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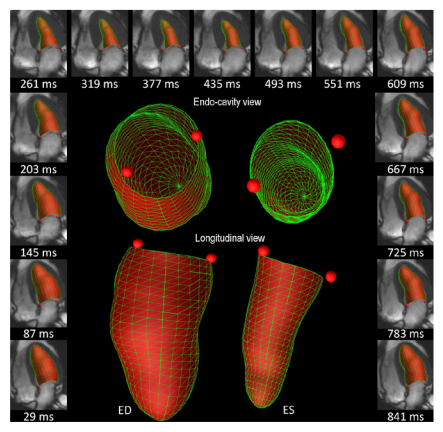

Figure 3 – *Three-dimensional displays of the model fits throughout the cardiac cycle in one R-R interval of 870 ms (outside images) for volume- and derivative-curve assessment (mL/s). Septal and lateral guide points motion can be evaluated through time, calculating the distance between the defined point and the model apex for myocardial longitudinal relaxation rate (mm/s). The endocardial surface is shaded in red and drawn with green lines. Page 555*

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The Concept of Clinical Economics and its Relation with Effectiveness

Franz Porzsolt[1,2] and Luis C. L. Correia[3,4]

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Clinical Economics should be an essential component of medical education and practice. In defining Clinical Economics, we should make clear that economical thinking is not primarily a monetary issue.

A classical economic analysis considers four aspects: first, the costs, i.e. what somebody has to give away; second, the consequences, i.e. what somebody gets back; third, the comparison of the relation of both costs and consequences of alternative ways of actions; fourth, the perspective of the person who makes the economic analysis.

To provide an example we start with the perspectives. From a patient's perspective, the alternative ways of action may be either immediate surgery or watchful waiting if there is a realistic chance of spontaneous regression. The costs for the patients will be an increased risk of complications in case of watchful waiting. The consequence (advantage for the patients) in this situation is the chance to avoid surgery. The perspective of the hospital manager will be different. He will also consider costs and consequences, but of different types, such as monetary costs and monetary consequences. Doctors and managers of a hospital have to do different jobs and to make different decisions. In some places the same person is responsible for both decisions. This is like somebody who is playing chess against himself.

Economic decisions are based on values, and values are different in different people. Clinical Economics is focusing on the from the perspectives of patients and doctors, but not from the perspectives of managers. It is obvious that no hospital will survive and no healthcare system will be affordable unless the perspectives of economists, managers and politicians will be considered. The difficult consensus process among people with different perspectives and values is shown in Figure 1.

Before thinking monetarily, physicians and patients need to figure out how much they have to give away (the costs) and what they get back (the consequences or benefit). Clinical investment is the "cost" a patient pays for accepting a treatment, such as pain, side effects, time spent, possible adverse events, or psychological distress. The "profit" is the value the patient gets back from his or her investment. Usually physicians do not consider this trade off, disregarding how much is the investment and overestimating the returned value (effect size). In addition, price and profit vary according to patient preferences. The value a pianist takes from a surgical repair of his or her hand is much higher than the value a lawyer would take back from the same surgery, because the proper function of the hand is more important to the first.

Clinical Economics is about efficiency, which can be defined as a cost-effective trade-off. A key moment in the history of Clinical Economics was the question of my teacher at the Ontario Cancer Institute in Toronto/Ontario about the German word for 'efficiency'. He was amused when I mentioned the word "Effizienz" in my response to him. He concluded the word 'efficiency' does obviously not exist in the German language. This terrible conclusion was a real strong motivation to demonstrate what efficiency means from a German perspective. Our group started to clarify the difference of efficacy and effectiveness and its relation to efficiency that was by far not as clear 20 years ago as it is today.

Efficacy versus Effectiveness

We underlined that efficacy and effectiveness describe two different types of information: efficacy is the demonstration that a new principle can theoretically work, which comes from studies under ideal controlled conditions; effectiveness is how the concept proven by efficacy studies works under real world conditions (RWC).[1,2] For demonstration of efficacy, one should select the optimal scenario for the proof of principle. It requires an experimental study design, with random allocation of treatments, to eliminate confounding bias and proper assessment of causality, it means the trial is explanatory.

The demonstration of effectiveness is pragmatic and takes place in the scenario in which the new principle will be used (RWC). The design is observational and treatment allocation is under the discretion and preferences of physician and patient. It allows assessment of the two main determinants of effectiveness: practical issues regarding adequate applicability of treatment and the impact of individualized choices. The interaction of these two forces determines whether the effectiveness of a treatment will be smaller than its proven efficacy (loss of beneficial effect in the real world) or whether the treatment will be even more effective than efficacious. The first situation should be a concern when logistic issues impair the treatment to be ideally applied (a not well trained doctor, a patient not educated enough to properly take an anticoagulant, a system not able to provide adequate door-to-balloon time in primary angioplasty for acute myocardial infarction), what tends to happen when the treatment is somewhat complex. The second situation takes place when physicians and patients provide a better solution than a simple randomization can do allocation.

Keywords

Clinical Trials as Topic / analysis; Cost-Benefit Analysis; Treatment Outcome.

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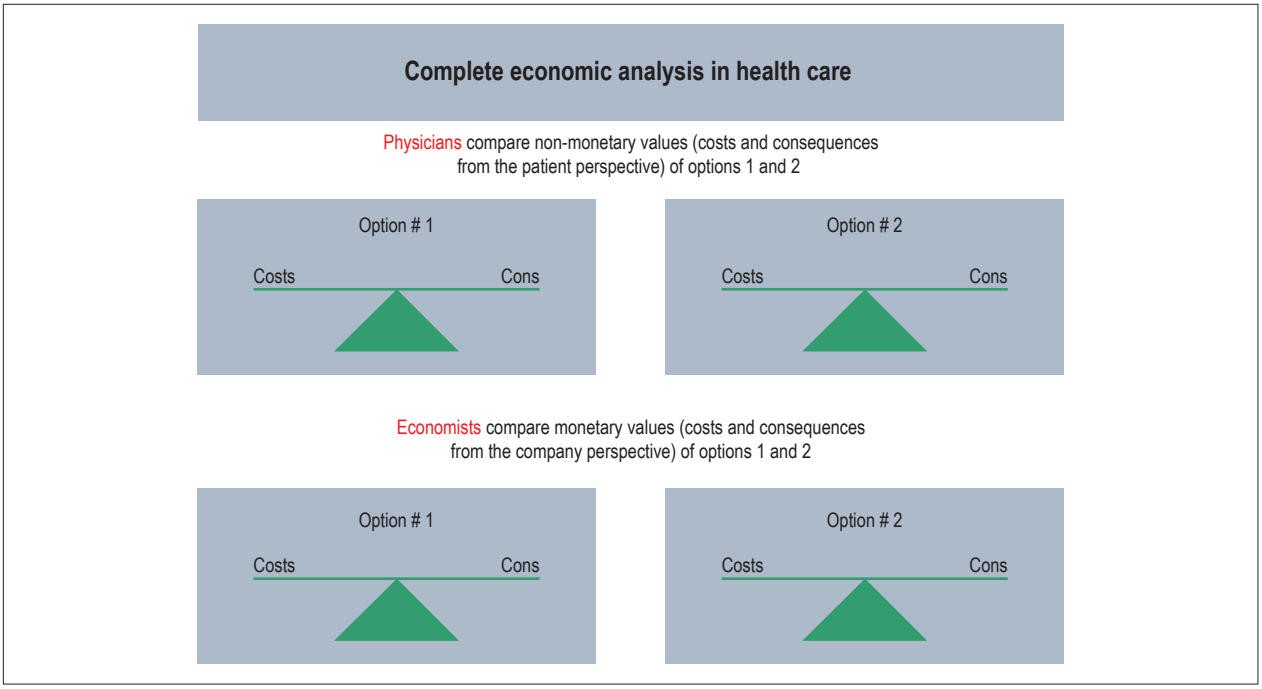

Figure 1 – *The complete economic analysis includes costs and consequences of different options. In medicine there are two important parties who's perspectives have to be considered and combined: first, the individual perspectives of the patients and their doctors and second, the natural perspectives of the patient without or with surgical operation.*

The actual effectiveness study

A pragmatic controlled trial (PCT), but not a randomized control trial (RCT), should be used for demonstration of effectiveness as a RCT can never reflect RWC.[3] To understand the contribution of PCTs to the existing RCTs we list the differences of these two trials:

1) Instead of randomization, the patients are stratified in a PCT to different risk and treatment groups.
2) The factors that characterize the risk groups are selected before start of the trial for each of the study endpoints.
3) A PCT can investigate multiple primary endpoints, e.g. mortality, specific aspects of quality of life, and cost of care, while a RCT can investigate only a single primary endpoint, but several secondary endpoints. This secondary endpoint cannot confirm or reject a hypothesis, but may generate new hypotheses.
4) The individual risks of the included patients are known in a PCT, but not in a RCT. The efficacy observed in a RCT reflects the average efficacy only related to the mix of risks in the investigated group. In a PCT, the effectiveness is described separately for each endpoint, for each risk group and for each treatment group.
5) A PCT uses inclusion, but no exclusion criteria, because a patient who meets the inclusion criteria cannot be excluded from care which may sometimes be 'wait and see' under RWC.
6) A PCT is a descriptive study in contrast to a RCT which is an explanatory study. Power calculation is not possible in a descriptive study as neither sample size, nor effect size, nor alpha-error and beta-error are known prospectively.
7) The approval by an institutional review board is necessary in a PCT for systematic collection and for publication of patient data.
8) An intent-to-treat analysis is not necessary in a PCT, as the patients cannot change the allocation to the risk group even if the treatment strategy is changed in the ongoing study.
9) The calculation of the statistical significance is not necessary for results that are clinically irrelevant. Statistical confirmation of a clinically irrelevant result is a waste of statistical power.

The bottom-line message is that RWC are essential for making reliable clinical decisions. The results obtained by RCTs under ideal world conditions are essential to justify the use of a new intervention under RWC. In addition, we need the effectiveness and the efficiency under RWC to justify a new intervention in recommendations and clinical guidelines.

We are not expecting that the described tools developed with several colleagues in the last decade[4,5] offer optimal solutions, but we hope that the offered tools and strategies will trigger a discussion on the further development of this growing discipline.

Blindness to effectiveness and overuse

The problem of *overuse* was recently addressed in *The Lancet* as one of the important challenges of the next decade.[6,7] *Overuse* takes place when useless tests or treatments are utilized, leading to *overdiagnosis* or *overtreatment*. *Overuse* is typically related to lack of efficacy. We believe the concept of *overuse* should be expanded beyond efficacy. An efficacious treatment not properly tested for effectiveness is also at risk to be an *overtreatment*. However, physicians are normally blind to effectiveness, missing the need of test for it. Especially in situations in which applicability of the treatment is complex, effectiveness studies should be mandatory to avoid *overuse*. Among other important steps in the development of evidence-based Medicine, the addition of PCTs to the existing RCTs may be an important development.

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Long-term Results of a Cardiology Postgraduate Program

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Introduction

Research and innovation help to drive economic growth and address socioeconomic challenges like poverty and health.[1] Many developed and developing countries have introduced policies and systems to increase research and innovation.

In Brazil, a system was created on 1951 with the objectives of improving technology and innovation and strengthening scientific research.[2,3] Similar to postgraduate doctorate programs in developed countries, postgraduate programs with broader and more in-depth scientific research objectives have been developed in Brazil.[4] In fact, a linear relationship has been demonstrated between the number of students graduating from these programs and the number of scientific publications produced by them.[5] Beyond scientific output, publishing a high-impact paper or in a journal with a high-impact factor seems to be an important requirement for innovation and technology growth. Considering that postgraduate students play an important role in scientific production in Brazil, a study including the characteristics of the scientific production of these students is justifiable.

We retrospectively investigated the scientific and academic production of students after their graduation from a cardiology postgraduate program. Because cardiovascular disease is the leading cause of death in developed countries and in Brazil, a postgraduate program focused on cardiology is a good target for innovation. Also, the knowledge of the characteristics, weaknesses, and strengths of a postgraduate program may help develop new strategies promoting innovation and publication in high-impact journals.

Methods

The protocol of this study was submitted to our institution's Ethics Committee on May 14, 2010, and received the number 3434/10/023. The Committee approved the study on December 15, 2010, with the number 385/10.

Objectives

The primary objective of this study was to investigate the number of publications of each graduate of a cardiology postgraduate program in Brazil and the corresponding impact factor of the journals in which the graduates' research was published.

The secondary objectives included the evaluation of the students' characteristics, *h*-index, total citations, citations per article, and academic position.

Study design

This was a retrospective study developed at *Instituto do Coração* (InCor), São Paulo. We defined as a graduate any postgraduate student obtaining a certificate at the end of the program between 1977 and 2010. The postgraduate program during the period of the study followed the rules set by the University of São Paulo for this type of program. The program was also evaluated from its beginning according to the criteria established by the *Coordenação de Aperfeiçoamento de Pessoal de Nível Superior* (CAPES, a Brazilian federal agency for the support and evaluation of postgraduate education). The students' baseline characteristics used in this study were obtained at the time of the students' registration in the program and included age, sex, and other data reported at baseline. These data were retrieved from the Cardiopulmonary Department program files in 2010.

A systematic review was carried out through a quantitative, retrospective, and documentary design for each student during the period that followed the completion of their postgraduate degree. The review included scientific papers published from 1977 to October 2015 and included in the Scopus and ISI Web of Science databases, as indicated by each postgraduate student in his or her Lattes curriculum. This curriculum is part of a Brazilian database created in 1999 and is supported by the *Conselho Nacional de Desenvolvimento Científico e Tecnológico* (CNPq) in which researchers may include information about their academic and scientific production (lattes.cnpq.br/). The name of each student was used for the review. The Lattes curriculum may also include data about the students' affiliated institutions and research teams.

Scientific papers were excluded from the analysis if comprising abstracts, medical guides, technical and scientific reports, dissertations, ministerial and government information, or any other type of document not complying with the standard IMRDC structure (introduction, methods, results, discussion, and conclusion) applied to scientific papers, except for reviews, editorials, and comments addressing cardiovascular issues published in journals indexed in PubMed. Any article in which the student was the first author or a coauthor was included in the analysis.

Statistical analysis

The data were statistically analyzed with GraphPad Prism 6 for Windows. The Shapiro-Wilk test was applied to verify the data's Gaussian distribution. Descriptive statistical analysis

Keywords

Health Postgraduate Programs; Scientific and Technological Activities; Program Evaluation.

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included simple distribution of frequencies, calculation of proportions, and median and respective interquartile ranges (IQRs). Continuous variables are expressed as median and IQR, and categorical variables are expressed as percentage. For group comparisons, Mann-Whitney or Wilcoxon tests was used, when appropriated. All tests were performed 2-tailed, and a p level < 0.05 was considered indicative of statistical significance.

Results

Characteristics of the postgraduate students

The study included 505 students who had completed the postgraduate cardiology program. Most students were male, white, and had previously obtained a medical degree (Table 1). Figure 1 shows the recent incremental increase in women as postgraduate students in the cohort. The absence of the Afro-Brazilian ethnicity is remarkable in the student population, given the high numbers of Afro-Brazilians in the Brazilian population (Table 1). Most students had no prior master's degree. Female students were younger than male ones, mainly in the last decade (Figure 2). The number of postgraduate students increased over the decades, and a recent increase in graduates without a medical degree was observed (Figure 3). We would also like to point out the low number of foreign students.

Publications and corresponding impact of the publications' journals

From 1977 to October 2015, a total of 14,398 manuscripts were published in which the cardiology postgraduate students were first authors or coauthors. Figure 4 shows the number of publications per year by all postgraduate students and the impact factor of the journals in which the articles were published. A progressive increase in the number of publications may be observed until 2007, followed by a decrease from 2008 to 2015. The journals' impact factors increased until 2011. Figure 5 shows the number of publications from 1977 to 2015 adjusted for the number of postgraduate students with a theoretical ability to publish. A decline in the number of publications may be observed from 1995 to 2000, after which it remained stable until 2013. A tendency towards a reduction in the number of publications may also be observed between 2014-2015.

Table 2 shows scientific indices and academic indicators related to the postgraduate students over the decades. The data show a small total number of articles published by year. The total number of citations was low, and the number of citations per article was not expressive. Likewise, the *h*-index was not high, according to the ISI and Scopus databases (Figure 6). Analysis of the *h*-index distribution revealed that 12.8%, 54.06%, 20.99%, 7.33%, 2.97%, and 2.57% of the students had *h*-index values of 0, 1–5, 6–10, 11–15, 16–20, and >20, respectively. University training in biology and biomedicine was associated with a lower *h*-index value and fewer published articles (Table 3). The median number of published articles and the *h*-index were higher among students with prior training in medicine ($p < 0.0001$ and $p = 0.0042$, respectively).

Following the end of the postgraduate cardiology program, only 42.3% of the students continued their research activities. Remarkably, 42.2% of the students did not follow research or teaching activities (Table 2).

Discussion

To the best of our knowledge, this is the first study reporting the scientific output of graduates from a cardiology postgraduate program in Brazil. Our findings are relevant because cardiovascular disease is the most frequent cause of death in some developing and developed countries.[6] The graduates of the largest cardiology program in Brazil had a progressive incremental in the total number of publications until 2007, mainly as a consequence of the expansion of the community of researchers. Also, the articles were published in journals with progressively higher impact factors until 2011, but these impact factors may be considered low. Moreover, the number of publications adjusted by the number of students reduced until 2000 and remained stable afterward. We observed that the scientific output per student was not homogeneous. The *h*-index, number of citations, and the number of publications of each graduate were poor. Only 42% of the graduates embraced research activities after the program, and the research they performed had a low impact. The population of postgraduate students also had special characteristics, including a low number of Afro-Brazilian students and foreigners, a progressive incremental rise in the number of students with a higher percentage of younger woman and students without prior medical training credentials.

Despite the success of the increase in the journals' impact factors until 2011 and the total number of publications until 2007 (which declined as the number of graduate students increased), the scientific productivity by cardiology postgraduate students and its impact are concerning. The heterogeneity of the scientific production was also worrisome because it seems to have followed the Pareto principle, in which a minority is responsible for the greater part of the production. Brazilian scientific publications have increased significantly in number, but the citation indices have remained at approximately 60% of the world's mean citations (Thomson Reuters). Despite this fact, the performance of Brazilian researchers is high among some developing and emerging countries.[7] In a comparison with other countries, a recent bibliometric analysis demonstrated that the number of cardiovascular publications from Latin America increased from 1999 to 2008.[8] Brazil was the country with the greatest increase in the number of publications. However, the citation index by year of publication in Brazil was 9 in 1999 and 9.1 in 2008, while in Argentina, this index increased from 9.2 to 25.6. The causes of poor scientific and academic output by cardiology postgraduate students are complex and largely unknown. Unfortunately, we lack published data from other postgraduate courses for the purpose of comparison. Many factors could be hypothesized to explain our findings. Although they might be interconnected, two periods can be

Table 1 – Baseline characteristics of the postgraduate students

Variable	N (%) or median (IQR)
Total number	505 (100)
Male sex	316 (62.6)
Female sex	189 (37.4)
Ethnicity	
White	260 (51.5)
Afro-Brazilian	0 (0)
Mulatto	6 (1.2)
Yellow (Asian)	16 (3.1)
Ethnicity not provided	223 (44)
Median age (all)	
Female sex	37 (34-43)
Male sex	39 (35-44)
Nationality	
Brazilian	500 (99)
Non-Brazilian	5 (1)
University graduation	
Medicine	397 (78.6)
Non-medicine	
Biology	8 (1.6)
Biomedicine	8 (1.6)
Nursing	12 (2.4)
Electronic engineering	1 (0.2)
Pharmacy	5 (1)
Physiotherapy	5 (1)
History	1 (0.2)
Psychology	5 (1)
Nutrition	6 (1.2)
Chemistry	1 (0.2)
Veterinary	3 (0.6)
Physical education	6 (1.2)
Unknown	38 (7.5)
Previous master's degree	64 (12.7)
Ph.D. without previous master's degree	441 (87.3)

IQR: Interquartile range.

considered to explain the causes of our findings: the training period for research during the postgraduate program, and the time after the program. During the training period in the postgraduate program, the initial module is provided to a potentially future researcher, whereas after the conclusion of the program, the student faces a real-world research scenario.

The cardiology postgraduate program was developed according to guidelines developed by CAPES, which may have influenced the training period of the program. CAPES has established criteria for the development of programs, measuring the scientific output of graduates from postgraduate programs and imposing goals for these individuals. The current CAPES criteria for evaluation of postgraduate programs in Brazil were initially established in 1998.[9] The evaluation of each program is currently complex and includes an appraisal of the program's proposal, faculty, students, intellectual output, and social inclusion. For the evaluation of the program, the impact of the scientific journals in which the articles are published is measured by a specific national index called *periódicos Qualis*. The Qualis system is an imperfect solution that considers the

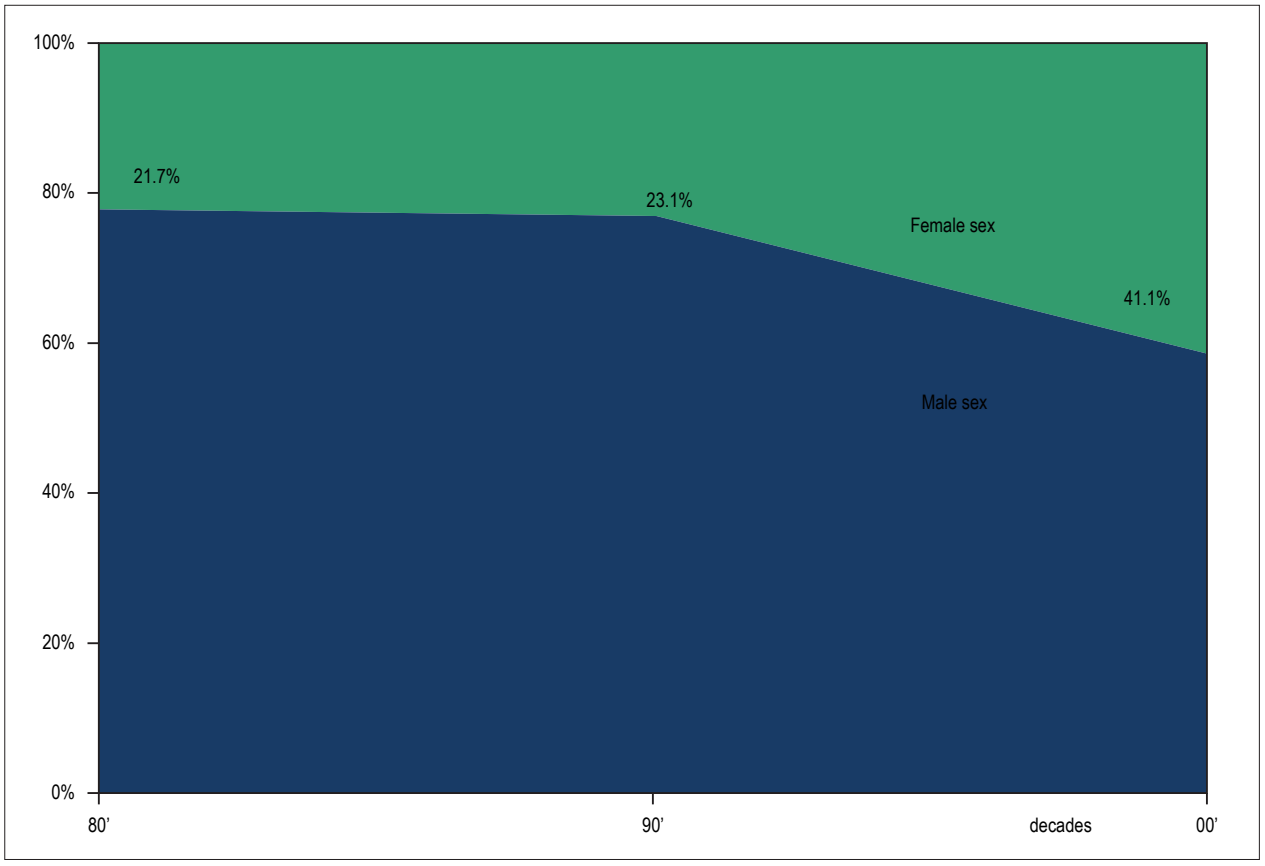

Figure 1 – *Gender distribution of the postgraduate students.*

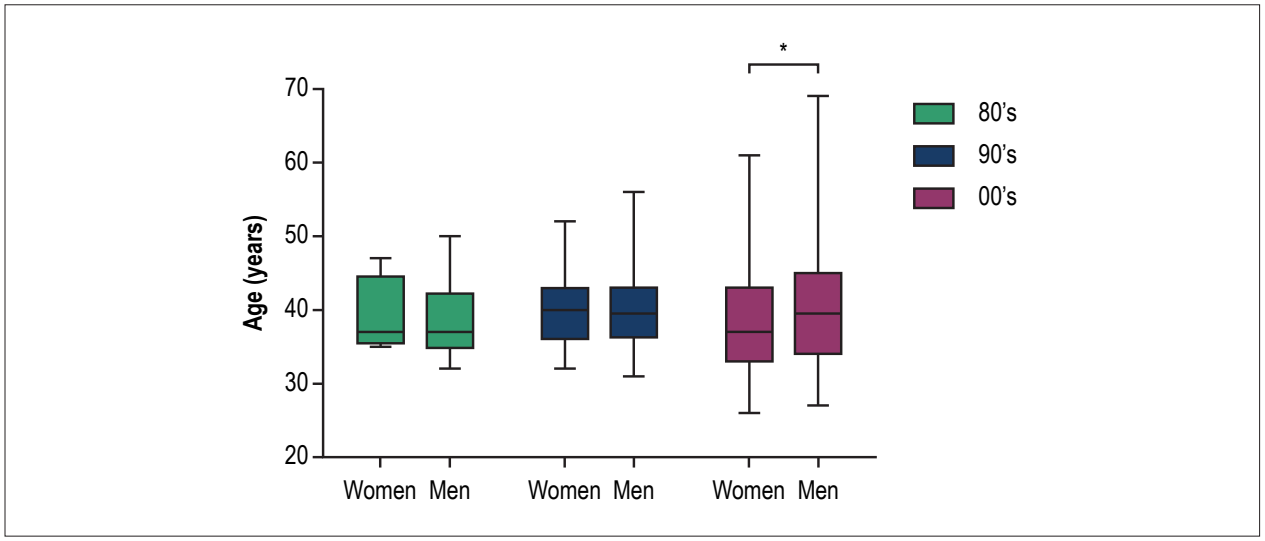

Figure 2 – *Mean age of the postgraduate students.*

importance of the article according to the journal in which it is published, regardless of the number of citations.[7] This evaluation criterion has never been validated prospectively and raises many concerns. Instead of focusing on strengthening scientific bases, technology, and innovation, CAPES has developed other objectives, such as the postgraduate training of teachers of all education levels and training of qualified human resources personnel for the non-academic market. Therefore, the rules established by CAPES may stimulate the training of more but low-impact cardiology researchers.

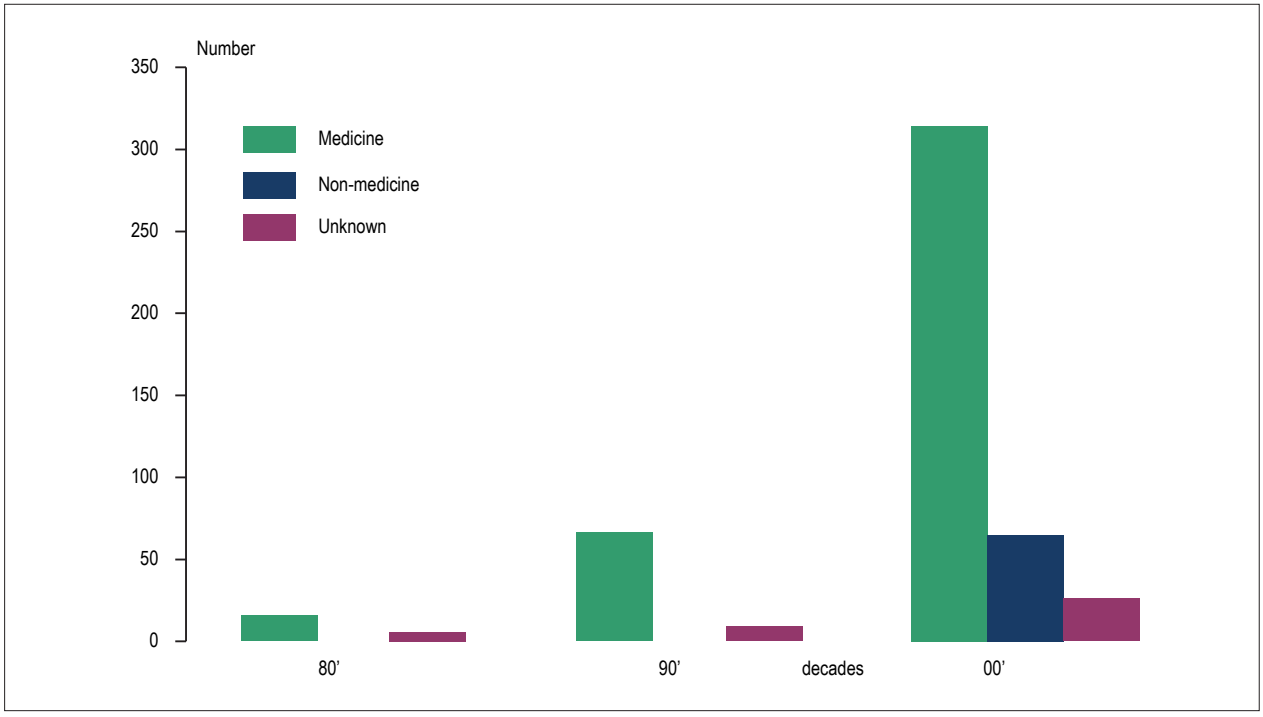

Figure 3 – *Postgraduate students with previous medical training versus no medical training.*

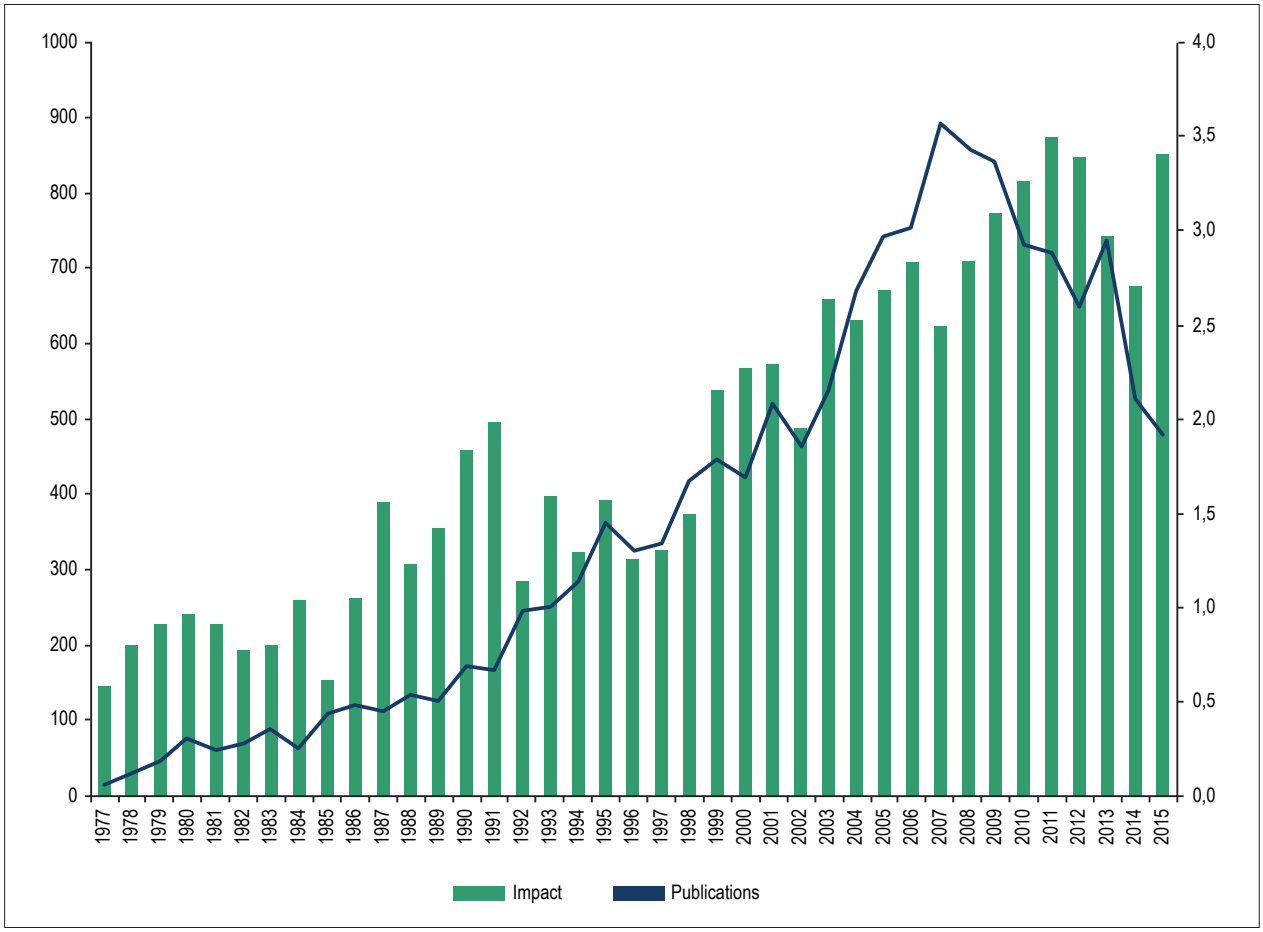

Figure 4 – *Number of publications per year by all postgraduate students and corresponding journal impact factors from 1977 to 2015.*

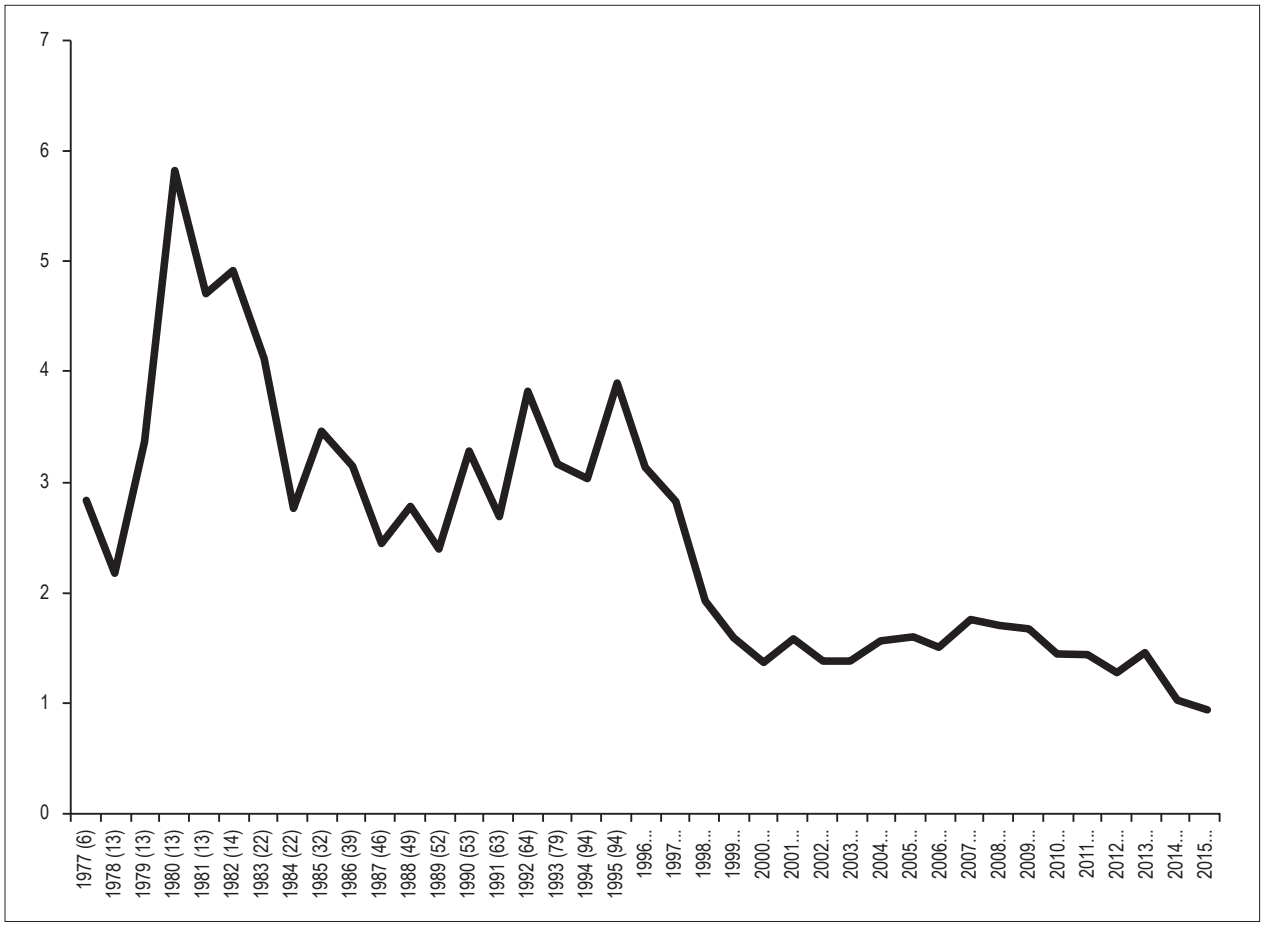

Figure 5 – *Number of publications from 1977 to 2015 adjusted for the number of postgraduate students with a theoretical capacity to publish.*

Table 2 – Scientific indexes and academic indicators of the postgraduate students over decades after completion of the program

Scientific index	Scopus	ISI	Lattes
H-index	4 (2-7)	3 (1-6)	___
Published articles	10 (3-25)	7 (2-16.5)	13 (4-35)
Total number of citations	54 (11-244)	39 (5-167)	___
Citations per article	6 (2-12)	5.6 (2-12)	___
Published articles per year	1 (0.3-2.2)	0.6 (0.2-1.6)	1.5 (0.5-3.2)
Impact factor	___	___	1.5 (0.8-2.4)
Academic indicators			
Research			16%
University teaching			15.5%
Research and teaching			26.3%
Others			42.2%

In addition to the rules established by CAPES, the postgraduate program is also influenced by the university's environment. The university's postgraduate board supports high-impact research, but this is actually not a top priority of the cardiology postgraduate program in the real world.[10] One important factor seems to be the form of the final assessment of the scientific production of each postgraduate student. Rather than assessing the work done during the

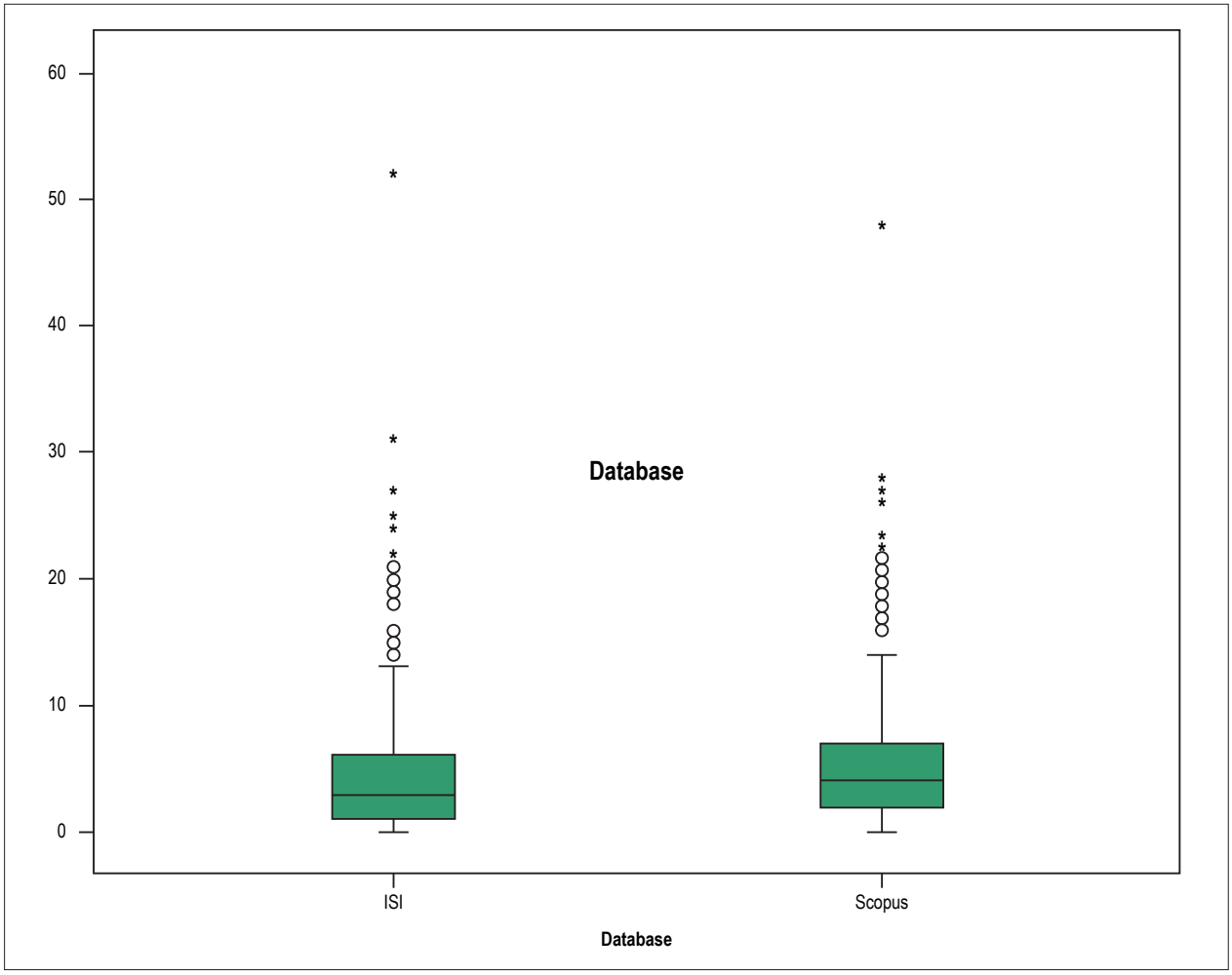

Figure 6 – *H-index values of the postgraduate students according to the ISI and Scopus databases.*

Table 3 – Scientific indexes and academic indicators of the postgraduate students according to the graduation program

Graduation	*H*-index		Impact factor	Articles
	ISI	Scopus		
Medicine	3 (1-6)	4 (2-6)	1.4 (0.8-2.5)	16.5 (5-40.3)
Non-medicine	2 (1-4.3)	2 (1-5)	1.8 (0.5-3)	4 (2-11.5)
Biology	1 (0-3)	3 (0-5)	2.9 (1-3.1)	3 (2-9)
Biomedicine	1.5 (0.3-2.8)	2.5 (0.5-3.8)	2.8 (1.2-3.3)	3.5 (2.3-9.3)
Physical education	4.5 (1-8.3)	4.5 (0-9)	1.8 (1.1-2.1)	15.5 (1.8-36.5)
Nursing	3 (2-5.8)	4 (1.3-5)	2.2 (0.7-3.7)	9.5 (5.8-14.5)
Pharmacy	4 (1-6)	4 (1-6.5)	3.5 (0.6-5)	8 (5-13.5)
Physiotherapy	1.5 (0.8-8.5)	2 (0.8-8.3)	1.2 (0.4-2.5)	5 (1.5-52)
Other	1.5 (0.8-3)	2 (0-3)	1.1 (0.2-3.1)	3 (1-5)

postgraduate program through the impact of its publications or the impact of the peer-reviewed journal in which the article was published, the evaluation is performed through a panel of local professors. As a confirmation of this fact, the rate of disapprobation of the theses presented as part of the program is almost nonexistent. In some situations, the

publications are accepted for approval but are hindered by bureaucratic complexities. For example, the university's postgraduate committee points out innovation as one of the objectives of the program but prioritizes other objectives instead, such as the teaching of training, leadership skills, and knowledge of the study field to postgraduate students. In addition, Brazilian universities have low classifications in international rankings, and this low ranking does not provide an enabling environment for high-impact research.[11] Some other characteristics of the postgraduate program may contribute to that, such as a scenario of low-risk taking, lack of proper environment for boldly innovative ideas, no priority for innovation in the real world, submission of a research protocol before research training courses, attempt to prepare students for high-impact research using low-impact training, absence of environment or time for revolutionary or innovative ideas or high-impact research, lack of training by international researchers, replication of science rather than development of original science, and necessity of publication as early as possible regardless of the impact that such publication will obtain. In fact, after an analysis of the criteria and objectives established by CAPES and the universities, one might assume that high-impact publications and innovation are not the highest priorities of these institutions in the real world, and the methods used by them are not enough to secure publication in high-impact journals.[9,10] Additional factors to explain the finding that high-impact research in the real world is not a priority for Brazilian universities are some lingering distortions from the French school model with its historical professional origin, institutions not integrating teaching and research, elitist attitude,[12] and threat to creativity perceived by the privileged model because of the generation of new values as a consequence of innovations and technology. The persistence of remnants of the cathedral structure without consideration of merits for career growth also hinders high-impact scientific accomplishments.[13]

Regarding the time after the program completion, the national scenario of research institutions is not attractive for cardiology students in terms of the development of a research-oriented career and does not contribute to retaining research talent. Many factors may contribute to that, such as a historical culture lacking research encouragement, low income, accomplishments not properly recognized, the necessity of multiple jobs to obtain adequate income, and promotion of scientific and academic career and choice of leaders not based on merit.

