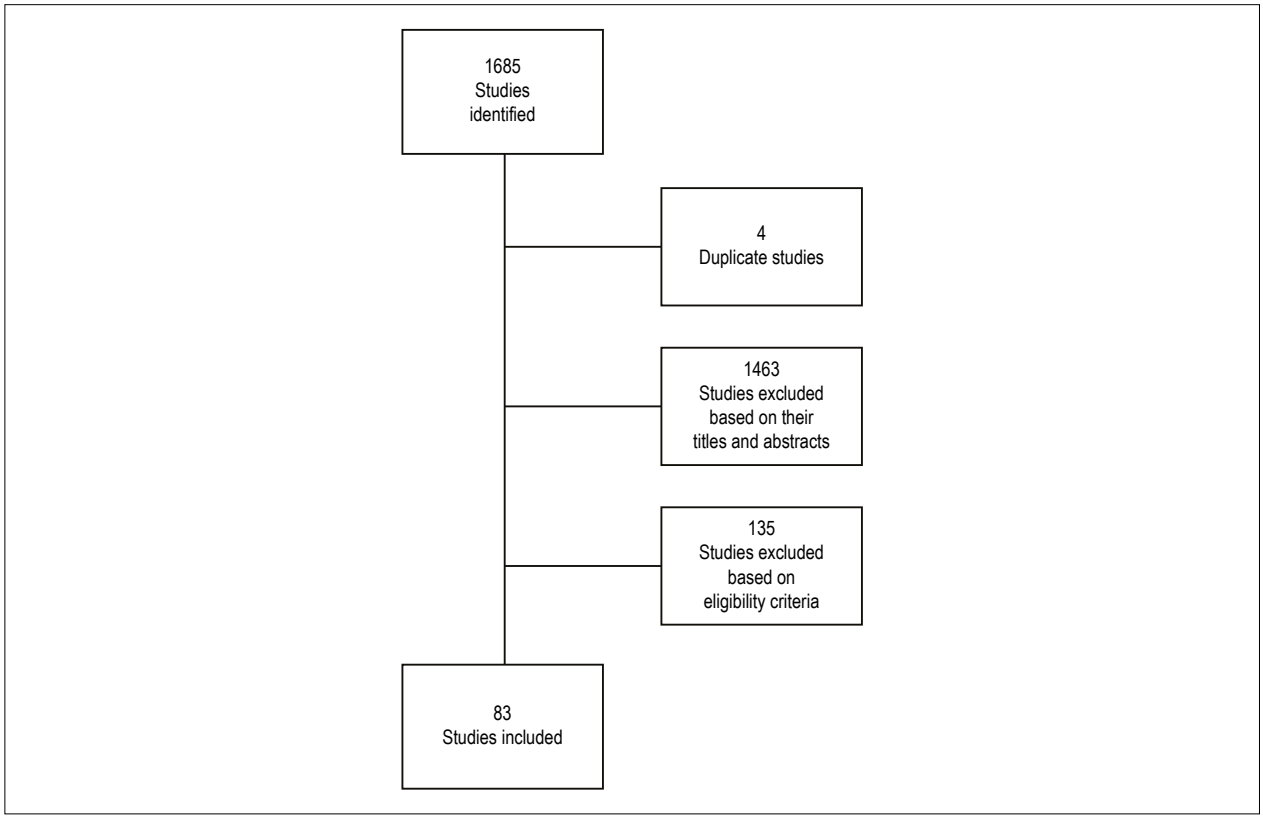

Figure 1 – *Flowchart of the studies included in this review.*

Table 1 – Common genetic syndromes associated with cardiologic and ophthalmologic disturbances

Condições Genéticas			Down	Tumer	Cat eye	Velo-cardio-facial/DiGeorge	Williams	WAGR	Rubinstein-Taybi	Alagille	Charge	Kabuki	Marfan	Noonan	Smith-Lemi-Opitz	Goldenhar	Poland-Mobius
Cardiologic findings		AP									+						
		EP				+	+			+				+			
		CAo		+													
		EAo					+				+			+			
		CIA	+	+	+	+		+	+	+	+	+					
		CIV	+		+		+				+	+				+	
		DSAV									+				+		
		AVCI			+												
		DAP												+			
		Dext														+	+
		PVCSE			+												
		PCA	+						+		+						
		PVM											+				
		RVPA			+												
		TOF	+			+			+		+						
		VAoB		+		+											
		VMP									+						
Ophthalmologic findings	Extrinsic	An. Lacrimal	+			+											
		An.Pab Formal/Posição	+	+		+		+			+					+	
		Colob. P														+	
		Estrabismo	+	+	+	+	+		+		+						+
		Hiper/Tel	+		+						+			+		+	
		Nistagmo	+		+			+	+								
		Oft. Ext				+											+
		PregaEp	+	+	+									+	+	+	
	Refractive errors and anterior segment abnormalities	Anir						+									
		Alt. Córnea e Limbo				+				+						+	
		Catarata ou An. de Posição	+	+		+		+					+		+		
		Colob. I			+						+	+					
		ErrosRef	+	+	+	+								+			
		Glaucoma							+								
		Hipop.I								+							
		M. Brush	+														
		Nód.I				+											
		ProemNC				+											
		Alt.VRet	+	+		+											
	Posterior segment abnormalities	An. Disco Op								+							
		Colob. RNC			+						+						
		Desc. Ret		+									+				
		Drus.N.Op								+							
		Hem.V		+													
		Hipop.DFO								+							
		Hipop.M														+	
		M. NeovC									+						
		OACRet											+				
		Ret.P												+			
		Retinob	+														
		DispEPR								+							

Cardiologic findings: PA: pulmonary atresia; AIVC: absent inferior vena cava; IAC: interatrial communication; IVC: interventricular communication; CoA: coarctation of the aorta; PAD: pulmonary artery dilation; ASD: atrioventricular septal defect; AoS: aortic stenosis; PLSVC: persistent left superior vena cava; MVP: mitral valve prolapse; APVR: anomalous pulmonary venous return; TOF: tetralogy of Fallot; BAV: bicuspid aortic valve; PMV: parachute mitral valve;
Ophthalmologic findings: Extrinsic: Lacrimal An.: lacrimal anomalies; Changes in eyelid shape/position; Eyelid coloboma; Hyper/Tel: hypertelorism/telecanthus; Ext.Opht: external ophthalmoplegia; EF: epicanthic fold.
Refractive errors and anterior segment abnormalities: Anir: aniridia; Changes in cornea and limbus; Cataract or position abnormalities; I Colob.: Iris coloboma; RE: refractive errors; IHypop: iris hypoplasia; Brushfield spots; INod.: Iris nodules; Prom.CN: prominent corneal nerves;
Posterior segment abnormalities: Abn.RV: abnormal retinal vessels; OD Abn.: optic disk abnormalities; Ret/Optic/Choroid/Nerve Colob.: Retinal/ Optic/ Choroid nerve coloboma; Ret det.: retinal detachment; ODD: Optic Disk Drusen; Vit. Hem.: Vitreous hemorrhage; DH Fundus.: Diffuse hypopigmentation in the fundus; M Hypop.: macular hypoplasia; C Neov M.: choroidal neovascular membrane; Ret CAO: retinal central artery occlusion; Rret P.: retinitis pigmentosa; Retinob: retinoblastoma; spots in the retinal pigment epithelium.

