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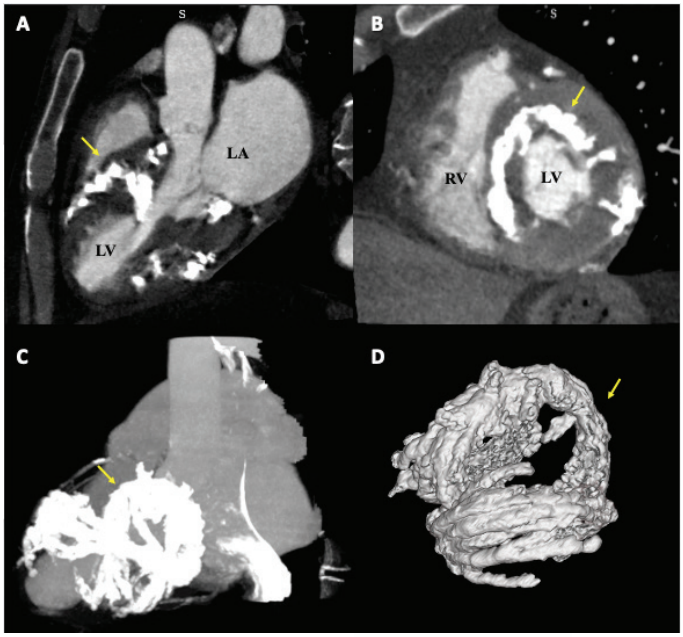

Figure 1, page 993

ABC Cardiol
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Contents

Review Article

Research Letter

Image

Letter to the Editor

Erratum

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ABC Cardiol
Arquivos Brasileiros de Cardiologia

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What is the Current Scenario of Cardiac Rehabilitation in Brazil and Portugal?

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Brazil and Portugal have a great deal in common, and they are bound by strong ties, with a history that began to be written over five centuries ago. They share a language, although there are pronounced differences in accent, as well as vocabulary. Air traffic between both countries is intense (much lower during the Covid-19 pandemic), and citizens from both sides of the Atlantic Ocean inhabit or visit cities on the other side. Finally, Portuguese blood runs in the veins (and arteries) of many Brazilians, and, in recent years, a wave of Brazilians have immigrated to Portugal, retracing the path taken by Pedro Álvares Cabral, when he and his 13 vessels first arrived in the land that would receive the name "*Terra Brasilis*".

Confused readers may now be asking themselves, "What is the relationship between the last paragraph and cardiac rehabilitation (CR)? What is the real reason that this text was written by one Portuguese and two Brazilian authors, who are all cardiologists and advocates of CR?" In truth, the objective is to sketch a brief profile of what is taking place with CR in both countries, attempting to inform readers about a reality that is absolutely disconnected from what we see in other areas of cardiology. Speaking not out of envy, but rather out of concern as rehabilitators, we see cardiology flourish in terms of medications and devices that change the quality and quantity of patients' lives,[1] therapies based on the best evidence described in the guidelines, and invasive procedures that save lives or significantly reduce damage, in addition to observing that personalized medicine is "knocking on the door" and promising a potential revolution in the management of monogenic and polygenic diseases. In short, wherever there is investment, dissemination, and marketing, cardiology is an unmistakable example of success.

It is important to underscore that, even though it is still behind the scenes in cardiological therapy, CR, in different clinical scenarios,[2,3] is a health strategy for which both the class of recommendation and the level of evidence have left no doubt, when compared to auspicious situations such as those described in the preceding paragraph. Systematic reviews and meta-analyses[4,5] have shown that the implementation of CR can have an immense impact on people's lives, and it is a useful action for society as a whole. Now, we ask: If a patient with ischemic heart disease does not receive antiplatelet therapy (with any medication whatsoever), what would people think of the cardiologist taking care of this patient? Or what if a patient with dyslipidemia, with total cholesterol of 267 mg/dL and LDL of 191 mg/dL, did not receive a statin prescription? Or, to push things even further, if a patient with an acute myocardial infarction (AMI) with ST elevation did not receive reperfusion therapy, while a hemodynamist and a hemodynamics room were available? The case would imaginably end up before the medical ethics board, and rightfully so! However, few people in the medical field are able to envision the enormous void that remains regarding a conduct based on the best evidence, namely, *not* referring patients who are ischemic after an AMI or patients with heart failure (HF) of any etiology to a CR service. In this case, although the indication is fully understood in theory, it is extremely under-applied in practice, both in Portugal and in Brazil, as we will see in the following paragraphs.