The limited research resources offered by the government and private initiatives,[14] the type of distribution of these resources, characteristics of the funding agencies, definitions of priority without enough social scientific transparency, and controversial criteria for the selection of the research to be supported may all influence cardiology graduates during the training period and after the completion of the postgraduate program. Unfortunately, high-impact research, with rare exceptions, is expensive. The popularity of providing research funds with low monetary value is contrary to high-impact research that results in innovation. Also, the low investment in research by private companies in Brazil is remarkable.

To worsen this scenario, foreign companies and institutions have developed in Brazil competitive and financially supported clinical research originating from other countries (without a "local technological value") generating unfair competition with local, unfunded original research. Unfortunately, this type of research is generally designed in foreign countries without a true Brazilian authorship, and the Brazilian researchers participating are therefore subordinated. At the most, Brazilian researchers may secure the position of coauthors without becoming main authors. This may contribute to local laboratory discoveries remaining in what has been termed as the "valley of death" – a gap between bench research and clinical application.[15] Additionally, there is not a critical mass of high-impact researchers acting in funding agencies as peer reviewers who can choose high-impact projects.

In general, the priorities and application of funds from funding agencies are not socially and scientific transparent. The lack of upgrading in funding agencies hinders them from rapidly adapting to new required strategies, considering that these agencies do not make bids for boldly innovative ideas. A cultural change is necessary for agencies considering innovation as a risky activity frequently not resulting in success. However, low investment in research and funding may not be enough to explain the low impact of the publications. In fact, the budget of the Brazilian Ministry of Science, Technology, and Innovation (MCTI) doubled from 2005 to 2010, but this fact was not associated with proportional relevant increments in publication impact.[16] The current decrease in research investment following the 2014 economy stalling in Brazil is worrisome. One might suggest that Brazil is a "young" country with regards to research, which could explain the country's limitations. However, other similarly young countries in terms of research, such as South Korea and China, have found success in innovation.[17]

The expectations of the cardiology postgraduate student also are important for low-impact publication, because the purpose of the program may sometimes be to complete and refine a previous learning deficiency mainly in research development and interpretation. Also, independently of a research career, graduates with a diploma from a postgraduate program will have better professional opportunities.

Finally, access to publishing in high-impact journals may have undisclosed obstacles, as such journals may prefer to publish manuscripts originating from developed countries. Research developed by Brazilian authors also has a low rate of true international collaboration. Some Brazilian researchers have attempted to overcome this limitation with the inclusion of foreign researchers without a well-defined international cooperation; fortunately, this is not a widespread procedure. Of note, articles with at least one foreign author may attract more citations.[7] It has been recently reported that the country from where an article originates affects the perception of the article's quality and relevance.[18] Thus, Brazilian researchers may be compelled to publish in Brazilian journals without a high international prestige, therefore without attracting many citations.[7] The median impact factor of most Brazilian journals is below those of thematic fields under international indexes.[7] A vicious circle or Matthew effect could be influencing this scenario.

Limitations

Since this retrospective study was conducted in the cardiology field, the internal validity of its results could be considered applicable only for a population of graduates of a cardiology postgraduate program. However, the finding that Brazilian publications have a low impact factor and the important role of the Brazilian postgraduate system in increasing the number of Brazilian publications are evidence of an external validity of our findings, at least in the medical area of cardiology. In other medical areas, the same low impact may be verified.[19] On the other hand, it is possible that select postgraduate programs may have different characteristics and, consequently, diverse results.

Much of the Lattes curricula data were included by the graduates themselves; therefore, they could not be entirely verified. Excellent articles, mainly on the areas of Tropical Medicine and Public Health, are not accepted in foreign journals, especially articles considered of "regional interest." Then, extremely important information is oftentimes not properly propagated because the information is not considered as a "universal science."

In contrast, some researchers probably have their research impact increased by participating as coauthors in international trials without resulting in Brazilian innovation or contribution to national technological development (absence of creation of Brazilian value). In fact, an unacceptable disproportion between first authorship and coauthorship can be verified. Moreover, some researchers are not necessarily considered among those with ideas or innovative initiatives, and they often play a supporting role, albeit not a major one, in the research.[20] Culturally, it may happen in Brazil, although uncommon, the inclusion of coauthors based on honor (in which the coauthors had no active participation in the research), either because of their hierarchical position at the institution where the research was performed, or for their referral of patients to the study, which is not compliant with the guidelines of the International Committee of Medical Journal Editors.[21] The evaluation of the increased impact of the journals in which all scientific research was published may have limitations due to the historical increase in the number of journals in which cardiology articles are generally published.

We did not investigate the number of downloads of each article, which is being increasingly used to assess a publication's impact. However, download statistics may have limitations. The number of downloads is not offered by most journals and may also include counts derived from search engine crawlers and downloads by non-scientific individuals. Therefore, the number of citations by other articles currently remains the gold standard for evaluation of the impact of an individual scientific article. Also, controversial results have been published concerning the correlation between the number of downloads and citations.[22,23]

Finally, we did not evaluate the publications' economic output, including patents, device approvals, and value created. However, considering the low-impact of these publications, positive findings in this area are unlikely. Other variables, such as the *h*-index of the study advisor, appear to be also important predictors of publication success.[24]

Implications

In addition to policies designed to increase scientific production, strategies to increase high-impact publications targeting innovation warrant changes to cardiology postgraduate programs and the period following completion of the program. Similar to the philosophical dilemma of the chicken or the egg coming first, the components are integrated and interdependent, but urgent modifications involving many factors should be planned, including related to CAPES, university rules, funding agencies, and the country's scenario. In fact, the postgraduate system should be reconsidered. Also, a better balance between scientific output and high impact should be obtained.

Other important decisions depend on whether the current cardiology model is cost-effective to the country in training students in research with the knowledge that less than half of the graduates will actually pursue research careers, even low-impact ones. The development of separate programs for high-impact research and teaching should be tested as an alternative. Advanced Medical Education Research and Innovation (MERI) units are an example.[25] At the postgraduate level, content should be more innovative, as in the UK.[26]

The assessment of academic and scientific output by graduates should be mandatory and extended to all postgraduate programs. In the evaluation criteria, scientific output by graduates should be required.

Conclusion

The Scientific output of graduates should be considered in the evaluation criteria of postgraduate programs. Policies for access to socially vulnerable students and international students should be encouraged. Despite the success in increasing the total number of publications, the current proposed mechanisms to increasing publication in high-impact journal through this current postgraduate system seem to be ineffective. Our findings showing a low scientific output from graduates of a cardiology postgraduate program in regards to the low number of publications, impact factor, and *h*-index values warrant modifications in postgraduate programs' plans, funding agencies, and the country's scenario for research.

Author contributions

Conception and design of the research: Bocchi EA; Acquisition of data: Borges DP, Oliveira-Carvalho VR; Analysis and interpretation of the data and Critical revision of the manuscript for intellectual content: Bocchi EA, Borges DP, Oliveira-Carvalho VR; Statistical analysis: Oliveira-Carvalho VR; Writing of the manuscript: Bocchi EA, Oliveira-Carvalho VR.

Potential Conflict of Interest

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

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There were no external funding sources for this study.

Study Association

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

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Healthy School, Happy School: Design and Protocol for a Randomized Clinical Trial Designed to Prevent Weight Gain in Children

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Abstract

Background: **Schools have become a key figure for the promotion of health and obesity interventions, bringing the development of critical awareness to the construction and promotion of a healthy diet, physical activity, and the monitoring of the nutritional status in childhood and adolescence.**

Objectives: **To describe a study protocol to evaluate the effectiveness of an intervention designed to improve knowledge of food choices in the school environment.**

Methods: **This is a cluster-randomized, parallel, two-arm study conducted in public elementary and middle schools in Brazil. Participants will be children and adolescents between the ages of 5 and 15 years, from both genders. The interventions will be focusing on changes in lifestyle, physical activities and nutritional education. Intervention activities will occur monthly in the school's multimedia room or sports court. The control group arm will receive usual recommendations by the school. The primary outcome variable will be anthropometric measures, such as body mass index percentiles and levels of physical activity by the International Physical Activity Questionnaire.**

Results: **We expect that after the study children will increase the ingestion of fresh food, reduce excessive consumption of sugary and processed foods, and reduce the hours of sedentary activities.**

Conclusion: **The purpose of starting the dietary intervention at this stage of life is to develop a knowledge that will enable for healthy choices, providing opportunities for a better future for this population. (Arq Bras Cardiol. 2017; 108(6):501-507)**

Keywords: **Schools; Health Promotion; Health Behavior; Obesity; Motor Activity; Diet, Food and Nutrition; Body Weight; Prevention & Control.**

Introduction

The increased prevalence of obesity and its complications reinforces the global need for improved prevention strategies.[1-3] In Brazil, population-based surveys indicate that overweight was present in 6% of children between 5 and 9 years in 1974-1975, rising steeply to 34.8% in 2008-2009.[4] Globally, overweight in children increased 47.1% over the past 20 years.[5] In 2010, it was estimated that overweight and obesity were responsible for 3.4 million deaths worldwide.[6] Chronic diseases remain a public health challenge in Brazil. The medical costs associated with diseases related to overweight and obesity are substantial in Brazil, reaching nearly US$ 2.1 billion annually.[7]

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Overweight in children and adolescents generates great concern because it is a risk factor for the development of hypertension, type 2 diabetes mellitus, dyslipidemia and other cardiovascular risk factors,[8,9] which, if not prevented or treated at an early age, tend to persist during adulthood.[10]

Nutritional intervention studies have shown a positive effect on preferences for healthy foods and a decrease in daily consumption of sugary drinks.[11,12] Permanent changes in diet quality, energy intake and physical activity demand preventive actions.[13] On that account, promotion of a healthy diet, physical activity, and monitoring of the nutritional status in childhood and adolescence are essential elements in public health. Being an educational environment that contributes to build personal values, schools become a key figure for health promotion and obesity interventions, bringing the development of critical awareness to the construction and modification of eating habits.[14,15]

A number of international agencies, such as the Centers for Disease Control and Prevention (CDC) and the Institute of Medicine (IOM), launched campaigns with guidelines for health promotion in schools aiming to address the epidemic of obesity and its consequences.[16-18] In Brazil, the School Health Program is designed to promote the comprehensive

health care of public school students and is structured in four blocks that seek to: assess health conditions; perform actions of prevention and promotion of health conditions; promote continuing education for professionals and the young; present evaluation and monitoring of health conditions of the students. The responsibility for planning and carrying out these actions is upon the primary care health team, and the objective is to integrate the educational system and the Brazilian Unified Health System (SUS).[19] However, this government action does not have coverage of all schools in the country yet.

In order to implement educational interventions in a large scale, it is important to adequately test their effectiveness. It is also important to look for simple and low-cost alternatives that can reach the largest possible number of schools. Improving the knowledge about food choices may be an important basis for children to acquire and maintain a healthy lifestyle from an early age, and possibly to sustain these healthy habits in subsequent stages of life.

Thus, the purpose of this study protocol is to evaluate the effectiveness of an intervention designed to improve knowledge of food choices in the school environment.

Methods

This protocol is reported according to the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) statement.

Study design

Overview

This is a cluster-randomized parallel two-arm study conducted in Brazil. The units of observation are individual children, and the units of randomization are schools. Randomization will be performed at the school level to avoid contamination. After the baseline assessment, enrolled schools are randomized to one of two study arms: the intervention arm focusing on changes in lifestyle, and the control group arm, that receives usual recommendations by the health care team. A summary of the study design, interventions and timelines is shown in Figure 1.

The primary outcome for the participants is change in body mass index (BMI = kg/m^2), and the secondary outcomes are behaviors related to healthy eating, increased preferences for fruits and vegetables, increased physical activity and reduced screen time. The Institutional Research Ethics Committee approved the protocol for the study, which is registered in the Brazilian Registry of Clinical Trials, Register Number RBR-97bztb, and named "Intervention program for health promotion in schools of public elementary school in the state of Rio Grande do Sul: randomized clinical study". The Universal Trial Number of this study is U1111-1155-7731.

Inclusion criteria

Children between the ages of 5 and 15 years, from both genders, enrolled in the public schools participating in this study, attending from the 1st to the 9th grades of the elementary and middle school will be eligible for the study (Table 1). The child and parent(s) or legal guardian(s) are required to sign the assent term and the informed consent.

Exclusion criteria

Children are excluded if they have conditions or other circumstances that could interfere with participation in the measurements or the interventions or if the parent does not give or is unable to give consent or the child does not assent. Participants are also excluded if they do not complete baseline assessments in 3 weeks.

Screening and recruitment

The screening and recruitment activities will be developed during the course of 4 weeks. During the first week, the school electronic files of student enrollment will be consulted to identify potential participants (the eligibility criteria can be seen in Table 1). During the following two weeks, recruitment letters will be sent to the student's guardians, with explanation of the study and attached Informed Consent Form. During the fourth week, individuals who agree to participate in the study will undergo anthropometric assessment, provided that there is no impediment for physical evaluation.

Randomization

Cluster randomization will be performed with distribution of two schools for the control group and two schools for the intervention group. A biostatistician who does not have direct contact with study participants will generate the random allocation sequences using a computerized random number generator. After the inclusion of each cluster, the allocation of that particular cluster will be provided to the study coordinator. Due to the characteristics of the intervention, it is not possible to mask participants or interventionists to group assignment. There will be no crossover between study arms, but the intervention will be offered to the control group at the end of the study, if proved to be effective.

Assessments

Measures are conducted at baseline (month one) and post-treatment (month 9).

Anthropometric measures

Weighing electronic scales with a maximum capacity of 150 kg and precision of 100 g, properly checked for tare weight, will be used for weight measures. The individual will be weighted barefoot and wearing light clothes. A metallic measuring tape with a capacity of 2 m/0.1 cm, set in an existing flat wall in the room, will be used to measure height, with the individual in the upright position, during maximum inspiration, barefoot and with empty pockets. These data will be used for the following calculation of BMI, obtained by weight, measured in kilograms, divided by the square of the height, measured in meters (kg/m^2). That will be calculated and nutritional status will be classified, both using the *Anthro Plus* software, according to the reference of the World Health Organization (WHO) 2006/2007.

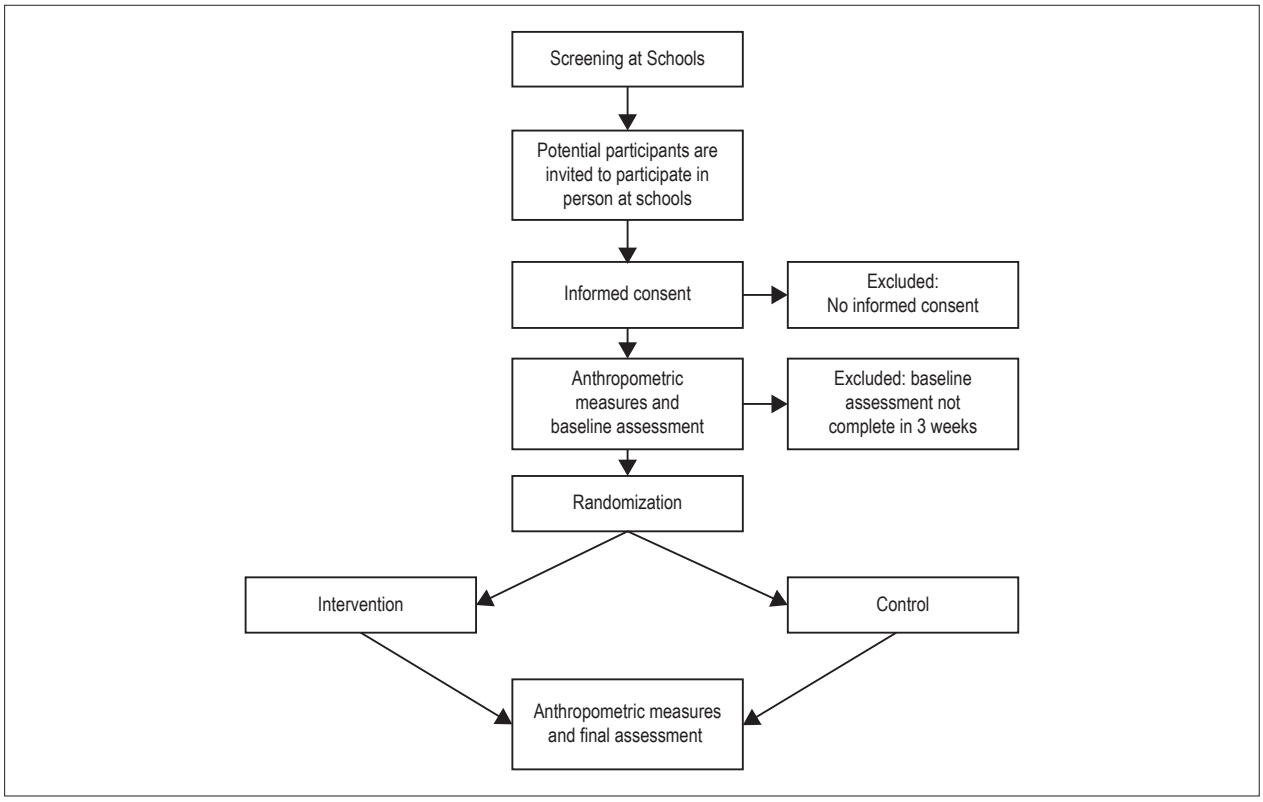

Figure 1 – *Flowchart of the study phases (enrolment, intervention allocation, and final assessments).*

Table 1 – Inclusion criteria and assessment methods.

Inclusion criteria	Assessment method
Age 5-15 years	In person screening
Enrolled in one of the participant schools, attending a course from the 1st to the 9th grade of the elementary and middle school.	Electronic school review
Agreeing to participate in all the meetings of the study	In person screening

Dietary intake

The collection of dietary data, referring to the eating habits of the participants, will be assessed by a Food Frequency Questionnaire (FFQ),[20] previously validated for the study population, designed to collect information on the frequency of food consumption and/or food groups for further association with other study variables, such as lifestyle and anthropometric measurements.

Physical activity

International Physical Activity Questionnaire (IPAQ)[21,22] will be used for all ages to classify the level of physical activity, in spite of the fact this instrument has being validated only for adults and adolescents, since there is not yet a validated questionnaire that can suit the needs of this study and adequately classify physical activity levels in Brazilian children.

Screen Time

Screen time refers to the amount of time individuals spend in front of television, video games and computer, and is considered to be a sedentary activity. It will be measured by hours per day and number of days in the week of screen time.

Knowledge of healthy habits

The acquisition of knowledge about healthy habits will be evaluated through a questionnaire validated for age,[23] consisted of knowledge about food and healthy activities in daily life.

Demographics measures

During baseline assessment, parents will be asked about a series of demographic data included in the Brazilian

Economic Classification Criterion by the Brazilian Association of Research Companies,[24] which includes: age; educational attainment of the family head; questions about household appliances and other family properties; street paving and treated water in the house.

Sample size

The sample size was calculated to detect a difference in 0.2 kg/m² on BMI, with a standard deviation of 0.05, statistical power of 90% and alpha error of 0.05. An estimate of mean 19 kg/m² is used as obtained from our pilot study. A number of 99 participants per group was estimated using these parameters. To compensate for losses, the sample size will be increased by 10%.

Planned data analyses

Collected data will be entered and analyzed using the Statistical Package for Social Sciences, version 17.0. Quantitative variables will be expressed as mean and standard deviation in the presence of normal distribution or median and interquartile range in the presence of asymmetric distribution. Qualitative variables are expressed as absolute and relative frequencies.

Adjusted analysis for primary and secondary outcomes will be performed using generalized estimating equations (GEE). The comparison between secondary outcomes will be performed using the nonparametric Wilcoxon test.

The level of significance for all tests will be 95% ($\alpha = 0.05$) and will follow the intention to treat principle. P-values will be reported up to three decimal places with p-values < 0.005 reported as $p < 0.005$. The outcomes will be evaluated by a blind adjudicator.

Interventionists

The interventions in this study will be delivered by the nutritionists of the Children and Adolescents Cardiovascular Prevention Group (PREVINA),[25] nutrition graduate students and health professional contributors employed by the City Hall (psychologists, physical education teachers, nurses). All interventionists will undergo extensive training on: intervention protocol; overall intervention objectives, content and format; and specific instructions for each intervention session.

Intervention description

Intervention activities will occur monthly in the school multimedia room or sports court (Table 2). All activities will be offered in different school shifts and schedules so that all students in all classes can participate.

Usual care comparator

Participants randomized to the control group will not receive any guidance during the study. Children will receive the usual care and recommendations through the school and health authorities.

Should the intervention prove to be effective, at the end of the study, the institutions allocated to the control group will receive all intervention activities if they wish.

Discussion

This randomized clinical trial is intended to help filling a gap in the literature regarding simple, low-cost and effective interventions to deal with the epidemic of obesity and overweight in developing countries. Numerous studies show that overweight and obesity rates in the young in Latin America bring important economic and health consequences.[26] In spite of the need for individual approaches for children who are already overweight or obese, the international consensus is that prevention is the most realistic approach and the best value for money.[27] It is therefore necessary to develop preventive interventions that can reach a larger number of children.

Facilitators and barriers for the development of healthy habits should be considered when designing a childhood overweight program. Adaptation to local culture and reality should also be a concern. One of the most important challenges of this study will be changing the approach to nutrition and physical activity. On that account, we designed interventions that include parents, teachers and students aimed at creating a positive impact on the health of children and adolescents.

The young need appropriate information to make healthy choices and change their sedentary behavior, but their parents and teachers are not always prepared to give that information. Therefore, involvement of trained health professionals specialized in the field is necessary in order to adequately provide that information. Given that children are exposed to the environment we create for them and that in Brazil they usually spend about 25 hours a week in school, it is important to design actions that seek to improve the school environment and create a healthy growth strategy.

The study also has some limitations, that must be addressed in future work. First, there is a possibility of cross-contamination of participants in the two intervention arms, since both interventions are delivered in a small city. Second, the trial does not evaluate the pubertal maturation, whose changes may impact on the body composition in childhood and early adolescence, such as weight gain in girls and a decline of body fat in pubertal boys.

In conclusion, we have described the basic rationale and design of the ongoing Healthy School, Happy School cluster-randomized trial. The study intervention aims to increase the ingestion of fresh food, reduce excessive consumption of sugary and processed foods, and reduce the hours of sedentary activities. The purpose of starting the dietary intervention at this stage of life is to develop a knowledge that will enable for healthy choices, providing opportunities for a better future for this population.

Author contributions

Conception and design of the research: Schuh DS, Barbiero SM, Sica C, Pellanda LC; Acquisition of data: Goulart MR, Borges R; Analysis and interpretation of the data: Schuh DS, Goulart MR, Moraes DW, Pellanda LC;

Table 2 – Description of intervention activities

Intervention	Type	Description	Moment
Presentation of the program to students, parents and teachers.	Seminar	A seminar approaching the following topics will be conducted: epidemiological data on obesity and noncommunicable disease risk factors; dyslipidemia tracking; importance of school intervention; presentation of the activities that will be developed during the school year; reading and clarification of the Informed Consent Form.	1st Month
Knowing what we eat.	Seminar	The seminar will succinctly address the composition of food, approaching macronutrients, fibers and food groups. As a task for the week, each class should study the vitamins and prepare a poster on that topic during class time. As a homework assignment, all students should create, with the help of parents, a list of five fruits and six vegetables they like to eat. Three of them should be cooked vegetables and three of them raw vegetables.	2nd Month
The importance of water.	Seminar	The seminar will address the importance of water in our health and the consequences of high consumption of sugary drinks. Soft drink consumption has increased in recent decades in Latin America, and that is being referred as a contributor to the population weight gain. Many schools sell soft drinks in the cafeteria and some children end up consuming them daily without parents' knowledge. The "Week without soda" challenge will be launched, in which children, parents and teachers will commit to spend a week without drinking soft drinks, which will require the family interaction and commitment for the accomplishment of the goal.	3rd Month
Revolution in the kitchen: first you taste, and then you like it.	Workshop	The workshop aims to propose an interaction among students, teachers, kitchen staff and the food. Various whole foods (fruits, vegetables, breads, cakes, cookies) will be placed on a table. Participants will be blindfolded and will have to randomly taste a food, describe their sensory characteristics and perceptions (whether it is soft or hard, if it has good or bad smell, if they like it or not) and try to guess what it is. After that, participants will be invited to prepare their own snack with some of the vegetables they planted earlier in the year, according to their preferences. As homework assignment, students will be asked to help parents to make the salad for the family for a day, starting with the choice of food in the supermarket. During class time, teachers, helped by a nutritionist, will work on the dynamics of the traffic light food, where the food is classified according to the colors of the traffic light. Green represents foods we should eat daily; yellow foods that can be eaten more than once a week, but in moderation; and red are the forbidden foods to eat daily, but which can be eaten on special occasions, like parties or the weekend. There will also be a seminar for parents in order to provide information and ideas for preparation of healthy snacks for school lunches best suited for the needs of children.	4th Month
Let's Move! Physical Activity in all moments!	Seminar	The seminar will address the importance of physical activity in our health, and it will present the physical activity programs that are available in the city. Activity ideas to do either outdoors or at home, alone or in groups, will be suggested. A challenge will be launched: "one disconnected day", in which students, parents and teachers will be invited to reduce television and internet time to only two hours for a day. Reducing sedentary behaviors, such as spending too much time watching television and using the computer, appears to contribute to the reduction of daily calorie intake. Activity suggestions will be given for that day.	5th Month
Where does my food come from?	Workshop	The workshop will have the participation of a city vegetable producer who will teach students how to plant and take care of a small vegetable garden at school. In addition, each student will receive seeds of green seasoning (parsley) to plant in a little vase previously decorated during arts education class.	6th Month
Milk every day!	Seminar	The seminar will address the importance of milk and dairy products in our diet and the recommended amounts of ingestion. It will also address certain disorders related to milk digestion, such as lactose intolerance and allergy to cow's milk protein.	7th Month
Bullying: we have to talk about it!	Seminar	A psychologist will conduct the seminar and address the meaning of the theme, bullying types, and what to do if you fall victim. There will be a special meeting with teachers to answer questions.	8th Month
German dances course	Workshop	It will be offered fortnightly lessons of German dances in school during one school year. This course also aims to rescue the traditions and culture of the city, which was settled mostly by Germans.	Ongoing activity during the year

Statistical analysis: Schuh DS, Goulart MR; Obtaining funding and Writing of the manuscript: Schuh DS; Critical revision of the manuscript for intellectual content: Barbiero SM, Sica C, Borges R, Moraes DW, Pellanda LC.

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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Cardiovascular Risk Stratification and Statin Eligibility Based on the Brazilian vs. North American Guidelines on Blood Cholesterol Management

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Abstract

Background: **The best way to select individuals for lipid-lowering treatment in the population is controversial.**

Objective: **In healthy individuals in primary prevention: (1) to assess the relationship between cardiovascular risk categorized according to the V Brazilian Guideline on Dyslipidemia and the risk calculated by the pooled cohort equations (PCE); (2) to compare the proportion of individuals eligible for statins, according to different criteria.**

Methods: **In individuals aged 40-75 years consecutively submitted to routine health assessment at one single center, four criteria of eligibility for statin were defined: BR-1, BR-2 (LDL-c above or at least 30 mg/dL above the goal recommended by the Brazilian Guideline, respectively), USA-1 and USA-2 (10-year risk estimated by the PCE ≥ 5.0% or ≥ 7.5%, respectively).**

Results: **The final sample consisted of 13,947 individuals (48 ± 6 years, 71% men). Most individuals at intermediate or high risk based on the V Brazilian Guideline had a low risk calculated by the PCE, and more than 70% of those who were considered at high risk had this categorization because of the presence of aggravating factors. Among women, 24%, 17%, 4% and 2% were eligible for statin use according to the BR-1, BR-2, USA-1 and USA-2 criteria, respectively ($p < 0.01$). The respective figures for men were 75%, 58%, 31% and 17% ($p < 0.01$). Eighty-five percent of women and 60% of men who were eligible for statin based on the BR-1 criterion would not be candidates for statin based on the USA-1 criterion.**

Conclusions: **As compared to the North American Guideline, the V Brazilian Guideline considers a substantially higher proportion of the population as eligible for statin use in primary prevention. This results from discrepancies between the risk stratified by the Brazilian Guideline and that calculated by the PCE, particularly because of the risk reclassification based on aggravating factors. (Arq Bras Cardiol. 2017; 108(6):508-517)**

Keywords: **Cardiovascular Diseases; Cholesterol; Anticholesterelemic Agents; Risk Assessment; Hydroxymethylglutaryl-CoA Reductases; Practice Guidelines as Topic.**

Introduction

Although the relationship between the reduction in serum low-density lipoprotein cholesterol (LDL-c) levels and the reduction in cardiovascular events is indisputable,[1] the best way to select individuals in the population for treatment with lipid-lowering drugs is controversial, and the recommendations vary in different guidelines.[2–7]

The V Brazilian Guideline on Dyslipidemia and Atherosclerosis Prevention (V Brazilian Guideline), published in 2013, is based on the classical precept, used for many years, of establishing more aggressive LDL-c goals for individuals at higher cardiovascular risk.[2]

The American College of Cardiology (ACC)/American Heart Association (AHA) guideline, from now on referred to as North American Guideline, also published in 2013, does not advocate meeting LDL-c goals, but elects groups of individuals who benefit from statin use, based on their clinical antecedents or absolute risk for major cardiovascular events.[3] In addition, the North American Guideline proposes new equations to calculate the cardiovascular risk, the pooled cohort equations (PCE), derived from cohorts representative of the North American population.[8]

Both the way of stratifying the cardiovascular risk and the criteria for statin eligibility can vary substantially, depending on the guideline used, which impacts the individual therapeutic decision-making and has an expressive repercussion to the health system.

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The objectives of this study, carried out with mainly healthy individuals in primary prevention and with no clinical manifestation indicative of high cardiovascular risk, were: (1) to assess the relationship between cardiovascular risk categorized according to the V Brazilian Guideline recommendations and the risk calculated by use of the PCE; (2) to compare the proportion of individuals eligible for statins, according to either the V Brazilian Guideline or the North American Guideline criteria.

Methods

Population studied

The present study included individuals consecutively evaluated at the Preventive Medicine Center of the Albert Einstein Israeli Hospital (São Paulo-SP) from 01/2009 to 12/2015. Data were prospectively collected. The study protocol comprises complete clinical history and physical examination performed by a clinician, treadmill exercise test and blood tests (lipid profile, fasting glycemia, high-sensitivity C-reactive protein [hs-CRP]), as previously detailed.[9]

Individuals with the following characteristics were excluded: age < 40 years or > 75 years; self-reported antecedents or detection of significant clinical or subclinical cardiovascular atherosclerotic disease, abdominal aortic aneurysm or diabetes mellitus; LDL-c ≥ 190 mg/dL; and current use of lipid-lowering drugs. In addition, individuals with parameters outside the recommended range for using the cardiovascular risk equations (total cholesterol < 130 mg/dL or > 320 mg/dL, high-density lipoprotein cholesterol [HDL-c] < 20 mg/dL or > 100 mg/dL, systolic blood pressure < 90 mm Hg or > 200 mm Hg) were excluded, as were those whose missing data prevented risk calculation.

Cardiovascular risk according to the V Brazilian Guideline

As recommended by the V Brazilian Guideline, the Framingham general cardiovascular risk score was calculated by using the proper equation with continuous variables (age, systolic blood pressure, total cholesterol, HDL-c) and categorical variables (sex, arterial hypertension treatment or non-treatment, presence or absence of diabetes mellitus and smoking).[10] That score calculates the risk of death from coronary artery disease, myocardial infarction, angina, ischemic or hemorrhagic stroke, transient ischemic attack, peripheral vascular disease or heart failure in 10 years.[10]

In addition, the presence or absence of aggravating risk factors, capable of re-stratifying cardiovascular risk, based on the V Brazilian Guideline recommendations, was assessed.[2] The following aggravating risk factors were considered: hs-CRP > 2 mg/L and < 10 mg/L in the absence of inflammatory conditions (not related to atherosclerosis); family history of premature coronary artery disease (male first-degree relative < 55 years or female first-degree relative < 65 years); metabolic syndrome (according to the *International Diabetes Federation* criteria[11]); and subclinical atherosclerosis (detected on ultrasound of the carotid arteries or computed tomography of the coronary arteries).[2] The assessment of subclinical atherosclerosis is not part of the routine protocol at our service, so its request was up to the clinician in charge or to the patient's attending physician.

Individuals with a Framingham general cardiovascular risk score < 5% were considered at low or intermediate risk, depending on the absence or presence of a family history of premature coronary artery disease, respectively. Women with a general risk score between 5% and 10%, as well as men with a general risk score between 5% and 20%, were classified as at an intermediate or high risk, depending on the absence or presence of aggravating factors, respectively. Women and men with global risk scores > 10% and > 20%, respectively, were stratified as at high risk.[2]

Cardiovascular risk according to the PCE

The cardiovascular risk was also calculated by use of the PCE, as recommended by the North American Guideline.[3,8] The PCE used a more modern statistical modeling that allows greater flexibility in accommodating the clinical variables used for risk prediction, which are the same described above for the Framingham general risk score, in addition to ethnicity.[8] Differently from the general risk score, the PCE calculate the risk of major cardiovascular events, such as death from coronary artery disease, non-fatal myocardial infarction and fatal or non-fatal stroke, in 10 years.[8]

Statin eligibility criteria

Based on the V Brazilian Guideline, two criteria of eligibility for statin use were arbitrarily considered: LDL-c above the goal advocated by the V Brazilian Guideline (BR-1 criterion) or LDL-c at least 30 mg/dL above that goal (BR-2 criterion).

The following LDL-c goals are recommended by the V Brazilian Guideline: < 100 mg/dL for individuals at intermediate risk and < 70 mg/dL for those at high risk.[2] Individuals at low cardiovascular risk, according to the V Brazilian Guideline, to whom the guideline recommends an individualized LDL-c goal, were not considered eligible for statin use according to the BR-1 and BR-2 criteria.

According to the North American Guideline, statin should be considered for individuals aged between 40 and 75 years, not diagnosed with clinical atherosclerotic cardiovascular disease or diabetes mellitus, with LDL-c between 70 mg/dL and 189 mg/dL, and cardiovascular risk by using PCE ≥ 7.5% in 10 years. Those with risk between 5.0% and < 7.5% can also be considered for statin use.[3]

Thus, this study considered two criteria of eligibility for statin use based on the North American Guideline: cardiovascular risk by using the PCE ≥ 5.0% (USA-1 criterion) or ≥ 7.5% (USA-2 criterion).

Statistical analysis

Knowing in advance that the data bank used in this study is mainly composed of male individuals and does not represent the general Brazilian population, the cardiovascular risk stratification was planned to be evaluated separately for women and men. Likewise, statin eligibility was analyzed in subgroups defined by sex, age group and cardiovascular risk categories.

Categorical variables were expressed as percentages, and the chi-square test was used for comparisons. Continuous variables were expressed as means and standard deviations; non-paired Student *t* test was used to compare baseline characteristics between men and women, while analysis of variance (ANOVA) was used to compare the cardiovascular risk obtained from the PCE among the low, intermediate and high risk categories. Considering the large sample size and the central limit theorem, according to which the distribution of the sample means always tends to normality, we assumed that all variables had a normal distribution and could be analyzed by use of parametric tests.

The analyses were performed with Microsoft Office Excel tools and Stata statistical program, 13.0 version. A p value < 0.05 was considered statistically significant.

Ethical aspects

The study was approved by the Ethics Committee in Research of the Albert Einstein Israeli Hospital (CAAE 54537916.2.0000.0071). Considering that this is a retrospective study using a data bank and involving a large number of individuals, many of whom seen several years before this study began, the written informed consent could not be used and the Ethics Committee approved its waiver.

Results

Population studied and its characteristics

Figure 1 details the individuals included in and excluded from the study. From the 32,532 individuals initially identified in the data bank, 18,585 (57%) were excluded, most of whom (76%) because of age < 40 years.

Of the final sample of 13,947 individuals, 9,901 (71%) were male. Table 1 shows the main characteristics of the population studied. Most women were at low cardiovascular risk. Despite the comparable mean age, the male population was characterized by a less favorable lipid profile, higher frequency of metabolic syndrome-related changes and higher cardiovascular risk as compared to women.