Table 2 – Rare genetic syndromes associated with cardiologic and ophthalmologic disturbances

Condições Genéticas			Adams-oliver	Alstrom	Botalli	Duane	Hutchinson-Gilford	Leber	McDonough	Mowat-Wilson	Óculo-facio-cardio-dental	Okihiro	Oto-palato-digital	Peters	PHACE	Sjogren-Larsson-like
Cardiologic findings		AP								+						
		CIA	+					+			+	+	+		+	
		CIV		+			+			+	+	+		+		+
		CoAo								+					+	
		Dext				+								+		
		DAo			+								+			
		DSVa											+			
		DSAV													+	
		EVM											+			
		EAo							+							
		EVAo								+						
		EP						+		+						
		FE						+								
		PCA			+					+				+	+	
		RM													+	
		TOF								+				+	+	
		VAOB								+						
Ophthalmologic findings	Extrinsic	Al.Cil					+								+	
		An.Palp Formal/ Posição				+		+		+		+			+	
		Estr	+		+	+			+	+	+	+		+	+	
		Hiper/Tel												+		+
		Microf									+			+		
		Nist		+				+		+						
		PregaEp				+										
	Refractive errors and anterior segment abnormalities	An.Corneana					+							+		
		An.Palp Forma/ Posição							+							
		An. Pulpilares			+			+								
		Caratarata ou An. de Posição									+		+	+	+	
		Colob.I												+		
		ErrosRef			+			+		+					+	+
		Glaucoma									+		+	+		
		HeterI								+					+	
		HipopI													+	
	Posterior segment abnormalities	Alt.VRet					+	+						+		
		An.Disco Óptico						+							+	
		Colob.C												+		
		DeslRet												+		
		HemanI													+	

Cardiologic findings: PA: pulmonary atresia; IAC: interatrial communication; IVC: interventricular communication; CoA: coarctation of the aorta; Dext: dextrocardia; AoD: aortic dilatation; DSVa: Dilatation of sinus of Valsalva; ASD Atrioventricular septal defect (AVSD); TMV: thickened mitral valve; AoS: aortic stenosis; AoVS: aortic valve stenosis; PS: pulmonary stenosis; EFE: endocardial fibroelastosis; PDA: patent ductus arteriosus; MR: mitral regurgitation; TOF: tetralogy of Fallot; BAV: bicuspid aortic valve

Ophthalmologic findings: Extrinsic: eyelash Abn: Eyelash abnormalities; Changes in eyelid shape/position; Str: strabismus; Hyper/Tel: hypertelorism/telecanthus; Microph: microphtalmia; Nyst: nystagmus; EF: epicanthic fold

Refractive errors and anterior segment abnormalities: Corneal Abn: corneal abnormality; Changes in eyelid shape/position; Pupillary Abn: pupillary abnormalities; Cataract or position abnormalities; I Colob.: Iris coloboma; RE: refractive errors; Glauc: glaucoma; IHeter: iris heterochromia; IHypop: iris hypoplasia

Posterior segment abnormalities: Abn.RV: abnormal retinal vessels; OD Abn.: optic disk abnormalities; CColob: Choroid nerve coloboma; Ret det.: retinal detachment; IHeman: intraorbital hemangioma

Phace syndromes, whereas the posterior segment was more frequently affected in the Turner, Alagille, Marfan, Bloch and Peters syndromes. Ocular findings associated with these syndromes were: strabismus (43.4%), cataract (28.0%), abnormalities of eyelid position and shape (28%), nystagmus (21.7%), refractive errors (19.5%), glaucoma (19.5%), and hypertelorism (19.5%).

Discussion

Due to their clinical variability, congenital cardiac malformations may progress asymptomatically to severe heart defects associated with high morbidity and mortality. For this reason, the identification of extra-cardiac characteristics that may somehow contribute to the diagnosis of the disease or reveal its severity is of great relevance. However, so far, few studies have investigated more specific extracardiac factors, such as ophthalmologic ones. In light of the potential associations between cardiologic and ophthalmologic changes, both cardiologist and ophthalmologist should be aware of concomitant signs that may indicate certain syndromes or their severity. Among these genetic syndromes, the most frequently described cardiac manifestations were interatrial and interventricular communications, patent ductus arteriosus, pulmonary artery stenosis, and tetralogy of Fallot, whereas the most common ocular diseases were strabismus, cataract, eyelid disturbances, nystagmus, glaucoma, refractive errors and hypertelorism. Mean number of ocular findings per genetic syndrome associated with heart disease was 3.5 among uncommon syndromes, and 4.6 among the most common syndromes.

A recent systematic review[39] showed that few studies have assessed the prevalence of ocular findings in CHD that are not associated with genetic syndrome. The prevalence was estimated at 32.5%, with cataract, strabismus, and retinopathy as the main consequences described.[39] In case of genetic syndromes, such estimation is limited due to the scarcity of series and reports.

Down syndrome had the highest number of patients described – more than 6,000 patients in the 6 articles analyzed. This is the most common syndrome in newborns with an incidence of 1/660 live births. In 95% of cases, Down syndrome is caused by nondisjunction during maternal meiosis I, resulting three copies of chromosome 21 in each cell; 4% of these cases are related to gene translocations and 1% to mosaicism. The frequency of CHDs in children with trisomy 21 is variable in the literature, varying from 20% to over 60%.[40] These children are known to be prone to strabismus, hypertelorism, upslanted palpebral fissures, epicanthic fold, supernumerary retinal vessels, Brushfield spots, refractive errors, cataract, nystagmus, amblyopia.

In general, the approach of children with genetic syndrome is more complex, requiring the simultaneous involvement of many medical specialties. These children should be followed-up by a multidisciplinary staff, which would be responsible for the diagnosis, the therapeutic project and patients' follow-up.

Among these study's limitations, the most important is the publication bias of the reviewed articles. Although available published data do not enable a meta-analysis, the summary of these findings enables the compilation of data published in sporadic reports into a unique text, resizing the problem dimension and demanding more comprehensive studies. We performed an extensive article search, without language restrictions, and this sensitivity was a strength of this study. However, an intrinsic limitation of a systematic review is the quality of the studies included.

Conclusion

This study demonstrated the variety of cardiologic and ophthalmologic findings associated with these genetic syndromes, emphasizing the importance of this simultaneity, and that signs in the eye and appendages and cardiac signs require an integrated approach. Since these cases can cause severe functional disturbances and high morbidity, their routine assessment should include an ophthalmologic examination. Primary detection of any of these ocular signs can determine the investigation of a so far unrecognized cardiac change.