What is the current scenario of cardiac rehabilitation in Brazil?

The scenario in Brazil is alarming. The number of documented CR programs is extremely insufficient in relation to the clinical need, and this is certainly harmful to the health of the Brazilian population with chronic heart diseases. Let's look at the evidence: In a study published in 2020, Britto et al.[6] estimated that, in Brazil, there is only 1 spot in a CR service for every 99 patients with ischemic heart disease, meaning that the availability is almost 3 times lower than that observed in another 32 countries evaluated (1 spot for every 32.7 patients). In another study that evaluated the worldwide availability and density of CR,[7] this type of service was identified in 111 out of 203 countries, and the global ratio of spots for each patient with ischemic heart disease was 1 to 11, which demonstrates a sad reality.

Unpublished data on the availability of CR[8] identified the operation of only 59 CR programs in Brazil; most of them (71%) were concentrated in the South (20%) and Southeast (51%) Regions of the country, which demonstrates not only the scarcity, but also the heterogeneity in the national distribution. In relation to available spots, the situation is even more concentrated, since 69% of them are in the Southeast Region, which exposes the large gap in spots and

Keywords

Rehabilitation; Secondary Prevention; Exercise; Heart.

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services in other Brazilian regions. Based on these data, the authors also calculated the national availability of CR spots for care after hospital discharge. The number of spots to provide care for these patients after a cardiovascular event represented less than 2% of the need.[8]

To further complicate the already critical situation in Brazil, with regard to the limited availability of CR services, the beginning of the COVID-19 pandemic has had a serious impact on the functionality of these services, with 81% of CR programs reporting interruption or termination of their care activities, in addition to another 14% of services that reduced the number of spots that were available up to that time.[8] There is no scientific information regarding the return of these services to date; however, informally, it is estimated that the service capacity has not yet returned to the pre-pandemic level. Furthermore, the CR services that resumed their activities began to receive a new flow of post-COVID-19 patients, which may have further reduced the availability of spots for patients with chronic or acute heart diseases after hospital discharge, making the "catastrophic" scenario of CR in Brazil even worse.

What is the current scenario of cardiac rehabilitation in Portugal?

In recent years, CR has shown progressive improvement, both in number and in quality. However, it is known that it is still far from ideal. In this scenario, the Study Group on Exercise Physiology and Cardiac Rehabilitation of the Portuguese Society of Cardiology has applied recurring questionnaires at CR centers to assess the evolution of CR in Portugal.[9-13] In the latest survey, dated 2019,[13] 25 centers with CR programs were registered (a 33% increase in relation to 2014),[12] which is thus considered in accordance with national and European standards.[14,15] Concerning these centers, 11 are located in the North Region, 1 in the Central Region, 12 in the Greater Lisbon Region, and 1 in the South Region. This concentration of centers is related to larger cities and the coastal region of the country, which reflects the great heterogeneity, with a manifest lack of rehabilitation centers in rural regions, small towns, and villages, as well as in the interior, which goes against the recommendations of the World Health Organization for equal access to health.[16] If we consider that approximately 10,000 people in Portugal are discharged from the hospital annually due to myocardial infarction, and, if they were evenly distributed throughout the national territory (which is not the case), theoretically, each rehabilitation center would have to rehabilitate 400 patients, only in relation to this disease (excluding other causes of cardiovascular disease). Assuming that phase 2 programs last 3 months, how many and which centers would be able to rehabilitate 100 patients at a time, adding to that the numbers of patients with other diseases? And how to achieve phase 3 in the long term?