A significant percentage of individuals was re-stratified into a higher-risk category because of the presence of an aggravating factor. Of the 577 women at intermediate risk based on the V Brazilian Guideline, 332 (58%) had a Framingham general risk score < 5% and family history of premature coronary artery disease. However, that situation occurred in only 187 (5%) of the 3,775 men stratified as at intermediate risk.

In addition, of the 500 women at high risk according to the V Brazilian Guideline, 366 (73%) had a Framingham general risk score between 5% and 10%, and were re-stratified due to the presence of an aggravating factor. Of the 4,046 men at high risk, 3,221 (80%) had a Framingham general risk score between 5% and 20% and an aggravating factor. Metabolic syndrome was the major single aggravating factor responsible for re-stratification into high risk, for both sexes (Figure 2).

Cardiovascular risk by the V Brazilian Guideline versus risk calculated by the PCE

Figure 3 shows the distribution of the cardiovascular risk categories calculated by using the PCE, according to the stratum of cardiovascular risk determined by the V Brazilian Guideline. For both sexes, a high proportion of individuals with PCE risk < 5% in 10 years was observed, even in the categories of intermediate and high risk, according to the V Brazilian Guideline. However, only a minority of individuals stratified as at high risk, according to the V Brazilian Guideline, had a PCE risk ≥ 7.5% in 10 years.

Among women, the means ± standard deviations of cardiovascular risks according to the PCE were as follows: 0.8 ± 0.6% in the low-risk category; 1.8 ± 1.6% in the intermediate-risk category; and 4.3± 3.4% in the high-risk category ($p < 0.01$). Among men, the respective values were 1.2 ± 0.4%, 4.1 ± 2.4% and 6.9 ± 5.4% ($p < 0.01$).

Statin eligibility

Statin eligibility was significantly higher according to the BR-1 and BR-2 criteria, as compared to the USA-1 and USA-2 criteria, for both women and men. According to the BR-1, BR-2, USA-1 and USA-2 criteria, 975 (24%), 705 (17%), 156 (4%) and 63 (2%) women, respectively, would be eligible for statin use ($p < 0.01$). The respective numbers for men were 7,381 (75%), 5,704 (58%), 3,050 (31%) and 1,696 (17%, $p < 0.01$).

A higher proportion of women eligible for statins according to the V Brazilian Guideline criteria as compared to those of the North American Guideline was observed in all age groups analyzed, and in those both at intermediate and high risks, according to the V Brazilian Guideline (Figures 4 and 5). The proportion of candidates for statin was 10 times greater according to the BR-1 criterion, as compared to the USA-1 criterion, for women aged between 50 and < 60 years (Figure 4), 19 times greater in those classified as at intermediate risk according to the V Brazilian Guideline, and 4 times greater in those at high risk (Figure 5).

In men, the higher rate of statin eligibility according to the Brazilian criteria was also observed in those at intermediate risk and at high risk (Figure 5) and aged < 60 years, but this was not detected in the subgroup aged 60-75 years (Figure 4). As compared to the USA-1 criterion, statin eligibility according to the BR-1 criterion increases by 7 times in men aged between 40 and < 50 years (Figure 4), triples in those at intermediate risk, and doubles in those at high risk (Figure 5).

Agreement and disagreement between the statin eligibility criteria

The BR-1 and USA-1 criteria were used to assess agreement and disagreement regarding statin eligibility based on the Brazilian and North American guidelines.

Among women, there was agreement between the criteria to not indicate statin in 76% of the population, while both criteria considered statin in only 4% of the cases.

Among men, there was agreement between the criteria in 54% of the cases: in 24% statin would not be considered by any criterion, while 30% of the individuals would be candidates for statin according to both criteria.

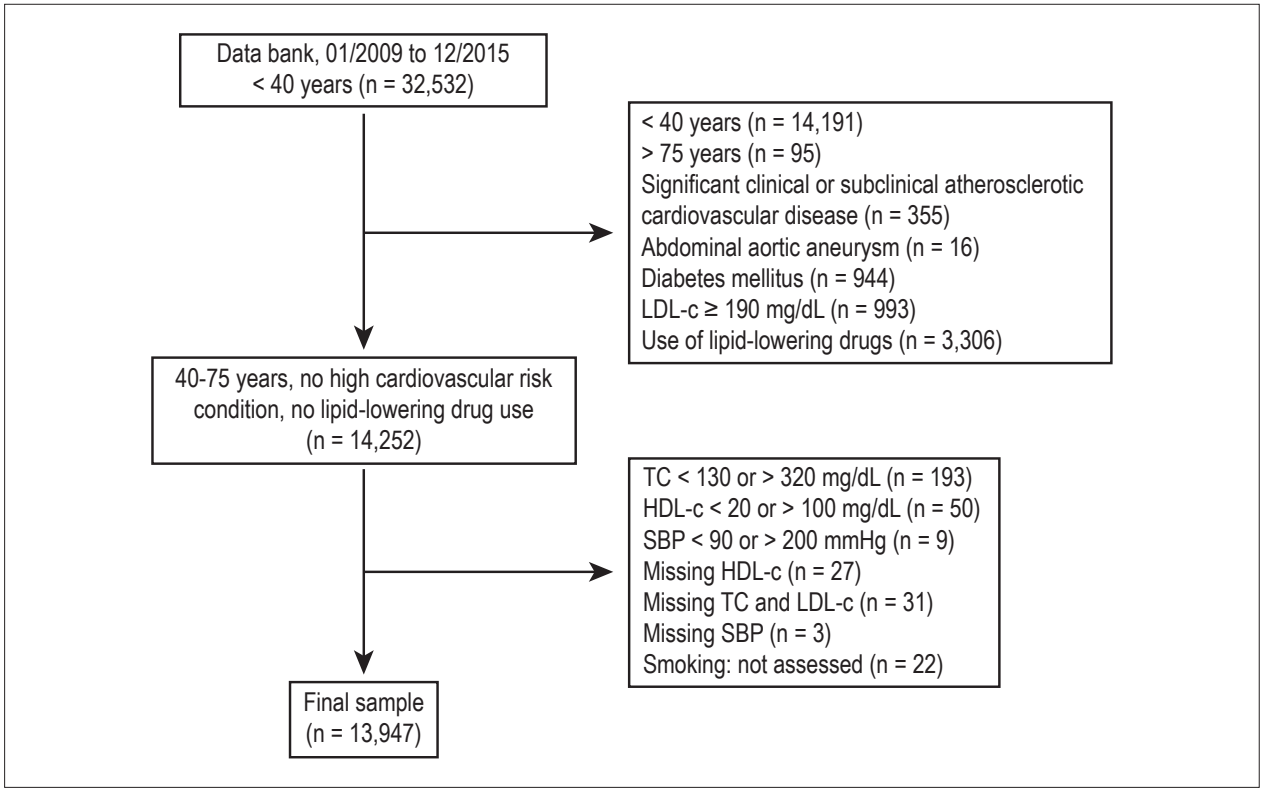

Figure 1 – *Flowchart detailing individuals included in and excluded from the study. SBP: systolic blood pressure; TC: total cholesterol.*

Table 1 – Characteristics of the study population

		Total (n = 13,947)	Women (n = 4,046)	Men (n = 9,901)	p (women vs men)
Age (years)		48 ± 6	48 ± 6	48 ± 7	< 0.01
BMI (kg/m²)		26.8 ± 4.2	25.3 ± 4.5	27.5 ± 3.9	< 0.01
Total cholesterol (mg/dL)		203 ± 31	198 ± 31	205 ± 31	< 0.01
LDL-c (mg/dL)		127 ± 28	119 ± 28	130 ± 28	< 0.01
HDL-c (mg/dL)		49 ± 13	58 ± 14	45 ± 11	< 0.01
Triglycerides (mg/dL)		137 ± 85	106 ± 57	150 ± 91	< 0.01
Fasting glycemia (mg/dL)		89 ± 11	85 ± 9	90 ± 11	< 0.01
hs-CRP (mg/L)*		2.7 ± 5.5	3.1 ± 5.9	2.5 ± 5.3	< 0.01
Arterial hypertension		2,117 (15)	419 (10)	1,698 (17)	< 0.01
Metabolic syndrome		3,557 (26)	613 (15)	2,944 (30)	< 0.01
Smoking		1,268 (9)	335 (8)	933 (9)	0.04
Family history of premature coronary disease		1,399 (10)	432 (11)	967 (10)	< 0.11
Cardiovascular risk (V Brazilian Guideline)	Low	5,049 (36)	2,969 (73)	2,080 (21)	< 0.01
	Intermediate	4,352 (31)	577 (14)	3,775 (38)	
	High	4,546 (33)	500 (12)	4,046 (41)	
Framingham general cardiovascular risk (% in 10 years)		8.0 ± 6.7	3.5 ± 2.8	9.8 ± 7.0	< 0.01
Cardiovascular risk (PCE, ACC/AHA 2013, % in 10 years)		3.7 ± 4.1	1.4 ± 1.8	4.6 ± 4.3	< 0.01

*Data expressed as mean ± standard deviation or n (%). ACC/AHA: American College of Cardiology/American Heart Association; BMI: body mass index; hs-CRP: hogh-sensitivity C-reactive protein; PCE: pooled cohort equations. * Data on hs-CRP were available in 96% of the study participants.*

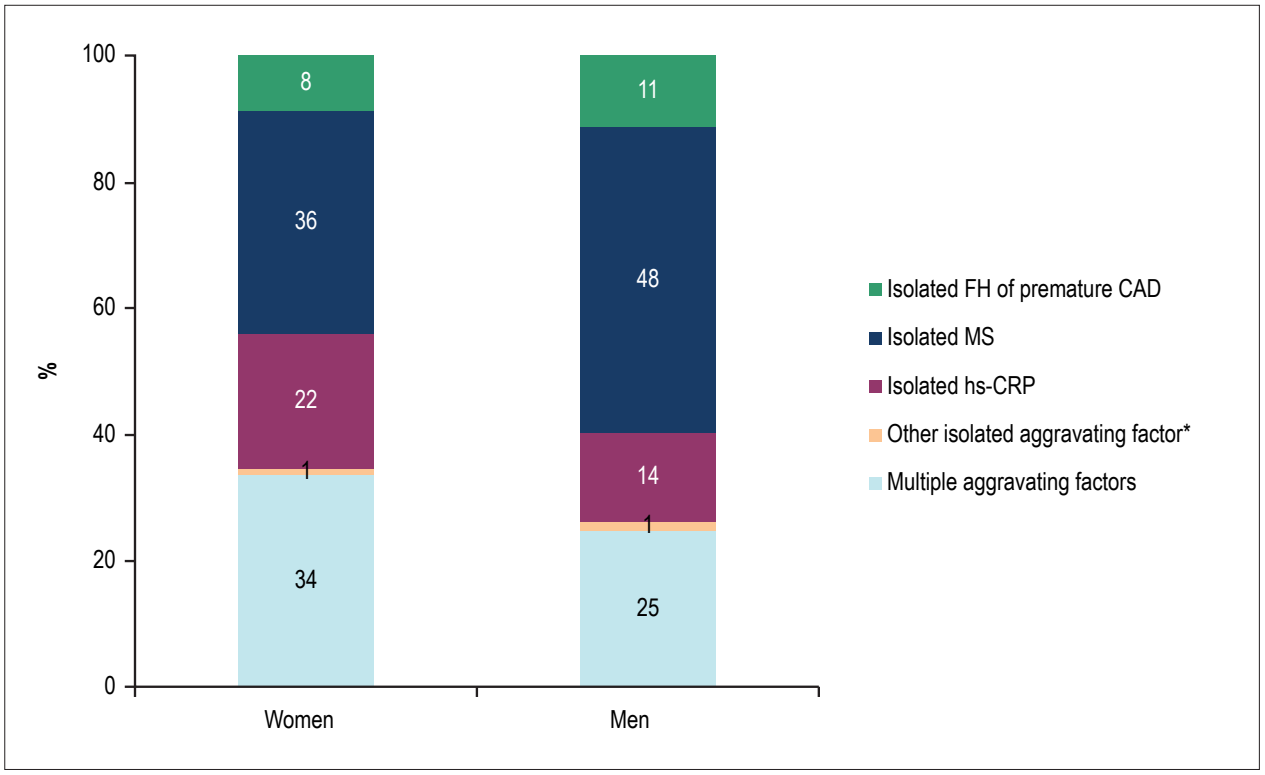

Figure 2 – *Aggravating cardiovascular risk factors responsible for risk re-stratification from intermediate to high risk. CAD: coronary artery disease; FH: family history; hs-CRP: high-sensitivity C-reactive protein; MS: metabolic syndrome. *Albuminuria, left ventricular hypertrophy, carotid intima-media thickness or coronary calcification.*

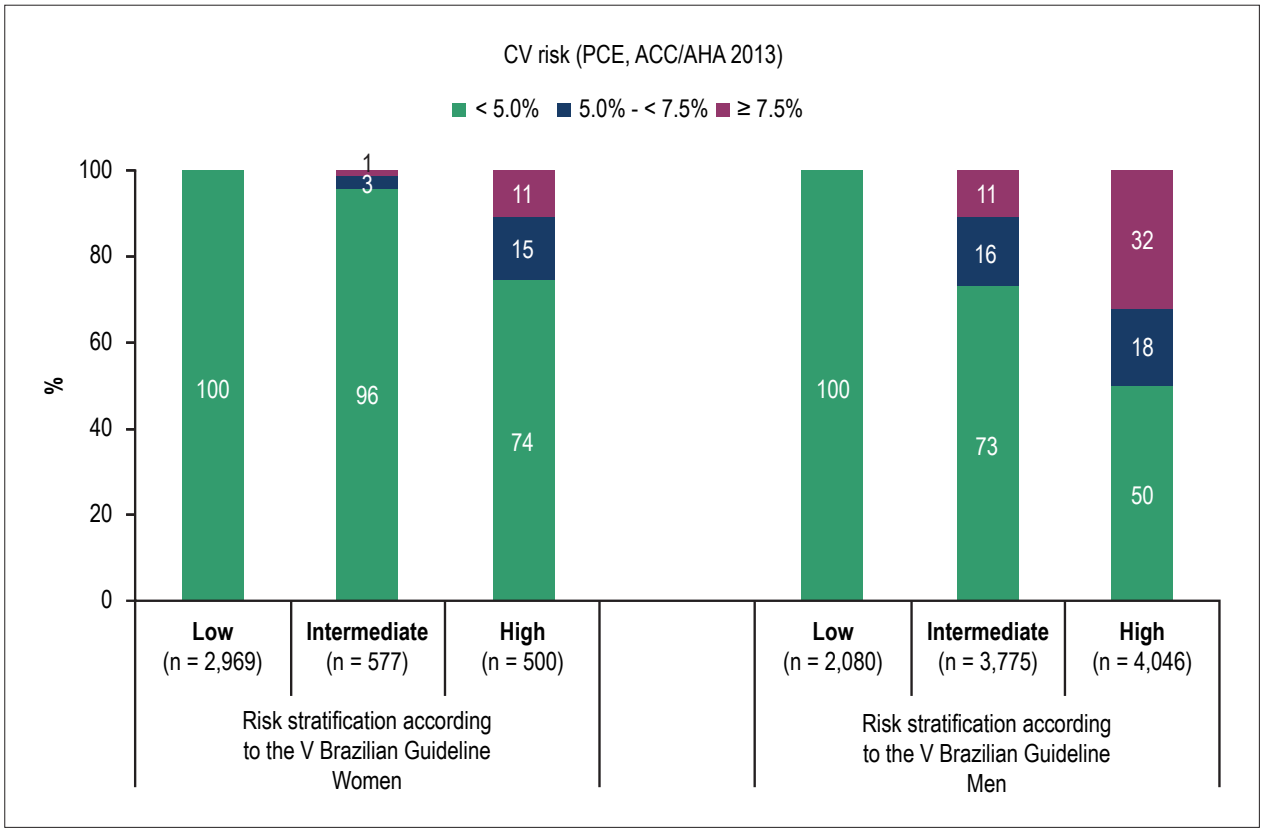

Figure 3 – *Categories of cardiovascular (CV) risk based on the pooled cohort equations (PCE) (ACC/AHA 2013), by sex and CV risk category according to the V Brazilian Guideline.*

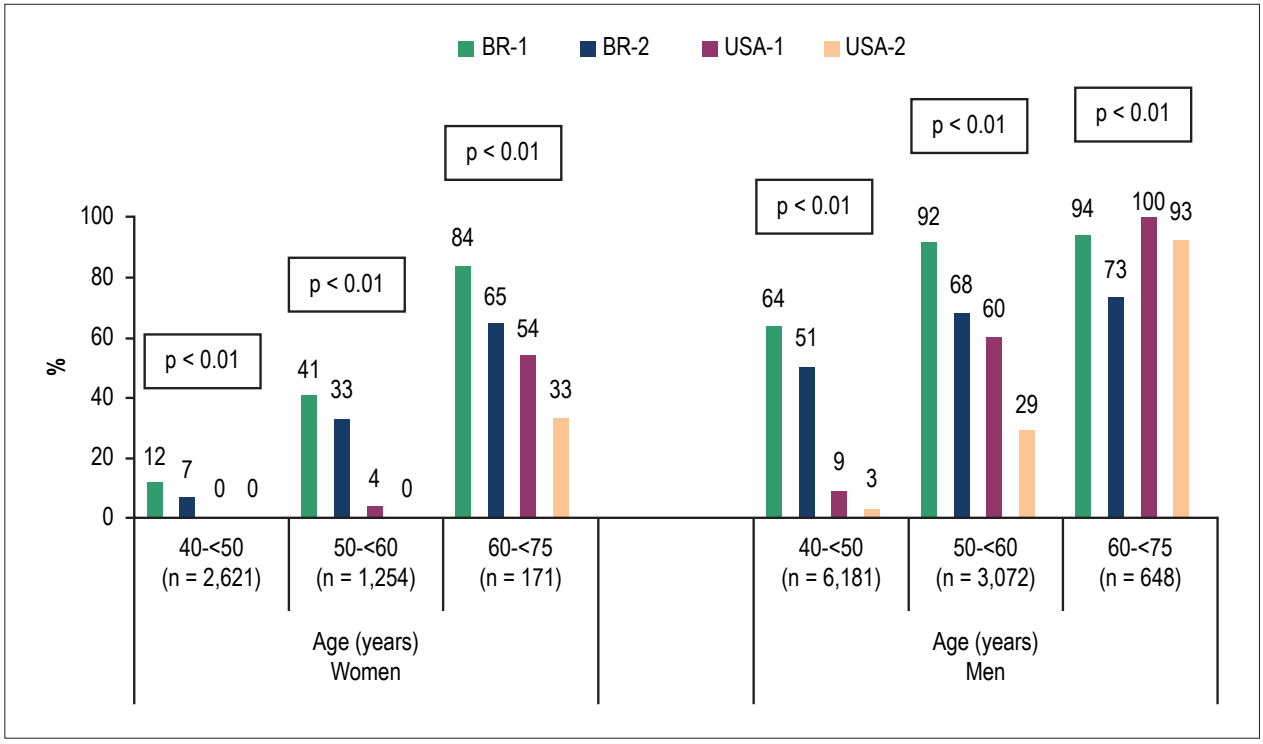

Figure 4 – *Proportion of individuals eligible for statin based on different criteria, by sex and age group.*

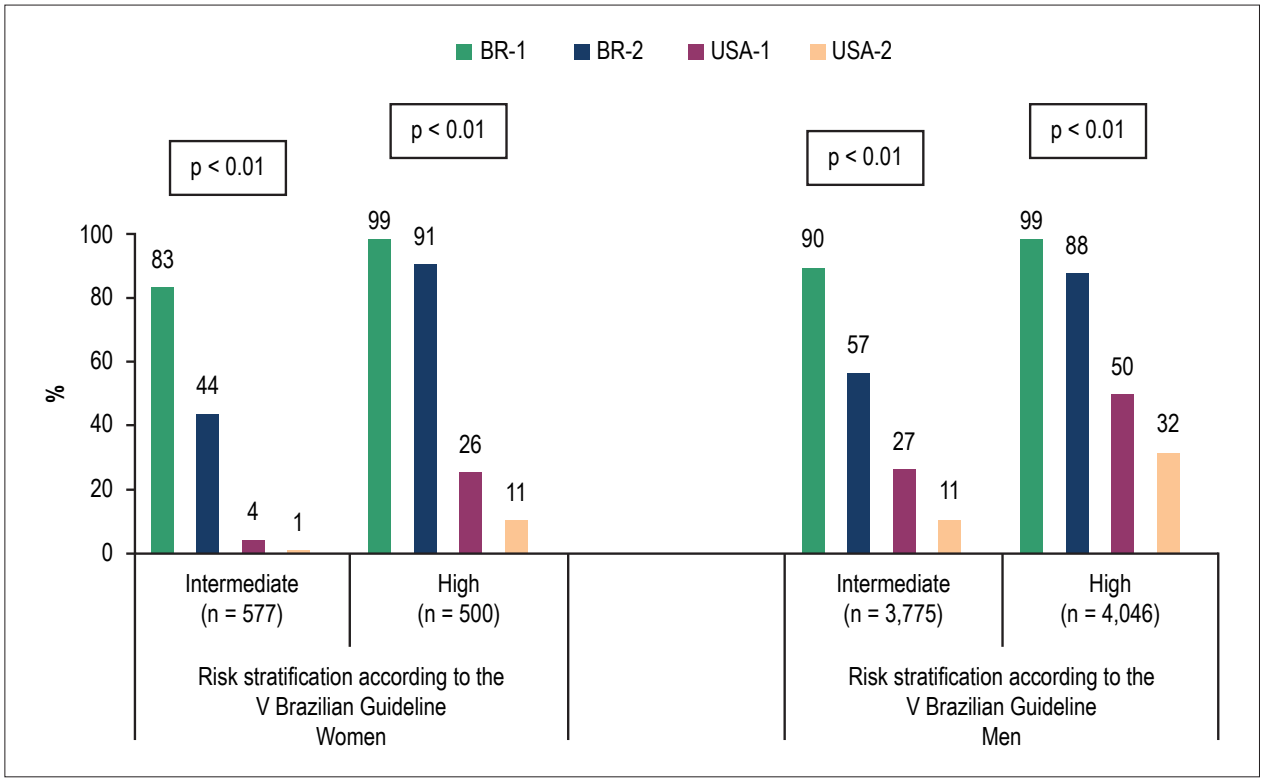

Figure 5 – *Proportion of individuals eligible for statin based on different criteria, by sex and cardiovascular risk according to the V Brazilian Guideline.*

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Eighty-five percent of women and 60% of men who were eligible for statin based on the BR-1 criterion would not be candidates for statin based on the USA-1 criterion (Figure 6). However, almost all individuals eligible for statin use based on that North American criterion would also be eligible based on that Brazilian criterion (Figure 6). The rare cases eligible for statin based on the USA-1 criterion, but not on the BR-1 criterion, were mainly observed among the elderly (Figure 7).

Analyzing the subgroups defined by age group, the disagreement rate between the BR-1 and USA-1 criteria increases with age in women, but decreases in men (Figure 7). While for most (88%) women between 40 and < 50 years there was agreement regarding the non-indication for statin, for men of the same age group there was 50% disagreement between the criteria (Figure 7). However, while the criteria agreed in considering statin for 94% of the men aged 60-75 years, for women of the same age group disagreement between the criteria reached 40% (Figure 7).

Among individuals classified as at intermediate risk and, to a lower extent, at high risk according to the V Brazilian Guideline, the disagreement rate between the BR-1 and USA-1 criteria was high, with an expressive number of cases of statin eligibility by the BR-1 criterion, but not by the USA-1 criterion, mainly among women (Figure 7).

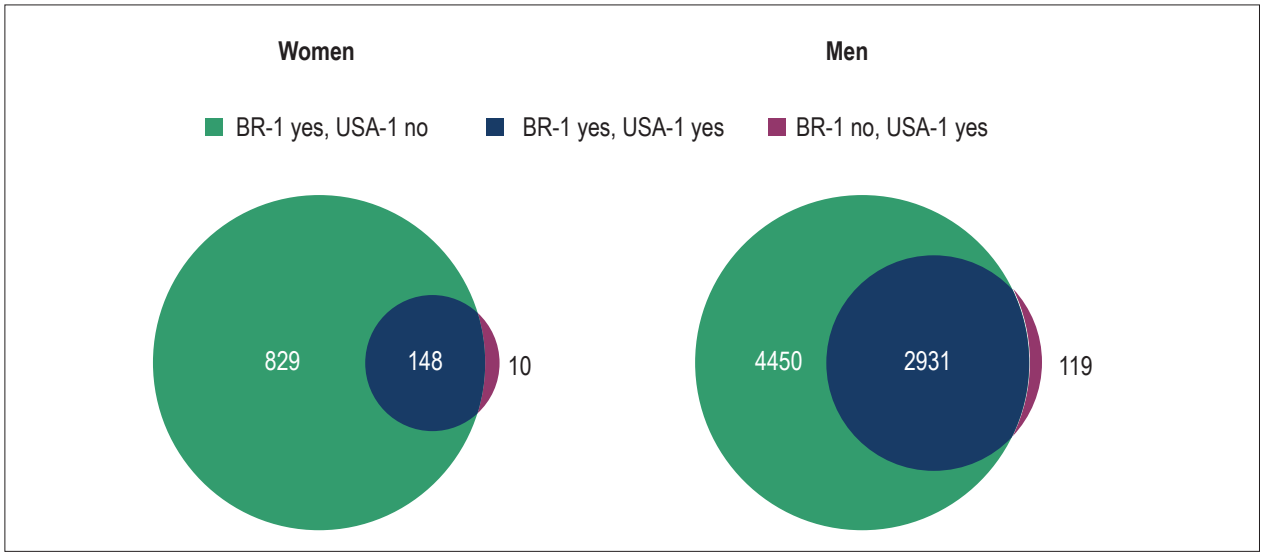

Figure 6 – *Venn diagram showing the number of eligible ("yes") or non-eligible ("no") individuals for statin use based on the BR-1 and USA-1 criteria, by sex.*

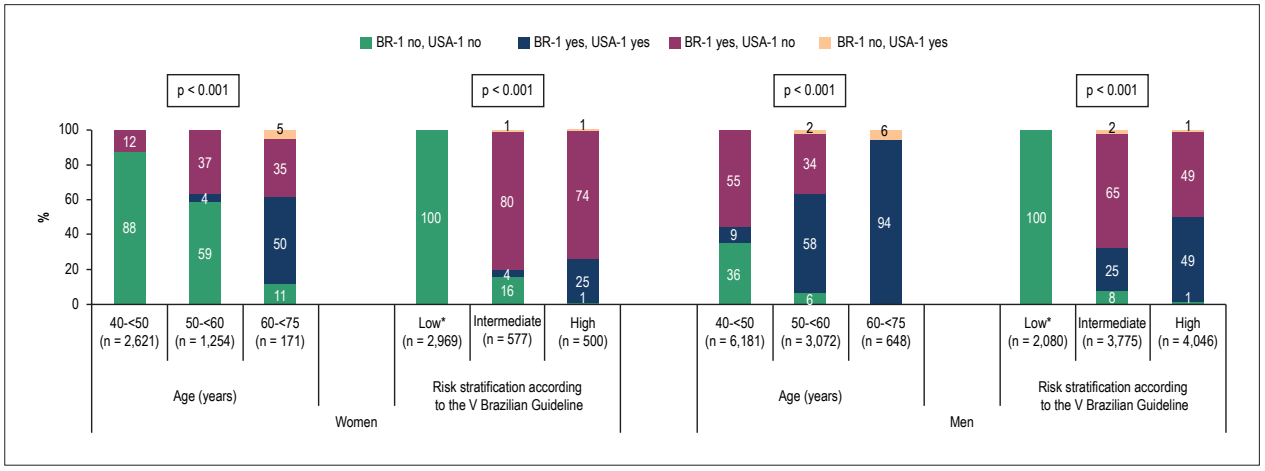

Figure 7 – *Proportion of eligible ("yes") or non-eligible ("no") individuals for statin use based on the BR-1 and USA-1 criteria, by sex, age group and cardiovascular risk according to the V Brazilian Guideline. *Individuals classified as at low risk based on the V Brazilian Guideline were considered non-eligible for statin use according to the BR-1 criterion (see Methods).*

Discussion

In the present study, we observed a large discrepancy in statin eligibility between the V Brazilian Guideline and the 2013 ACC/AHA Cholesterol Guideline, the number of candidates for statin being significantly higher following the recommendations of the Brazilian Guideline.

Among individuals stratified as at intermediate or high risk, according to the V Brazilian Guideline, the number of those eligible for statin based on the Brazilian Guideline, but not on the North American Guideline, is high mainly among women. This is directly related to the fact that most individuals considered at intermediate or high risk by the V Brazilian Guideline has a low risk calculated with the PCE. For those classified as at high risk according to the Brazilian Guideline, for example, the mean risk in 10 years calculated with the PCE was < 5% for women and < 7% for men, while North American guidelines consider individuals at high risk those with risk ≥ 15% or ≥ 20% in 10 years.[4,12]

That discrepancy between the risk stratifications recommended by the V Brazilian Guideline and the North American Guideline is associated with the finding that most individuals classified as at high risk by the V Brazilian Guideline has a Framingham general risk score at intermediate levels, being re-stratified due to the presence of an aggravating factor, mainly metabolic syndrome and hs-CRP elevated levels.

The magnitude of risk reclassification observed in this study might be overestimated as compared to that of clinical practice. The hs-CRP measurement was performed as part of this study protocol and was available in 96% of the participants, a proportion certainly higher than that in the real world. In addition, hs-CRP was measured only once. Among individuals reclassified due to hs-CRP elevation, there might be cases in which that elevation would not repeat, if a second measurement was performed, and cases in which the hs-CRP increase occurred due to incipient or subclinical inflammatory conditions, not diagnosed or not reported by the attending physician.

The highest rate of statin eligibility according to the Brazilian Guideline as compared to the North American Guideline can also be related to changes in the V Brazilian Guideline[2] as compared to the previous one,[13] which made it more "aggressive": a reduction in the LDL-c goals, a reduction in the thresholds to categorize intermediate and high risks (mainly in women), and the adoption of the Framingham general risk score in the place of the risk score for "hard" coronary outcomes. The Canadian guideline, for example, which also recommends risk stratification based on the same general cardiovascular risk score, although modified (the risk is doubled in the presence of family history of premature cardiovascular disease), uses higher cutoff points than those of the V Brazilian Guideline to separate the risk categories: low-risk individuals are those with score < 10%, intermediate-risk individuals are those with score ≥ 10% and < 20%, and high-risk individuals are those with score ≥ 20% in 10 years, with no distinction between men and women.[6]

Our results differ from those of a recent publication that reports a higher number of candidates for statin according to the North American Guideline, as compared to the IV Brazilian Guideline on Dyslipidemia,[13] in participants of the ELSA-Brasil Study.[14] The North American recommendations have also shown higher statin eligibility as compared to the European guidelines,[15,16] but not to the Canadian guideline.[17]

The only subgroup analyzed in this study that showed a high agreement between the Brazilian and North American criteria was that of men aged 60-75 years, whose proportion of statin eligibility was very elevated, regardless of the criterion used. Other analyses have also detected a high rate of statin eligibility for the elderly, when applying the North American Guideline.[16] In addition, that finding might be related to the possibility that PCE overestimate the cardiovascular risk in the subgroups of higher risk, such as the elderly, which has been reported in some cohorts.[18,19]

More individuals on statins would mean a lower mean LDL-c level and greater cardiovascular benefit for the population, because of the unquestionable relationship between those two factors, even in populations at lower cardiovascular risk.[20] That benefit, however, would be provided at the expense of higher costs, higher incidence of statin-related side effects, and especially a greater number needed to treat (NNT) to prevent one cardiovascular event, which foster discussions on medical overtreatment.[21] Cost-effectiveness analyses might help to better define the advantages of following one or the other guideline.

Limitations

This study was based on theoretical considerations that might not reflect precisely the real world. For example, this study considered non-eligible for statin those stratified as at low cardiovascular risk, according to the V Brazilian Guideline, but part of those individuals could receive a drug prescription in clinical practice. Conversely the present study did not include the North American Guideline recommendation to consider statin use for individuals with a low calculated cardiovascular risk, but with some conditions known to increase the risk, such as LDL-c ≥ 160 mg/dL, family history of premature atherosclerotic cardiovascular disease, hs-CRP elevation, and significant coronary calcification on computed tomography.[3]

Conclusions

For healthy individuals in primary prevention, management of blood cholesterol based on the V Brazilian Guideline on Dyslipidemias or the 2013 ACC/AHA Cholesterol Guideline can vary substantially. Among those classified as at intermediate or high risk according to the V Brazilian Guideline, there is a high proportion of individuals eligible for statin according to the Brazilian Guideline criteria, but not according to the North American Guideline criteria. This finding is associated with the fact that most individuals at intermediate or high risk according to the Brazilian Guideline

have a low risk calculated by the PCE, in addition to the fact that most individuals classified as at high risk owe that to the presence of an aggravating factor.

Our results can allow a critical reflection on the current guidelines and continuous improvement of the recommendations. In addition, they can help attending physicians with clinical judgement and therapeutic decision making.

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Author contributions

Conception and design of the research, Acquisition of data, Analysis and interpretation of the data and Writing of the manuscript: Cesena FHY; Statistical analysis: Cesena FHY, Bittencourt MS; Critical revision of the manuscript for intellectual content: Laurinavicius AG, Valente VA, Conceição RD, Bittencourt MS, Santos RD.

Potential Conflict of Interest

Dr. Fernando Henpin Yue Cesena received honoraria for participating in a clinical trial sponsored by Sanofi. Dr. Antonio Gabriele Laurinavicius is a Sanofi employee. Dr. Raul D. Santos receives honoraria as a consultant and speaker of the following companies: Amgen, Astra Zeneca, Biolab, Boehringer Ingelheim, Cerenis, Genzyme, Eli-Lilly, Kowa, Akcea, Pfizer, Praxis, Sanofi Regeneron, Merck and Unilever. The other authors report no conflict of interest.

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.

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The Expected Cardiovascular Benefit of Plasma Cholesterol Lowering with or Without LDL-C Targets in Healthy Individuals at Higher Cardiovascular Risk

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Abstract

Background: There is controversy whether management of blood cholesterol should be based or not on LDL-cholesterol (LDL-c) target concentrations.

Objectives: To compare the estimated impact of different lipid-lowering strategies, based or not on LDL-c targets, on the risk of major cardiovascular events in a population with higher cardiovascular risk.

Methods: We included consecutive individuals undergoing a routine health screening in a single center who had a 10-year risk for atherosclerotic cardiovascular disease (ASCVD) ≥ 7.5% (pooled cohort equations, ACC/AHA, 2013). For each individual, we simulated two strategies based on LDL-c target (≤ 100 mg/dL [$S_{target-100}$] or ≤ 70 mg/dL [$S_{target-70}$]) and two strategies based on percent LDL-c reduction (30% [$S_{30\%}$] or 50% [$S_{50\%}$]).

Results: In 1,897 subjects (57 ± 7 years, 96% men, 10-year ASCVD risk 13.7 ± 7.1%), LDL-c would be lowered from 141 ± 33 mg/dL to 99 ± 23 mg/dL in $S_{30\%}$, 71 ± 16 mg/dL in $S_{50\%}$, 98 ± 9 mg/dL in $S_{target-100}$, and 70 ± 2 mg/dL in $S_{target-70}$. Ten-year ASCVD risk would be reduced to 8.8 ± 4.8% in $S_{50\%}$ and 8.9 ± 5.2 in $S_{target-70}$. The number of major cardiovascular events prevented in 10 years per 1,000 individuals would be 32 in $S_{30\%}$, 31 in $S_{target-100}$, 49 in $S_{50\%}$, and 48 in $S_{target-70}$. Compared with $S_{target-70}$, $S_{50\%}$ would prevent more events in the lower LDL-c tertile and fewer events in the higher LDL-c tertile.

Conclusions: The more aggressive lipid-lowering approaches simulated in this study, based on LDL-c target or percent reduction, may potentially prevent approximately 50% more hard cardiovascular events in the population compared with the less intensive treatments. Baseline LDL-c determines which strategy (based or not on LDL-c target) is more appropriate at the individual level. (Arq Bras Cardiol. 2017; 108(6):518-525)

Keywords: Cholesterol, HDL / blood; Cholesterol, LDL / blood; Hypercholesterolemia / blood; Risk Factors; Coronary Artery Disease.

Introduction

Lowering low-density lipoprotein-cholesterol (LDL-c) levels is a well-established way to reduce the risk of cardiovascular events[1] and more aggressive LDL-c lowering strategies are recommended for subjects at higher risk.[2-7] However, risk stratification, as well as recommendations for the management of blood cholesterol, differs across different guidelines.[2-7]

The latest documents from the European Society of Cardiology (ESC),[3] European Atherosclerosis Society (EAS),[4] National Lipid Association (NLA),[5] Canadian Cardiovascular Society,[6] and the Atherosclerosis Department of the Brazilian Society of Cardiology[7] maintain the long-standing principle of establishing LDL-c target concentrations according to the absolute risk of cardiovascular events.

In 2013, however, the American College of Cardiology (ACC)/American Heart Association (AHA) cholesterol management guidelines changed this concept, abolishing the historical LDL-c targets and recommending statin prescription, at moderate or high intensity, according to the predicted absolute risk of events.[2]

Whether we should pursue LDL-c target levels or prescribe fixed-dose statins aiming at a percent LDL-c reduction is a subject of debate. Moreover, there is no consensus on how aggressive the lipid-lowering strategies should be at different risk levels, and the incremental benefit of more aggressive therapies should be counterbalanced by higher risk of adverse events and higher costs.

In order to address these issues, the purpose of this study was to compare the estimated impact of different cholesterol-lowering strategies on the risk of major cardiovascular events in

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healthy subjects considered to be at higher cardiovascular risk. Specifically, we simulated cholesterol-lowering approaches at different intensities and based on LDL-c target or fixed percent reduction.

Methods

Subjects and estimation of cardiovascular risk

Participants were selected from a large database of individuals undergoing a routine health screening at the Preventive Medicine Center of the Hospital Israelita Albert Einstein, São Paulo, Brazil, from January 2006 to June 2013. Data were prospectively collected from consecutive predominantly healthy individuals who underwent interview with a clinician, physical examination, treadmill stress test, and blood collection, among several procedures, as described elsewhere.[8] History of cardiovascular events and current use of medication were verified. Fasting blood glucose and lipids were performed, among other tests. LDL-c was calculated using the Friedewald equation,[9] except for the cases in which the triglyceride level was higher than 400 mg/dL, when LDL-c was measured by a direct method.

We included subjects with a calculated 10-year risk for atherosclerotic cardiovascular disease (ASCVD) ≥ 7.5%, according to the 2013 ACC/AHA risk calculator derived from the pooled cohort equations.[10] This quantitative risk assessment method predicts the 10-year risk of developing a first cardiovascular event, defined as nonfatal myocardial infarction, coronary heart disease death, or fatal or nonfatal stroke, among people without cardiovascular disease.[10]

Exclusion criteria were as follows:

- individuals in secondary prevention, defined as history of clinical ASCVD, subclinical ASCVD deemed significant by the assistant physician, or aortic aneurysm;
- current use of lipid-lowering medication;
- presence of variable(s) out of the recommended range to use the pooled cohort equations: age < 40 years or > 79 years, total cholesterol < 130 mg/dL (3.4 mmol/L) or > 320 mg/dL (8.3 mmol/L), high-density lipoprotein-cholesterol (HDL-c) < 20 mg/dL (0.5 mmol/L) or > 100 mg/dL (2.6 mmol/L), or systolic blood pressure < 90 mmHg or >200 mmHg;
- missing data not allowing calculations needed for risk estimation or predicted cardiovascular benefit.

The study was approved by the Research Ethics Committee of the Hospital Israelita Albert Einstein, São Paulo, Brazil (CAAE: 53641916.9.0000.0071).

Simulated strategies and assumptions

For every subject, two strategies based on LDL-c target ($S_{target\text{-}100}$ and $S_{target\text{-}70}$) and two based on fixed percent LDL-c reduction ($S_{30\%}$ and $S_{50\%}$) were simulated. Table 1 depicts the simulated treatments and the expected final LDL-c after the adoption of each strategy. In the strategies with LDL-c target, to reflect the common clinical practice, it was assumed that medication would be prescribed only if LDL-c was at least 20% higher than the target, and drug therapy would reduce LDL-c by at least 30%. In the strategies based on percent reduction, medication would be prescribed only if baseline LDL-c was ≥ 70 mg/dL (1.8 mmol/L), as recommended by the 2013 ACC/AHA guideline.[2]

Estimation of cardiovascular risk reduction

The expected variation in LDL-c allowed us to estimate the absolute cardiovascular risk reduction for every individual in each of the simulated strategies. For these calculations, we considered a 22% relative risk reduction (risk ratio [RR] equal to 0.78) in major cardiovascular events for each 39 mg/dL (1 mmol/L) of LDL-c lowered, based on the Cholesterol Treatment Trialists' (CTT) Collaboration meta-analysis.[1] Accordingly, if LDL-c lowers 78 mg/dL (2 mmol/L), the relative risk reduces 39% (RR = 0.78 x 0.78 = 0.61). If LDL-c lowers 117 mg/dL (3 mmol/L), the relative risk is expected to reduce 53% (RR = 0.78 x 0.78 x 0.78 = 0.47).[1] Therefore, the final cardiovascular risk was given by the following formula:

$$\text{final cardiovascular risk} = \text{baseline cardiovascular risk} \times 0.78^{n},$$

where n is the amount of LDL-c reduction expressed in mmol/L and the baseline cardiovascular risk is the ASCVD risk derived from the pooled cohort equations.[10] Contemporary risk calculators and cost-effectiveness studies also use CTT results in order to estimate the benefits of lipid-lowering therapy.[11–14]

The number of events prevented in 10 years per 1,000 individuals assigned to a simulated strategy was calculated by dividing 1,000 by the number needed to treat (NNT), which was calculated directly as the reciprocal of the absolute difference between the baseline and the final cardiovascular risks. Calculations were also performed for subgroups defined by baseline LDL-c concentration.