Author contributions

Conception and design of the research: Oliveira PHA, Souza BS, Pacheco EN, Menegazzo MS, Corrêa IS, Zen PRG, Rosa RFM, Cesa CC, Pellanda LC, Vilela MAP; Acquisition of data, Analysis and interpretation of the data, Statistical analysis, Obtaining financing, Writing of the manuscript and Critical revision of the manuscript for intellectual content: Souza BS, Pacheco EN, Menegazzo MS, Corrêa IS, Zen PRG, Rosa RFM, Cesa CC, Pellanda LC.

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Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Fundação Universitária de Cardiologia do Rio Grande do Sul under the protocol number 101593/2013-9. 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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Cognitive Deficit in Heart Failure and the Benefits of Aerobic Physical Activity

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Abstract

Heart Failure is a clinical syndrome prevalent throughout the world and a major contribution to mortality of cardiac patients in Brazil. In addition, this pathology is strongly related to cerebral dysfunction, with a high prevalence of cognitive impairment. Many mechanisms may be related to cognitive loss, such as cerebral hypoperfusion, atrophy and loss of gray matter of the brain, and dysfunction of the autonomic nervous system. The literature is clear regarding the benefits of aerobic physical activity in healthy populations in the modulation of the autonomic nervous system and in brain functions. Studies have shown that in the population of patients with heart failure, exercise is associated with an improvement in cognitive function, as well as in cardiac autonomic regulation. However, little emphasis has been given to the mechanisms by which aerobic physical activity can benefit brain functioning, the autonomic nervous system and result in better cognitive performance, particularly in patients with heart failure. Therefore, the present work presents the ways in which brain areas responsible for cognition also act in the modulation of the autonomic nervous system, and emphasizes its importance for the understanding of cognitive impairment in relation to the pathophysiology of heart failure. It is also described the way in which aerobic physical activity can promote benefits when it is integrated into the therapy, associated to a better prognosis of the clinical picture of these patients.

Heart Failure (HF) accounts for about 50% of all hospitalizations occurring in South America[1] and is one of the most frequent causes of hospitalization for cardiovascular diseases.[2] In addition to the direct influence on cardiac autonomic control, HF is strongly related to the presence of cerebral dysfunction and cognitive impairment, affecting approximately 75% of this population.[3] This cognitive deficit is associated with executive functions, including difficulties in the planning and execution of actions, low ability to solve problems and inhibit behaviors.[4] In practice, this results into less ability to perform daily activities such as shopping, feeding and locomotion - including walking - in addition to being related to lower self-care levels, higher hospitalization rates, increased expenses with more frequent hospitalizations, and, finally, there is an increase in morbidity and mortality in this pathology. In this sense, several treatments are performed in order to mitigate the deleterious effects caused by HF. However, such treatments usually involve invasive and / or medicamentous procedures such as heart transplantation, left ventricular assist device, beta-blockers, aldosterone antagonists, and angiotensin converting enzyme inhibitors. All these drugs, despite having proven beneficial results, can develop several types of side effects such as renal failure and hyperpotassemia.[2] In this sense, physical exercise has been pointed out as an important auxiliary tool in the treatment of patients with HF, however, little has been analyzed about its benefits to brain function. In the present work, the pathways by which the prefrontal cortex (PFC) is closely linked to the regulation of cardiac autonomic control and its influence on cognitive impairment in HF patients are presented. In addition, it is described how the regular practice of physical activity can promote benefits to brain function and cognitive performance in this population, as well as the contribution on cardiac autonomic control already widely described.

In the search for the genesis of this problem, many mechanisms may be related to cognitive loss, such as cerebral hypoperfusion, atrophy and loss of gray matter of the brain, as well as autonomic nervous system (ANS) dysfunction.[5] A neuroimaging study in FC II patients found that individuals with this syndrome had impairment in several brain areas such as the hippocampus (short-term memory conversion in long-term memory), caudate nucleus (modulation of body movements), PFC (executive functions: decision-making, planning, inhibitory control) and hypothalamus, fundamental areas in cognitive processes and autonomic control.[5] In this perspective, it is worth mentioning the existence of a recent pathophysiological model of cognitive decline in this population, which states that a set of factors such as hypoperfusion, hypoxia, inflammatory cytokines increase, thromboembolic diseases and hemodynamic abnormalities can lead to brain mass atrophy, generating cognitive deficits.[6] Another important point to emphasize about the pathophysiology imposed by HF is the severe dysfunction in ANS, characterized by increased sympathetic tone and decreased parasympathetic[7] and may be related to vasoconstriction.[8] As a consequence of this autonomic balance with sympathetic overlap, there is difficulty in the arrival of blood in various systems of the body, including the brain. Cerebral hypoperfusion in patients with HF may lead to reduced functional capacity[9] and cognitive deficits.[5] More specifically, permanent impairment of cerebral perfusion and chronic ischemia in deep areas may result in cognitive impairment and difficulty performing

Keywords

Heart Failure; Indicators of Morbidity and Mortality; Cognition; Exercise.

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routine activities. The hippocampus, for example, has neural plasticity in front of the lower supply of oxygen and may have decreased mass and possibly cause memory impairment.[10]

It has been demonstrated that FC I-III patients have low cerebral blood flow (CBF) in the sitting position and this is related to low cardiac output, which can cause intense hypoperfusion in the accomplishment of simple tasks, such as the act of leaving a position lying to a sitting.[9] Therefore, with less supply of oxygen to the brain, cognitive impairments are virtually unavoidable. In addition, it has already been observed that the degree of cognitive dysfunction may serve as a predictor of cardiovascular complications in patients with HF. In the study, 246 FC II - IV patients performed the Montreal Cognitive Assessment to evaluate cognitive ability and it was shown that the worst performance in the test was those with the greatest possibilities of cardiovascular events in up to 180 days.[11] Thus, cognition seems to be closely related to the degree of cerebral oxygenation, and the more hypoperfused the brain, the greater the dysfunction of the nervous system, indicating a greater impairment in cardiac output and a lower ability to modulate autonomic activity, increasing the risk of cardiovascular and cerebrovascular events.

Literature is clear on the benefits of aerobic physical activity (APA) in healthy populations, on SNA modulation, and on brain and cognitive functions. Evidence shows that chronically performed APA has the potential to promote beneficial effects on cardiovascular health, mediated by increased vagal tone and decreased sympathetic activity in the sinus node, with improved vascular function, cardiac remodeling, and renal-adrenal functions.[12] However, regular APA has also demonstrated an important role in the modulation of some brain regions of fundamental importance in cognitive processes, through the increase of CBF in PFC,[13] increased volume in the hippocampus,[10] increased concentrations of vascular endothelial growth factors (VEGF) (new capillary growth) and brain-derived neurotrophic factor (BDNF) (strengthening of synaptic connections)[14], as well as angiogenesis in lobofrontal regions.[15] Therefore, these functional, biochemical, and morphological changes in the brain are strongly linked to cognitive improvement.