It is not only in the geographical distribution of centers throughout the territory of Portugal that this great heterogeneity is observed, but also in the types of programs instituted, with varying design and duration. Most phase 2 programs have a weekly frequency of 2 to 3 exercise sessions (ranging from 12 to 36 weeks). In turn, phase 3 programs have a frequency of 1 to 3 sessions per week, with a very long-term option in some cases. All centers have multidisciplinary teams, always including a cardiologist, who often coordinates the programs. In addition to exercise, the programs always included nutritional counseling, most with risk factor control, some with smoking cessation and psychological intervention. In other words, this demands the preparation of teams capable of intervening through the various components of CR, which is already a reality in some hospitals and universities, as is the case with the Masters in Cardiovascular Rehabilitation at the Faculty of Medicine of the University of Lisbon,[17] a postgraduate program geared toward different specialists. In fact, the availability of qualified professionals may even be a key factor in the emergence of new CR programs.

Another interesting piece of data is that, in 2019,[13] a 13% increase was found in the number of patients who were referred for CR, when compared to the previous questionnaire from 2014,[12] especially in the public health system. However, despite the increase in the number of rehabilitated patients, only 9.3% of patients with acute coronary syndrome (ACS), which is the most frequent cause of rehabilitation, were actually rehabilitated. Therefore, if we consider that 100% of these patients should participate in CR programs to improve their quality of life and reduce reinfarction and mortality,[4,18] we are facing a truly suboptimal scenario. In turn, HF of different etiologies was the second most frequent indication for phases 2 and 3 (with 1.8% increase in relation to the previous 2014 questionnaire),[12] including rehabilitation after implantation of cardiac devices (a 3.1% increase). Certainly, the referral to CR programs of patients after ACS or patients with diagnosis of HF needs to be improved, in addition to the availability and training of the centers.

The causes for non-adherence of patients to CR programs in Portugal, as in other countries, are transportation difficulties, distance to the rehabilitation center, financial problems, lack of family support, lack of motivation, lack of knowledge regarding the benefits and risks of exercise, and labor problems. Further posing difficulties, in the past 2 years, the COVID-19 pandemic has been added to the causes of non-adherence, leading some centers to develop distance programs to attempt to minimize the obstacle of social isolation.

Finally, in spite of significant improvements, CR in Portugal is still far from what would be desirable, both in terms of referral and in terms of better distribution of programs throughout the country.

Conclusion

The scenario of CR in Brazil and Portugal is still inadequate, and it requires great investment, especially if we consider that this secondary prevention intervention is essential and can save lives. In this context, for effective implementation we need the following:

To promote adequate dissemination of CR through the media and to encourage health policies through scientific societies and health professionals, both individually and institutionally;

To increase referral by means of prevention education for health professionals and the creation of a patient referral system, with indication as early as hospital discharge;

To combat the causes of non-adherence of patients to CR programs, such as: a) transportation difficulties and distances to rehabilitation centers; b) financial problems and lack of family support; c) lack of motivation and lack of knowledge regarding the benefits and risks of exercise; d) work problems.

Finally, it is clear to us that if all the agents potentially involved in the process of implementing rehabilitation programs in both countries (governments, health agents, civil society, and others) invest a fair share, the returns will far exceed the principal. In other words, by practicing medicine based on the best evidence, with a relatively low cost, the result can be a substantial gain in lives, reduced suffering, and even a significant decrease in population health expenditures.