Statistical analyses

Categorical variables were expressed as proportions and the chi-square test was used in the comparisons. Continuous variables were assumed to have a normal distribution due to the large sample size and were expressed as means and standard deviations. The different strategies for cholesterol reduction were compared by multilevel mixed effects models with Bonferroni´s adjustment for multiple comparisons. Analyses were carried out with the use of the Stata software, version 13.0. P values < 0.05 were considered statistically significant.

Results

Study population

From an initial population of 24,874 individuals, we first excluded 171 (0.7%) subjects with history of clinical ASCVD, significant subclinical ASCVD or aortic aneurysm. Among 24,712 individuals in primary prevention of ASCVD,

Table 1 – Simulated treatments and the expected final LDL-c, according to strategies and baseline LDL-c

Strategy	Baseline LDL-c	Treatment	Final LDL-c
$S_{30\%}$	< 70 mg/dL (1.8 mmol/L)	None	= baseline LDL-c
	≥ 70 mg/dL	30% LDL-c reduction	= baseline LDL-c – 30%
$S_{50\%}$	< 70 mg/dL (1.8 mmol/L)	None	= baseline LDL-c
	≥ 70 mg/dL	50% LDL-c reduction	= baseline LDL-c – 50%
$S_{target-100}$	< 120 mg/dL (3.1 mmol/L)	None	= baseline LDL-c
	≥ 120 mg/dL	≥ 30% LDL-c reduction	= baseline LDL-c – 30% or 100 mg/dL (2.6 mmol/L)*
$S_{target-70}$	< 84 mg/dL (2.2 mmol/L)	None	= baseline LDL-c
	≥84 mg/dL	≥ 30% LDL-c reduction	= baseline LDL-c – 30% or 70 mg/dL (1.8 mmol/L)*

** The lower value was considered.*

we excluded 22,156 (89.7%) subjects with a 10-year risk for ASCVD < 7.5%. From the remaining 2,556 individuals, all of them with a 10-year risk for ASCVD ≥ 7.5%, we excluded 545 (21.3%) on current use of lipid-lowering drugs. The final study population consisted of 1,897 individuals (7.6% of the initial population, Figure 1).

Baseline characteristics

Table 2 shows the baseline characteristics of the study subjects. The mean age was 57 ± 7 years, 96% were men, mainly white, and the mean 10-year ASCVD risk was 13.7 ± 7.1%.

Medication use

According to the LDL-c thresholds to prescribe medication showed in Table 1, the percentage of individuals receiving a lipid-lowering drug would be 99% in strategies $S_{30\%}$ and $S_{50\%}$, 74% in $S_{target-100}$, and 96% in $S_{target-70}$ ($p < 0.001$).

LDL-c and absolute cardiovascular risk predicted reductions

The mean LDL-c achieved in the population would be significantly lower if participants were subjected to any of the more aggressive strategies ($S_{50\%}$ or $S_{target-70}$), compared with the less intensive approaches ($S_{30\%}$ and $S_{target-100}$, Figure 2A). The adoption of $S_{50\%}$ and $S_{target-70}$ would result in numerically comparable mean LDL-c in the population (71 ± 16 mg/dL [1.8 ± 0.4 mmol/L] and 70 ± 2 mg/dL [1.8 ± 0.1 mmol/L], respectively, p = 0.039). Also, the final mean LDL-c in the population would be comparable in $S_{30\%}$ and $S_{target-100}$ (99 ± 23 mg/dL [2.6 ± 0.6 mmol/L] and 98 ± 9 mg/dL [2.5 ± 0.2 mmol/L], respectively, p = 0.171). Of note, the distribution pattern of LDL-c in the population would be very different according to the strategy, with a wider distribution in the approaches based on percent reduction, compared with the modalities based on target concentration (Figure 2A).

In parallel to LDL-c reduction, $S_{50\%}$ and $S_{target-70}$ would similarly decrease the average population cardiovascular risk (to 8.8 ± 4.8% and 8.9 ± 5.2%, respectively, p = 1.000), whereas both $S_{30\%}$ and $S_{target-100}$ would reduce the mean cardiovascular risk to a comparable level (10.5 ± 5.6% and 10.6 ± 6.1%, respectively, p = 0.090). The expected final cardiovascular risk in the more aggressive strategies would be significantly lower than the risk predicted in the less intensive approaches (Figure 2B).

The number of major cardiovascular events prevented in 10 years per 1,000 individuals assigned to the strategy would be 32 in $S_{30\%}$, 31 in $S_{target-100}$, 49 in $S_{50\%}$, and 48 in $S_{target-70}$.

Despite resulting in similar mean values of final LDL-c and cardiovascular risk, the more aggressive strategies ($S_{50\%}$ and $S_{target-70}$) would be quite different depending on the way blood cholesterol is managed in the population. Indeed, the percentage of individuals achieving LDL-c ≤ 70 mg/dL (1.8 mmol/L) would be 98% in $S_{target-70}$, but only 49% in $S_{50\%}$ ($p < 0.001$). On the other hand, while 99% of the subjects would lower LDL-c by 50% in $S_{50\%}$, this proportion would be only 52% in $S_{target-70}$ ($p < 0.001$).

Influence of baseline LDL-c on the predicted absolute risk reduction

The superiority of a strategy based on LDL-c target over percent reduction, or vice-versa, is expected to be dependent on the baseline LDL-c.

In the intermediate LDL-c tertile of our population, $S_{30\%}$ and $S_{target-100}$ would prevent a comparable number of events, whereas $S_{50\%}$ and $S_{target-70}$ would also be similarly effective in reducing cardiovascular events (Figure 3). The more aggressive strategies would prevent approximately 50% more hard cardiovascular events than the less intensive modalities (Figure 3).

Subjects with lower LDL-c would benefit more from $S_{30\%}$ than from $S_{target-100}$, and more from $S_{50\%}$ than from $S_{target-70}$. In the lower LDL-c tertile, compared with $S_{target-70}$, $S_{50\%}$ would prevent 39% more hard cardiovascular events (Figure 3).

In individuals with higher LDL-c, $S_{target-100}$ would prevent more events than $S_{30\%}$, and $S_{target-70}$ would prevent 13% more cardiovascular events compared with $S_{50\%}$ (Figure 3).

Discussion

The present study highlights relevant aspects of the management of blood cholesterol in individuals at higher cardiovascular risk: (1) the cardiovascular benefit in the population would be similar for a strategy based on a 50% LDL-c reduction or targeting LDL-c ≤ 70 mg/dL (1.8 mmol/L); (2) the cardiovascular benefit would also be similar for a strategy based on a 30% LDL-c reduction or targeting LDL-c ≤ 100 mg/dL (2.6 mmol/L); (3) LDL-c lowering strategies based on target level or percent reduction

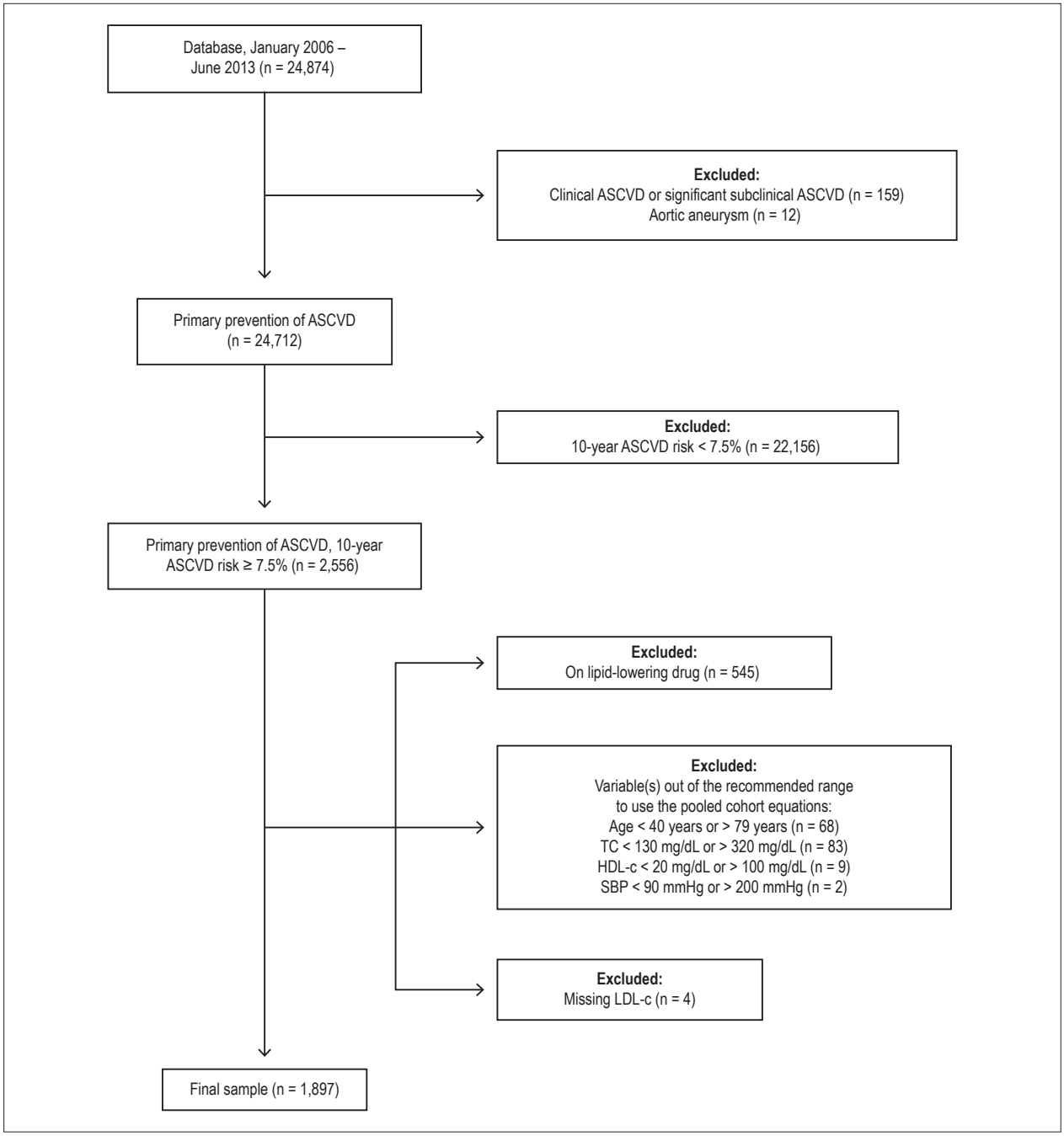

Figure 1 – *Schematic flowchart depicting included and excluded subjects. ASCVD: atherosclerotic cardiovascular disease; SBP: systolic blood pressure; TC: total cholesterol.*

may promote similar overall cardiovascular benefit despite resulting in different LDL-c distribution patterns in the population; (4) the more aggressive modalities (based on a 50% LDL-c reduction or targeting LDL-c ≤ 70 mg/dL) would prevent approximately 50% more hard cardiovascular events compared with the less intensive treatments; (5) baseline LDL-c determines which modality of treatment (based on target concentration or percent reduction) would prevent more cardiovascular events.

Since the publication of the 2013 ACC/AHA cholesterol management guidelines[2] recommending a switch from a treat-to-target approach to a statin dose-based strategy, intense debate has taken place both inside and outside the USA.[15–17] In the absence of randomized clinical trials directly comparing the outcome of different strategies, with or without LDL-c target concentrations, simulations may be of value to provide information that may help guide therapy and develop guidelines.

Table 2 – Baseline characteristics of participants

Characteristic	Value
Male gender	1,827 (96)
Age, years	57 ± 7
Total cholesterol, mg/dL (mmol/L)	221 ± 36 (5.7 ± 0.9)
LDL-c, mg/dL (mmol/L)	141 ± 33 (3.6 ± 0.9)
HDL-c, mg/dL (mmol/L)	43 ± 10 (1.1 ± 0.3)
Triglycerides, mg/dL (mmol/L)	190 ± 120 (2.1 ± 1.4)
Blood glucose, mg/dL (mmol/L)	102 ± 29 (5.7 ± 1.6)
Diabetes mellitus	208 (11)
Arterial hypertension	749 (40)
Smoking	590 (31)
BMI, kg/m^2	28.4 ± 4.0
10-year ASCVD risk, %	13.7 ± 7.1

Values are expressed as mean ± SD or n (%). BMI: body mass index; ASCVD: atherosclerotic cardiovascular disease.

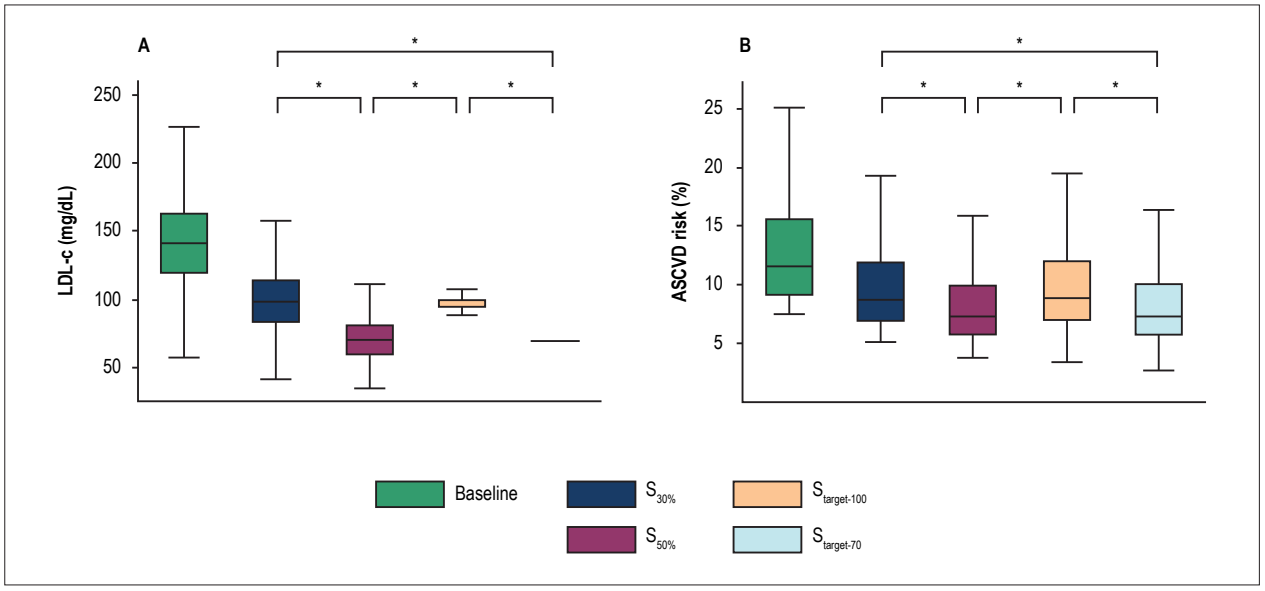

Figure 2 – *Distribution of LDL-c (A) and the 10-year risk for atherosclerotic cardiovascular disease (B) at baseline and according to the simulated strategy. ASCVD: atherosclerotic cardiovascular disease. * p <0.001.*

When recommending LDL-c target levels, guidelines differ on the goal for individuals in primary prevention at higher cardiovascular risk (< 70 mg/dL [1.8 mmol/L),[3,4,7] < 77 mg/dL [2.0 mmol/L)[6] or < 100 mg/dL [2.6 mmol/L][5]). An aggressive LDL-c target (< 70 mg/dL [1.8 mmol/L]) for these patients is supported by the CTT meta-analysis,[1] as well as by extrapolation of subanalyses of randomized clinical trials in patients with cardiovascular disease.[18,19] Accordingly, our study, which is based on assumptions derived from the CTT study,[1] showed a robust difference between achieving LDL-c ≤ 70 mg/dL or ≤ 100 mg/dL. This finding, however, contrasts with a recent population-based study that reported no additional benefit by achieving LDL-c 70 mg/dL or less in individuals with stable ischemic heart disease taking statins.[20]

One of the main criticisms of the abolishment of LDL-c target levels is the possibility of undertreating individuals with higher baseline LDL-c. Indeed, subjects with LDL-c > 140 mg/dL will not achieve 70 mg/dL even if they reduce LDL-c by 50%, approximately the expected mean reduction with high-intensity statin. In our simulations, this phenomenon was not negligible, as more than half of the study population simulated to a 50% LDL-c reduction would not attain LDL-c ≤ 70 mg/dL. This result compares with those of a meta-analysis of statin trials showing that more than 40%

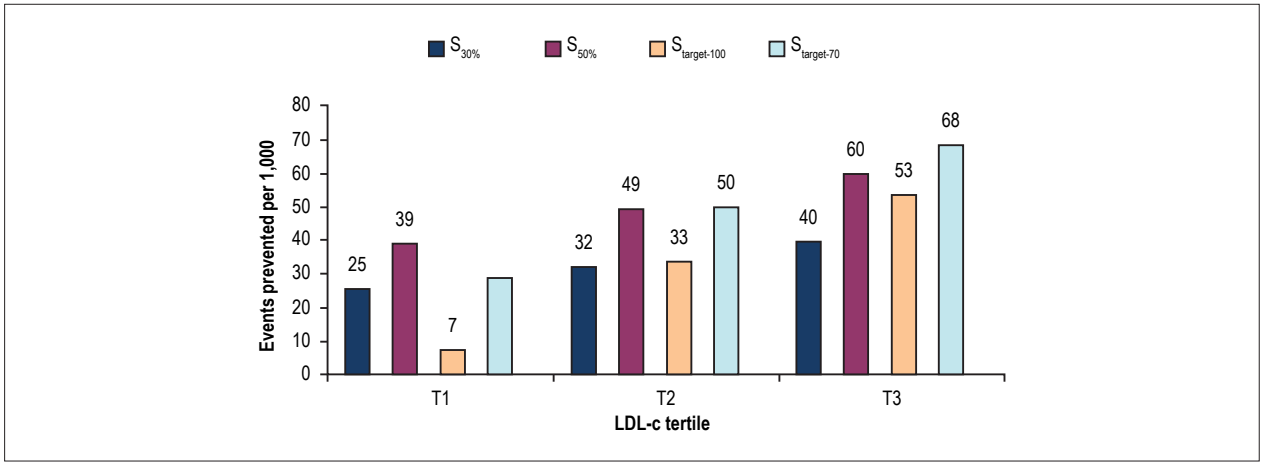

Figure 3 – *Estimated number of events prevented in 10 years per 1,000 individuals assigned to the simulated strategy, according to baseline LDL-c (lower tertile [T1]: < 129 mg/dL [3.3 mmol/L]; intermediate tertile [T2]: 129-155 mg/dL [3.3-4.0 mmol/L]; higher tertile [T3]: > 155 mg/dL [4.0 mmol/L]).*

of subjects assigned to high-dose statin therapy did not reach LDL-c target < 70 mg/dL.[21] In this regard, it is noteworthy that the expert consensus published by the ACC in 2016 states that a non-statin drug (ezetimibe) may be considered for primary prevention patients with 10-year ASCVD risk ≥ 7.5% and high-risk markers who have not achieved LDL-c < 100 mg/dL on maximally tolerated statin therapy.[22]

On the other hand, under an LDL-c target-based strategy, many individuals with baseline LDL-c in the lower range would not need high-dose statins to reach the lipid goal. These individuals may also be considered undertreated, since high-dose statins would promote higher absolute LDL-c lowering and higher cardiovascular risk reduction. Our data demonstrate that this situation should not be underestimated. Indeed, in perfect agreement with our results, the recently published European guidelines recommend, for very high-risk patients, an LDL-c goal < 70 mg/dL (1.8 mmol/L) or a reduction by at least 50% if LDL-c is between 70 and 135 mg/dL (1.8 and 3.5 mmol/L).[3,4]

The importance of a percent LDL-c reduction is also supported by a recent publication by Bangalore et al.[23] In a large cohort of patients included in randomized trials, the authors reported that the percent LDL-c reduction added incremental prognostic value over statin dose and attained LDL-c levels, but achieved LDL-c did not provide incremental prognostic value over statin dose and percent LDL-c reduction.[23]

Therefore, the present study supports treating those individuals with relatively higher LDL-c plasma concentration to aggressive LDL-c target levels and prescribing high-dose statin, aiming for a great percent LDL-c reduction, for those with relatively lower LDL-c level. Our data suggest that the debate should shift from the "with or without target" issue to a broader discussion about how to customize the management of blood cholesterol in order to minimize the impact of cardiovascular diseases in the population.

Limitations

This study has several limitations inherent to simulation analyses. We had to make some assumptions arbitrarily and we cannot exclude the possibility of different results if other assumptions were used. We also simulated 30% and 50% LDL-c reductions as strategies roughly representative of moderate- and high-intensity statin therapies, respectively. It is widely known, however, that there is a substantial interindividual variability in the response to statin therapy.[21,24,25]

Our study population was almost exclusively male because of intrinsic characteristics of the preventive service where data were collected, which is attended predominantly by businessmen. Different results may be seen in populations with a more balanced male/female ratio. Ethnic issues also have to be considered, since we studied an almost exclusively white population. Importantly, we predict that results may significantly vary according to mean LDL-c in the population. Therefore, we cannot extrapolate our findings to other communities.

Conclusions

In a simulation study based on real-world individuals considered to be at higher risk for cardiovascular events, we observed that LDL-c lowering strategies based on target level or percent reduction may promote similar overall cardiovascular benefit, despite resulting in different distribution patterns of LDL-c in the population. Importantly, both aggressive approaches simulated ($S_{50\%}$ and $S_{target\text{-}70}$) may potentially prevent approximately 50% more hard cardiovascular events in the population compared with the less intensive treatments ($S_{30\%}$ and $S_{target\text{-}100}$).

However, these strategies may be very different at the individual level depending on the baseline LDL-c. An aggressive target-based strategy is the best option when LDL-c is relatively high, while percent LDL-c reduction is superior when LDL-c is relatively low.

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Author contributions

Conception and design of the research, Acquisition of data, Analysis and interpretation of the data and Writing of the manuscript: Cesena FHY; Statistical analysis: Cesena FHY, Bittencourt MS; Obtaining funding: Laurinavicius AG; Critical revision of the manuscript for intellectual content: Laurinavicius AG, Valente VA, Conceição RD, Bittencourt MS, Santos RD.

Potential Conflict of Interest

Dr. Fernando Henpin Yue Cesena has received honoraria for participating in a study funded by Sanofi. Dr. Antonio Gabriele Laurinavicius is employee at Sanofi. Dr. Raul D. Santos has received honoraria for consulting and speaker activities from Amgen, Astra Zeneca, Biolab, Boehringer Ingelheim, Cerenis, Genzyme, Eli-Lilly, Kowa, Akcea, Pfizer, Praxis, Sanofi Regeneron, Merck, and Unilever. All other authors declare that there is no conflict of interest.

Sources of Funding

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Study Association

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

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Discordant Lipid Pattern and Carotid Atherosclerotic Plaque. Importance of Remnant Cholesterol

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Abstract

Background: Subjects with levels of non-HDL-C 30 mg/dL above those of LDL-C (lipid discordance) or with high remnant cholesterol levels could have a greater residual cardiovascular risk.

Objectives: 1) To determine the prevalence of lipid discordance in a primary prevention population and analyze the clinical variables associated with it; 2) To investigate the association between lipid discordance and remnant cholesterol with the presence of carotid plaque.

Methods: Primary prevention patients without diabetes or lipid-lowering therapy were included. Regardless of the LDL-C level, we define "lipid discordance" if the non-HDL-C value exceeded 30 mg/dL that of LDL-C. Remnant cholesterol was calculated as total cholesterol minus HDL-C minus LDL-C when triglycerides were < 4.0 mmol/L. Ultrasound was used to assess carotid plaque occurrence. Multiple regression logistic models were performed.

Results: The study included 772 patients (mean age 52 ± 11 years, 66% women). The prevalence of lipid discordance was 34%. Male sex and body mass index were independently associated with discordant lipid pattern. The prevalence of carotid plaque was higher in subjects with lipid discordance (40.2% vs. 29.2, p = 0.002). The multivariate analysis showed that the discordant lipid pattern was associated with the greater probability of carotid plaque (OR 1.58, 95% CI 1.08-2.34, p = 0.02). Similarly, a significant association between calculated remnant cholesterol and carotid plaque was found.

Conclusion: Lipid discordance and presence of a higher level of calculated remnant cholesterol are associated with subclinical atherosclerosis. Our findings could be used to improve the residual cardiovascular risk evaluation. (Arq Bras Cardiol. 2017; 108(6):526-532)

Keywords: Atherosclerosis / complications; Plaque, Atherosclerotic; Carotid Arteries; Cholesterol, LDL; Lipoproteins, LDL; Cholesterol, VLDL.

Introduction

Elevations in triglyceride-rich lipoproteins are associated with an increased risk of atherosclerotic cardiovascular events even in patients with well-controlled levels of low-density lipoprotein cholesterol (LDL-C) achieved by statin regimens.[1,2]

Although LDL-C has typically been the primary target of therapy, several guidelines recognize non–HDL-C as a secondary therapeutic target.[3-6] The US National Lipid Association (NLA) in its recent published recommendation recognizes both non–HDL-C and LDL-C as primary therapeutic targets.[7] In this scene, the non-HDL-C targets were 30 mg/dL higher than the recommended LDL-C goals.

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The non–HDL-C comprises cholesterol carried by all potentially atherogenic particles that include LDL-C, intermediate density lipoproteins, very low-density lipoproteins, remnant lipoproteins and lipoprotein(a). Additionally, in several meta-analyses, it was found that non-HDL-C correlated more closely with cardiovascular risk than LDL-C both at baseline and during therapy.[8,9]

In the same way, the "atherogenic dyslipidemia" is associated with increased cardiovascular risk. Its main findings include hypertriglyceridemia, low HDL-C levels, qualitative changes in LDL particles, accumulation of remnant lipoproteins, and postprandial hyperlipidemia.[10] Remnant cholesterol is the cholesterol content of triglyceride-rich remnant lipoproteins, which in the fasting state comprise very low-density lipoproteins and intermediate-density lipoproteins, and, in the non-fasting state, those two lipoproteins together with chylomicron remnants. Likewise, remnant lipoproteins carry large amounts of cholesterol and share with LDL the potential to enter and get trapped in the intima of the arterial wall.[11]

On the other hand, the diagnosis of carotid atherosclerotic plaque is a surrogate objective and constitutes an independent

predictor of coronary events.[12] Our working group has previously reported a considerable prevalence of carotid plaque in patients in primary prevention.[13,14]

Given the above, we raised the possibility that subjects with non-HDL-C levels 30 mg/dL above the LDL value (lipid discordance) or with higher calculated remnant cholesterol value may show a higher prevalence of carotid atherosclerosis.

Hence, the objectives of our study were: 1) To determine the prevalence of lipid discordance in a primary prevention population and to analyze the clinical variables associated with it; 2) To investigate the association of lipid discordance and calculated remnant cholesterol with the presence of carotid plaque.

Methods

A multicenter, descriptive, cross-sectional study was performed on consecutive samples obtained in the cardiovascular prevention outpatient clinics of six cardiology centers in the Autonomous City of Buenos Aires. Primary prevention subjects were included. Exclusion criteria were: 1) previous cardiovascular disease; 2) history of diabetes mellitus; and 3) prior hypolipidemic therapy.

Colorimetric and turbidimetric assays were used to measure non-fasting plasma levels of triglycerides, HDL-C and total cholesterol. The Friedewald equation was used to calculate LDL-C. Remnant cholesterol was calculated as total cholesterol minus HDL-C minus LDL-C when triglycerides were < 4.0 mmol/L.

Regardless of the LDL-C level, "lipid discordance" was defined as a non-HDL-C level exceeding 30 mg/dL that of LDL-C.

Carotid atherosclerotic plaque was recorded when atherosclerotic plaque was found in the carotid arteries on noninvasive, 2D-mode ultrasound images. Presence of plaque was defined as: a) abnormal wall thickness (defined as intima-media thickness >1.5 mm); b) abnormal structure (protrusion towards the lumen, loss of alignment with the adjacent wall); and c) abnormal wall echogenicity.

Three cardiovascular risk scores were calculated: 1) The Framingham Score for coronary events using the third National Cholesterol Education Program (NCEP) expert panel report on elevated blood cholesterol detection, assessment and treatment in adults (Adult Treatment Panel III - ATP III),[15] defining low, moderate and high risk as values < 10%, between 10% and 19%, and ≥ 20%, respectively; 2) The new score used by the last 2013 ACC/AHA Guidelines for cholesterol management;[16] 3) The European SCORE for fatal events, using the specific score corresponding to low risk countries.[17] The choice of this score was arbitrary, based on the fact that most Argentine immigrant population comes from those countries. Risks < 1%, between 1% and 4.9%, 5% and 9.9% or ≥ 10% were classified as low, moderate, high or very high, respectively.

Statistical analysis

Variable normality was explored analyzing the mean, standard deviation, median, skewness, kurtosis and histogram, and using the Shapiro-Wilk test. Continuous data were compared between groups using the unpaired *t* test for normal distribution or the Mann-Whitney-Wilcoxon test for non-normal distribution. The analysis of categorical data was performed using the chi-square test. The correlation between LDL-C and non-HDL-C was performed with the Pearson test.

A multiple regression logistic model was performed to identify independent characteristics associated with discordant lipid pattern, including all variables with $p < 0.05$ in the univariate analysis or those considered clinically relevant (age and smoking). Similarly, another multiple regression logistic model was performed to explore the association between the discordant lipid pattern and the presence of carotid plaque, including all variables with $p < 0.05$ in the univariate analysis or those considered clinically relevant (sex). Finally, a third multivariate model was performed to analyze the association between highest and lowest quartiles of calculated remnant cholesterol and the presence of carotid plaque, adjusting for age, sex, body mass index, smoking and antihypertensive medication.

Continuous variables were expressed as mean (standard deviation) if the distribution was normal and as median (interquartile range) if the distribution was abnormal. Categorical variables were expressed as percentages. A two-tailed p value < 0.01 was considered as statistically significant. STATA 11.1 and 3.1 EPIDAT software packages were used for statistical analysis.

Sample size calculation: Looking to have a power of 80% and an alpha error of 0.05 to detect an absolute difference equal to or greater than 7% in the prevalence of carotid plaque among subjects with or without lipid discordance, we estimate that it would be necessary a sample of 513 subjects. Assuming a loss of 15%, the number was 604 patients.

Ethics considerations

The study was conducted following the recommendations in medical research suggested by the Declaration of Helsinki, Guidelines for Good Clinical Practice and valid ethical regulations. The ethical issues have been evaluated and approved by the Area of Investigation of the Argentine Society of Cardiology.

Results

A total of 772 patients (mean age 52 ± 11 years, 66% women) were included in the study. Average body mass index was 26.9 ± 4.5 and mean cholesterol, LDL-C and HDL-C values were 219 ± 45 mg/dL, 142 ± 43 mg/dL and 50 ± 14 mg/dL, respectively. The median triglyceride level was 117 mg/dL (80-173). Thirty-six percent of patients were receiving antihypertensive treatment, and 20.5% were active smokers.

Thirty-four percent of the population showed lipid discordance (non-HDL-C > LDL-C+30 mg/dL). Relationship between LDL-C and non-HDL-C in the population is shown in Figure 1.

Patients with lipid discordance showed a higher proportion of men and subjects on anti-hypertensive medication, and higher body mass index compared with subjects with lipid concordance. Moreover, a smaller proportion of low-risk individuals according to different

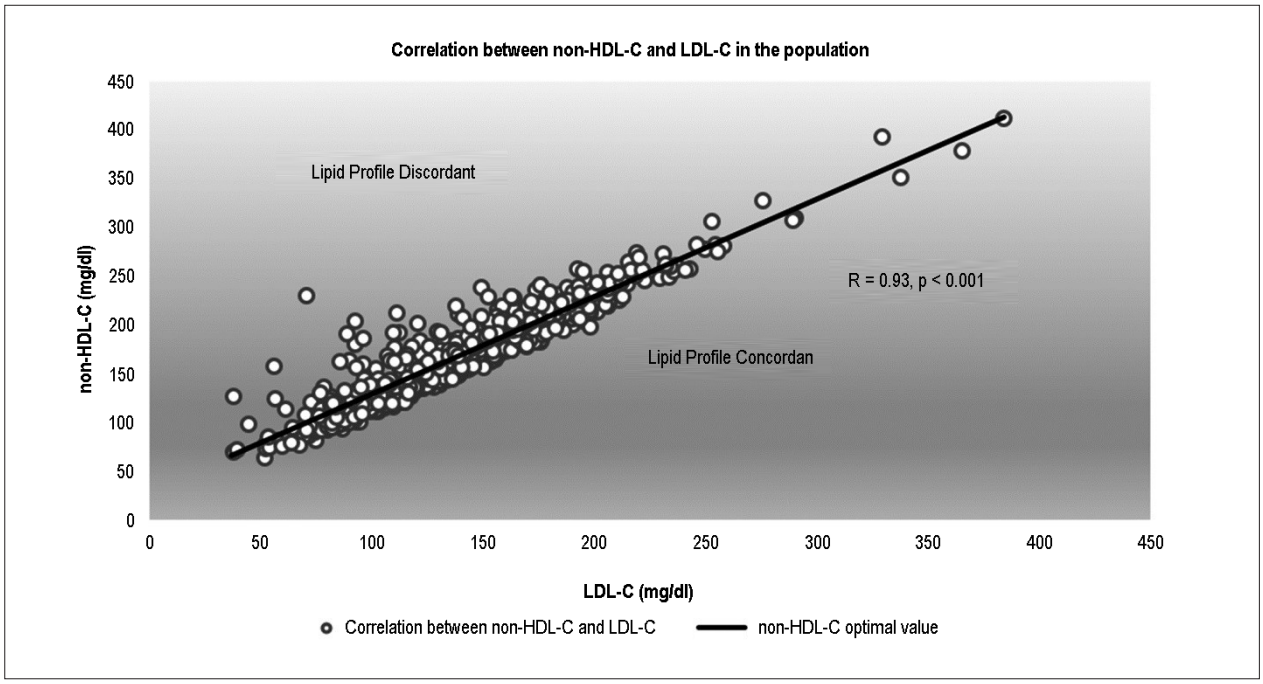

Figure 1 – *Relationship between LDL-C and non-HDL-C in the population. The black line represents the value of non-HDL-C (30 mg/dL above) associated with each value of LDL-C.*

cardiovascular scores was observed in the group with lipid discordance. The characteristics of the population according to the lipid pattern are shown in Table 1. Also, lipid values according to the lipid pattern are displayed in Table 2.

In the multivariate analysis, male sex (OR: 1.50; 95% CI: 1.07-2.11, p = 0.02) and body mass index (OR: 1.12; 95% CI: 1.08-1.17, p < 0.001) were independently associated with greater probability of being a discordant lipid pattern.

Table 3 displays the characteristics of the population (non-lipid risk factors) according to the presence or absence of carotid plaque. The prevalence of carotid plaque was significantly higher in subjects with lipid discordance (40.2% vs. 29.2, p = 0.002). In univariate analysis, a significant association between discordant lipid pattern and the presence of carotid plaque was observed (OR: 1.61; 95% CI: 1.17-2.19, p = 0.003). In the same way, the multivariate analysis showed that the discordant lipid pattern was independently associated with greater probability of exhibiting carotid plaque (OR: 1.58; 95% CI: 1.08-2.34, p=0.02). This finding occurred after adjusting for age, sex, body mass index, systolic blood pressure, antihypertensive treatment, active smoking and family history of early coronary disease.

Similarly, a significant association between calculated remnant cholesterol and the presence of carotid plaque was found in the univariate analysis (upper vs. lower quartile: OR: 1.82; 95% CI: 1.19-2.79, p = 0.006). This association remained after adjusting for other risk factors (upper vs. lower quartile: OR: 1.84; 95% CI: 1.11-3.05, p = 0.02). Figure 2 shows the association between quartiles of calculated remnant cholesterol and the presence of carotid plaque.

Discussion

Discordance analysis is an analytical technique in which biologically linked variables are analyzed by groups of concordance or discordance between their relative distributions.[18] In our work, we have defined "lipid discordance" arbitrarily but in an original way. For each patient, we categorize the lipid pattern as discordant if the non-HDL-C level exceeded 30 mg/dL that of LDL-C. Thus, the clinical value of this analysis is more closely related to the number of atherogenic particles than to the total mass of cholesterol.

In our study, male patients or subjects with a higher body mass index were more likely to show lipid discordance. Coinciding with our findings, in a study that analyzed a population of Barcelona, the prevalence of atherogenic dyslipidemia was higher in men compared to women (using the HDL-C cutoff recommended by the European guidelines).[19] Also, a study conducted in primary health care users of Portugal showed a higher prevalence of hypertriglyceridemia and low HDL-C levels in males.[20] In another study, Williams et al.[21] demonstrated that non-diabetic men showed higher levels of apolipoprotein B, non-HDL-C and small LDL particles than women without diabetes. On the other hand, the association between overweight or obesity and high non-HDL-C levels was widely demonstrated.[22,23]

Our analysis showed an association between discordant lipid pattern and higher prevalence of carotid plaque. Similarly, Holewijn et al.[23] showed that subjects with high non-HDL-C levels had a lower ankle-brachial index, increased mean intima-media thickness and more atherosclerotic plaques than patients with low

Table 1 – Association between different non-lipid risk factors and lipid pattern

	Concordant n = 510	Discordant n = 262	p
Continuous variables, mean (SD)			
Age, years	52.8 (10.8)	51.6 (11.3)	0.15
Systolic blood pressure, mm Hg	127.5 (15.3)	129.1 (14.5)	0.16
Body mass index, kg/m^2	26.0 (4.2)	28.6 (4.6)	< 0.001
Categorical variables, %			
Male sex	39.0	54.6	<0.001
Anti-hypertensive medication	33.1	42.8	0.01
Smoking	20.2	21.0	0.79
Family history of early cardiovascular disease	26.5	26.4	0.98
Framingham score (ATP III)			
Low risk	80.6	69.4	0.001
Intermediate risk	13.9	24.5	
High risk	5.5	6.1	
New Score (ACC/AHA 2013)			
< 5%	55.1	40.8	0.001
5-7.5%	10.8	16.8	
> 7.5%	34.1	42.4	
European SCORE			
Low risk	53.3	46.2	0.04
Intermediate risk	36.9	47.0	
High/Very high risk	9.8	6.8	

SD: standard deviation.

Table 2 – Lipid values according to the lipid pattern

Variable (mg/dL)	Concordant n = 510	Discordant n = 262	p
Total Cholesterol, mean (SD)	213.3 (44.3)	232.2 (44.9)	< 0.001
LDL-C, mean (SD)	141.5 (41.8)	142.8 (44.1)	0.58
Non-HDL-C, mean (SD)	160.0 (42.9)	188.4 (43.1)	< 0.001
HDL-C, mean (SD)	53.3 (14.7)	43.8 (11.3)	< 0.001
Triglycerides, median (interquartile range)	89.0 (72.0-116.0)	199.0 (172.0-252.0)	< 0.001
Calculated remnant cholesterol, mean (SD)	18.5 (5.8)	45.1 (16.3)	< 0.001

SD: standard deviation.

non-HDL-C levels. Moreover, high non-HDL-C/low LDL-C discordance was associated with higher coronary artery calcium score measured by computed tomography.[24] Consequently, several factors arise to explain the association between discordant lipid pattern and higher prevalence of subclinical atherosclerosis. First, some triglyceride-rich lipoprotein remnants enter the arterial wall similarly to LDL-C, contributing to the initiation and progression of atherosclerosis. Second, non–HDL-C correlates more closely with the total burden of all atherogenic particles. Finally, elevated levels of triglycerides and very low-density lipoprotein-C could reflect the hepatic overproduction of atherogenic and dense particles characterized by a slower clearance from the circulation.

Another finding of our study was the association between calculated remnant cholesterol and the presence of carotid plaque. This association remained even after adjusting for non-lipid risk factors.