Following this line of reasoning, in a study with FC III patients and ejection fraction ≤ 35%, an 18 week intervention (twice a week) of physical exercises was performed alternating between treadmill, cycle ergometer and stair simulator. The results demonstrated that exercise improved the cognitive functions of selective attention and psychomotor speed.[16] In addition, the performance of the six-minute walk test and the Mini Mental State Exam score have been directly correlated, indicating that the lower the functional cardiovascular capacity of the subject, the lower their cognitive ability.[17] In the meantime, it is worth mentioning that patients usually leave the doctors' offices having heard that the practice of physical exercises is important to combat the sedentary lifestyle, improve the function of the heart muscle and, therefore, become healthier and with a better quality of life. However, the low emphasis on cognitive benefits and the improvement in brain function that physical activity can provide for HF patients is of concern.

In this context, a recent review addresses the practice of APA as a beneficial factor in preventing and even reversing the cognitive impairment caused mainly by the decrease in CBF in this population. This benefit would be a consequence of both the improvement in cardiac muscle contractile activity and the decrease in peripheral vascular resistance due to a decrease in sympathetic activation.[18] Furthermore, the possible effects of APA on the ANS of patients with heart disease have been demonstrated, as in the case of HF, indicating the possible sympatovagal modulation with increased parasympathetic tone and a decrease in sympathetic activity, which is an extremely important and decisive clinical condition for this population.[19] However, little emphasis was given to the integration between the CBF and the autonomic nervous system, as well as in the modulation of the ANS as a result of exercise in patients with HF, besides the possible integration pathways resulting from this modulation of the ANS and its influence on activity in general, implying greater benefits for the individual.

The pathways through which frontal regions, such as the PFC, act in the modulation of the ANS are important for the understanding of the pathophysiology of HF, as well as to understand how the APA can interfere in these two aspects (cognition and cardiac autonomic control). In this sense, a neurovisceral model was proposed by which the PFC has an inhibitory function on the amygdala[20] (an integrative area that receives sensory afferents, confers an emotional characteristic and emits eferences to cortical areas). However, when this region is uninhibited, a situation that can occur due to the lower CBF in the PFC, allows the activation of sympathetic neurons and a decrease in the action of parasympathetic neurons, both in the brainstem[20], triggering a nervous autonomic balance with sympathetic predominance. It is known that APA plays an active role, especially in CPF[13] and autonomic modulation[12], creating a feedback system in which APA acts in several spheres, culminating in the cognitive improvement of patients (Figure 1) and, consequently, improving the prognosis.

Thus, it can be observed that the damages caused in the cognitive aspects are often reversible and, therefore, possible to improve the executive functions,[18] increasing the quality of life of these patients. It is worth mentioning, then, that APA is a useful tool as part of the treatment of these patients, besides being a non-pharmacological alternative and low cost. Although APA is easy to perform in healthy subjects, the same cannot be said for patients with HF. FC IV patients, for example, are not advised to perform physical activity. In addition, some procedures should be done before the practice, such as performing the maximum effort test for physical and clinical condition analysis. The prescription should be made based on evaluations performed periodically by the cardiologist and on the risk stratification of the patient and the practice should not be performed without supervision.[2]

Therefore, the importance of physical activity in a much broader context that goes beyond the improvement of the heart, which is the benefit of the brain function of patients with heart failure, through functional and morphological

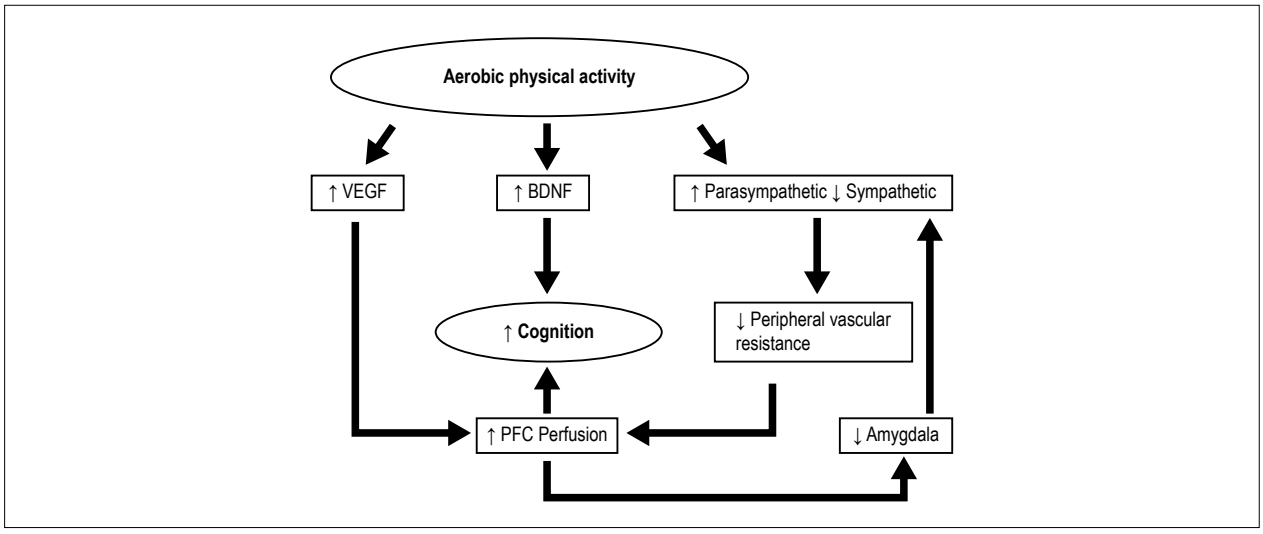

Figure 1 – *Aerobic physical activity promotes an increase in the concentrations of VEGF and BDNF, which can improve cognitive processes, increase the parasympathetic tone, and decrease the sympathetic activation. This condition may decrease peripheral vascular resistance and lead to increased cerebral blood flow in the prefrontal cortex, positively interfering with cognitive ability. With increased cerebral blood flow in the prefrontal cortex, there may be an inhibition of the amygdala promoting a vagal increase and sympathetic decrease, feedback system. VEGF: vascular endothelial growth factor; BDNF: brain-derived neurotrophic factor*

changes in the brain and ANS, is clear, implying greater efficiency in cognitive processes. Therefore, it is valid to emphasize once again the prescription of APA with a focus on cognition, with the justification of enhancing performance in the basic and instrumental activities of this population and explaining its practical benefits and its contribution to the possibility of greater well-being of the patients during the evolution of the clinical condition.

Finally, in addition to combating sedentary lifestyle and improved heart muscle, APA prescription should be focused on cognitive benefit, with repercussion in the management of possible daily limitations, such as shopping, compromising understanding, communication and interpersonal relationships. This can be a way to increase the patient's adherence to this therapeutic component, aiding in his treatment and bringing more benefits and quality of life.

Author contributions

Conception and design of the research, Writing of the manuscript and Critical revision of the manuscript for intellectual content: Rêgo MLM, Cabral DAR, Fontes EB.