Elevated remnant cholesterol is associated with ischemic heart disease.[25] Similarly, increased concentrations of both calculated and measured remnant cholesterol were associated

Table 3 – Association between non-lipid risk factors and carotid plaque

	Without plaque n = 517	With plaque n = 254	p
Continuous variables, mean (SD)			
Age, years	49.8 (11.3)	57.7 (11.3)	< 0.001
Systolic blood pressure, mm Hg	125.2 (13.8)	133.8 (15.9)	< 0.001
Body mass index, kg/m^2	26.3 (4.5)	27.9 (4.4)	< 0.001
Categorical variables, %			
Male sex	42.0	48.9	0.07
Anti-hypertensive medication	28.4	52.8	<0.001
Smoking	15.1	31.1	<0.001
Family history of early cardiovascular disease	23.8	32.0	0.016

SD: standard deviation.

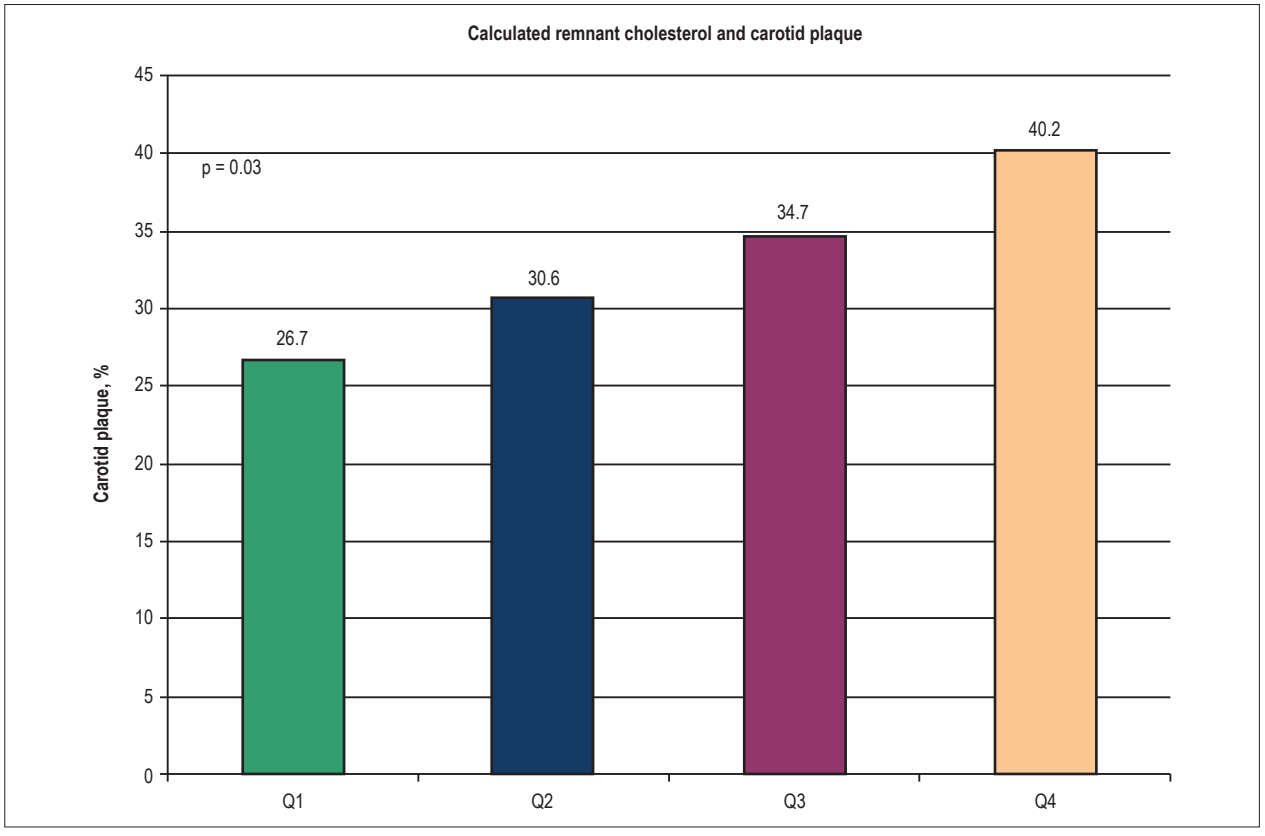

Figure 2 – *Association between quartiles of calculated remnant cholesterol and the presence of carotid plaque. Q: Quartile.*

with increased all-cause mortality in patients with ischemic heart disease.[26] The main explanation for a causal effect of elevated remnant cholesterol on ischemic heart disease risk could be that remnants enter and get trapped in the intima of the arterial wall.[27] Even more, remnants may not need to be oxidized to be taken up by macrophages to cause foam cell formation and atherosclerosis.[28] Therefore, the findings of our research are consistent with pathophysiological and clinical data previously reported.

Our findings, regarding that patients with discordant lipid patterns and higher remnant cholesterol levels are associated with atherosclerotic plaque, highlight the role of non-HDL-C in clinical practice. In the real world, patients with very high cardiovascular risk have a significant prevalence of atherogenic dyslipidemia despite having achieved LDL-C goals.[29]

However, the recommendations of the guidelines are confusing and not always consistent.[30] The 2013 ACC/AHA guidelines for cholesterol management do not consider HDL-C

and triglycerides in cardiovascular prevention. However, the NLA emphasizes the relevance of atherogenic dyslipidemia and the Canadian guidelines introduced non-HDL-C and apolipoprotein B as alternative targets. The International Atherosclerosis Society and National Institute for Health and Care Excellence (NICE) guidelines promote the importance of non-HDL-C. The European guidelines highlight HDL-C and triglycerides, but with the limitation that the main evidence comes from sub-analysis of clinical studies.

Our study has some limitations. First, as in any cross-sectional study, the possibility of bias (mainly selection bias) potentially influencing the results cannot be ruled out. We believe a selection bias may exist in our sampling, as patients attending the cardiovascular prevention clinic do not necessarily represent the general population. Second, we did not measure remnant lipoprotein cholesterol directly. However, the measurement of calculated remnants has been used in several previous studies. Finally, in our study, carotid plaque was defined according to the Atherosclerosis Risk in Communities study criteria. Changing the definition of plaque could modify our results.

Conclusion

In our analysis, the lipid discordance and the presence of a higher level of calculated remnant cholesterol are associated with subclinical atherosclerosis. Our findings expand the strategies in primary prevention to evaluate the residual cardiovascular risk.

Author contributions

Conception and design of the research, Acquisition of data, Analysis and interpretation of the data, Writing of the manuscript and Critical revision of the manuscript for intellectual content: Masson W, Lobo M, Molinero G, Siniawski D; Statistical analysis: Masson W, Lobo M.

Potential Conflict of Interest

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

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Systemic Arterial Hypertension in Patients Exposed to Cesium-137 in Goiânia-GO: Prevalence Study

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Abstract

Background: Systemic Arterial Hypertension (SAH) in the Brazilian population, in populations not exposed to Césio-137, presents a prevalence of 28% nationwide. However, in the group of radioactivity victims, these values are unknown.

Objective: To analyze the prevalence of hypertension in patients exposed to Cesium-137 in Goiânia, enrolled in the Sistema de Monitoramento dos Radioacidentados (SISRAD) (Radioactivtity Victims Monitoring System) of the Centro de Assistência aos Radioacidentados (C.A.R.A) (Assistence Center for Radioactivity Victims).

Methods: This is a descriptive, observational cross-sectional epidemiological study carried out in Goiânia-Goiás, from August 2013 to October 2014, with a group of patients enrolled in the Sistema de Monitoramento dos Radioacidentados (SISRAD) of the Centro de Assistência a Radioacidentados (C.A.R.A.). A total of 102 radioactive patients were divided into two groups: group 1 with 40 and group 2 with 62 participants. A field survey was conducted with a closed and semi-structured questionnaire in which the following contexts were addressed: sociodemographic profile, life habits and personal background. A database was created using the Google Forms application from the Google Web technologies company. The duly collected and stored data were imported and analyzed in the statistical software SPSS, version 21.

Results: The prevalence of SAH reached a total of 25% (12 individuals) of the 48 interviewees, 50% of women (24) and 50% of men (24), of which 22.9% (11) of the radioactivity victims revealed to be smokers.

Conclusion: The prevalence of SAH in the radioactivity victims population is similar to that of the population in general. (Arq Bras Cardiol. 2017; 108(6):533-538)

Keywords: Hypertension; Cesium; Cesium, Radioisotopos; Cardiovascular Diseases.

Introduction

In September of 1987 occurred in the state of Goiás, in the city of Goiânia, the radiological accident involving the cesium-137. It was caused by the rupture of a radiotherapy device containing cesium-137 (radioactive isotope), incorrectly handled by lay people and that was abandoned in an inactive medical clinic.[1]

About 112,000 people were involved in this accident, of which 249 were externally or internally contaminated.[1] The government of Goiás State, through the Municipal Health Department, set up a dedicated service to care for this contaminated population.

Thus, they were categorized in groups I, II and III according to *International Atomic Energy Agency* (IAEA) standards, taking into account classification criteria according to the severity of the cutaneous lesions and the intensity of internal and external contamination.[2,3] The *Centro de Atendimento aos Radioacidentados* (C.A.R.A.), through the IAEA standards, classifies the radioactivity victims into three groups as follows:

- **Group I (booking each 6 months):** 40 patients with radiodermatitis and/or cytogenetic dosimetry above 0.20 Gy (20 rad) and/or body activity ≥ ½ LIA, corresponding to 1.85 GBq (50 mCi) ;
- **Group II (annual schedule):** 62 patients with cytogenetic dosimetry between 0.05 and 0.20 Gy (5 and 20 rad) and or body activity below ½ LIA; and
- **Group III:** 880 professionals who dealt and deal with contaminated material or patients irradiated or contaminated by cesium-137 and of neighboring population of contamination outbreaks.

The C.A.R.A. is the successor of part of the attributions of the extinct SuLeide (Leide das Neves Superintendence).[2] This coordinates the referral and counter-referral system of the radioactivity victims and also monitors their health. In addition, it acts in the production of epidemiological data about exposure to ionizing radiation by Cesium-137.[2]

Radiation causes a series of changes in the human body, being of physical, physicochemical, chemical and biological

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characteristics.[4] Understanding cellular responses to ionizing radiation is essential for the development of predictive markers useful for assessing human exposure, scarce in the literature.[5]

The threshold dose for circulatory diseases is 0.5 Gy for morbidity and mortality.[4] Cardiovascular lesions are varied and include accelerated atherosclerosis, pericardial and myocardial fibrosis, conduction abnormalities, and heart valve lesions.[6] The risk of cardiovascular diseases radiation-related may be correlated to the risks of hypertension and other secondary disorders, such as the risk of atherosclerotic disorders.[6-8]

Systemic Arterial Hypertension (SAH) is considered a chronic, multifactorial degenerative disease whose blood vessel wall pressure values are > 140 mmHg for systolic pressure and > 90 mmHg for diastolic blood pressure.[9]

As a polygenic syndrome, it comprises genetic, environmental, vascular, hormonal, renal and neural aspects.[10] The control of SAH begins with the detection and continuous observation of blood pressure, prevention of modifiable risk factors and greater access to medicines, Especially, by the unified health system (SUS).[11,12]

The importance of knowing the SAH for the scientific community and for the studied group, is determinant in the systematic follow-up of the victims of the cesium accident for the prevention and monitoring of injuries, since these patients are unique in the world.

It is also relevant to deepen the study because the relationship between hypertension and radioactivity victims patients has been little explored in medical literature. Other studies conducted with radioactivity victims, such as the reflection of psychosocial aspects on the victims of the accident, were well exploited. However, so far there are few publications linking SAH with radioacticity victims. This study aims to contribute with studies that address the primary prevention and early diagnosis for SAH.

The study aimed to know the prevalence of SAH in patients exposed to Césio 137 in an accident in Goiânia-Goiás, registered in the SISRAD of C.A.R.A.

Methods

this is an epidemiological study of descriptive, observational, cross-sectional design, carried out in Goiânia-Goiás, from August 2013 to November 2014, with patient groups enrolled in C.A.R.A. SISRAD, a unit of the of Health State Department of Goiás.

After the approval of the Ethics and Research Committee, data collection was started, guided by SISRAD, with 102 registered patients referring to groups I and II, respectively 40 and 62 patients. 9 of these died, 8 migrated to other states, 4 migrated out of the country, 2 with not found address and 2 resident in other cities in the state of Goiás and were not found, totaling 25 victims.

However, during the data collection in visits at home in the capital and metropolitan region of Goiânia, 23 patients refused to participate in the study, and it was not possible to locate the address of 3 and 3 were not found after two visits.

In this context, the study was carried out with 48 victims whose SISRAD information used were: name, address and date of birth.

The data collection instrument consisted of the sociodemographic profile, life habits and personal antecedents with structured and semi-structured queries, containing 41 questions.

For the sociodemographic profile, 18 questions were used to characterize the radioactivity victim patient. The remaining 23 questions were divided into life habits and personal antecedents. Concerning life habits, there were questions related to smoking (Fagerstrom test), alcoholism, physical activity and food. As for the personal history, there were questions identifying patients with a previous diagnosis of systemic arterial hypertension and its control with the use of antihypertensives.

The variables were represented by means of descriptive statistics with frequency (absolute and relative) analysis for all participants. Cross-checking between these variables was also performed using statistical software SPSS version 21.

The data was transported to *Google Forms* and stored, being exported to the statistical software SPSS, version 21.

Results

The study consisted of 48 individuals belonging to groups I and II, according to classification previously mentioned. Of these, 24 (50%) are women and 24 (50%) are men, with a minimum age of 18 and a maximum of 89 years, being the largest number of patients between the ages of 30 and 59 years. The children of individuals in groups I and II were enrolled in these groups and are followed up by C.A.R.A.

About the monthly income, 26 patients (54.2%) receive up to 2 minimum wages; 13 patients (27.1%) have income from 4 to 10 minimum wages with reference to the minimum wage amount of R $ 724.00. Of these, 25 (64.1%) declared as economic activity to be pensioners, as explained in Table 1.

In terms of life habits, 27 patients reported frequent use of alcohol, 12 (44.4%) reported drinking 1 to 2 times a week; 11 (22.9%) patients stated that they are smokers; 42 (87.5%) reported not considering their salt-rich diet; And 39 (81.2%) reported never or rarely practicing physical activity. When asked if they had already been diagnosed with any disease before the accident with Cesium-137, 44 (91.6%) said they did not.

When questioned about having a clinical diagnosis of hypertension, 36 (75%) of the total of interviewees stated that they did not have the diagnosis and 12 (25%) knew they were hypertensive, and of these 7 (29.2%) were female and 5 (20.8%) male, as shown in Table 2.

Also in Table 2, the frequency distribution according to the gender of patients who report having a medical diagnosis of SAH with an estimated monthly income is shown. According to the data presented, the income of up to 2 minimum wages corresponds to 7 (58.3%) interviewed, from 2 to 4 minimum wages equals 1 (8.3%) and from 4 to 10 wages minimum is equal to 4 (33.3%).

Table 3 shows the systolic and diastolic blood pressure, in the first and second measurements, according to the classification of the VI Brazilian Guidelines for Hypertension (DBH).

Table 1 – Sociodemographic characteristics of the 48 participants investigated for Systemic Arterial Hypertension (SAH), radioactivity victims with Césio 137, living in Goiânia-Goiás, Brazil

Characteristics	HYPERTENSE	NON HYPERTENSIVE
Mean age (years): 49 (18 a 89)	61	45
Age range		
18-29	01	04
30-39	00	11
40-49	03	05
50-59	03	11
60-69	01	03
70-79	01	02
80-89	03	00
Gender		
Male	05	19
Female	07	17
Get to know SAH normal band		
Yes	46	----
No	2	----
Civil status		
Single	06	-----
Marriage/unmarried union	31	----
Divorced/widowed	10	-----
Family income		
2 minimum wage	26	
2 to 4 minimum wage	08	
4 to 10 minimum wage	13	
> 10 minimum wage	01	

In the first measurement, the optimal classification represents 23 (47.91%) interviewees; The normal classification is equal to 1 (2.08%); The borderline classification is equal to 7 (14.58%). Already the classification stage 1 hypertension represents 10 (20.83%) interviewed; Stage 2 equals 6 (12.5%) and stage 3 equals 1 (2.08%).

In the second measure, the optimal classification represents 24 (50%) interviewees; The normal classification is equal to 4 (8.3%); The borderline classification is equal to 5 (10.4%). The classification of stage 1 hypertension corresponds to 9 (18.7%); Stage 2 corresponds to 5 (10.4%) and stage 3 corresponds to 1 (2.08%).

Considering the clinical diagnosis of hypertension, 15 (31.25%) individuals were identified as hypertensive in the second measurement and 5 (10.42%) presented borderline results.

Table 4 represents the frequency of smoking patients by age group with a predominance of age between 50 and 59 years with 5 (45.5%) smokers.

Among those who do not smoke, there is a prevalence in the age group of 30 to 39, with 11 (29.7%) smokers, followed by age groups of 50 to 59 years old, with 9 (24.3%).

Discussion

The results showed that most of the radioactivity victims had no medical diagnosis of SAH. However, there was a prevalence of SAH identified in these subjects of 25%, that is, similar to that of hypertensive individuals in Brazil.

Therefore, it is relevant to study chronic diseases such as hypertension, since its prevalence in populations not exposed to Césio-137 is 28% in Brazil.[12]

It is possible to infer that low income is a socioeconomic factor that interferes in the early diagnosis and control of hypertension, since those with income less than 2 minimum wages have less access to consultations, and less financial condition for the purchase of medications.[16-17] Several are the determinants

Table 2 – Distribution of frequency of interviewees according to gender, estimated monthly income and medical diagnosis of SAH.

	You have medical diagnosis for SAH		Total
	No	Yes	
Gender			
Female	17	7	24
	70,8%	29,2%	50%
Male	19	5	24
	79,2%	20,8%	50%
Total	36	12	48
	75,0%	25,0%	100%
Up to 2 minimum wage	19	7	26
	52,8%	58,3%	54,2%
From 2 to 4 minimum wage	7	1	8
	19,4%	8,3%	16,7%
From 4 to 10 minimum wage	9	4	13
	25,0%	33,3%	27,1%
From 10 to 20 minimum wage	1	0	1
	2,8%	0%	2,1%
Total	36	12	48
	75,0%	25,0%	100%

Table 3 – Frequency distribution of the interviewees according to the blood pressure measurement in the first and second measurements according to the classification of the VI Brazilian Guidelines for Hypertension

Blood Pressure Levels	1st measure		2nd measure	
	Freq.	Percent	Freq.	Percent
Excellent	23	47.92%	24	50.00%
Normal	1	2.08%	4	8.33%
Bordering	7	14.58%	5	10.42%
Hypertension stage 1	10	20.83%	9	18.75%
Hypertension stage 2	6	12.50%	5	10.42%
Hypertension stage 3	1	2.08%	1	2.08%
Total	48	100.00%	48	100.00%

for non-adherence to treatment, such as the patient's lack of knowledge about the disease, low socioeconomic status, and high cost of medications.[9]

Another relevant risk factor for SAH in radioactivity was smoking, because smoking causes an acute increase in blood pressure and heart rate, which persists for more than 15 minutes after smoking a cigarette, as a consequence of stimulation of the sympathetic nervous system, at the central level and at the nerve endings.[13]

"The prevalence of smokers was 17.2% of the population aged 15 years or more in 2008, demonstrating the decline that occurred along these 20 years."[14]

A study conducted in the state of Rio Grande do Sul clames that men still smoke more than women, 38% to 29.6%, and smokers with more than 20 cigarettes/day make up the majority: 17.8% of the 33,9%.[11] These data corroborate with the study presented here, since it reveals that the number of smokers is higher in patients over 50 years and may be influencing the increase of the index of hypertensive in the radioactivity victims.

Researchers from the city of Goiânia recommend the continuation of the studies since the late effects of the radiological accident.[1] This is because, until the present day, the monitoring reports do not indicate statistically significant

Table 4 – Frequency Distribution of interviewees' according to age group and use of tobacco

		You smoke		Total
		No	Yes	
Faixa Etária	18 to 29	5	1	6
		13,5%	9,1%	12,5%
	30 to 39	11	1	12
		29,7%	9,1%	25,0%
	40 to 49	5	2	7
		13,5%	18,2%	14,6%
	50 to 59	9	5	14
		24,3%	45,5%	29,2%
	60 to 69	3	1	4
		8,1%	9,1%	8,3%
	70 e mais	4	1	5
		10,8%	9,1%	10,4%
Total		37	11	48
		100,0%	100,0%	100,0%

data for morbidity and mortality associated with the effects of ionizing radiation, and the somatic effects can be divided into acute or in short-term and late or in long-term effects, depending on the duration of this effects, which is a function of the absorbed dose.[1,4]

The study presented limitations in terms of population and sample. The loss of individuals enrolled as group III in the SISRAD decreased the impact of this study identified as a potential sampling selection bias between groups I and II included in the sample used. Another limitation was the impossibility of reaching individuals of groups II and III, who would have larger samples. It was also not possible to define the causality of hypertension in radioactivity victims patients.

Therefore, the lack of information about cesium-137 on the risk of causing SAH, allows us to affirm that the complications of this disease are irreversible and possibly the level of ionizing radiation has caused long-term changes associated with comorbidities such as hypertension.

Final considerations

The dissemination of information about cesium-137, concerning the risk of causing hypertension, allows us to affirm that the complications of this disease are significant. Based on this exploratory study, it was not possible to identify that the level of ionizing radiation causes long-term changes associated with comorbidities such as hypertension.

The lack of studies about the health situation of this population, not only in relation to systemic arterial hypertension, but also of other pathologies, especially related to mental health, encourages the development of new researches. This was confirmed by the authors when the data collection instrument was applied, and it was possible to infer to this condition the difficulty found for adherence to this study.

This way, the study concludes that in the population of radioactivity victims the SAH occurs in a similar way to the population in general.

Author contributions

Conception and design of the research: Lima H, Pinto MM, Figueiredo RMP, Rodrigues JVR. Acquisition of data: Pinto MM, Figueiredo RMP. Analysis and interpretation of the data: Pinto MM. Obtaining financing: Pinto MM, Figueiredo RMP, Rodrigues JVR. Writing of the manuscript: Lima H, Pinto MM. Critical revision of the manuscript for intellectual content: Lima H, Sacchetim SC, Pinto MM, Rodrigues JVR. Supervision / as the major investigador: Lima H, Sacchetim SC, Souto R.

Potential Conflict of Interest

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

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The Effect of Physical Resistance Training on Baroreflex Sensitivity of Hypertensive Rats

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Abstract

Background: Baroreceptors act as regulators of blood pressure (BP); however, its sensitivity is impaired in hypertensive patients. Among the recommendations for BP reduction, exercise training has become an important adjuvant therapy in this population. However, there are many doubts about the effects of resistance exercise training in this population.

Objective: To evaluate the effect of resistance exercise training on BP and baroreceptor sensitivity in spontaneously hypertensive rats (SHR).

Method: Rats SHR (n = 16) and Wistar (n = 16) at 8 weeks of age, at the beginning of the experiment, were randomly divided into 4 groups: sedentary control (CS, n = 8); trained control (CT, n = 8); sedentary SHR (HS, n = 8) and trained SHR (HT, n = 8). Resistance exercise training was performed in a stairmaster-type equipment (1.1 × 0.18 m, 2 cm between the steps, 80° incline) with weights attached to their tails, (5 days/week, 8 weeks). Baroreceptor reflex control of heart rate (HR) was tested by loading/unloading of baroreceptors with phenylephrine and sodium nitroprusside.

Results: Resistance exercise training increased the soleus muscle mass in SHR when compared to HS (HS 0.027 ± 0.002 g/mm and HT 0.056 ± 0.003 g/mm). Resistance exercise training did not alter BP. On the other hand, in relation to baroreflex sensitivity, bradycardic response was improved in the TH group when compared to HS (HS –1.3 ± 0.1 bpm/mmHg and HT –2.6 ± 0.2 bpm/mmHg) although tachycardia response was not altered by resistance exercise (CS –3.3 ± 0.2 bpm/mmHg, CT –3.3 ± 0.1 bpm/mmHg, HS –1.47 ± 0.06 bpm/mmHg and HT –1.6 ± 0.1 bpm/mmHg).

Conclusion: Resistance exercise training was able to promote improvements on baroreflex sensitivity of SHR rats, through the improvement of bradycardic response, despite not having reduced BP. (Arq Bras Cardiol. 2017; 108(6):539-545)

Keywords: Hypertension; Exercise; Heart Rate; Baroreflex; Muscle Hypertrophy.

Introduction

According to the World Health Organization, hypertension is a major risk factor related to death and disability worldwide, affecting billions of people and killing about 9.4 million individuals every year.[1] In Brazil, about 31 million people are hypertensive, disease responsible for 1,683 in-hospital deaths.[2]

Hypertension occurs when the body loses the ability to maintain homeostasis of blood pressure (BP). The human body has many different mechanisms for BP control, among them: central nervous system ischemic response, renin-angiotensin-aldosterone system and the baroreflex system.[3,4] The baroreflex system consists in receptors located in the carotid arteries and aorta, which are sensitive to BP changes.[5] When there is an elevation in BP, baroreceptors send a signal to the nucleus of the solitary tract, which, in turn, excites the caudal ventrolateral medulla, inhibiting the premotor neurons of the rostral ventrolateral medulla, thus decreasing the cardiac contractility and consequently the BP. However, when there is a decrease in BP, baroreceptors increase sympathetic activity by decreasing the transmission of inhibitory signals to the pressure-regulating center. But, when BP is continuously high, an adaptive response of these receptors occurs, which shifts the normal BP threshold upward, making this regulatory system ineffective to deal with abnormal pressures.[6,7]

In order to reduce BP levels and health problems, the main guidelines advocate lifestyle changes, through nutritional education and physical activity as recommendations to everyone, while drug therapy should be used only by patients diagnosed with hypertension or with borderline hypertension with high global cardiovascular risk.[8]

Several studies have shown that aerobic exercise training of mild or moderate intensity is effective in reducing BP by improving baroreflex control of HR significantly in hypertensive rats, as well as controlling risk factors associated

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with hypertension.[9-11] Although there is no consensus in the literature on the effects of resistance training on BP,[12-14] practicing this type of training can be beneficial to hypertensive patients, especially elderly people, since muscle strength decreases with age, thus decreasing the quality of life.[15] Therefore, the aim of this study was to evaluate the effect of resistance exercise training on BP and the sensitivity of baroreceptor in spontaneously hypertensive rats (SHR).

Methods

Reagents

Epinephrine (Sigma-Aldrich Co., USA), sodium nitroprusside (Sigma-Aldrich Co., USA) and potassium chloride (Synth).

Animals

SHR (n = 16) and Wistar rats (n = 16) were obtained from the CEDEME (Center for the Development of Experimental Models for Biology and Medicine) at the University UNIFESP. All rats were male and 8 weeks of age at the beginning of the experiment. Cages held four animals each, and the animals were fed with a standard diet for laboratory rodents (Nuvilab) and water *ad libitum*. Room temperature was kept between 22-23°C and a light/dark cycle of 12:12 hours was adopted, with the light period beginning at 8:00 a.m. All experiments were carried out in accordance with National Research Council's Guidelines for the Care and Use of Laboratory Animals and were conducted after approval by the Ethics and Research Committee of the UNIFESP (CEP #0233/12). The animals were randomly divided into four groups, as follows: sedentary control (CS, n = 8); trained control (CT, n = 8); sedentary SHR (HS, n = 8) and trained SHR (HT, n = 8).

Murinometrics and evaluated vital signs

The body mass in all groups was evaluated in semi-analytical balance (Gehaka), in the last day of experimental protocol, before the animals were anesthetized for euthanasia. The BP was evaluated by tail plethysmography (1day/week, during 8 weeks) using a specific system for rats (Visitech Systems: BP-2000 - Series II - Blood Pressure Analysis System) on days that the rats were not subjected to training session.

Training protocol

After adaptation, all animals were habituated to the act of climbing steps for 5 consecutive days before the maximal load test. The test consisted of an initial load of 75% of the body mass, which was attached to the base of the tail. The load was progressively increased by 50 g increments in subsequent climbs.[16] The resistance exercise training was then performed using the normalized value of the individual maximal load (load of the last complete climb/body weight) for each rat, and was adjusted in the fourth week according to the new test maximal load. Resistance exercise was performed 5 days/week, during 8 weeks at moderate intensity (40-60% of maximal load). The rats performed 15 climbs per session with a 1-min interval between climbs.[16]

Baroreflex sensitivity

48 hours after the last exercise session, the animals were anesthetized with xylazine (20 mg/kg, ip) and ketamine (40 mg/kg, ip) and catheters made of polyethylene tubing PE-10 and PE-50 (Clay Adams, Parsipanny, NJ, USA) were introduced into carotid artery and vein. Mean arterial pressure (MAP) and heart rate (HR) were registered online, 48 hours after the last training session, through an analog-digital plate PowerLab (ADInstruments, Australia). The baroreflex control of HR was evaluated by bradycardia responses (vagal component) compared to a pressor and tachycardia stimulation (sympathetic component) after a depressant stimulus. This was accomplished by the administration of bolus doses of epinephrine (3, 5 and 10 μg - ev) and depressor dose of sodium nitroprusside (5, 15 and 20 μg - ev), respectively, with 10-minute interval between doses.

Cardiac baroreflex gain was determined by the ratio of the ΔHR/ΔMAP induced by vasoactive drugs, and thus expressed as heart beats per millimeter of mercury (bpm/mmHg).

Euthanasia

The animals were deeply anesthetized with urethane (1.7 g/kg - ev) followed by administration of 5% KCl (ev). The soleus and extensor digitorum longus (EDL) were removed for weighing the masses and had their values corrected by tibial length.

Statistical analysis

The statistical analysis was performed in GraphPad Prism 5.0. The distribution of the data obtained in this study was verified by Shapiro-Wilk test. The data showed Gaussian distribution and were presented as mean ± standard error of the mean and compared using analysis of variance. MAP, body mass, muscle mass and HR were analyzed with analysis of variance (ANOVA), followed by post-hoc Tukey's tests. Systolic blood pressure (SBP), diastolic blood pressure (DBP) and the maximum load tests were analyzed by two-way ANOVA followed by post-hoc Bonferroni's tests. In all analyses, statistical significance was established when $p < 0.05$.

Results

Murinometrics and evaluated vital signs

At the end of the experimental protocol, hypertensive animals (HS and HT) showed a decrease in body weight compared to the control groups (CS and CT). However, there was no significant change between HS and HT (Figure 1).

At the end of the eighth week of exercise training protocol, it was possible observe the significant increase in the maximum strength in all groups. In addition, we could see that tolerance to weight at the end of the experimental protocol was lower in the HS group in comparison to other groups (Figure 2).

The mass of the soleus muscle in the HS group (0.027 ± 0.002 g/mm) was lower compared to the CS group (0.046 ± 0.005 g/mm, Figure 3A). Although the exercise has promoted increased muscle mass in the trained groups, only the HT group showed significant increase in relation to

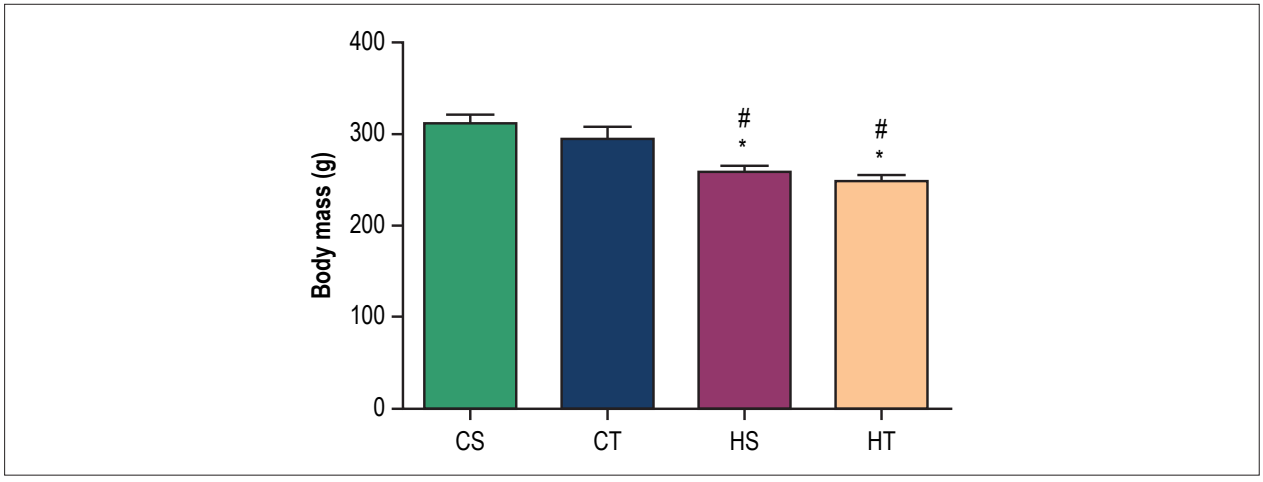

Figure 1 – *Body mass in grams (g) in sedentary control (CS), trained control (CT), sedentary SHR (HS) and trained SHR (HT) after 8 weeks of either sedentary or resistance exercise training protocol. * p < 0.05 vs. CS; # p < 0.05 vs. CT.*

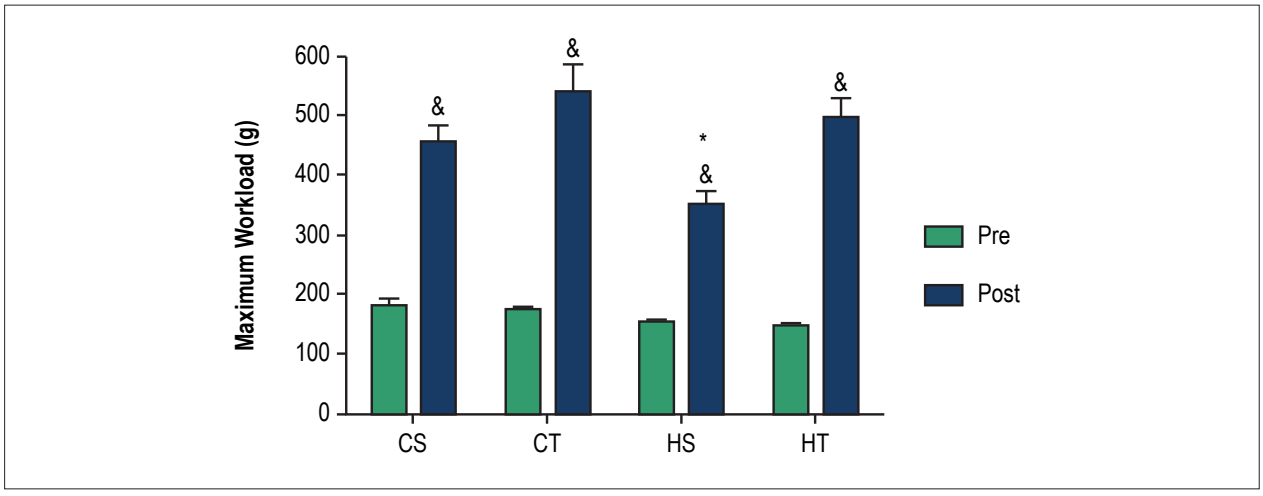

Figure 2 – *Maximum load test in grams (g) in sedentary control (CS), trained control (CT), sedentary SHR (HS) and trained SHR (HT) pre and post 8 weeks of either sedentary or resistance exercise training protocol. & p < 0.05 vs. same group at pre moment; * p < 0.05 vs. all groups at post moment.*

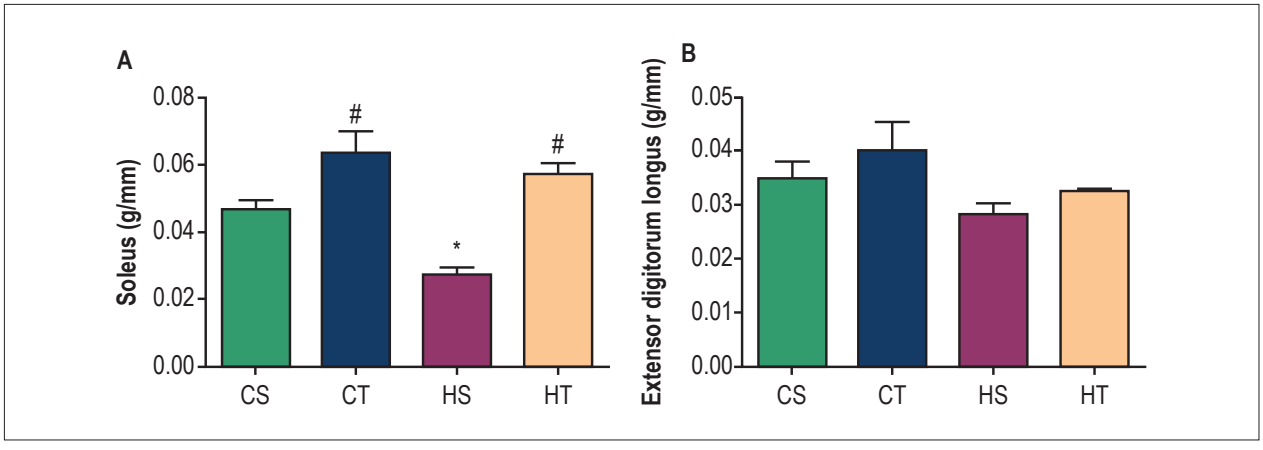

Figure 3 – *Muscle mass in grams corrected by tibia length (g/mm) in sedentary control (CS), trained control (CT), sedentary SHR (HS) and trained SHR (HT) after 8 weeks of either sedentary or resistance exercise training protocol. A) Soleus mass; B) Extensor digitorum longus mass. * p < 0.05 vs. CS; # p < 0.05 vs HS.*

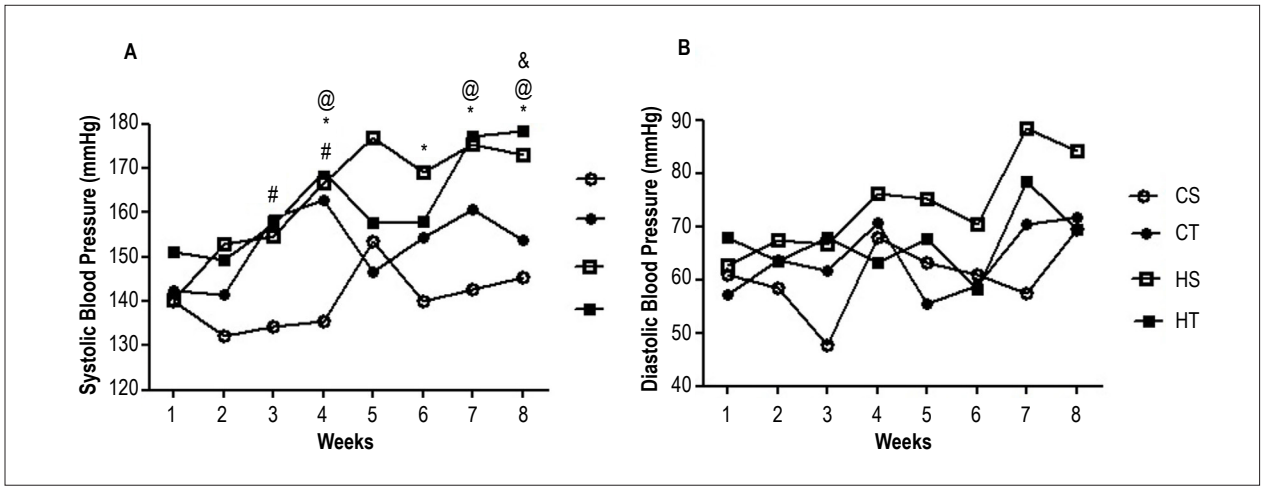

Figure 4 – *Blood Pressure measurements in sedentary control (CS), trained control (CT), sedentary SHR (HS) and trained SHR (HT) during or after 8 weeks of either sedentary or resistance exercise training protocol. A) Systolic blood pressure in mmHg evaluated by tail plethysmography; B) Diastolic blood pressure in mmHg evaluated by tail plethysmography. (*) There was significant difference between the groups HS vs. CS ($p < 0.05$); (#) There was significant difference between the groups CT vs. CS ($p < 0.05$); (@) There was significant difference between the groups HT vs. CS ($p < 0.05$); (&) There was significant difference between the groups CT vs. HT ($p < 0.05$). Significance based on two-way ANOVA with Bonferroni's post-hoc test.*

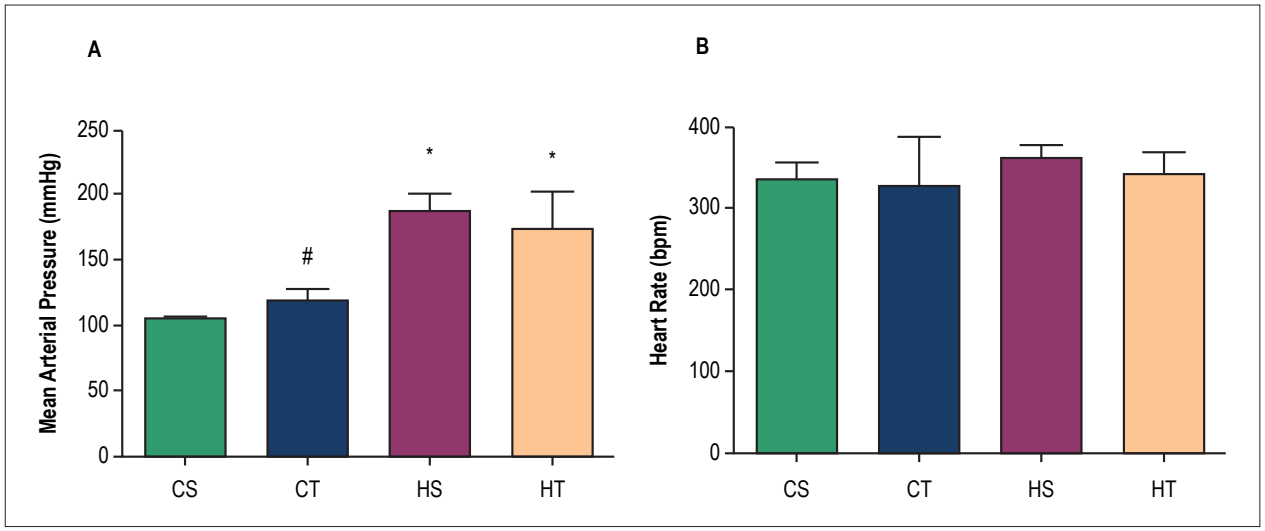

Figure 5 – *Mean arterial pressure and heart rate evaluated directly after experimental protocol. A) Mean arterial pressure (*) $p < 0.05$ vs. CS. (#) $p < 0.05$ vs. CT. and B) Heart rate. Significance based on one-way ANOVA with Tukey's post-hoc test. There was no significant difference.*

its control (0.056 ± 0.003 g/mm HT). Regarding the EDL muscle, there were no significant differences between groups (Figure 3B).

Figure 4 shows the indirect measurements SBP and DBP over the eight weeks of the experimental protocol, and demonstrate the MAP and HR of the animals directly at the end of the protocol. Figure 4A demonstrates that the hypertensive groups (HS and HT) showed a significant increase in SBP from the fourth week compared to the CS group. Although the blood pressure of the CT group was higher compared to the CS in the third and fourth week, pressure levels showed no significant difference from the fifth week onwards. It was observed that the HT group showed significant reductions in SBP for two weeks (5th and 6th week), however, the decrease in SBP was not sustained.

There were no significant differences in DBP (Figure 4B). Figure 5A shows that MAP of HS group (188 ± 14 mmHg) and HT group (174 ± 29 mmHg), assessed directly, showed significantly higher values in comparison to the CS group (106 ± 3 mmHg). Resistance exercise training had no effect on MAP in groups CT or HT. No significant differences were found in the HR evaluated directly in animals (CT = 336 ± 20 bpm, HS = 362 ± 17 bpm, CT = 328 ± 60 bpm and HT = 342 ± 27 bpm), (Figure 5B).

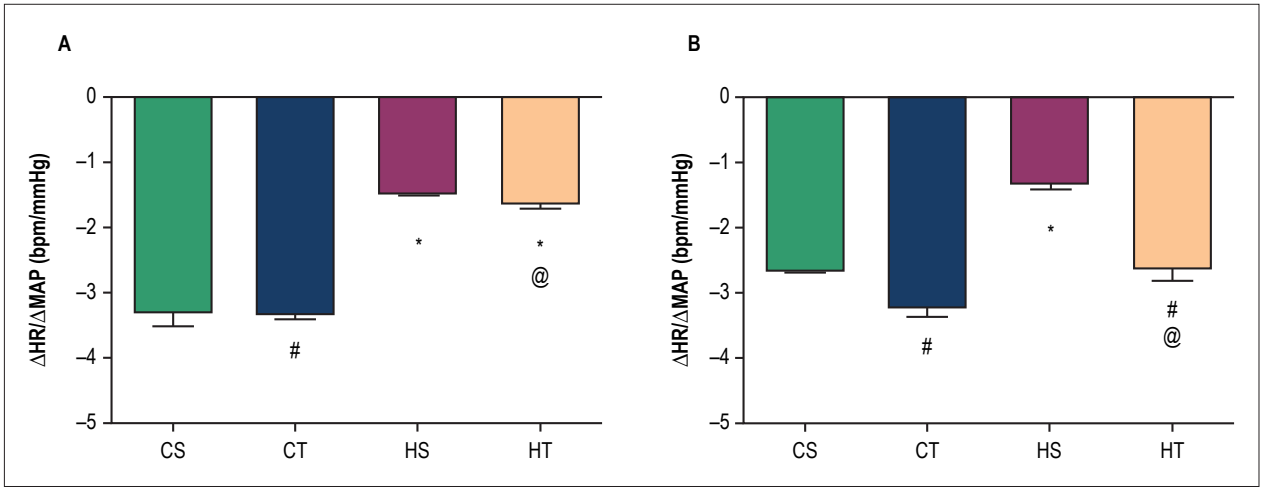

Figure 6 – *Baroreflex sensitivity (difference between ΔHR and ΔMAP) in sedentary control (CS), trained control (CT), sedentary SHR (HS) and trained SHR (HT) after 8 weeks of either sedentary or resistance exercise training protocol. A) Tachycardic sensitivity; B) Bradycardic sensitivity. * p < 0.05 vs. CS; # p < 0.05 vs. respective control group; @ p < 0.05 vs. CT. HR: heart rate; MAP: mean arterial pressure.*

Baroreflex sensitivity

We found that exercise was not effective in promoting improved tachycardia sensitivity in hypertensive groups (CS –3.3 ± 0.2 bpm/mmHg, CT –3.3 ± 0.1 bpm/mm Hg, HS –1.47 ± 0.06 bpm/mmHg, HT –1.6 ± 0.1 bpm/mmHg) (Figure 6A). In relation to the bradycardic response, we observed a decrease in the HS group (–1.3 ± 0.1 bpm/mmHg) compared to the CS group (–2.67 ± 0.06 bpm/mmHg). Moreover, mean values of ΔHR/ΔMAP and bradycardic sensitivity were also higher in the HT group (–2.6 ± 0.2 bpm/mmHg) in relation to the HS group (Figure 6B).

Discussion

It was found that hypertensive animals showed a decrease in body mass compared to control groups, and that resistance exercise training did not promote changes. The HS group also presented a reduced mass of the soleus muscle when compared to the CS group. Although it had no effect on body mass, resistance exercise training promoted an increase in soleus muscle mass in the HT group in comparison to the HS group. Therefore, we can infer that the lower body mass observed in HT rats was due to the likely reduction of adipose tissue, since resistance training promotes increased expression of genes related to lipid catabolism.[17,18]

The HS group showed less strength compared to the other groups in maximum load test; however, the resistance exercise training promoted increase in muscle strength after the exercise training period in both groups. Recent studies in humans have shown that there is a strong correlation between decreased handgrip performance with hypertension.[19-21] Previous studies have related functional alteration of skeletal muscle with decreased nitric oxide bioavailability caused by increased reactive oxygen species (ROS), endothelin receptor type A and increased activation of protein catabolism due to increased angiotensin- II (ANG II).[22-25] Such changes may explain the decrease in strength that was observed in the HS group. Concerning the increase in strength observed in all groups, when we compare post-experimental to pre-experimental data, animal growth can be cited as a factor responsible for this increase, as well as the adaptation of the animals to the test.

In fact, resistance exercise training is able to promote increased muscle mass, especially in the soleus.[26] However, there were no significant changes in the EDL, as observed in other studies.[27,28] According to Neves et al.,[28] the type of training can justify these results, since the climbing training exercises promote little action in the EDL muscle and greater action in the soleus, because of the greater need of force employed by the rat to perform plantar flexion while up the stairs. A fact that contributes to this hypothesis is that training with electrical stimulation for muscle contraction promotes significant increase in mass of the EDL, while the soleus presents atrophy with this type of stimulus.[29]

Regarding hemodynamic parameters, it was found that the SHR animals developed spontaneous hypertension, with significant increase in SBP from the fourth week of the experimental protocol and thirteenth week of life, which was expected for the model as reported by other authors.[30-32] Elevation of SBP observed in CT group at 3rd and 4th week of training is possibly related to the stress of the load that was increased in the half time of the training protocol and due to the beginning of the reproductive phase of the animals, between the 10th and 12th week of life, since testosterone increases the ANG II sensitivity.[33,34]

At the end of the experimental protocol, resistance exercise training did not promote alterations in MAP measured directly. Previous studies also found no significant effects of resistance training on BP.[35-37]

About the baroreflex sensitivity, it was found that the HS group showed a reduction in both bradycardic and tachycardia response, which was expected, as was noted earlier in experimental models[38,39] and in humans.[40] Resistance exercise training was able to promote significant improvement only

in the bradycardic response. When analyzing the effect of resistance exercise training in rats with metabolic syndrome induced by hypercaloric diet, Valenti et al.[41] obtained similar results to ours, demonstrating that this type of exercise is ineffective in improving the tachycardic response, regardless of the experimental model. Thus, the resistance exercise training seems to work mainly with the improvement of the sensitivity of the carotid baroreceptors, since the bradycardic response demonstrates strong correlation with the integrity of carotid sinus.[38-40] Furthermore, increased bradycardic response collaborates with decreasing sympathetic activity in the heart, leading to a reduction in HR at rest, decreasing cardiac output and finally decreasing BP.[42]

Conclusion

With the data obtained in this study, we can conclude that resistance exercise training, despite not promoting a significant decrease in BP in SHR, improves bradycardic response. However, more studies are needed to understand the mechanisms that lead to this improvement.

Author contributions

Conception and design of the research: Borges ME, Medeiros A; Acquisition of data: Borges ME, Rossi VA, Moura EOC; Analysis and interpretation of the data: Gomes MFP; Statistical analysis and Writing of the manuscript: Gomes MFP; Obtaining funding: Medeiros A; Critical revision of the manuscript for intellectual content: Gomes MFP, Medeiros 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.

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Pacemaker Implants in Children and Adolescents with Chagas Disease in Brazil: 18-Year Incidence

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Abstract

Background: Chagas disease continues to be a serious public health problem, and accounts for 25-30% of the indications for cardiac stimulation in Brazil.

Objective: To assess clinical and epidemiological characteristics of patients with Chagas disease, younger than 18 years, who had undergone pacemaker implantation in Brazil between 1994 and 2011, and its temporal trend.

Methods: This was a cross-sectional analysis of data from the Brazilian Pacemaker Registry database. The following variables were analyzed: year when pacemaker was implanted, location, age, sex, ethnic group, functional class and the main electrocardiographic findings at baseline.

Results: In a total of 183,123 implants performed between 1994 and 2011, 214 implants of cardiac stimulation device in Chagas disease patients aged younger than 18 years were identified. Mean age at implantation was 5.6 ± 6.2 years. Second- and third-degree atrioventricular blocks corresponded to 71% of indications for pacemaker implantation. Fifty-six percent of the procedures were performed in the southeast region. Regarding the total number of pacemaker implants per year, there was a remarkable increase in the implants for all causes. However, time series analysis of the implants in Chagas disease patients younger than 18 years revealed a significant reduction in the annual number of implants.

Conclusion: There has been an important reduction in the number of pacemaker implantations among children and adolescents with Chagas disease, suggesting a reduction in the vertical transmission of the parasite. (Arq Bras Cardiol. 2017; 108(6):546-551)

Keywords: Retrospective Studies; Pacemaker,Artificial; Child; Adolescents; Chagas Disease; Chagas Cardiomyopathy; Epidemiology.

Introduction

Endemic in South America and emerging in Europe and in the United States, Chagas disease continues to be a serious public health problem. Estimates indicate that there are 2.9 - 7.2 million people with Chagas disease in Brazil,[1] which accounts for approximately 6 thousand deaths per year.[2,3] According to the Brazilian Pacemaker Registry (BPR), 25%-30% of cardiac stimulation are performed for Chagas disease in Brazil.[4]

In addition to transmission via infected feces of the hematophagous triatomine insect, Trypanosoma cruzi may also be transmitted by blood transfusion, consumption of contaminated food or drinks, and congenital transmission (from mother to child).[5] Due to a more effective control of both vector and transfusional transmission, congenital route has emerged as the most important way of transmission in most endemic areas.[6,7]

Prevalence of *T.cruzi* infection in pregnancy varies from 1% to 40%,[8-12] and congenital transmission may reach 28.6%.[7] Recent estimates indicate that annually, more than 14 thousand babies are born with congenital Chagas disease in Latin America. A Brazilian study conducted between 2001 and 2008 on 105 thousand children aged from 0 to 5 years living in rural areas reported a 0.03% prevalence of *T. cruzi,* 0.02% for probable congenital transmission and 0.01% for vectorial transmission.[13]

Although most cases of congenital infection of *T.cruzi* are asymptomatic, it may cause premature death, low birth weight, stillbirths and clinical manifestations of Chagas disease at birth.[14,15] Since congenital transmission cannot be prevented, early diagnosis and treatment of congenital cases are the main goals of the programs for Chagas disease control.[16,17]

Considering changes in demography and transmission pathways, in particular the rising importance of vertical transmission, information on how these changes may affect patients' treatment and outcome are still scarce. Therefore, aiming to contribute to the knowledge on the

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theme, the objective of this study was to evaluate clinical and epidemiological characteristics of Chagas disease patients younger than 18 years, who had undergone a permanent pacemaker implantation in Brazil in the period between 1994 and 2011.

Methods

Data of the BPR database were analyzed in this study. This database system, officially created by the Ministry of Health decree no. 41, of December 17th, 1994, is maintained by the Department of Artificial Cardiac Stimulation of the Brazilian Society of Cardiology Surgery. The system holds information of permanent cardiac stimulation procedures performed in Brazil by means of a standardized, specific form about generator implants performed in the country. Completed forms were forwarded to the central, where the information was registered.

The following variables were analyzed: year when implant was performed, place of origin, age, sex, ethnic group, heart failure functional class according to the New York Heart Association (NYHA) criteria, and the main electrocardiographic finding that indicated the need for a pacemaker.

Categorical variables were expressed as absolute and relative frequencies, and continuous variables as mean and standard deviation. Statistical analysis was performed using the SPSS (*Statistical Package for the Social Sciences*) software.

Temporal variation in the number of pacemaker implants was assessed by the Jonckheere's trend test, and the alpha error was set at 0.05.

Results

Between 1994 and 2011, a total of 183,123 patients undergoing first pacemaker implantation were identified. Of this total, 35,204 were performed in patients with Chagas disease, and 214 of them consisted of surgical implantation of cardiac stimulation devices in patients aged 17 years or less.

In the group of patients with Chagas disease younger than 18 years, who had undergone a pacemaker implant, mean age at procedure was 5.6 ± 6.2 years. Forty-five percent of these patients were women (5.2 ± 5.8 years), and 55% were men (6.1 ± 6.5 years). The Figure 1 shows the absolute frequency of implants performed per year throughout the period assessed (18 years), with a remarkable reduction in the number of implants. Mean number of implants was 20.6 implants/year in the first triennium (1994-1996), and 4.3 implants/year in the last triennium, indicating a 79.1% decrease between these periods.

Distribution of procedures by geographic area revealed a considerable diversity. Most patients came from the southeast of Brazil; in fact, most of Chagas disease patients were from this region (55.6% of the cases), followed by the central west region (25.7% of the cases).

Regarding ethnic characteristics of the patients, most of them were white (49.5% of the implants), followed by mestizos (21.1%) and black individuals (14%). With respect to symptoms, most patients were NYHA class III and IV. One hundred patients (46.7%) were symptomatic during moderate/little efforts and 68 (31.8%) had symptoms at rest (Table 1).

Seventy-one percent of the electrocardiographic indications for implantation of cardiac stimulation system were second- and third-degree atrioventricular block (AVB). Most of them were complete AVB with a wide QRS complex (42% of incidence), whereas complete AVB with a narrow QRS complex was reported in 10% of patients (Figure 2).

Considering the total number of pacemaker implants per year (Figure 3), there was a relevant, statistically significant increase in the number of implants for all causes. Time series analysis of the number of implants in Chagas disease patients of all ages showed a slight, non-significant variation. The possibility that this variation has occurred by chance cannot be ruled out (p trend = 0.5). Nevertheless, time series analysis of the implants in Chagas disease patients younger than 18 years revealed a significant reduction in the number of implants through the years (p trend < 0.001) (Figures 1 and 3).

Discussion

In 1999, the Pan-American Health Organization (PAHO) declared that Triatoma infestans, the vector insect of *T. cruzi*, had been completely eliminated from human dwellings in Brazil, Chile, Uruguay, and large portions of Argentina, Bolivia, and Paraguay.[19] Nevertheless, despite recent advances in the control of T.cruzi transmission, Chagas disease continues to be an important public health problem in Latin America, with an annual impact of 430,000 DALYS (Disability-Adjusted Life Years) in the region.[18] Two hypotheses may be raised from this fact: (1) there have been continuous or increasing expenses on the treatment of chronic Chagas disease, particularly on patients with chronic Chagas cardiomyopathy (CCC), or (2) the parasite transmission modes have not been effectively controlled yet, which causes concern regarding blood transfusion transmission and vertical transmission of *T.cruzi*.

Data of the Brazilian Pacemaker Registry reflect CCC morbidity and hence yield useful information. Approximately 20% of infected patients develop CCC, and are at high risk for AVB and cardiac sudden death.[20] Interestingly, here we describe that, despite the increase in the number of pacemaker implants in Brazil, the number of procedures performed in Chagas disease patients per year did not change in the same period. This reflects a relative reduction of CCC and increase of other causes – such as senile degeneration of the conduction system – as indications for artificial stimulation of the heart. This finding may be due to a more effective control of vectorial and transfusional transmission of Chagas disease, as well as to an increase in life expectancy in the Brazilian population.[21]

Our most important finding was the drastic decrease in the use of artificial cardiac stimulation in individuals younger than 18 years, which may suggest a better control of Chagas disease transmission in Brazil in the last decades. As previously mentioned, this result may be partly explained by the control of the vector. However, the decrease in blood transfusion transmission in addition to the continuous,

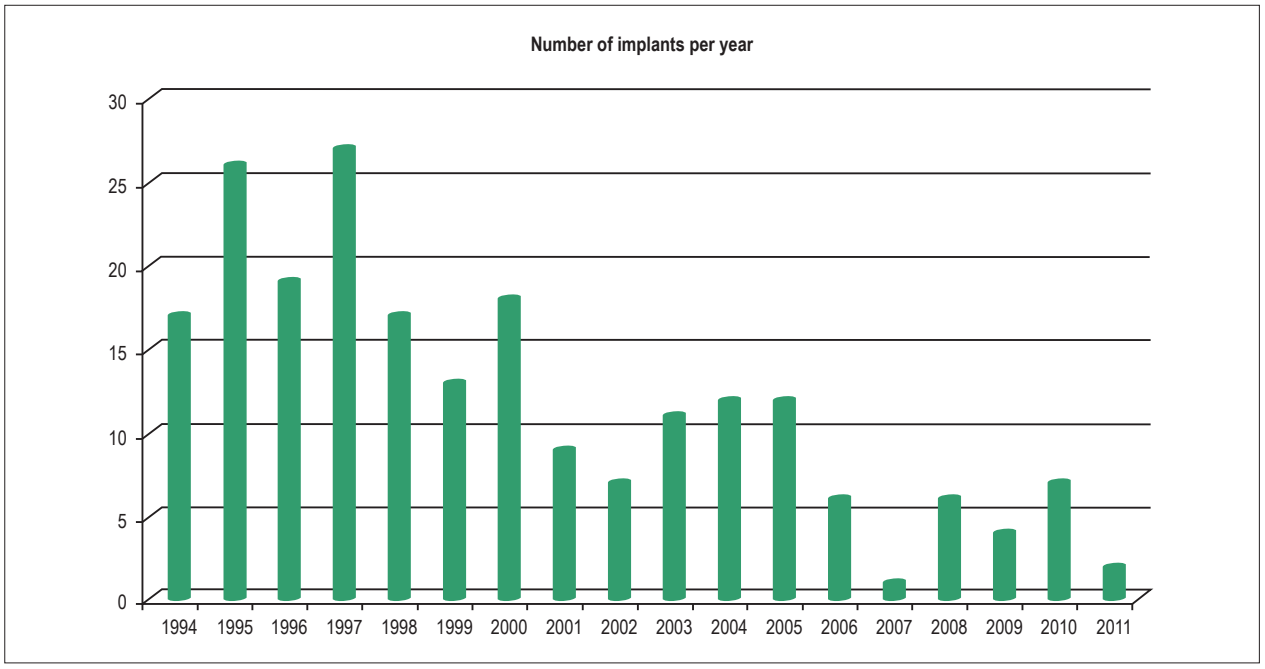

Figure 1 – *Annual distribution of pacemaker implantations in Chagas disease patients younger than 18 years. Source: Brazilian Pacemaker Registry.*

Table 1 – Baseline characteristics of Chagas disease patients younger than 18 years who had undergone implantation of cardiac stimulation devices between 1994 and 2011

Patients (n)		214
Age (years)		5.62 ± 6.2
Sex	Male	118 (55.2%)
	Female	96 (44.8%)
Federative unit of origin	Sao Paulo	59 (27.6%)
	Minas Gerais	59 (27.6%)
	Goias	36 (16.8%)
	Distrito Federal	19 (8.9%)
	Parana	13 (6.1%)
	Bahia	8 (3.7%)
	Alagoas	5 (2.3%)
	Pernambuco	5 (2.3%)
	Others	10 (4.7%)
Ethnic group	White	106 (49.5%)
	Mestizo	43 (20.1%)
	Black	30 (14.0%)
	Not declared	35 (16.3%)
Symptoms	Asymptomatic	19 (8.9%)
	Symptoms during great efforts	22 (10.3%)
	Symptoms during light/moderate efforts	100 (46.7%)
	Symptoms during rest	68 (31.8%)
	Not declared	5 (2.3%)

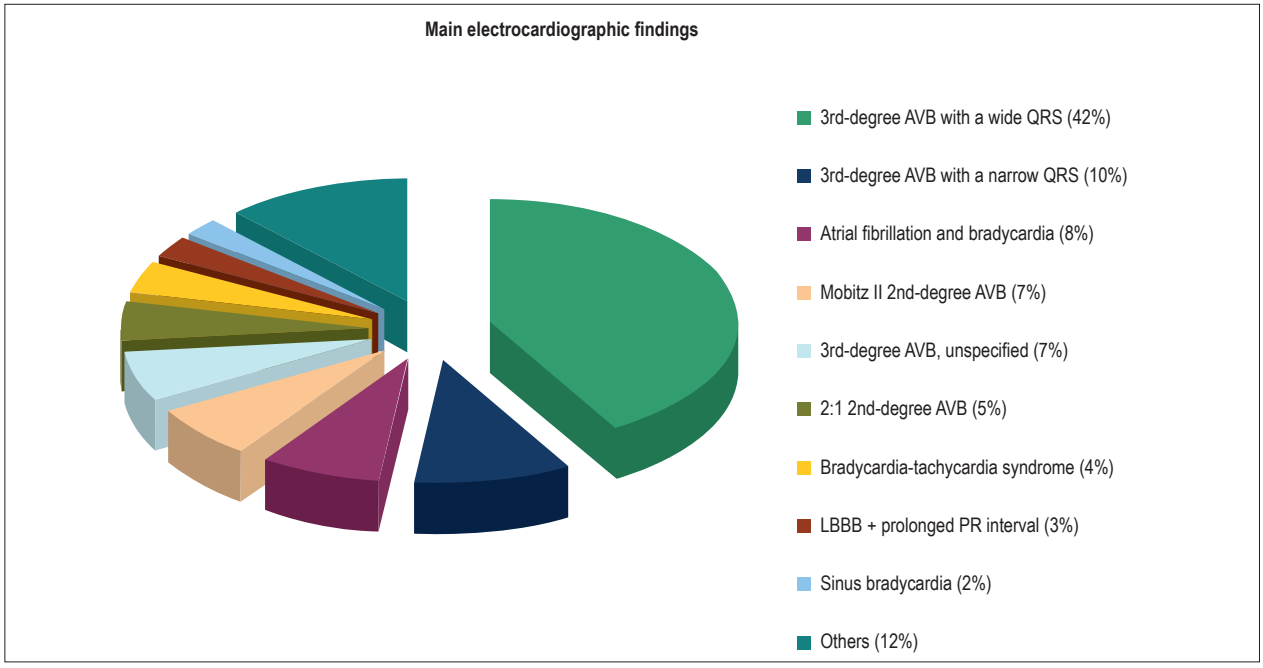

Figure 2 – *Electrocardiographic findings suggesting the need for pacemaker implantation in Chagas disease patients younger than 18 years. AVB: atrioventricular block; LBBB: left bundle branch block. Source: Brazilian Pacemaker Registry.*

effective control of vertical transmission of *T.cruzi* may have also contributed to it. At the end of the eighties, screening of blood donors for *T.cruzi* infection became compulsory in Brazil and, before this measure was implemented, approximately 20,000 new cases of Chagas disease were attributable to transfusional transmission per year. Today, the estimated risk of contamination of blood components by *T.cruzi* may be lower than 1 in 1,000,000 of transfusions.[21]

Although the relevance of vertical transmission of Chagas disease has increased since the control of other transmission modes of the disease in Brazil, there are no conclusive data about its real magnitude. According to a recent systematic review,[1] the infection prevalence among pregnant women varies from 0.1 to 8.5%, and the vertical transmission rate varies from 0 to 5.2%. The decrease in vertical transmission is also corroborated by the fact that conduction system diseases require years for its establishment, occurring in last stages of CCC.

Another finding that deserves attention is the uneven geographical distribution of the number of pacemaker implants across the national territory, not following the regions of higher prevalence of CCC. In addition to the concentration of main public health services in the big cities, the lack of trained experts in artificial cardiac pacing in children could also lead to the concentration of these procedures in tertiary health centers in capitals like Sao Paulo.

This study has some limitations inherent to the study design. First, accuracy of data may be affected by the inter-subject variability of individuals responsible for feeding the database. Second, the study only allows us to formulate causal hypothesis related to the management of Chagas disease in the last years, not only for the retrospective nature of the study, but also for the adoption of a variable that does not represent the whole. Despite these considerations, we believe that our study provide useful information for the planning of health systems.

Conclusion

There has been an important reduction in the number of pacemaker implantations among children and adolescents in Brazil, suggesting a better control of Chagas disease transmission in Brazil in the last two decades and a reduction in the vertical transmission of the parasite.

Author contributions

Conception and design of the research: Mizzaci CC, Souza TGS, Mateos JCP, Mateos JCP; Acquisition of data: Mizzaci CC, Targueta GP, Tótora APF; Analysis and interpretation of the data: Souza TGS, Targueta GP, Tótora APF; Statistical analysis: Souza TGS; Writing of the manuscript: Mizzaci CC, Souza TGS, Targueta GP, Tótora APF, Mateos JCP; Critical revision of the manuscript for intellectual content: Mizzaci CC, Mateos JCP, Mateos JCP.

Potential Conflict of Interest

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

Sources of Funding

There were no external funding sources for this study.

Study Association

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

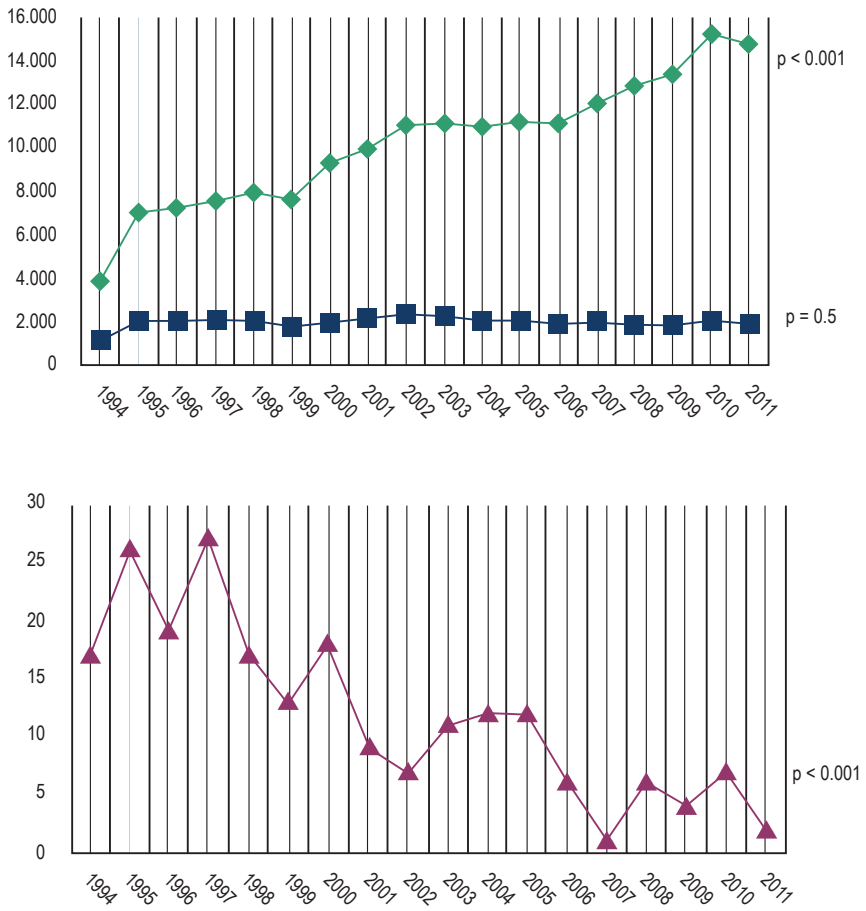

Figure 3 – *Comparative graph of total pacemaker implants for all causes performed in Brazil per year (diamonds), total number of pacemaker implants in Chagas disease patients (square) and total pacemaker implants in Chagas disease patients younger than 18 years (triangle). P value of variation trend in each series through the years. Source: Brazilian Pacemaker Registry.*

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Original Article

Three-Dimensional Volumetric Assessment of Diastolic Function by Cardiac Magnetic Resonance Imaging: The Multi-Ethnic Study of Atherosclerosis (MESA)

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Abstract

Background: **Cardiac Magnetic Resonance is in need of a simple and robust method for diastolic function assessment that can be done with routine protocol sequences.**

Objective: **To develop and validate a three-dimensional (3D) model-based volumetric assessment of diastolic function using cardiac magnetic resonance (CMR) imaging and compare the results obtained with the model with those obtained by echocardiography.**

Methods: **The study participants provided written informed consent and were included if having undergone both echocardiography and cine steady-state free precession (SSFP) CMR on the same day. Guide points at the septal and lateral mitral annulus were used to define the early longitudinal relaxation rate (E'), while a time-volume curve from the 3D model was used to assess diastolic filling parameters. We determined the correlation between 3D CMR and echocardiography and the accuracy of CMR in classifying the diastolic function grade.**

Results: **The study included 102 subjects. The E/A ratio by CMR was positively associated with the E/A ratio by echocardiography ($r = 0.71$, $p < 0.0001$). The early diastolic relaxation velocity by tissue Doppler and longitudinal relaxation rate for the lateral mitral annulus displacement were positively associated ($p = 0.007$), as were the ratio between Doppler E/e' and CMR E/E' ($p = 0.01$). CMR-determined normalized peak E (NE) and deceleration time (DT) were able to predict diastolic dysfunction (areas under the curve [AUCs] = 0.70 and 0.72, respectively). In addition, the lateral E/E' ratio showed good utility in identifying diastolic dysfunction (AUC = 0.80). Overall, echocardiography and CMR interobserver and intraobserver agreements were excellent (intraclass correlation coefficient range 0.72 – 0.97).**

Conclusion: **3D modeling of standard cine CMR images was able to identify study subjects with reduced diastolic function and showed good reproducibility, suggesting a potential for a routine diastolic function assessment by CMR. (Arq Bras Cardiol. 2017; 108(6):552-563)**

Keywords: **Ventricular Function; Evaluation; Magnetic Resonance; Imaging Three Dimensional; Echocardiography, Three –Dimensional.**

Introduction

the prevalence and cost of treatment of heart failure (HF) in the United States are high. In 2008, this condition was estimated to affected 5.3 million adults and was associated with a total spending of 34.8 billion dollars.[1,2] Approximately 50% of the patients were reported to have diastolic HF.[1,2] Diastolic dysfunction is an increasingly recognized component of a variety of diseases of the myocardium,[3,4] and its recognition is necessary for patient management.[5]

Echocardiography is currently used as the standard of reference to evaluate diastolic dysfunction.[6-10] With cardiac magnetic resonance (CMR) imaging, diastolic function is assessed using special pulse sequences such as phase-contrast analysis or myocardial tissue tagging.[5,6,8,11-16] These assessments require additional time and software for acquisition and analysis. As a result, the diastolic assessment with CMR is not routinely applied.[5,17,18] Thus, CMR is in need of a simple and robust method for diastolic function assessment that can be done with routine protocol sequences.

A three-dimensional (3D) model of myocardial function has been developed to assess the myocardial function based on standard steady-state free precession (SSFP) CMR cine

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images.[19] A model-based analysis of the systolic function is relatively fast (~15 minutes per CMR study) and allows extraction of time-varying function parameters that may characterize the diastolic function.[19-23]

Thus, the purpose of this study was to perform an intraindividual analysis to develop and validate a 3D model-based volumetric assessment of diastolic function using CMR imaging and compare the results obtained with this model with those obtained by echocardiography.

Methods

Study population

The study included participants who underwent both echocardiography and CMR between 2008 and 2009 in a substudy of the Multi-Ethnic Study of Atherosclerosis (MESA) at the Johns Hopkins Hospital. Details of the MESA study have been previously described.[24] In brief, 1096 participants free of clinically apparent cardiovascular disease and aged 45-84 years, were enrolled at the Baltimore field center at baseline in 2000-2002. A total of 149 consecutive participants were invited to participate in the CMR-echocardiography substudy. Participants were excluded if they had not undergone both studies at the same day; if they had a heart rate variability of more than 15 beats per minute between both studies, severe mitral annular calcification or mitral valve regurgitation; or if the qualitative assessments of the left ventricular (LV) function was impaired by arrhythmias or poor image quality by either modality (Figure 1). The study was approved by the local ethics committee, and all subjects gave a written informed consent for participation.

Since this study included a correlation between echocardiography and CMR, not all variables were used in the analysis. We will describe the variables that can be acquired by echocardiography and the 3D model-based volumetric assessment of diastolic function using CMR.

Echocardiography

Echocardiograms were obtained by expert sonographers according to the recommendations of the American Society of Echocardiography (ASE).[10] The examinations were reviewed offline by two readers. Readers 1 (A.L.C.A.) and 2 (A.C.A.) had 20 and 5 years of experience, respectively, in reading echocardiograms. Two-dimensional (2D) echocardiograms were recorded using an Aplio scanner (Toshiba Medical Systems Corp, Tochigi, Japan). The images were acquired from an LV apical four-chamber view. Image acquisitions were performed using B-mode harmonic images adjusting transducer frequencies (1.7-3.5 MHz), frame rate (40-80 frames per second), focus, sector width (as narrow as possible), sector depth (minimal), and gain, in order to optimize myocardial image quality. The images were digitally recorded, stored on compact discs, and transferred to a computer terminal for post processing.

Mitral inflow velocities: All Doppler measurements were assessed according to the ASE recommendations.[25] From the transmitral recordings, the following measurements were carried out: a) transmitral early peak filling velocity during diastole (early peak filling rate [E]), in centimeters per second; b) (transmitral late peak atrial filling velocity during diastole [peak atrial velocity [A]), in centimeters per second; c) time elapsed between E and the point where the extrapolation of the deceleration slope of the E velocity crosses the zero baseline (deceleration time [DT]), in milliseconds; d) time elapsed between the systolic peak to E (time to peak E [relative TPE]), in milliseconds; e) time elapsed between the systolic peak to A (time to peak A [relative TPA], in milliseconds.

Tissue Doppler measurement of mitral annular velocity: Pulsed wave tissue Doppler imaging (TDI) was performed in the apical views to acquire the mitral annular velocities according to the ASE recommendations.[25] The sample volume was placed in the ventricular myocardium immediately adjacent to the mitral annulus in the septal and lateral walls.

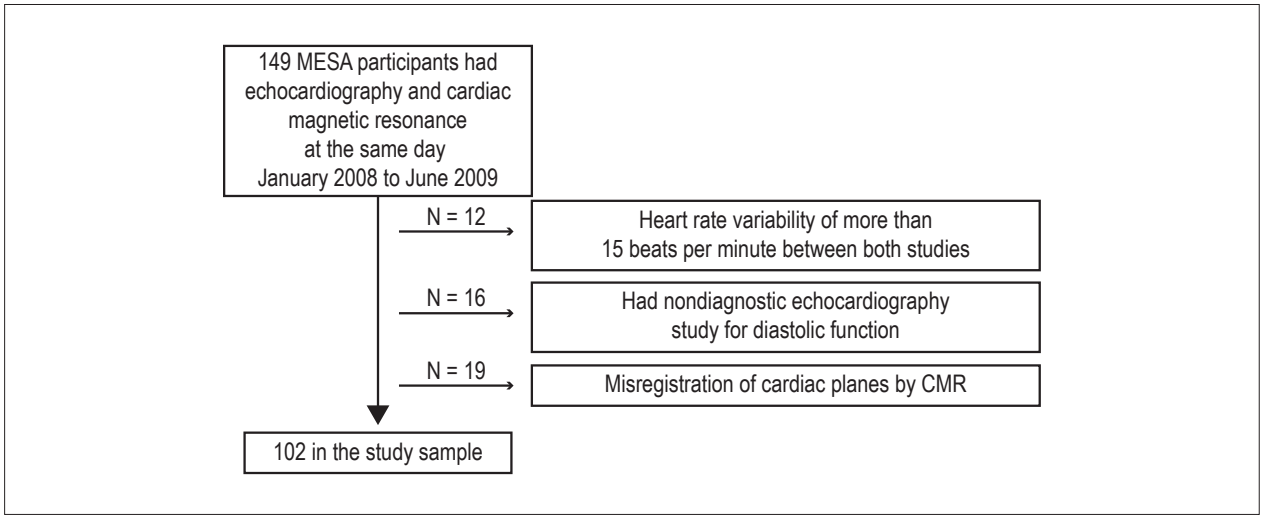

Figure 1 – *Flowchart of the study population. Abbreviation: CMR: cardiac magnetic resonance.*

With this method, the early diastolic myocardial relaxation velocity (e'; cm/s), as the annulus ascends away from the apex, was assessed in this study.

Cardiac magnetic resonance

Cine-CMR images were acquired on a 1.5 T scanner (Avanto, Siemens, Malvern, PA, USA) using a 2D SSFP acquisition in vertical long-axis, horizontal long-axis, and short-axis orientations with the following parameters: TE 1.16 ms, TR 3.2 ms, flip angle 60°, receiver bandwidth ±1220 kHz, FOV 36 cm, slice thickness 8 mm, slice gap 2 mm, acquisition matrix 205 × 256, number of averages = 1, number of frames = 30. The mean reconstructed temporal resolution (R-R interval/number of cardiac phases) was 30.43 ± 5.44 ms.

CMR images were analyzed using a research version of the CIM 6.2 program modified to assess diastolic function (Auckland MRI Research Group, University of Auckland, New Zealand).[19] CMR image analyses were done by two readers accredited by the Auckland MRI Research Group. Readers 1 (M.S.N.) and 2 (E.Y.) had 7 years and 1 year of experience, respectively, in reading CMR.

Time-volume curve: All timing measurements were defined semiautomatically with manual correction with the observer using a slider on the time/rate curve (Figure 2). The following measurements were assessed: a) diastolic volume recovery (DVR), defined as the time from end-systole (ES) to the time at which the volume has filled to 80% of the stroke volume (msec); b) E (mL/sec), the first maximum filling rate detected after ES. Peak E was also divided by the end-diastolic volume (EDV) to generate a normalized peak E filling rate (NE). Additional measurements included: c) relative time to early peak filling rate (RTPE) (msec), the trigger time to peak E from the ES phase; d) A (mL/sec), the second peak filling rate after ES. Peak A was also indexed by EDV to generate a normalized peak A filling rate (NA); e) relative time of atrial peak filling rate (RTPA; msec), the trigger time to peak A from the ES phase; and f) DT (msec), or the time delay of E subtracted from the E wave downslope intersecting the baseline.

Guide points at the junction of the LV wall with the septal mitral annulus and at the junction of the LV wall with the lateral mitral annulus in the four-chamber view were used to define g) E' septal, and h) E' lateral, respectively. The ratio between E and E' was also calculated (Figure 3).

Note that CMR rates are expressed as volume (mL) per unit of time, whereas echocardiographic parameters are expressed as distance (cm) per unit of time. However, CMR-derived E' is expressed as a linear velocity similar to its echocardiographic correlate.