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Case 1/2018 – Preponderant Left Ventricular Restrictive Syndrome in a 28-Year-Old Woman

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Clinical data: Increase in size of the left atrium known since 8 years of age, when she was labeled as carrier of idiopathic left ventricular restrictive syndrome. Since then, there was a progressive increase of this cavity with the appearance of fatigue to the efforts and atrial fibrillation five months ago, reversed in the occasion with electric shock and amiodarone. Despite a high dose of this drug, 400 mg/day, heart rate remained elevated, around 100 bpm, having developed thyroid dysfunction with TSH elevation and hormone diminution. The arrhythmia reappeared two months later and led to new clinical research.

Physical Exam: eupneic, acyanotic, normal pulses, HR = 96 bpm, BP = 100x70 mmHg.

Venous impulses in the neck. In the precordium, there were no impulses, normal heart sounds, no audible murmurs. Third sound sometimes inconstant. Clean lungs. Abdomen unchanged.

Additional tests

Chest X-ray: normal cardiac area with a clear increase of the left atrium in a double atrial contour and a more prominent pulmonary vascular weave in the upper fields (Figure1).

Electrocardiogram: atrial flutter and right bundle branch conduction disorder with rr1 morphology in V1. AQRS = +70° AT = + 110°.

Echocardiogram: exclusive increase of the left atrium. Ao = 28, LA = 53, RV = 22, LV = 40, septum = 8, posterior wall = 10, LVEF = 68%, SPRV = 53 mmHg. Enlarged superior vena cava without ventricular dyskinesias (Figure 1).

Magnetic nuclear resonance: no fibrosis in late enhancement.

Cardiac catheterization: showed signs of restriction to left ventricular filling with discrete pulmonary hypertension. LA = 12, RV = 35/10, PA = 35/20-28, Wedge = 20, LV = 80/5-18, Ao = 80/50-64, CO = 3.1 l/m, PVR = 2.58 W, SVR = 16.75 W Angiography clearly emphasized the left atrial emptying delay, right ventricular hypertrophy, and the left ventricular endocardial smooth wall (Figure 1).

Endomyocardial biopsy of the RV septum: Five fragments of the right ventricle myocardium with elastic consistency and brownish, measuring 4x3x1 mm, showed moderate and diffuse hypertrophy in cardiomyocytes, moderate and focal interstitial myocardial fibrosis, absence of inflammatory infiltrate, absence of amyloid protein deposition by the Red Congo histochemical method, negative histochemical investigation of glycogen and neutral mucopolysaccharides, and acids by the periodic acid method of Schiff, with and without diastase.

Clinical diagnosis: idiopathic restrictive syndrome with isolated increase of the left atrium size with atrial flutter and pulmonary hypertension, in addition to hypothyroidism due to the use of high dose of amiodarone.

Clinical reasoning: In an initially asymptomatic patient with an even slight increase in the left atrium, without other commemorative ones, the diagnosis of restrictive left ventricle syndrome becomes imperative. The progressive increase of this cavity further accentuates this diagnosis, even more with the advent of pulmonary congestive symptoms expressed by dyspnea, physical fatigue and enlargement of the pulmonary vascular network, in addition to the appearance of atrial flutter. Restrictive syndromes are classified into myocardial, non-infiltrative idiopathic, infiltrative amyloidosis type, sarcoidosis, Gaucher and Huler disease; storage diseases such as hemochromatosis, Fabry disease and glycogen storage. We can also mention the endomyocardial ones with fibrosis, eosinophilic syndrome, the carcinoid, those by irradiation, of malignant tumors and by anthracycline toxicity.

Differential diagnosis: symptoms of fatigue, atrial size increase, pulmonary arterial hypertension and ventricular diastolic dysfunction, assure the diagnosis of restrictive syndrome. Therefore, the cause should immediately be sought from those exposed above, through diagnostic imaging, allied to cardiac biopsy. Treatment depends on the cause, corticosteroids on sarcoidosis, chelation on hemochromatosis.

Conduct: having found mild pulmonary arterial hypertension, there was an indication for the use of metoprolol 100 mg/day adrenergic beta-blocker in order to improve the ventricular filling and to decrease the heart rate after the obligatory suspension of amiodarone. Atrial flutter ablation was also indicated to improve ventricular filling and to prevent the left atrial enlargement. Routine clinical follow-up aims to preserve the current condition in order to postpone cardiac transplantation.

Comments: The main characteristic of the restrictive syndrome is diastolic filling difficulty, with normal ventricular volume and more rigid ventricular walls despite normal thickness, and also with preservation of systolic function. Therefore, it provokes proportional increase of the left atrium, congestion and pulmonary arterial hypertension. Therapeutic options are rare and ineffective and cardiac transplantation should be considered in advanced phases.[1,2] Left atrial septum decompression by atriosseptostomy has been considered in order to reduce congestion and

Keywords

Cardiomyopathy, Restrictive; Atrial Fibrillation; Electroshock; Ventricular Dysfunction Left; Hypertension, Pulmonary.

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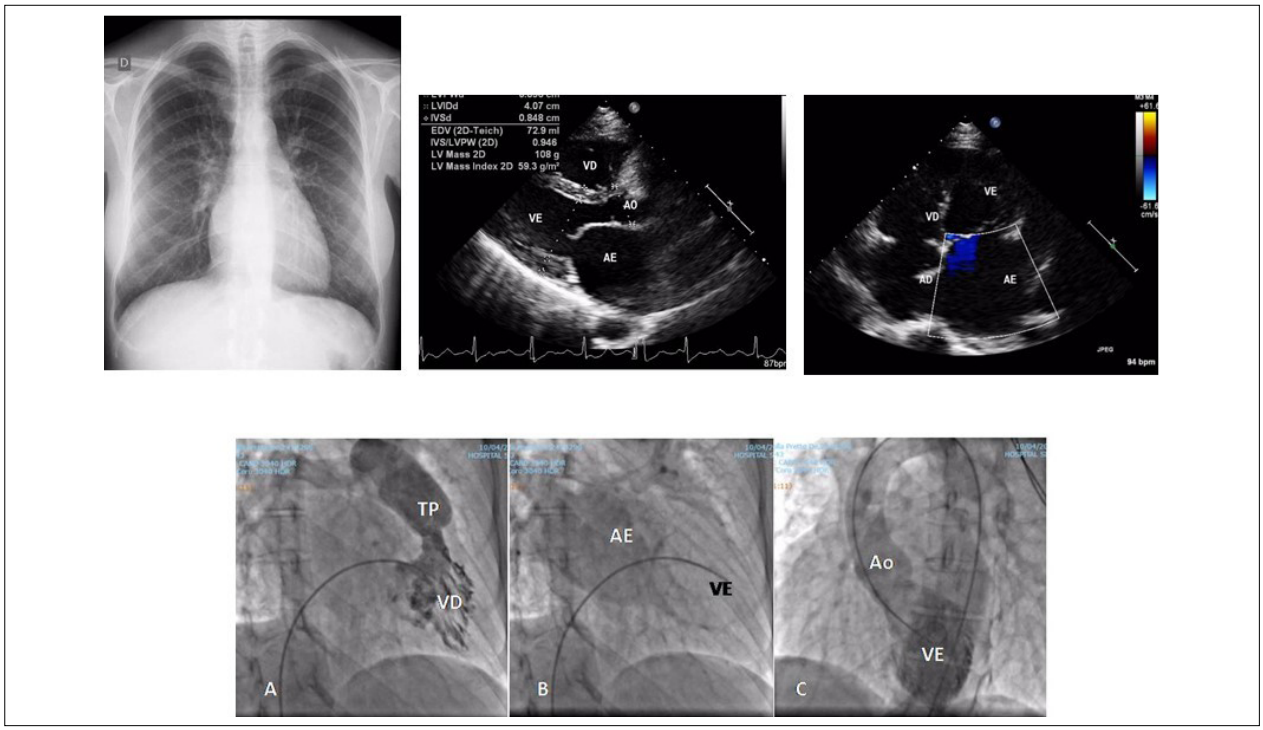