Data and statistical analysis

The diastolic function classification used three echocardiographic parameters recommended by the ASE for this purpose: (1) septal e' < 8 cm/s, (2) lateral e' < 10 cm/s, and (3) ratio between average E and average e' ≥ 10.[25] If all three criteria were present, the diastolic function was rated as type II (reduced). If only two criteria were present or one criteria plus LV hypertrophy, the diastolic function was rated as type I (impaired). The LV mass was assessed by echocardiography and divided by the body surface area to define the LV mass index (LVMi). LV hypertrophy was defined as an LVMi > 115 g/m² for men and > 95 g/m² for women, as recommended by the ASE.[26]

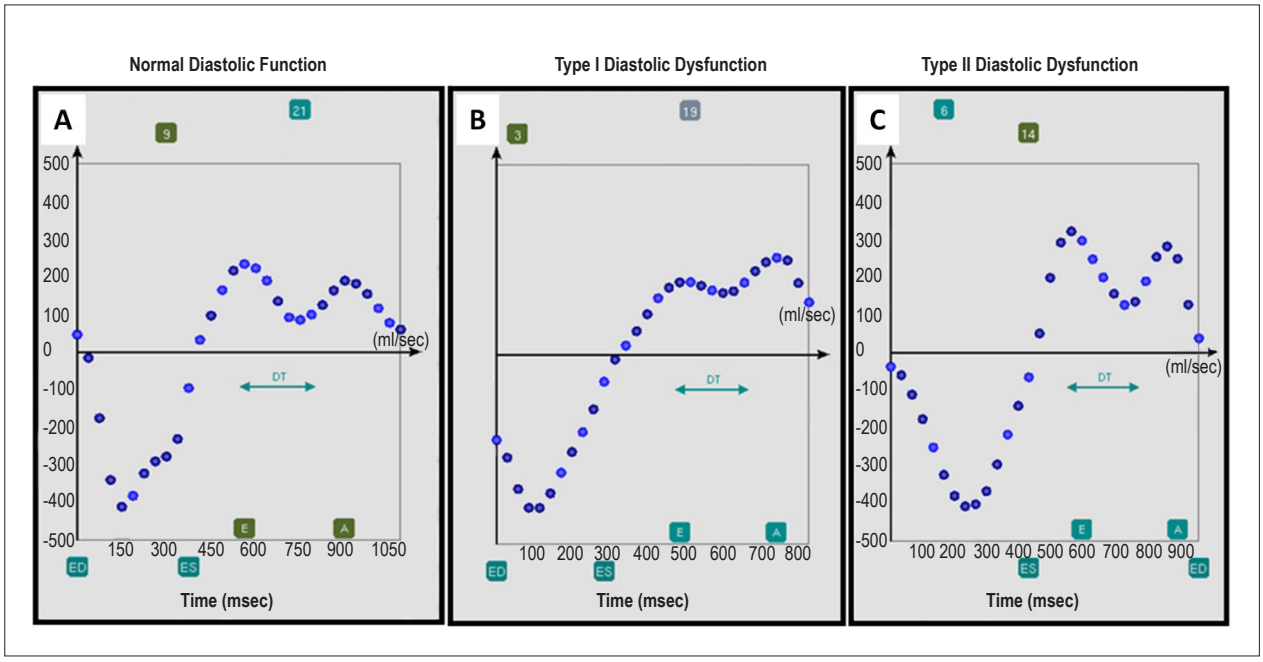

Figure 2 – *Screenshots of different diastolic function examples using the program CIM. A) Normal, B) impaired, and C) reduced. The following measurements were assessed: end-systole (ES), end-diastole (ED), early peak filling rate (E), atrial peak filling rate (A), and deceleration time (DT). All timing measurements were defined semiautomatically with manual correction with the observer using a slider on the time/rate curve.*

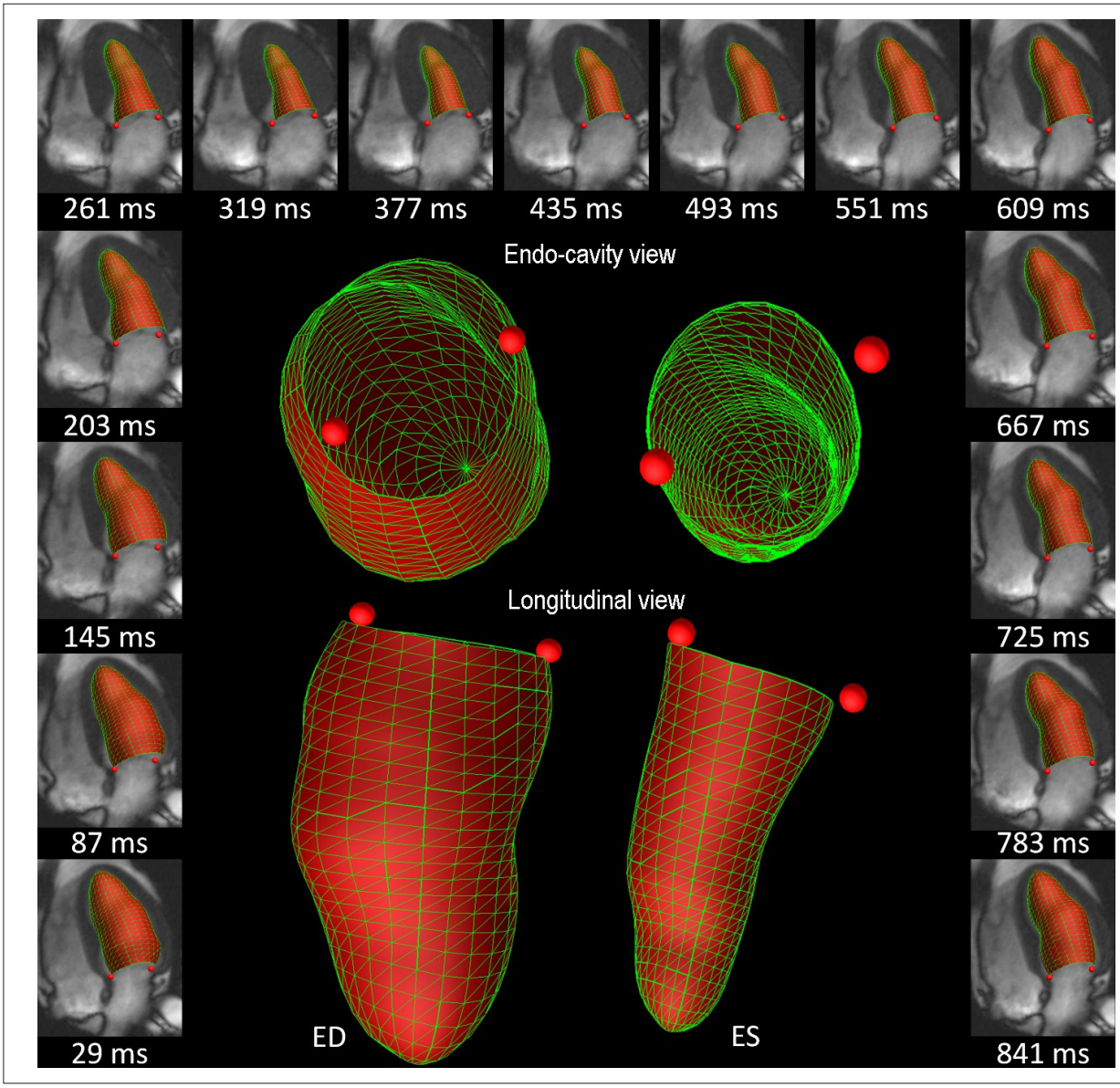

Figure 3 – *Three-dimensional displays of the model fits throughout the cardiac cycle in one R-R interval of 870 ms (outside images) for volume- and derivative-curve assessment (mL/s). Septal and lateral guide points motion can be evaluated through time, calculating the distance between the defined point and the model apex for myocardial longitudinal relaxation rate (mm/s). The endocardial surface is shaded in red and drawn with green lines.*

Data are presented as mean ± standard deviation (SD) for continuous variables and as percentage for categorical variables. Multiple comparisons were tested by one-way analysis of variance (ANOVA) with *post hoc* Bonferroni correction. Fisher's exact test was used to examine the differences between proportions. As the variables were normally distributed, linear regression analysis was performed using Pearson's correlation coefficient (r) and setting echocardiography as the predictor variable and CMR as the dependent variable. We used Bland-Altman to compare variables with the same units. However, in many cases, the CMR surrogates for echocardiographic parameters were represented in different units, so the Bland-Altman analysis was inappropriate.

Receiver operating characteristic (ROC) curve analysis was used to identify the diagnostic performance of CMR in predicting diastolic dysfunction. This was achieved by using the group with reduced diastolic function assessed by echocardiography as the "true positive" surrogate marker for diastolic dysfunction in this population, compared with the group with normal function as the "true negative" (area under the curve [AUC] ≥ 0.5 to < 0.7 = poor fit, AUC ≥ 0.7 to < 0.9 = good fit, and AUC ≥ 0.9 to 1.0 = excellent fit).

Intraobserver and interobserver agreements were assessed using intraclass correlation coefficient (ICC) with a two-way random model (ICC < 0.40 = poor agreement, ICC ≥ 0.40 to 0.75 = fair to good agreement, ICC > 0.75 = excellent agreement).

The statistical analysis was performed using Stata, version 12.0 (StataCorp LP, College Station, Texas, USA). A p value < 0.05 was considered significant.

Results

A total of 102 participants met the inclusion criteria (Figure 1). On echocardiography, the diastolic function was classified as normal in 66 (64.7%) patients, impaired in 21 (20.6%), and reduced in 15 (14.7%) of them. The mean duration of the CMR analysis (systolic and diastolic function) was 18.3 ± 4.5 minutes. Note that the CMR analysis also yields parameters such as LV volume and mass, since the analysis is performed over the full cardiac cycle. The mean duration of the echocardiographic analysis (diastolic function only) was 4.6 ± 0.6 minutes (p < 0.0001 compared with the CMR analysis). Reduced diastolic function was more frequent in diabetic and hypertensive participants. Major variables, *e.g.*, age, gender, body mass index (BMI), systolic blood pressure (SBP), LV mass, EDV, and heart rate, showed no significant variance between groups. The characteristics of the subjects and the clinical data related to their LV function are summarized in Table 1.

Echocardiographic parameters showed increasing mean values in association with diastolic dysfunction severity (p < 0.05, Table 2). However, A alone showed no statistically significant difference between groups. NE and DT obtained from derivative volume-curves by CMR showed trends toward diastolic dysfunction severity similar to those obtained by echocardiography (p < 0.05). The E/A ratio by CMR was 1.10 ± 0.38 in the normal group, and was lower in the impaired group (1.01 ± 0.26) and higher in the reduced diastolic function group (1.33 ± 0.45, p = 0.03). All other variables showed no difference between groups (Table 2).

Tissue Doppler velocities by echocardiography assessed e' and the E/e' ratio. In all regions (septal and lateral mitral annulus), e' showed significantly decreased mean values in the normal diastolic function group (e' lateral = 11.6 ± 2.4 cm/s) and in the reduced diastolic function group (e' lateral = 6.9 ± 1.8 cm/s, p < 0.05). Also, E/e' increased from the group with a normal diastolic function to the one with reduced diastolic function (6.65 ± 1.8 and 13.3 ± 5.2, respectively, p < 0.0001). Compared with CMR, E' and E/E' showed similar trends toward worse diastolic function for both septal and lateral walls (p < 0.05 and p < 0.001, respectively) (Table 2).

Table 3 highlights the associations between the diastolic function measured by echocardiography and CMR. E/A ratios on echocardiography were positively associated with E/A ratios on CMR (r = 0.71, p < 0.0001). The 95% limits of agreement between the two methods were -0.45% to +0.62%. A small bias (0.081%) toward a higher E/A ratio by CMR was detected (Figure 4).

Values of e' by tissue Doppler and E' for the lateral mitral annulus displacement were positively correlated (r = 0.26, p = 0.007), as were E/e' by CMR and echocardiography (r = 0.24, p = 0.01). However, both septal measurements were not correlated (p > 0.05).

Prediction of reduced diastolic function by cardiac magnetic resonance

Table 4 shows the ROC curve analysis for reduced diastolic function for all CMR parameters. CMR-determined NE and DT were able to predict diastolic dysfunction (AUCs = 0.70 and 0.72, respectively). In addition, the lateral E/E' ratio appeared to be useful in the classification of diastolic dysfunction (AUC = 0.80) (Table 4).

Diastolic time periods and cardiac cycle duration

No significant differences were detected in relative TPE and RTPA values obtained by CMR compared with those obtained by echocardiography (mean RTPA: 183.3 ± 47.32 ms *versus* 181.5 ± 27.45 ms, respectively, p = 0.90; mean TPE: 544.32 ± 145.62 ms *versus* 550.77 ± 196.19 ms, respectively, p = 0.91). The cardiac cycle duration (R-R interval) was also not significantly different by CMR *versus* echocardiography (mean 943.65 ± 135.11 ms *versus* 944.77 ± 135.42 ms, respectively, p = 0.95).

Interobserver and intraobserver agreements

Overall, echocardiography and CMR interobserver and intraobserver agreements were excellent (Table 5). The mean ICC for measurements by echocardiography was excellent (0.89) and slightly higher than those obtained by CMR (0.86).

Discussion

The purpose of this study was to evaluate the role of cine CMR for diastolic function assessment and compare values obtained with this method with those obtained with echocardiography. Using a relatively fast and reproducible method, CMR-derived parameters were shown to be comparable to those obtained by echocardiography, with good correlations. Importantly, this study demonstrated that CMR was capable of identifying diastolic dysfunction in most patients with diastolic dysfunction detected by echocardiography. This suggests a role for CMR in the assessment of LV diastolic function in the general population.

Echocardiography has long been used to evaluate diastolic dysfunction. The combination of mitral inflow velocity curves and tissue Doppler velocities of the mitral annulus are known to provide better estimates of LV filling pressures than other methods.[27] Although routinely reported by echocardiography, diastolic function by CMR is usually not routinely assessed due to the requirement of additional phase contrast or tagged sequences, as well as separate post processing. Automated segmentation of LV volumes for all temporal phases holds the potential to rapidly assess diastolic filling patterns;[28] however, this method alone only provides partial information regarding the diastolic physiology needed to differentiate all degrees of diastolic dysfunction severity.

Recently, CMR software innovations[19,29,30] have allowed the assessment of similar parameters using SSFP cine CMR with 3D post processing. HF with preserved ejection fraction

Table 1 – Population characteristics by diastolic function grades

	Normal n = 66 (64.70%)	Type I n = 21 (20.60%)	Type II n = 15 (14.70%)	p value
Age (years)	66.8 ± 8.9	65.5 ± 7.5	64.4 ± 9.7	0.60
45 to 64 years	24 (36.3)	11 (52.3)	7 (46.6)	0.48*
65 to 84 years	42 (63.6)	10 (47.6)	8 (53.3)	0.48*
Gender (male)	26 (39.3)	7 (33.3)	6 (40.0)	0.91
Race				
White, Caucasian	41 (62.0)	11 (55.0)	6 (40.0)	0.25*
Black, African-American	25 (38.0)	10 (45.0)	9 (60.0)	0.25*
Weight (kg)	77.5 ± 15.1	80.3 ± 19.4	80.3 ± 22.2	0.73
Height (cm)	168.0 ± 9.4	166.0 ± 11.2	166.1 ± 9.7	0.65
BMI (kg/m^2)	28.0 ± 4.4	29.1 ± 5.7	28.2 ± 7.1	0.71
BSA	1.8 ± 0.2	1.8 ± 0.2	1.8 ± 0.2	0.89
Smoking status				
Never	27 (40.9)	9 (42.8)	5 (33.3)	0.37*
Former	33 (50.0)	12 (57.1)	7 (46.6)	0.37*
Current	6 (9.0)	0 (0.0)	3 (20.0)	0.37*
Systolic blood pressure (mmHg)	121.8 ± 18.7	119.8 ± 14.6	121.3 ± 25.9	0.91
Diastolic blood pressure (mmHg)	71.2 ± 11.2	66.3 ± 10.6	69.1 ± 10.7	0.21
Hypertension (%)	33 (50.0)	7 (33.3)	9 (60.0)	0.28*
Any hypertension medication	31 (46.9)	6 (28.5)	9 (60.0)	0.20*
Diabetes (%)	3 (4.5)	2 (9.5)	3 (20.0)	0.11*
Triglycerides (mg/dL)	111.9 ± 60.5	100.3 ± 67.3	101.3 ± 54.8	0.68
LDL cholesterol (mg/dL)	111.5 ± 32.3	109.1 ± 34.2	112.4 ± 42.9	0.95
HDL cholesterol (mg/dL)	58.9 ± 18.4	62.4 ± 24.9	52.6 ± 12.0	0.33
Total cholesterol (mg/dL)	192.8 ± 38.5	191.5 ± 38.8	185.2 ± 52.7	0.81
Metabolic syndrome	21 (31.8)	4 (19.0)	2 (13.0)	0.26*
Echocardiographic measurements				
Heart rate (beats/min)	64.8 ± 9.6	65.0 ± 9.4	62.6 ± 5.7	0.66
End-diastolic diameter (mm)	4.4 ± 0.5	4.5 ± 0.5	4.6 ± 0.4	0.44
Diastolic septal thickness (mm)	1.0 ± 0.2	1.0 ± 0.1	0.9 ± 0.1	0.18
Diastolic inferolateral thickness (mm)	0.9 ± 0.1	0.9 ± 0.1	0.9 ± 0.1	0.66
CMR measurements				
Heart rate (beats/min)	65.2 ± 10.4	66.4 ± 9.7	61.6 ± 5.5	0.31
Ejection fraction (%)	69.0 ± 7.3	70.7 ± 7.0	70.6 ± 10.2	0.51
End-diastolic volume (mL)	106.8 ± 24.4	110.6 ± 28.7	99.6 ± 22.1	0.43
End-systolic volume (mL)	33.8 ± 13.6	33.5 ± 14.2	28.8 ± 10.6	0.42
LV mass (g)	124.8 ± 34.4	132.5 ± 38.2	121.8 ± 26.2	0.59
Stroke volume (mL)	73.0 ± 15.1	76.5 ± 18.0	73.1 ± 17.5	0.67

*BMI: body mass index; BSA: body surface area; CMR: cardiac magnetic resonance; LV: left ventricular. Note: * Fisher's exact test was used to compare proportions between diastolic severity grades.*

Table 2 – Diastolic measurements by echocardiography and cardiac magnetic resonance

	Normal n = 66 (64.70%)	Type I n = 21 (20.60%)	Type II n = 15 (14.70%)	p value
Echocardiography				
Mitral inflow velocities				
E (cm/s)	74.53 ± 16.43	74.89 ± 20.76	87.68 ± 20.94	0.03
DT (ms)	220.14 ± 45.19	247.95 ± 76.70	258.4 ± 77.69	0.03
A (cm/s)	77.66 ± 19.59	75.40 ± 19.55	77.18 ± 23.09	0.90
E/A	0.99 ± 0.24	1.02 ± 0.22	1.23 ± 0.47	0.01
Tissue Doppler velocities				
Septal				
e' (cm/s)	9.38 ± 1.69	8.33 ± 2.12	6.00 ± 1.26	<0.0001
E/e'	8.20 ± 2.24	9.23 ± 2.22	15.37 ± 5.91	<0.0001
Lateral				
e'(cm/s)	11.61 ± 2.45	8.23 ± 1.68	6.97 ± 1.80	<0.0001
E/e'	6.65 ± 1.82	9.37 ± 3.22	13.36 ± 5.21	<0.0001
Mean				
e' (cm/s)	10.47 ± 1.59	8.27 ± 1.45	6.48 ± 1.44	<0.0001
E/e'	7.25 ± 1.78	9.12 ± 2.06	14.19 ± 5.40	<0.0001
CMR				
Volume-curves				
E (mL/s)	189.30 ± 66.39	206.30 ± 62.58	213.60 ± 71.67	0.33
NE (s^{-1})	1.77 ± 0.46	1.89 ± 0.50	2.11 ± 0.43	0.03
DT (ms)	186.61 ± 43.94	211.08 ± 43.75	218.37 ± 42.59	0.01
TPE (ms)	504.86 ± 82.41	493.46 ± 68.75	517.54 ± 37.80	0.63
A (mL/s)	181.13 ± 72.08	211.09 ± 75.17	164.73 ± 43.96	0.11
NA (s^{-1})	1.70 ± 0.53	1.98 ± 0.76	1.71 ± 0.58	0.16
TPA (ms)	837.27 ± 193.40	861.57 ± 155.17	866.00 ± 115.64	0.78
E/A	1.10 ± 0.38	1.01 ± 0.26	1.33 ± 0.45	0.03
DVR (ms)	535.32 ± 117.96	542.44 ± 122.45	516.08 ± 78.16	0.80
Longitudinal relaxation rate				
Septal				
E' (mm/s)	75.35 ± 24.49	66.49 ± 25.31	58.22 ± 24.11	0.03
E/E' (mL/mm)	2.64 ± 0.96	3.45 ± 1.60	4.65 ± 3.38	0.0002
Lateral				
E' (mm/s)	82.36 ± 26.14	70.88 ± 28.45	61.06 ± 27.73	0.01
E/E' (mL/mm)	2.40 ± 0.83	3.32 ± 1.80	4.52 ± 3.54	0.0001
Mean				
E' (mm/s)	78.86 ± 24.85	68.69 ± 26.26	59.64 ± 25.45	0.02
E/E' (mL/mm)	2.50 ± 0.87	3.33 ± 1.53	4.55 ± 3.44	0.0001

E: early peak filling rate; DT: deceleration time; A: atrial peak filling rate; E/A:E/A ratio; e': early diastolic myocardial relaxation velocity; E/e': E/e' ratio; NE: normalized peak E filling rate; NA: normalized peak A filling rate; DVR: diastolic volume recovery; E': early longitudinal relaxation rate; CMR: cardiac magnetic resonance, TPE: time to peak E; TPA: time to peak A.

is increasing in incidence and has a high clinical relevance,[8] although a clear consensus for its diagnosis has yet to be established.[31] In this study, we decided to follow the ASE recommendations[25] to delineate normal *versus* reduced diastolic function groups.

CMR is considered a reference standard for ventricular systolic function, including the analysis of regional wall motion, mass, and volumes, and estimation of ejection fraction.[32] The assessment of diastolic function by CMR is usually not routinely performed in our clinical practice.

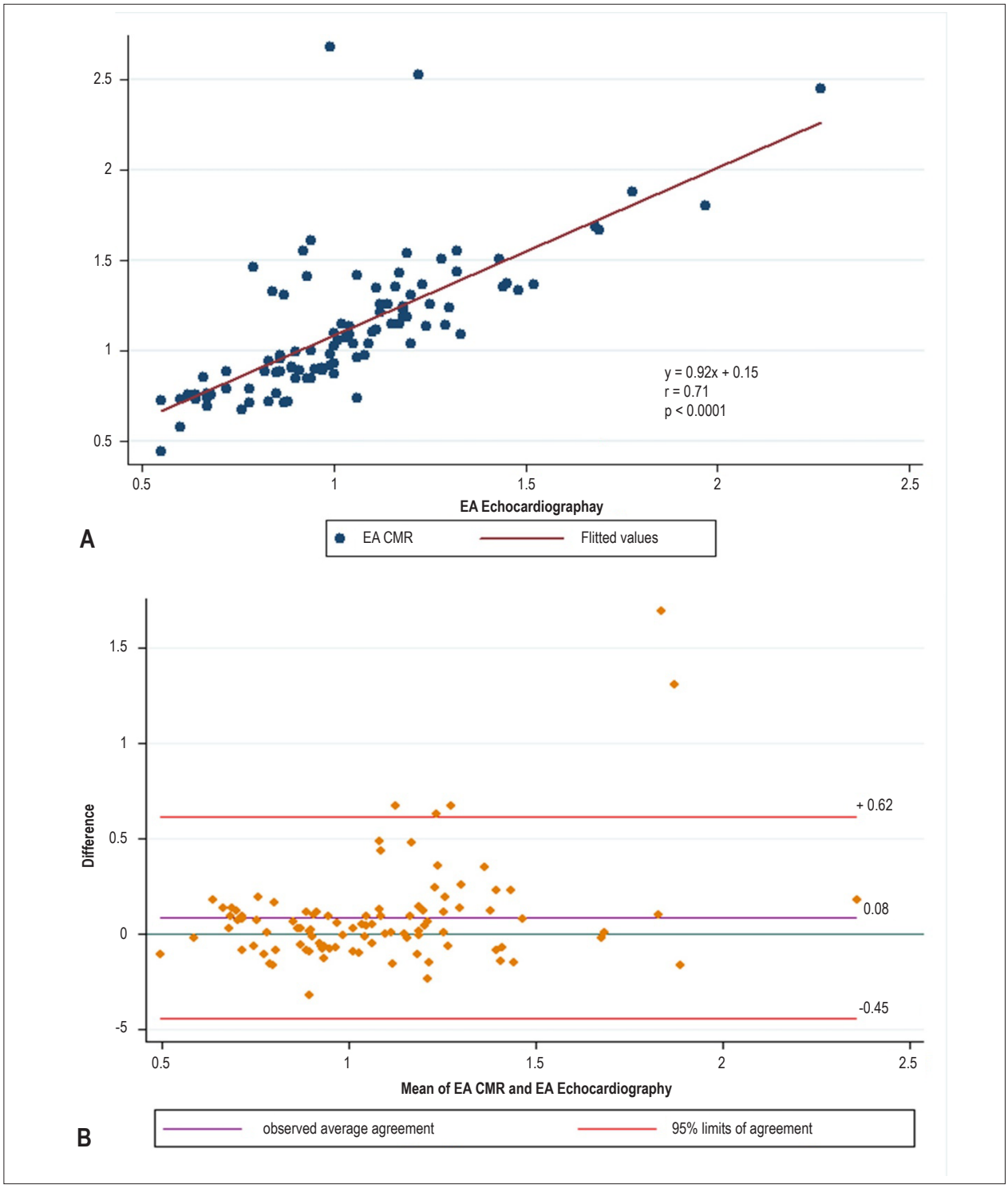

Figure 4 – *Results obtained using cardiac magnetic resonance (CMR) three-dimensional volume-curve and echocardiography Doppler mitral valve inflow. The ratio between the early peak filling (E) and atrial peak filling rate (A) using velocity (cm/s) by echocardiography and flow (mL/s) by CMR. (A) Linear regression and Pearson's correlation; (B) Bland-Altman analysis.*

CMR diastolic assessment typically requires an increased scan time for image acquisition (e.g., additional phase-contrast sequences), as well as a tedious imaging post-processing analysis. Automated segmentation of LV volumes for all temporal phases holds the potential to assess rapidly diastolic filling patterns;[28] however, this method relies on a sequential

Table 3 – Associations between measures of diastolic function by echocardiography and cardiac magnetic resonance (n = 102)

Echocardiography	CMR	Pearson's correlation coefficient (r)	p value
Mitral inflow velocities	**Volume-curves**		
E (cm/s)	E (mL/s)	0.06	0.51
E (cm/s)	NE (s^{-1})	0.1	0.18
A (cm/s)	A (mL/s)	0.22	0.01
A (cm/s)	NA (s^{-1})	0.28	0.003
E/A	E/A	0.71	< 0.0001
Tissue Doppler	**Longitudinal relaxation rate**		
Septal	**Septal**		
e' (cm/s)	E' (mm/s)	0.11	0.26
E/e'	E/E' (mL/mm)	0.11	0.30
Lateral	**Lateral**		
e' (cm/s)	E' (mm/s)	0.26	0.007
E/e'	E/E' (mL/mm)	0.24	0.01
Mean	**Mean**		
e' (cm/s)	E' (mm/s)	0.22	0.02
E/e'	E/E' (mL/mm)	0.17	0.07

CMR: cardiac magnetic resonance; early peak filling rate; A: atrial peak filling rate; e': early diastolic myocardial relaxation velocity; NE: normalized peak E filling rate; NA: normalized peak A filling rate; E/A: E/A ratio; E': early longitudinal relaxation rate. Echocardiography corresponds to Doppler echocardiography.

Table 4 – Prediction of reduced diastolic function by cardiac magnetic resonance (n = 81)

CMR	Area under the ROC curve	p value
Volume-curves		
E (mL/s)	0.60	0.21
NE (s^{-1})	0.70	0.008
DT (ms)	0.72	0.01
A (mL/s)	0.53	0.37
NA (s^{-1})	0.48	0.92
DVR (ms)	0.51	0.57
E/A	0.66	0.05
Longitudinal relaxation rate		
Septal		
E' (mm/s)	0.67	0.01
E/E' (mL/mm)	0.76	0.0003
Lateral		
E' (mm/s)	0.70	0.0004
E/E' (mL/mm)	0.80	< 0.0001
Mean		
E' (mm/s)	0.69	0.006
E/E' (mL/mm)	0.78	0.0001

CMR: cardiac magnetic resonance; ROC: receiver operating characteristic; E: early peak filling rate; NE: normalized peak E filling rate; DT: deceleration time; A: atrial peak filling rate; NA: normalized peak A filling rate; DVR: diastolic volume recovery; E/A: E/A ratio; E': early longitudinal relaxation rate; E/E': E/E' ratio.

Table 5 – Intraobserver and interobserver agreement (n = 20)

	Intraclass correlation coefficient (ICC)	Bias	95% limits of agreement
Echocardiography R1 *versus* R2			
Mitral inflow velocities			
E (cm/s)	0.93	-1.66	-11.70 to 8.36
DT (ms)	0.84	9.84	-38.67 to 58.36
A (cm/s)	0.95	-1.12	-14.84 to 12.59
Tissue Doppler velocities			
Septal			
e' (cm/s)	0.85	0.42	-1.84 to 2.68
Lateral			
e' (cm/s)	0.89	-0.37	-1.76 to 2.49
Echocardiography R1 *versus* R1			
Mitral inflow velocities			
E (cm/s)	0.95	-1.39	-9.22 to 6.44
DT (ms)	0.72	6.77	-62.40 to 75.96
A (cm/s)	0.96	-0.22	-12.85 to 12.39
Tissue Doppler velocities			
Septal			
e' (cm/s)	0.89	0.28	-1.78 to 2.35
Lateral			
e' (cm/s)	0.92	-0.59	-2.06 to 0.86
CMR R1 *versus* R2			
Volume-curves			
E (mL/s)	0.84	2.54	-79.77 to 84.86
DT (ms)	0.77	-21.52	-81.75 to 38.70
A (mL/s)	0.82	22.89	-51.20 to 97.00
Longitudinal relaxation rate			
Septal			
E' (mm/s)	0.75	-4.90	-32.59 to 22.63
Lateral			
E' (mm/s)	0.89	-5.48	-25.24 to 14.27
CMR R1 *versus* R1			
Volume-curves			
E (mL/s)	0.97	-1.36	-33.73 to 31.00
DT (ms)	0.84	12.93	-28.46 to 28.46
A (mL/s)	0.96	-15.51	-64.82 to 33.79
Longitudinal relaxation rate			
Septal			
E' (mm/s)	0.85	-2.93	-23.91 to 18.03
Lateral			
E' (mm/s)	0.94	-4.11	-18.93 to 10.70

Note: R1: reader 1 and R2: reader 2. E: early peak filling rate; DT: deceleration time; A: atrial peak filling rate; e': early diastolic myocardial relaxation velocity; E': early longitudinal relaxation rate.

cross-sectional analysis that only provides partial information regarding the diastolic physiology needed to differentiate all degrees of diastolic dysfunction severity.

In our study, we were able to overcome several limitations of CMR diastolic function analysis using a new 3D method with an average analysis time of fewer than 20 minutes with no need to add more sequences in our routine protocol. In our experience, this analysis time is comparable to that obtained for full 3D volumetric assessment of systole alone. For CMR, it appears that E/E', NE, DT, and E/A were the most useful parameters obtained from time-volume curves. When the longitudinal shortening was measured, both septal and lateral measurements were able to categorize diastolic dysfunction. However, E' at the lateral wall was shown to be more reproducible and easily measured by CMR. By comparison, septal E' had lower reader reproducibility.

This study had several limitations. Echocardiography was used as the reference standard, but reader variability and diastolic classification are known to be imperfect with this method.[31] The correlation between LV mitral valve inflow velocities and time-volume curves from CMR represents different physiological processes. The time-volume curves from CMR should not be adversely affected by mitral valve disease or angle of acquisition.[9,25] In this study population, hemodynamic data were not available. In addition, our study population did not include subjects with restrictive cardiomyopathy. CMR time-volume curves represent the average of several cardiac cycles, whereas echocardiography shows peak values for each cardiac cycle. Finally, although a good correlation of echocardiographic and CMR data appears to be present, outcome data is still needed to validate further the CMR approach.

Conclusion

The 3D CMR method was relatively fast, reproducible, and successfully applied to routine SSFP cine CMR data. CMR was able to identify most patients with reduced diastolic function identified by echocardiography. This suggests a role for CMR in the assessment of LV diastolic function in the general population and in patients with mild and moderate diastolic dysfunction.

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Author contributions

Conception and design of the research: Nacif MS, Young AA, Cowan BR, Lima JAC, Bluemke DA; Acquisition of data: Nacif MS, Almeida ALC, Young AA, Cowan BR, Armstrong AC, Yang E; Analysis and interpretation of the data: Nacif MS, Almeida ALC, Young AA, Cowan BR, Armstrong AC, Yang E, Sibley CT, Hundley WG, Liu S, Lima JAC, Bluemke DA; Statistical analysis: Nacif MS, Young AA, Cowan BR, Armstrong AC, Yang E; Obtaining funding: Lima JAC, Bluemke DA; Writing of the manuscript: Nacif MS; Critical revision of the manuscript for intellectual content: Nacif MS, Almeida ALC, Young AA, Cowan BR, Sibley CT, Hundley WG, Liu S, Lima JAC, Bluemke DA.

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Cirrhotic Cardiomyopathy: A New Clinical Phenotype

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Introduction

Hepatic cirrhosis is the final spectrum of several aggressions to the liver, with great relevance to public healthcare. National data estimate a prevalence of 0.14% to 0.35%, mortality of 3 to 35 per 100,000 individuals and an annual average of 30,000 hospital admissions in Brazil.[1,2] With the ageing population, the prevalence of chronic liver diseases, in particular steatohepatitis associated to obesity and metabolic syndrome, results in an increase in the number of hepatic cirrhosis cases.[3]

Cardiac manifestations of hepatic cirrhosis were first reported in the 20th century, with alterations on cardiac output.[4] With new information on the extra-hepatic repercussions of cirrhosis, cirrhotic cardiomyopathy (CCM) has been described as a spectrum of chronic morphofunctional alterations in the heart of cirrhotic patients with no previous cardiac diseases.[5-7] The cardiomyocyte lesion is provoked by an imbalance in hemeostasis that occurs in the progression of cirrhosis, with exhaustion of beta-adrenergic receptors, cytoplasmic impregnation by endocannabinoids, and imbalance of nitric oxide and endothelin.[7] CCM is asymptomatic; however, systolic and diastolic structural alterations are described in the electrocardiogram (ECG) and Doppler echocardiogram (ECHO).[8]

Because CCM is asymptomatic, except during situations of stress, prevalence studies are limited. Heart failure (HF) secondary to CCM is frequent in patients who undergo liver transplant, in which half the patients presents HF, and up to 21% die from cardiac causes.[9] Today, it is possible to identify myocardial compromise in up to 50% of cirrhosis patients,[10] but, in most cases, without clinical expression.

The objective of this review is to describe recent findings of the pathophysiology of the cardiovascular system in hepatic cirrhosis, and show the importance of biomarkers and cardiac imaging methods in the identification of a new clinical phenotype of CCM.

Cardiovascular system in hepatic cirrhosis

Hepatic cirrhosis evolution is insidious, being at times asymptomatic or oligosymptomatic until advanced stages. Signs and symptoms of liver failure tend to appear late, with subtle clinical and laboratory manifestations which are often hard to interpret.

Cardiologists may be faced with a patient complaining of dyspnea, presenting with ascites, without pathological jugular swelling, normal ECG, ECHO with normal ejection fraction, but with elevated B-type natriuretic peptide (BNP) – a condition that may be suggestive of CCM.[11] Considering it is different from a classic presentation of HF, it is necessary to know this syndrome (CCM) and have a degree of clinical suspicion for early identification, to prevent its evolution to related complications, such as suprarenal insufficiency and hepatorenal syndrome (HRS).

In the past, cardiomyopathy in alcoholic cirrhosis was understood as myocardial damage concomitant to liver damage, and had dilated cardiomyopathy as a phenotype.

It was believed that alcohol aggression to the heart always happened in the form of chronic disease with dilatation of cavities. With the discovery of viral hepatitis B and C, myocarditis from hepatitis B and C viruses was described, with variable clinical phenotypes, from the oligosymptomatic state, associated or not to dilated cardiomyopathy. The concept of CCM allows us to understand a new clinical phenotype: the asymptomatic patient, with no apparent functional limitations, but subclinical cellular and structural cardiac disease (Figure 1).

Cirrhotic patients have hyperdynamic circulation from the peripheral vasodilatation imposed by the neuroendocrine imbalance of hepatic cirrhosis, with increased cardiac output at rest and decreased peripheral vascular resistance.[12] There is a predominance of arterial vasodilatation, which induces the activation of the autonomic nervous and renin-angiotensin-aldosterone (RAAS) systems, so that peripheral perfusion is preserved. This hyperdynamic pattern is directly dependent on cardiac reserve (inotropic and chronotropic capacity), so cardiac output is preserved.

Figure 2 summarizes the main hemodynamic alterations in cirrhotic patients. There is a relative increase in cardiac output, sympathetic hyperstimulation, and elevation of heart rate and pulmonary blood flow, with a reduction of pulmonary vascular resistance. Conversely, there is a decrease in effective circulating arterial volume, systemic blood pressure, and afterload from vasodilatation.[12]

With the evolution of biochemical studies and morphofunctional cardiac evaluations, the concept of CCM started to represent the suboptimal ventricular response to stress, physiological or induced, even though the patient presents apparently normal cardiac output at rest, in the absence of previous heart disease.[13]

CMC`s pathogenesis involves cellular, neural and humoral factors, whose pathophysiological basis is in alterations of the plasma membrane of cardiomyocytes: influence in calcium

Keywords

Liver Cirrhosis / mortality; Obesity; Aging; Metabolic Syndrome; Fatty Liver; Cardiomyopathy, Alcoholic.

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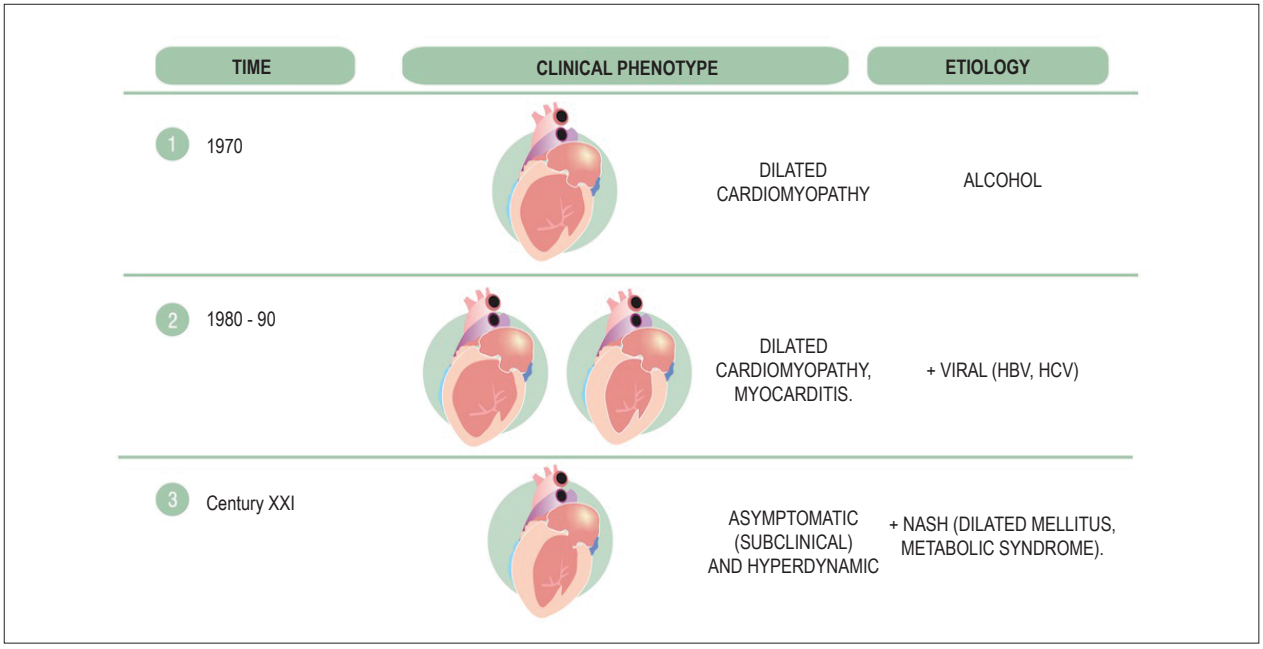

Figure 1 – *Evolution of cirrhotic cardiomyopathy concept. HBV: hepatitis B virus; HCV: hepatitis C virus; NASH: non-alcoholic steatohepatitis.*

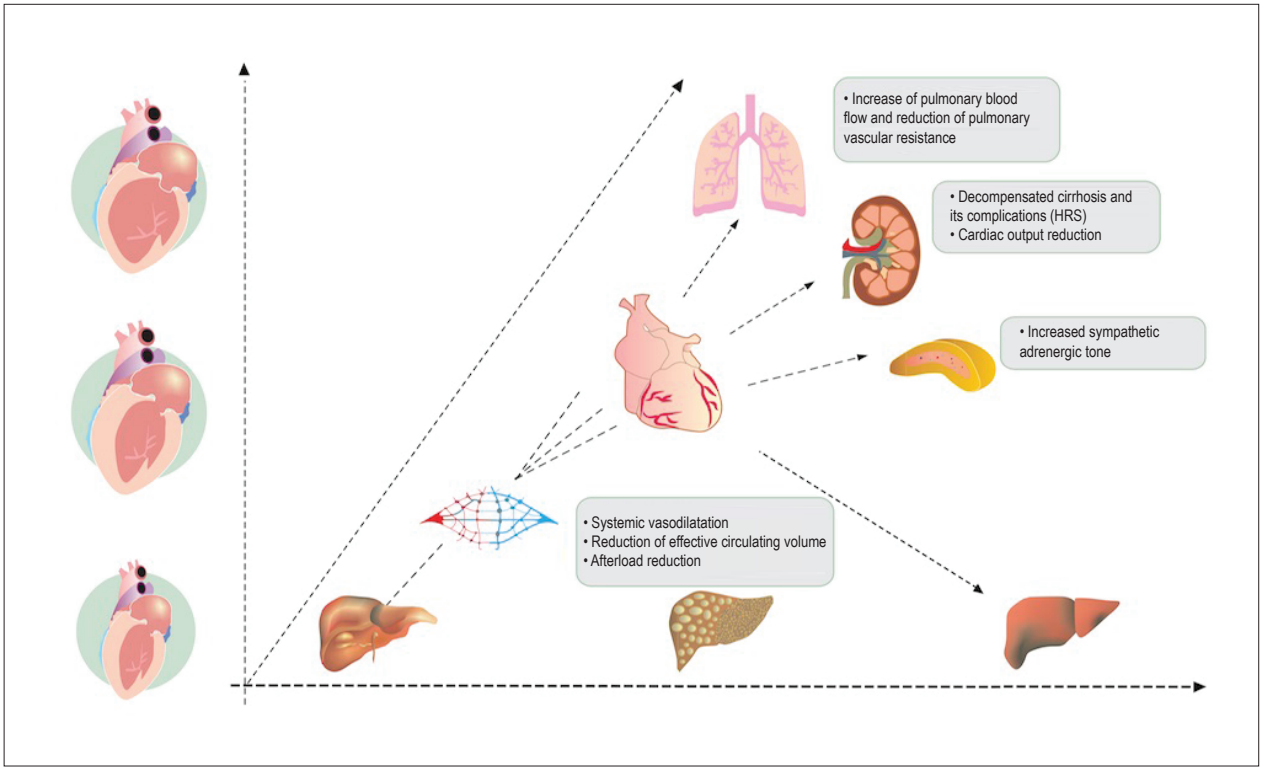

Figure 2 – *The progression of cardiac disease is concomitant to its evolution to hepatic cirrhosis, evolving from diastolic dysfunction, systolic dysfunction, and dilated cardiomyopathy. HRS: hepatorenal syndrome.*

signaling, hyperstimulation of beta receptors, action mediated by nitric oxide, carbon monoxide and endocannabinoids. There is an increase in circulating levels of vasoactive substances (endothelin, glucagon, vasoactive intestinal peptide, tumor necrosis factor, prostacyclins, and natriuretic peptide) which are usually elevated in cirrhosis due to liver failure and the presence of portosystemic collateral vessels.[14]

Concomitant to the progression of the hepatic disease, there is diastolic myocardial dysfunction (myocardial rigidity due to fibroses, myocardial hypertrophy and subendothelial edema) and systolic myocardial dysfunction (hyperdynamic circulation and splanchnic vasodilation, with increased arterial compliance).[14]

It is understood that diastolic and systolic dysfunction is directly related to the severity of liver dysfunction and portal hypertension.[5] Diastolic dysfunction usually precedes systolic dysfunction, which is generally observed in situations in which there is an increased demand for cardiac output associated to decreased myocardial contractility, such as in situations of hemodynamic stress – infectious processes, physical exercise, use of certain medication and surgery.[9]

Cardiac dysfunction can negatively interfere in the prognosis of cirrhotic patients, reducing survival and participating in the genesis of complications. HRS and post-paracentesis circulatory dysfunction, which a state of systemic hypoperfusion secondary to the quick removal of large volumes of ascitic fluid without adequate albumin intake, are the main complications associated to blunt myocardial response to stress.[15] Cardiac dysfunction is also manifested in situations of myocardial stress, such as preload increase secondary to transjugular intrahepatic portosystemic shunt (TIPS) insertion, generally indicated for pre liver-transplant patients.[10]

CCM diagnosis approach

Considering most patients are asymptomatic in the initial stages of CCM, they must undergo clinical, laboratory, electrocardiographic and imaging evaluations for early diagnosis.[11,16] Criteria for CCM identification are described in Table 1.

The use of biomarkers has been useful in clinical practice, especially troponin I, BNP, and N-terminal-pro-BNP (NT-pro-BNP), which may be found in abnormal levels in cirrhosis.[16-18] Troponin I elevation has been associated to a decrease in systolic output and left ventricular mass, but with no correlation to the severity of cihrrosis.[19] Pro-BNP elevation has been associated to intraventricular septum wall thickness and ventricular wall thickness. BNP and pro-BNP elevation is associated to the severity of cirrhosis and cardiac dysfunction, but not to hyperdynamic cuiculation.[20,21] The increase of BNP and pro-BNP in cirrhotic patients, compared to the control group and healthy individuals, has a direct correlation to the severity of the hepatic disease (by the Child-Pugh score and the hepatic venous pressure gradient) and to cardiac dysfunction markers (QT interval, heart rate, and plasma volume).[16] Elevated levels of BNP and pro-BNP in cirrhotic patients indicate a myocardial origin of these peptides due to the stretching of cardiomyocytes from left ventricular overload, which increases the expression of the gene responsible for BNP transcription.[17]

Table 1 – Diagnostic criteria for cirrhotic cardiomyopathy

Clinical-laboratory criteria
Absence of cardiopulmonary symptoms at rest
Low functional cardiac reserve
Signs of sympathetic hyperactivity and RAAS
El BNP, pro-BNP and/or troponin elevation
Electrocardiographic criterion
QT interval prolongation
Echocardiographic criteria
Diastolic dysfunction
E/A ratio < 1.0
Left atrial enlargement
Deceleration time > 200 ms
Isovolumetric relaxation time > 80 ms
Increased left ventricular end-diastolic diameter
Left ventricular hypertrophy
Systolic dysfunction
Left ventricular function at rest below 55%
Contractility deficit in situations of overload (stress)

RAAS: renin-angiotensin-aldosterone system; BNP: B-type natriuretic peptide. (*) Criteria that corroborate the diagnosis of CCM according to the World Congress of Gastroenterology in Montreal, Canada, 2005.

Tumor necrosis factor alpha and interleukins 1 and 6 are inflammatory cytokines hyperstimulated in hepatic cirrhosis and HF. The elevation of cardiac dysfunction biomarkers (troponin I, BNP, and pro-BNP) indicates, in the context of cirrhosis, myocardial compromise, which is related to the severity of the hepatic disease.[16]

Chest X-Ray evaluation is usually normal, or may reveal indirect signs of left atrial enlargement and, in advanced stages, left ventricular enlargement and cardiomegaly with pleural effusion. ECG may aid in the diagnosis by showing QT interval prolongation (earliest and most prevalent alterations), presence of multiple extrasystoles and, in more advanced stages, bundle branch block and ST segment depression. 24-hour holter has better sensitivity to identify bradyarrhythmia and tachyarrhythmia, and can aid in the diagnosis of subclinical or paroxysmal diseases.

ECHO is a non-invasive method whose findings are correlated to the degree of hepatic dysfunction: increase of LV diastolic diameter and decrease of peak systolic velocity, and LV systolic deformity rate evaluated by tissue Doppler. Other findings seen in CCM's diastolic dysfunction are: reduced early (E) and late (A) ventricular relaxation capacity, and decreased E/A ratio with prolongation of the E-wave deceleration time. In advanced stages, there is LV systolic dysfunction, with reduction of the ejection fraction. The strain rate (SR) is a new echocardiographic parameter able to identify a reduction in LV systolic function when the ejection fraction is still normal.[5]

MRIs have been increasingly used in the context of morphofunctional evaluation of liver and heart diseases. It can determine ejection fraction, volume of cardiac chambers (increase of LV mass and end diastolic volumes in the LA and LV) and myocardial morphologic alterations, including tissue alterations (areas of edema and fibrosis), identifying the lesion by using contrast such as gadolinium.[8] It can also help identify simultaneous compromise of both organs, such as in hemochromatosis and amyloidosis.

Recognizing the appropriate moment for a therapeutic approach in these patients is a challenge in the comprehension of CCM. Cardiac compromise is usually subclinical, and is manifested as left ventricular insufficiency (LVI) at times of increased demand, such as in situations of clinical or surgical stress. Congestive HF, with signs of pulmonary congestion, is the final spectrum of dilated CMPs of any etiology, in which CCM is included – clinical context of poor prognosis and high mortality. There is still no specific treatment for CCM. It is currently approached in the same way as HF, which includes water and sodium restriction, use of diuretics, RAAS inhibitors and beta-blockers.[19]

CCM approach in the course of hepatic cirrhosis is still a challenge in clinical practice because, when there is the diagnosis of dilated CMP with frank pulmonary congestion, prognosis is reserved. Recently, our group reported, for the first time, two cases of patients with elevated BNP, X-Ray with no pulmonary congestion, and ECHO with normal LVEF, but with a progression to HRS refractory to conventional treatment, in which there was benefit from the use of dobutamine, as rescue therapy of kidney function, with great clinical response.[22,23] The central idea is that HRS is a marker of bad systemic perfusion, and that cardiac output, despite being in the normal range in the ECHO, is insufficient for the demand. Thus, the inotropic would promote an increase in cardiac output and renal perfusion. In the published cases, there was good clinical response with recovery of kidney function.

Conclusion

Myocardial compromise, underdiagnosed in cirrhotic patients, and CCM represent a new clinical phenotype. Once cardiovascular repercussions are understood, the cardiologist should observe its manifestations, be them signs of congestion or clinical complications such as HRS, particularly in situations of clinical or surgical stress, stimulating its evaluation with cardiac imaging methods and biomarkers. There is still a lack of understanding of how to apply this knowledge, in daily practice, to benefit patients. There is a need for studies with the objective of identifying potential treatments that alter the natural history of cardiac disease in cirrhotic patients, especially in the asymptomatic phase.

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Author contributions

Conception and design of the research, Acquisition of data, Analysis and interpretation of the data, Writing of the manuscript and Critical revision of the manuscript for intellectual content: Mocarzel LOC, Rossi MM, Miliosse BM, Lanzieri PG, Gismondi RAC.

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Case 4/2017 - Double-Chambered Right Ventricle with Dextrocardia and Hypoxemia Due to Atrial Shunt in a 4-Year-Old Girl

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Clinical data

A premature female twin (33-week gestation), weighing at birth 1935 g, remained hospitalized for one month due to the diagnosis of atrial septal defect (ASD) + ventricular septal defect (VSD) + persistence of ductus arteriosus (PDA). The patient gained less weight than the average children, but maintained full and similar activity, receiving furosemide and captopril, up to the age of 3 years, when her mother noticed cyanosis.

Physical exam

Eupnea; mild cyanosis; normal pulses; weight, 11 kg; height, 89 cm; heart rate, 100 bpm; O_2 saturation, 83%. The aorta was not palpable at the suprasternal notch. Her chest showed mild bulging and mild systolic thrusts on the right sternal border (RSB). The 1st heart sound was more intense on the right midclavicular line (RMCL), and the 2nd heart sound, on the RSB with greater radiation to the RMCL. A rough systolic ejection murmur (4/6) was audible on the upper RSB, and a mild regurgitation systolic murmur (4/6) was audible on the lower RSB. The liver was palpated 1 cm from the right costal margin.

Complementary diagnostic tests

Electrocardiogram: sinus rhythm and signs of marked right ventricular overload. There were Rs complexes in V1 to V3, rsR´ in V5R and V6R, positive T wave in V1 to V6, and isoelectric T wave in V6R, signs of right ventricle (RV) located to the right. AP: +60º, AQRS: –150º, AT: +70º (Figure1).

Chest X-ray: enlargement of the cardiac silhouette to the right, and reduced pulmonary vascular bed. Rounded and long ventricular arch to the right (Figure1).

Echocardiogram: (Figure2) showed situs solitus with dextrocardia, normal systemic and pulmonary venous connections, concordant atrioventricular and ventriculoarterial connections. Dilatation of the inferior vena cava and suprahepatic veins. Ostium secundum ASD of 4 mm, with right-to-left shunt. Intact ventricular septum deviated to the left. Marked tricuspid regurgitation. Aneurysmatic right atrium with volume of 58 mL/m². Right ventricle markedly dilated and hypertrophied, with hypertrophied moderator band, narrow infundibulum due to hypertrophy, and two ventricular chambers with a 140-mmHg gradient between them. Normal pulmonary and aortic valves. Normal left cavities. PT = 20 mm, PA´s = 9 mm. Pulmonary ring = 15 mm and right ventricular anterior wall = 10 mm.

Clinical diagnosis

Stenosis of double-chambered right ventricular inlet with mild hypoxia due to right-to-left shunt through a small ASD.

Clinical rationale

The clinical elements were compatible with cyanotic congenital heart disease with reduced pulmonary flow resulting from an obstruction at the right and right-to-left shunt. An obstruction in the right ventricular inlet could be suspected based on the auscultation of a markedly rough and intense systolic murmur. However, the more intense 2nd heart sound raised the possibility of corrected transposition of the great arteries, mainly in the presence of dextrocardia with situs solitus. The electrocardiogram was not compatible with atrioventricular discordance, because the T wave indicated a RV located to the right (T wave axis to the left (+70 degrees) and greater intensity in V6 than in V6R). The echocardiogram was conclusive about the defect and its repercussion. The marked tricuspid regurgitation causing an aneurysmatic right atrium was due to marked obstruction inside the RV. It is worth noting the rarity of that anomaly in the presence of dextrocardia with situs solitus and no VSD, in addition to marked tricuspid regurgitation as an uncommon consequence from obstruction in the RV.

Differential diagnosis

The most likely differential diagnosis was corrected transposition of the great arteries.

Management

Because of the marked repercussion of the defect, surgery was performed immediately, eliminating the obstruction of the inlet of the hypertrophied RV.

Comments

The double-chambered RV or stenosis of the inlet of the RV is a rare congenital anomaly, in which an anomalous hypertrophied muscular band divides the RV into two cavities, the proximal being of high pressure, and the distal, of low pressure. Muscular obstruction develops over time, but rarely in adult age. The hypertrophied muscle is either the septoparietal or the septomarginal trabecula.

Keywords

Double Chambered Right Ventricle; Dextrocardia; Hypoxia.

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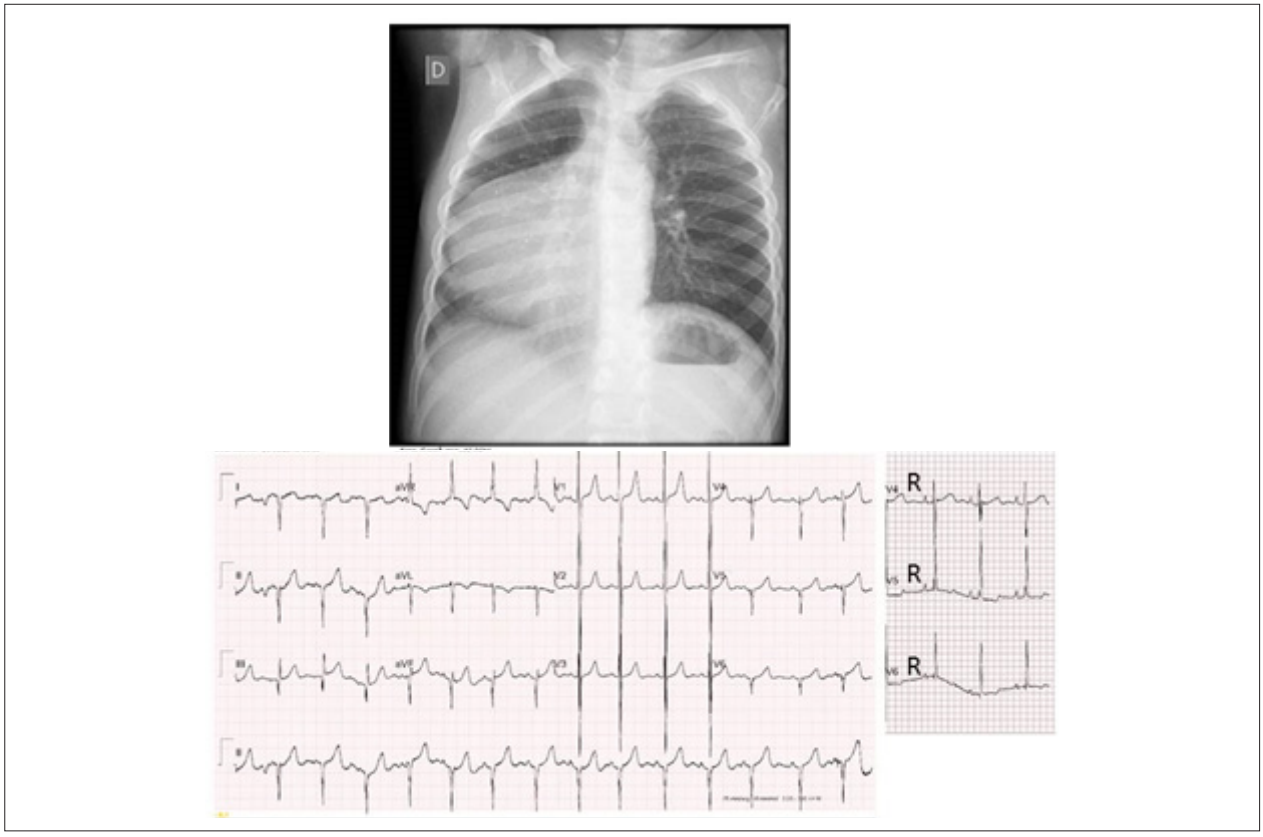

Figure 1 – *X-ray showing marked cardiomegaly with rounded and long ventricular arch to the right, situs solitus (gastric bubble to the left) and reduced pulmonary vascular bed. Electrocardiogram showing signs of marked right ventricular overload to the right, with preponderant R wave in V6R, S wave in V6, positive T wave in V6, and isoelectric T wave in V6R.*

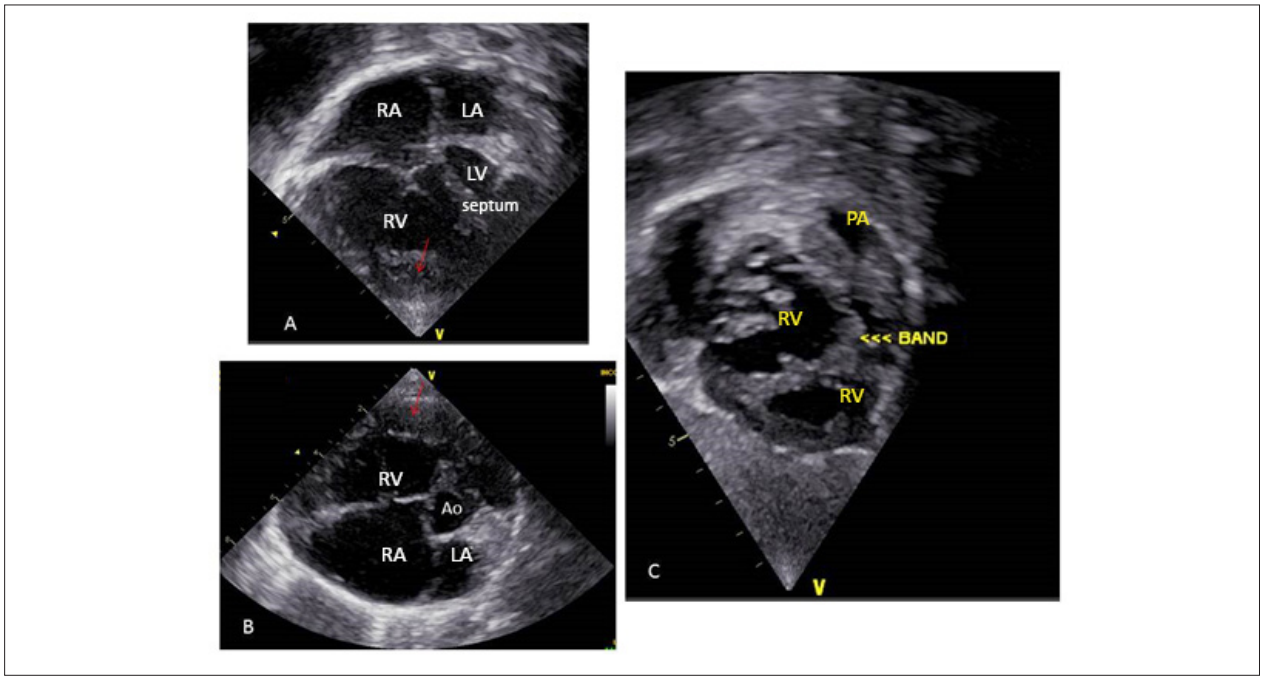

Figure 2 – *Echocardiogram: 4-chamber (A) and short-axis (B) views showing markedly enlarged right cardiac cavities with septa bulging to the left and marked ventricular hypertrophy (arrows), and moderator band dividing the two right ventricular chambers: proximal and distal chambers seen on subcostal view (C). RA: right atrium; LA: left atrium; Ao: aorta; RV: right ventricle; LV: left ventricle; PA: pulmonary artery.*

In over 95% of the cases, the stenosis of the inlet of the RV is associated with VSD, whose location determines the characteristic clinical findings. Thus, when the VSD is located before the obstruction, the clinical findings are similar to those of tetralogy of Fallot, and when the VSD is distal to the obstruction, those findings are similar to those of the VSD itself. It is worth noting that the grade of obstruction and the size of the VSD account for the magnitude of the findings.

To our knowledge, this is the first report on the association of double-chambered RV with dextrocardia and situs solitus and no VSD, whose clinical findings simulated those of marked pulmonary stenosis and consequent progressive tricuspid regurgitation.[1,2]

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Myocardial Bridge and Angiotomography of the Coronary Arteries: Perfusion under Pharmacological Stress

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Introduction

The myocardial bridge is one of the most prevalent congenital anomalies that involve the coronary circulation, and its incidence in the general population is high, affecting from 23 to 55% in necropsy studies.[1]The impairment of the anterior descending artery is more frequent, on its proximal 2/3.[1]In most patients, the myocardial bridges do not cause symptoms, because in order to have ischemia, there must be an imbalance between supply and consumption of oxygen. The superficial bridges, with small or slender muscle band, are the most common ones, and they may account for 75% of the cases, with average length of 1.5 cm and usually without causing symptoms. In approximately 24% of the cases, we observed deep myocardial bridges, with thicker muscle band.[1,2]

Atherosclerosis is the most common cause of ischemic heart disease. However, other causes for ischemia are frequent, and among them, we highlight the myocardial bridge, which may provoke typical or atypicalchest angina,acute myocardial infarction and sudden death.[3-5]

Angiotomography of the coronary arteries is an increasingly important diagnosis technique when assessing the myocardial bridge, with high spatial and temporal resolution. Thisnoninvasive imaging technique is a very useful tool for locating and defining the morphology of the myocardial bridge.[6]

Objectives

We describe the case of a female patient with myocardial ischemia detected through myocardial scintigraphy on which the determining mechanism for presence of the perfusion alteration was a bridge diagnosed by the angiotomography of the coronary arteries, which also confirmed the of the perfusion defect by evaluating resting perfusion images and those under pharmacological stress.

Keywords

Myocardial Bridge; Myocardial Ischemia; Perfusion; Radionuclide Imaging; Computed Tomography; Coronary Artery Disease.

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Case Report

Female patient, 52 years old, presenting atypical chest pain, witha 26.5 body mass index, diabetic, hypertensive, dyslipidemic, usingASA, ARBS, Insulin, Metformin. She was forwarded to the nuclear medicine sector with a Myocardial Scintigraphy request for ischemia survey.

The patient was invited to participate in the research project, approved by the ethics committee no. 392,966, which aims to compare the perfusion findings of the nuclear medicine exam to those from the angiotomography of the coronary arteriesat rest and under stress. The patient performed a specific myocardial scintigraphy procedure (Figure 1) on a 1-collimator Gamma Camera device (Millennium MPR, GE) and acomputed tomography scan of 64 detectors (Brilliance, Philips), to evaluate the calcium score, myocardial perfusion at rest and under stress associated with coronary anatomical evaluation. The stress acquisition was conducted following dipyridamole infusion at a dose of 0.56 mg/kg, in 4 minutes. On the sixth minute, 25 mCi of 2-methoxyl-isobuthyl-isonitrile-99 m Tc (sestamibi-99mTc) was administered. In the same minute, the perfusion images under pharmacological stress by angiotomography (Figure 2) were acquired, with infusion of iodinated contrast at a 70 ml dose under a 5 ml per second flow rate. The myocardial perfusion scintigraphy images, stress stage, were acquired 30 to 90 minutes after the administration of the radiopharmaceutical.

The stress scintigraphic images demonstrated reversible perfusion defectswithin the territory of the anterior descending artery. Theperfusion computerized tomography confirmed the presence of perfusion defects and did not evidence a presence of atherosclerotic lesion in coronary arteries. A significant myocardial bridge constricting the anterior descending artery was diagnosed by the angiotomography of coronary arteries (Figure 3), configuring the most probable mechanism for the observed perfusion defects.

Discussion

The myocardial bridge still shows various challenges to the clinical practice, because it may occur in patients on which the atherosclerotic disease is uncommon. This leads, in several situations, to failure to reach a diagnosis due to the low pretest probability of these patients. As it is a known factor for myocardial ischemia, the myocardial bridge may hamper the clinical correlation when linked to the atherosclerotic disease, complicating the planning of the best therapeutic management and monitoring of these patients. In the case of myocardial bridges, the mechanism responsible for the symptoms is uncertain and controversial. The irrigation of the vascular myocardium occurs almost exclusively during

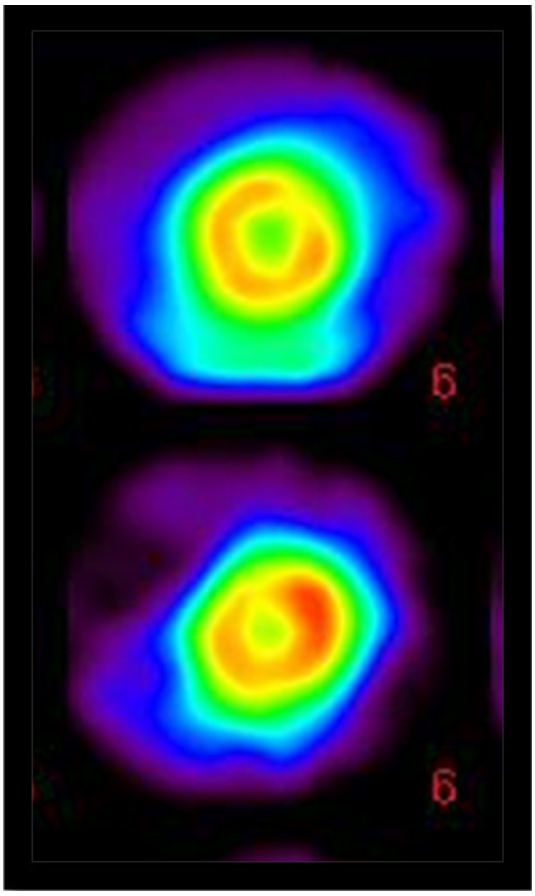

Figure 1 – *Myocardial scintigraphy with 2-methoxy isobutyl isonitrile -99mTc (sestamibi-99mTc) using protocol (rest-stress), with a 25 mCi dosein each step. The scintigraphic images reveal hypoperfusion in anteroapical and lateral-apical segments of the left ventricle in the post-stress images, with complete improvement of the uptake in relation to the rest images.*

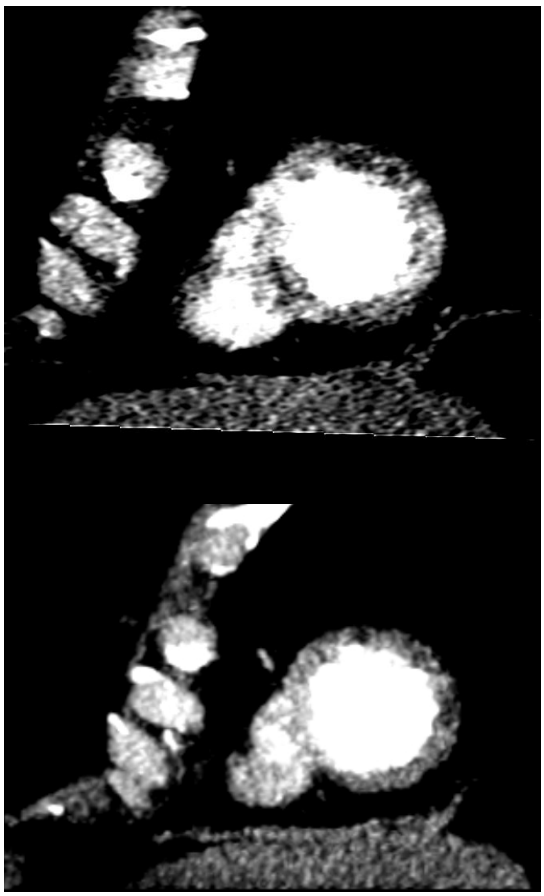

Figure 2 – *64-channel Cardiac Computed Tomography, effort and rest stage, reveals perfusion defect in the anteroapical and lateral-apical segments of the left ventricle in the post-stress images with normal perfusion in rest.*

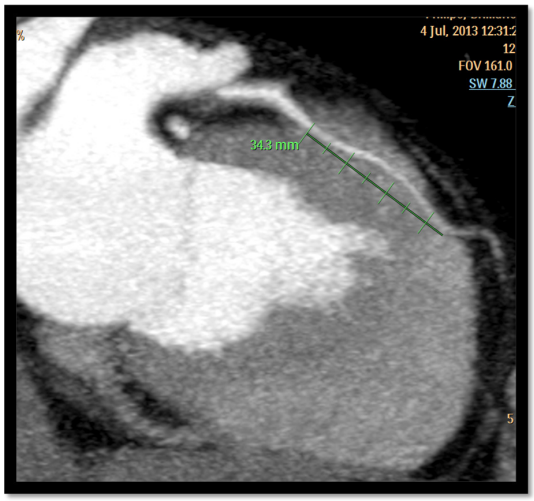

Figure 3 – *Myocardial CT angiography showing presence of a 34.3 mm myocardial bridge, in the projection of the anterior descending artery, responsible for the area of perfusion defect in the anteroapical and lateral-apical segments of the left ventricle, described in the myocardial scintigraphy and computed tomography.*

diastoles, and the bridge reduces the light of the artery, in most cases, only during systoles. As such, it is not easy to explain the physiopathology of myocardial ischemia.[7]

Among the various hypothesis, we may mention the distortion of the intramyocardial artery during systoles, provoking myocardial ischemia. The presence of symptoms only in individuals whose myocardial bridges are long and deep is favorable to this hypothesis. This mechanism could be aggravated when the oxygen consumption by the myocardium increased. The appearance of coronary spasm in the anterior descending artery in its intramyocardium path after intracoronary injection of acetylcholine appears to be another hypothesis, suggesting endothelial dysfunction located in that segment. This seems to be the reason for the symptoms to appear only in the fourth or fifth decade of live, a time on which alterations to the vascular tonus occur.[8,9]Theendothelial injury is also implied in the formation of thrombi at the proximal region of the coronary bridge.[10]

The diagnosis through clinical examination is difficult precisely because the symptoms are virtually identical to those of the atherosclerotic artery disease. Functional studies validating the effect of the myocardial bridge on the myocardial blood flow demonstrate that its restriction occurs both during the systoles as well as in diastoles, and that there is a link between reversible myocardial ischemia shown by scintigraphy or by the positron emission tomography.[11]Thevasodilator pharmacological stress may not be linked to ischemia because there is no increase in the coronary contractility and subsequent systolic compression.[11]The angiotomography (angio-CT) of the coronaries is an exam that allows viewing the cardiac anatomy, especially that of the coronary arteries, in addition to analyzing the vessel walls, the presence of plaques and the diameter and course of the arteries. Barros and collaborators demonstrated that angio-CT is highly accurate in the morphological evaluation of the myocardial bridge, allowing a noninvasive approach of its localization, length and depth, as well as of the presence of associated atherosclerosis.[12]The association of the coronary angio-CT with the functional study of the myocardial perfusion under stress with dipyridamole allows for a better definition of the physiological and clinical significance of this condition, as observedin the present case, where there is functional significance.[12]

In most cases of myocardial bridge, the prognostic is good, after the start of medication use, but there are reports of sudden death in in young people when exercising. The drug treatment is able to control the symptoms in the vast majority of cases, using beta-blockers and antagonists of calcium channels, providing better filling of the diseased coronary during diastoles, reducing the heart rate at rest and during efforts. Nitrates may aggravate the anginal symptoms and the ischemia when used in patients with myocardial bridge, because this drug promotes the reduction of the venous return and blood pressure with consequent adrenergic stimulation, increasing the systolic constriction of the myocardial band on the coronary artery. Currently, the drug treatment is the preferential for the myocardial bridges, because, in proper doses, it may control the angina episodes in most of the patients.[12,13]

We believe that the angiotomography of the coronary arteries, when used with protocol at rest and under pharmacological stress, may gather useful information for handling the patient withprecordial pain without significant obstructive coronary disease, be it diagnosed by catheterization or any other method of characterization of ischemia, as demonstrated by scintigraphy in the instant case.

Author contributions

Conception and design of the research, Acquisition of data and Analysis and interpretation of the data: Ker WS, Neves DG, Damas ASAA, Mesquita CT, NacifMS; Statistical analysis, Writing of the manuscript and Critical revision of the manuscript for intellectual content: Ker WS, Mesquita CT, NacifMS.

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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Exuberant Vasospastic Angina Simulating Severe Three-Vessel Disease

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A 56-year-old Caucasian male, came to our hospital complaining of thoracic oppression at exertion and sometimes occurring at rest, lasting for a few minutes. The patient was an active smoker, with a moderate alcohol consumption habit and had had an episode of unstable angina two months earlier. At that episode, two drug-eluting stents were implanted, one in the distal anterior descending artery and the other in the proximal first diagonal artery. The ECG showed mild ST-elevation in V1-V3 and a T-wave inversion in V3-V5. There was a slight increase in Troponin I up to 0.24 ng/mL but the blood tests were otherwise unremarkable. The patient was admitted at the coronary unit and was scheduled for urgent coronary angiogram. The exam revealed severe and diffuse stenosis in the territories of the right and left coronary arteries with slow flow (TIMI 1-2), sparing only the stented segments (picture/video 1). The administration of 2 mg of intracoronary isosorbite dinitrate reverted all the stenosis but slow flow (TIMI 2) was still observed in the left coronary artery. Hence, the diagnosis of vasospastic angina was made. The patient was successfully controlled with calcium antagonists and has remained asymptomatic.

Vasospastic angina is commonly misinterpreted as acute coronary syndrome. Although its pathophysiology is not fully understood, it usually has a favorable long-term prognosis, although coronary artery spasms may have an important role in arrhythmia generation and subsequent cardiac arrest.

Keywords

Angina, Stable / complications; Coronary Vasoespasm; Acute Coronary Syndrome; Coronary Angiography.

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Author contributions

Acquisition of data: Marmelo B; Writing of the manuscript: Marmelo B, Abreu L, Pereira J; Critical revision of the manuscript for intellectual content: Ferreira P, Cabral J.

Potential Conflict of Interest

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Sources of Funding

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Study Association

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

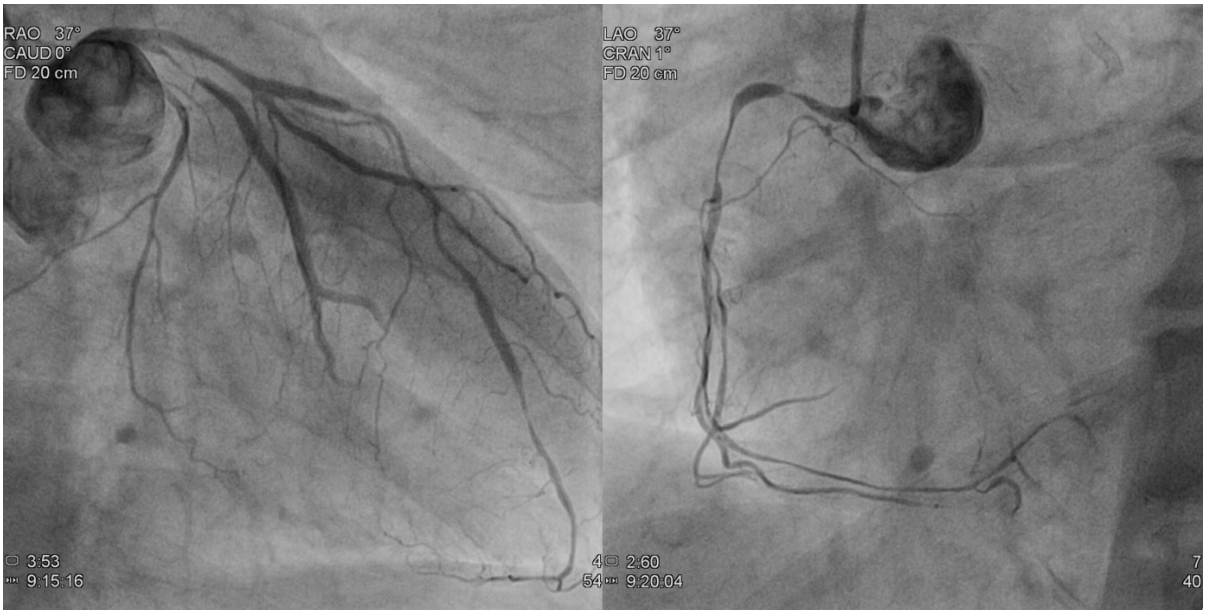
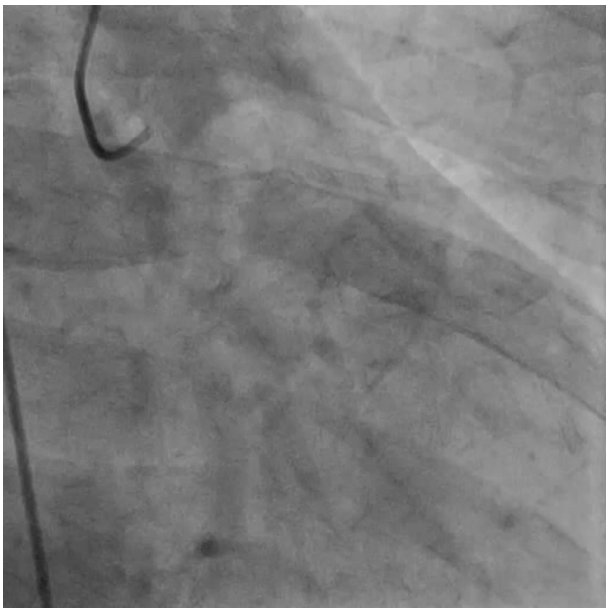


Figure 1 – *Left and right coronary angiogram showing multiple severe stenosis and slow flow.*



Video 1 – *Left and right coronary angiogram showing multiple severe stenosis and slow flow followed by administration of intracoronary isosorbide dinitrate and stenosis resolution. Access the video through the link: http://www.arquivosonline.com.br/2017/english/10806/video_ing.asp*

Erratum

August issue of 2012, vol. 99 (2), Suppl. 2, pages 1-28

In “First Brazilian Guidelines for Familial Hypercholesterolemia”, consider Lottenberg AM as the correct form for the name of the author Ana Maria Lottenberg.

May issue of 2017, vol. 108 (5), pages. 417-426

In the Original Article “Prognostic Value of Coronary Flow Reserve Obtained on Dobutamine Stress Echocardiography and its Correlation with Target Heart Rate”, pages 417-426, by authors José Sebastião de Abreu, Eduardo Arrais Rocha, Isadora Sucupira Machado, Isabelle Oliveira Parahyba, Thaís de Brito Rocha, Fernando José Villar Nogueira Paes, Tereza Cristina Pinheiro Diogenes, Marília Esther Benevides de Abreu, Ana Gardenia Liberato Ponte Farias, Marcia Maria Carneiro, José Nogueira Paes Junior, please be aware that the correct spelling for Isabelle O. Parahyba is Isabelle Oliveira Parahyba and Thais Brito Rocha is Thaís de Brito Rocha.

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