Figure 1 – *Chest X-ray in AP emphasizes normal cardiac area with a clear increase of the left atrium size in a double contour in the lower right arch and slightly congested pulmonary vascular weave in the upper fields. The echocardiographic images highlight the left atrial enlargement in longitudinal and 4-chamber projection. Angiocardiograms below show right ventricular hypertrophy (A), left atrial emptying delay (B) compatible with left ventricular restrictive syndrome and this cavity with smooth and normal-sized internal borders (C).*

pulmonary hypertension, allowing to postpose the indication for transplantation.[2] It is the least common cardiomyopathy of all types. The genetic spectrum points to mutations in sarcomeric genes in half of the cases.[1] Evolutionarily, sudden death occurs in 80%, heart failure in 15%, infective endocarditis in 5%, predominantly below 20 years of age.

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Pregnancy in Woman with Kawasaki Disease and Multiple Coronary Artery Aneurysms

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Introduction

Kawasaki disease (KD), first described in 1967, is a systemic vasculitis of unknown cause.[1] It is an important cause of cardiac diseases in children aged younger than five years.[2] KD is an autoimmune disorder whose clinical features include high fever, exanthema, conjunctivitis, cervical linfadenopathy and peripheral edema. Laboratory tests are compatible with acute inflammatory condition.

KD predominantly affects the coronary arteries, which is the most important clinical manifestation of the disease, varying from dilation and stenosis to aneurysm (incidence of 5% in patients with adequate treatment, and 25% in untreated patients). Giant coronary artery aneurysms (CAAs), i.e., CAAs with diameters > 8 mm, are associated with increased risk of thrombosis, acute myocardial infarction (AMI) and sudden death.[2]

Lack of diagnosis and treatment of KD at its acute phase during childhood contributes to increased prevalence of pregnant women with vascular sequelae of KD.[3] Management of these patients has not been established, especially in symptomatic patients and, in existing literature, premature labor has been performed in these cases. There are no Brazilian reports on the theme, which are more commonly found in the American and Japanese literature.

The aim of this study is to describe a successful management of a patient with giant CAA, sequela of KD with thrombotic complication, from the first trimester of pregnancy until term birth.

Case report

A 32-year old patient was admitted to the emergency care at week nine of first pregnancy, with dyspnea and slight, precordial pain during great efforts, of short duration and well tolerated. The patient had a history of ST-elevation myocardial infarction of inferior wall at the age of 30, with giant aneurysms and coronary artery thrombosis evidenced by coronary angiography (Figure 1C and 1D). The patient underwent coronary computed tomography angiography, which confirmed the previous findings, with evidence of coronary artery ectasia with multiple aneurysmatic dilatations and mural thrombus (Figure 2). The patient received the diagnosis of KD and was referred to outpatient follow-up. At the occasion, the patient was using simvastatin, clopidogrel, atenolol and acetylsalicylic acid (ASA). At physical examination on admission, the patient was eupneic, with blood pressure of 110/60 mmHg, heart rate of 80 bpm, normal heart sounds without murmurs, normal pulmonary auscultation, abdomen free of abnormal signs, and normal pulse rate. Regarding complementary tests, electrocardiography showed sinus rhythm with diffuse ventricular repolarization; transthoracic echocardiogram is depicted in Figure 1A and 1B.

Despite recommendations received in outpatient visits on contraindications for pregnancy, the patient got pregnant, and a close monitoring of the patient was started. A daily dose of 100 mg of ASA, 60 mg of propranolol and 40 mg of enoxaparin were prescribed, and routine obstetric exams showed normal fetal vital signs. After 29 weeks of pregnancy, the patient had progressive worsening of cardiac function to New York Heart Association (NYHA) class III, with daily, atypical palpitations, which caused the patient to get a sick leave to rest at home.

During the week 34, the patient had diffuse chest pain, dyspnea and uterine contractions. The patient was then hospitalized for a rest and adjustment of medication. Obstetric examination revealed irregular, weak contractions, fundal height of 33 cm, impenetrable cervix, a single fetus in longitudinal position, cephalic presentation, regular heart beat at 128 bpm. Fetal assessment was performed by fetal biophysical profile and normal doppler velocimetry of umbilical arteries. Estimated fetal weight was adequate (percentile of Hadlock growth curve). There was a marked improvement in clinical and obstetric conditions as result of adjustments in propranolol (80 mg/day orally) and enoxaparin (60 mg/2x day subcutaneously) doses, as well as administration of sublingual nitrate (only if needed) and vaginal tablets of natural micronized progesterone (200 mg/2x day). There were no changes in electrocardiographic or echocardiographic patterns during hospitalization. At week 37, cesarean section and tubal ligation were indicated. The procedure was successfully performed by the Central Institute obstetric staff at the Heart Institute (InCor) of the General Hospital of the University of Sao Paulo Medical School. Newborn was born healthy, weight 2,860 g, appropriate for gestational age, Apgar score of 9 and 10 at fifth and tenth minute of life, respectively. Tubal ligation was performed following delivery, with previous consent of the spouse. Enoxaparin was discontinued 12 hours before and restarted 24 hours after cesarean section. Forty-eight hours later, warfarin was prescribed and readjusted until the prothrombin international normalized ratio (INR) was 2;

Keywords

Pregnancy; Mucocutaneous Lymph Node Syndrome; Coronary Aneurysm.

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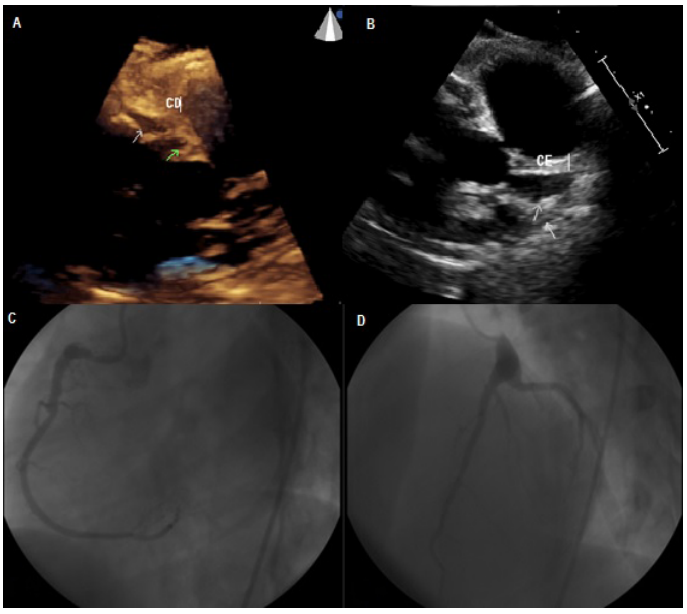

Figure 1 – *(A and B) Echocardiography: ejection fraction 68%; left atrium 35 mm; septum 8mm; posterior wall 8mm; left ventricular diastolic diameter 45mm; left ventricular systolic diameter 30 mm; PSAP 40 mmHg. Dilatation of left coronary artery (7 mm). Left ventricle with preserved systolic function and myocardial thickness, with no changes in segmental wall motion. (C and D) Cardiac catheterization (10/2013): coronary artery ectasia. Dominant coronary with 50% proximal, eccentric tubular lesion and coronary thrombosis; left coronary artery trunk with aneurysmatic dilatation at the distal third; anterior descending artery with ectasia at the proximal third, without obstructive lesions. Circumflex artery with proximal ectasia, without obstructive lesions.*

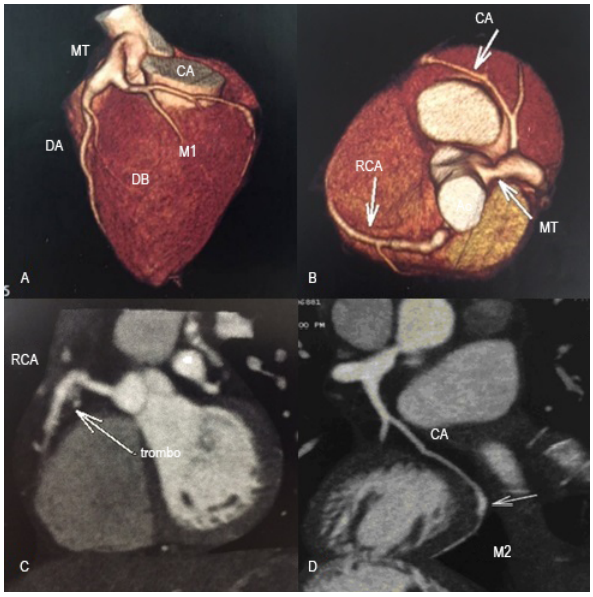

Figure 2 – *Coronary computed tomography angiography showed aneurysm at the distal third of the left coronary artery trunk (9mm) and anterior descending artery ostium (9.5 mm); circumflex artery with ectasia at the ostium (3.7 mm); marginal branch 2 with aneurysm at the distal segment; right coronary artery with saccular aneurysm (9.8 mm at the greatest diameter), mural thrombus and small regions of calcification. Total score of 23.81 (Agaston) and 38.59 (Volume). MT: main trunk of the left coronary artery; DA: anterior descending artery; DB: diagonal branch; CA: circumflex artery; M1: left marginal artery; M2: second marginal branch of circumflex artery; RCA: right coronary artery; LA: left atrium; Ao: aorta*

at this time, enoxaparin was suspended and the patient was discharged. At the clinical visit 60 days thereafter, the patient was asymptomatic, breast feeding and using warfarin (INR = 2) and ASA (100 mg/d).

Discussion

In the present case, strategies for prevention of complications of giant CAAs secondary to KD and acute infarction were successful in terms of maternal-fetal health.

Preventive therapy was planned during patient's first medical visit at week 9 of pregnancy. The strategy consisting of outpatient follow-up, hospitalization and delivery with interventional support at a cardiology hospital was chosen because of patient instability. However, such procedure is not considered routine in the literature in symptomatic patients.[3]

We also considered the influence of the hyperkinetic, hypercoagulable state of pregnancy on the occurrence of expected complications (thrombosis, myocardial infarction and sudden death) in this patient. The potential risk of arterial rupture and/or dissection is increased with presumed arterial changes including fragmentation of reticular fibers, decrease in mucopolysaccharide content and loss of normal elastic fiber structure.[4]

In the study by Wei et al.,[5] that included 38 cases of KD, thrombosis was seen in 17 patients, which has been hypothesized to be caused by insufficient anticoagulant therapy. In a meta-analysis including 159 children with giant CAA, Su et al.[6] reported that coronary occlusion, AMI and death were significantly lower in children treated with warfarin plus aspirin than in those treated with aspirin alone. In this line of thought, the progressive activation of coagulation factors in the second half of pregnancy, and the maximum activation at delivery made the authors recommend anticoagulation with dose adjustment combined with ASA. Enoxaparin was used in place of warfarin during pregnancy due to risk of hemorrhage and fetal toxicity, in prophylactic dose until week 34 and then therapeutic dose until 12 hours before delivery. The drug was then restarted until warfarin was reintroduced for maintenance of INR within target range.

The history of myocardial infarction increased the pregnancy risk, although ventricular function was preserved and was favorable to patient's progression. Increased myocardial metabolic demand, due to increased cardiac output and oxygen consumption related to pregnancy, was the cause of frequent complaints of angina and dyspnea, which were controlled by propranolol. At 60 mg/day, the drug did not affect fetal growth until week 32 of pregnancy. Arterial hypotension, resulting from a decrease in peripheral vascular resistance, limited the use of nitrates for the supposed risk of decreased uteroplacental blood flow.

During the third trimester of pregnancy, high-amplitude uterine contractions (Braxton Hicks) become more frequent and may be confused with premature labor, accounting for 75% of births before week 37 of pregnancy.[7] These contractions cause oscillations in venous return and in heart rate, and may cause instability in women with limited cardiac reserve, which was the cause of hospitalization of the patient in the week 32. Together with the obstetrician, a decision was made to not anticipate delivery, adjust medication for control of clinical obstetric symptoms until fetal maturity was reached.

With respect to the type of delivery chosen, a study on 13 women with KD[8] and coronary artery lesions, showed that vaginal deliveries under epidural anaesthesia in 9 patients, and caesarean section was performed in 3 symptomatic patients. These data corroborate the clinical decisions made in this case. Also, tubal ligation was chosen as the safest contraceptive method due to contraindications of a new pregnancy.

Conclusion

This report added to the literature one case of successful term pregnancy in a symptomatic patient with multiple CAAs secondary to KD and history of myocardial infarction. The study illustrated the importance of the multidisciplinary approach to reach the full-term of a high-risk pregnancy. However, family planning, including counseling on genetics and possibility of a new pregnancy, is still essential. The risk of complications cannot be neglected regardless of the therapeutic strategy adopted.

Author contributions

Conception and design of the research: Avila WS; Acquisition of data: Avila WS, Freire AFD, Soares AAS, Pereira ANRE; Analysis and interpretation of the data and Writing of the manuscript: Avila WS, Freire AFD, Soares AAS; Critical revision of the manuscript for intellectual content: Avila WS, Nicolau JC.

Potential Conflict of Interest

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Cor Triatriatum Sinistrum

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A 25-year-old male presented to clinic with complaints of palpitations. Transthoracic echocardiogram (TTE) showed presence of a membrane in left atrium suggestive of cor triatriatum [Figure 1A]. This finding was confirmed with transesophageal echocardiogram (TEE), which revealed a membrane in the left atrium attaching at the Coumadin ridge and the atrial septum, just caudal to the fossa ovalis [Figure 1B].

Cor triatriatum sinistrum (CTS) is a rare congenital malformation in which the left atrium is divided into two chambers by a fenestrated fibro-muscular septum. The posterior proximal left atrial chamber receives the pulmonary veins and the anterior distal left atrial chamber contains the mitral valve and left atrial appendage. Cor triatriatum accounts for 0.1% to 0.4% of congenital heart defects. This defect generally manifests during infancy and early childhood. However, some cases present well into adulthood as in our patient. The most common presenting symptoms are dyspnea, orthopnea, hemoptysis, palpitations and chest pain. Although cor triatriatum can be an isolated lesion as in our patient, it is frequently associated with other congenital cardiovascular anomalies, most often ASD. Echocardiography is the mainstay for diagnosis. CTS is first suspected by the presence of a linear structure in the left atrium on TTE. TEE is used for better visualization of the membrane, measurement of gradients across the membrane and to recognize ASD. In symptomatic patients, management consists of resection of the diaphragm and correction of the associated congenital heart defects. Conservative approach is often implemented in asymptomatic adults.

Keywords

Cor Triatriatum; Heart Defects, Congenital; Echocardiography, Transesophageal.

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Conception and design of the research and writing of the manuscript: Raheja H, Namana V; Acquisition of data: Raheja H; Critical revision of the manuscript for intellectual content: Raheja H, Namana V, Moskovits N, Hollander G, Shani J.

Potential Conflict of Interest

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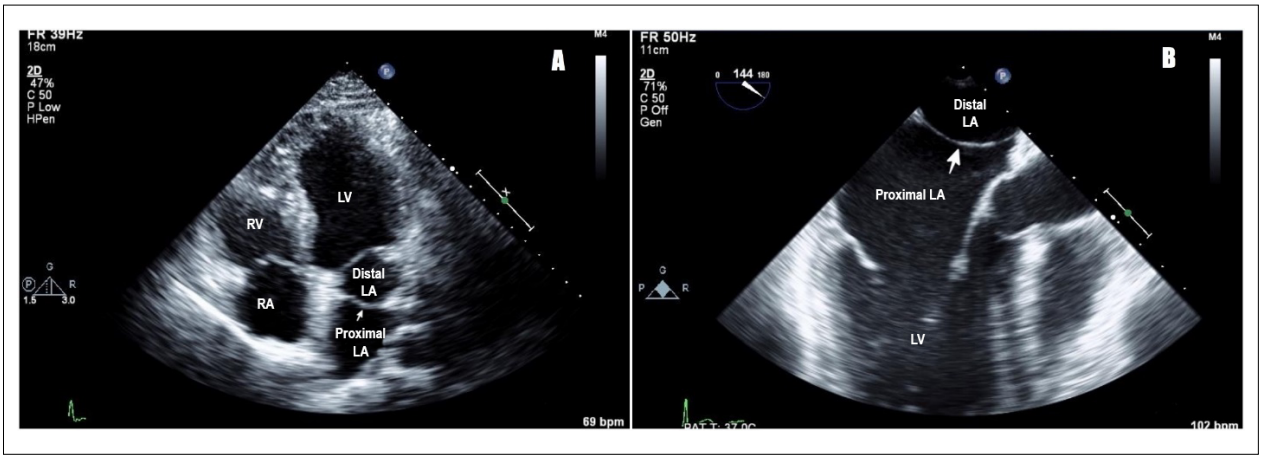

Figure 1 – *A) Transthoracic echocardiogram showing cor triatriatum: proximal and distal left atrium separated by a membrane (Pointing white arrow), LA: left atrium; LV: left ventricle; RV: right ventricle; RA: right atrium. B) Transesophageal echocardiogram showing cor triatriatum: proximal and distal left atrium separated by a membrane (Pointing white arrow), LA: left atrium; LV: left ventricle.*

Cardiac Cachexia – A Window to the Wasting Disorders

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To The Editor

I read with interest the recent review by Okoshi and colleagues in the journal.[1] This was a thoroughly enjoyable read that reviewed the main areas of focus. I would like, however, to reinforce some of the arguments. In the section on neurohormonal blockade there has also been a successful phase 2 trial of the fourth generation beta-blocker espindolol in cancer cachexia.[2,3] Clearly beta-blockers can be helpful also in cardiac cachexia given their crucial role in heart failure in general. Other cardiovascular drugs are also being explored for their beneficial or protective effects on skeletal muscle. These include, as the authors point out, the ACE inhibitor Imidapril. Others including trimetazidine are also being studied.[4] One issue of difficulty is that we are starting from the point of no effective therapies and testing therapies one by one. The true multi-system complexity of cachexia and yet its similarity across different organ failure syndromes implies it will be a multi-barrelled approach that may be needed to solve it. We may need to combine neurohormonal blockade, immune modulation, nutritional and exercise support with pro-anabolic agents to get real clinical benefits. Perhaps as the authors point out Cardiac Cachexia where several of these agents are already on board may be a good place to start. The time for a much greater focus on all cachexias, including of course cardiac cachexia, is truly here and now.[5]

Keywords

Cachexia; Wasting Syndrome; Exercise; Nutritional Physiological Phenomena.

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Reply

We truly appreciate the comments on our review manuscript published in the journal.[1] The authors reinforced our point of view by citing some papers published after the submission of our manuscript. We agree that we should immediately initiate a greater focus on cachexia of all causes aiming its prevention and treatment. While nutritional support has been long recommended for cachexia management, only more recently was exercise highlighted as a tool to manage muscle wasting and sarcopenia.[2-4] As correctly pointed out, due the capacity to prevent body weight loss in heart failure patients with reduced ejection fraction, neurohormonal blockade has also been evaluated in non-cardiac cachexia. However, concerning other therapies such as immune modulation and pro-anabolic agents, there is no convincingly evidence for a positive response[3,5,6] suggesting that additional studies are needed before we can effectively prevent and treat cachexia associated with different diseases including chronic heart and renal failure, cancer, and chronic obstructive pulmonary disease.

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