References

1. Précoma DB, Oliveira GMM, Simão AF, Dutra OP, Coelho OR, Izar MCO, et al. Updated Cardiovascular Prevention Guideline of the Brazilian Society of Cardiology - 2019. Arq Bras Cardiol. 2019;113(4):787-91. doi: 10.5935/abc.20190204.
2. Carvalho T, Milani M, Ferraz AS, Silveira ADD, Herdy AH, Hossri CAC, et al. Brazilian Cardiovascular Rehabilitation Guideline - 2020. Arq Bras Cardiol. 2020;114(5):943-987. doi: 10.36660/abc.20200407.
3. Ambrosetti M, Abreu A, Corrà U, Davos CH, Hansen D, Frederix I, et al. Secondary Prevention Through Comprehensive Cardiovascular Rehabilitation: From Knowledge to Implementation. 2020 Update. A position Paper from the Secondary Prevention and Rehabilitation Section of the European Association of Preventive Cardiology. Eur J Prev Cardiol. 2020:2047487320913379. doi: 10.1177/2047487320913379.
4. Anderson L, Oldridge N, Thompson DR, Zwisler AD, Rees K, Martin N, et al. Exercise-Based Cardiac Rehabilitation for Coronary Heart Disease: Cochrane Systematic Review and Meta-Analysis. J Am Coll Cardiol. 2016;67(1):1-12. doi: 10.1016/j.jacc.2015.10.044.
5. Taylor RS, Sagar VA, Davies EJ, Briscoe S, Coats AJ, Dalal H, et al. Exercise-Based Rehabilitation for Heart Failure. Cochrane Database Syst Rev. 2014;2014(4):CD003331. doi: 10.1002/14651858.CD003331.pub4.
6. Britto RR, Supervia M, Turk-Adawi K, Chaves GSDS, Pesah E, Lopez-Jimenez F, et al. Cardiac Rehabilitation Availability and Delivery in Brazil: A Comparison to Other Upper Middle-Income Countries. Braz J Phys Ther. 2020;24(2):167-76. doi: 10.1016/j.bjpt.2019.02.011.
7. Turk-Adawi K, Supervia M, Lopez-Jimenez F, Pesah E, Ding R, Britto RR, et al. Cardiac Rehabilitation Availability and Density around the Globe. EClinicalMedicine. 2019;13:31-45. doi: 10.1016/j.eclinm.2019.06.007.
8. Jardim ISC. Impactos da COVID-19 nos programas de reabilitação cardiovascular no Brasil: estudo observacional baseado em um questionário online [dissertation]. Brasília (DF): Universidade de Brasília; 2021.
9. Mendes M. National Survey of Cardiac Rehabilitation Programs in Portugal--Situation in 1999. Rev Port Cardiol. 2001;20(1):7-19.
10. Teixeira M, Sampaio F, Brízida L, Mendes M. Cardiac Rehabilitation in Portugal--Developments between 1998 and 2004. Rev Port Cardiol. 2007;26(9):815-25.
11. Abreu A, Bettencourt N, Fontes P. Overview of Cardiac Rehabilitation in Portugal 2007-2009. Rev Port Cardiol. 2010;29(4):545-58.
12. Silveira C, Abreu A. Cardiac Rehabilitation in Portugal: Results from the 2013-14 National Survey. Rev Port Cardiol. 2016;35(12):659-668. doi: 10.1016/j.repc.2016.06.006.
13. Fontes JP, Vilela EM, Durazzo A, Teixeira M. Current state of Cardiac Rehabilitation in Portugal: Results of the 2019 National Survey. Rev Port Cardiol. 2021;40(11):877-87. doi: 10.1016/j.repce.2021.10.024.
14. Abreu A, Mendes M, Dores H, Silveira C, Fontes P, Teixeira M, et a. Mandatory Criteria for Cardiac Rehabilitation Programs: 2018 Guidelines from the Portuguese Society of Cardiology. Rev Port Cardiol. 2018;37(5):363-73. doi: 10.1016/j.repc.2018.02.006.
15. Abreu A, Frederix I, Dendale P, Janssen A, Doherty P, Piepoli MF, et al. Standardization and Quality Improvement of Secondary Prevention Through Cardiovascular Rehabilitation Programmes in Europe: The Avenue Towards EAPC Accreditation Programme: A Position Statement of the Secondary Prevention and Rehabilitation Section of the European Association of Preventive Cardiology (EAPC). Eur J Prev Cardiol. 2020:2047487320924912. doi: 10.1177/2047487320924912.
16. World Health Organization. Governance for health equity: taking forward the equity values and goals of Health 2020 in the WHO European Region [internet]. Geneva: World Health Organization; 2013 [cited 2022 Apr 6]. Available from: https://www.euro.who.int/__data/assets/pdf_file/0020/235712/e96954.pdf
17. Universidade de Lisboa. Faculdade de Medicina. Cardiovascular Rehabilitation [Internet]. Lisboa: Faculdade de Medicina; 2022 [cited 2022 Apr 6]. Available from: https://www.medicina.ulisboa.pt/en/cardiovascular-rehabilitation.
18. Rauch B, Davos CH, Doherty P, Saure D, Metzendorf MI, Salzwedel A, et al. The Prognostic Effect of Cardiac Rehabilitation in the era of Acute Revascularisation and Statin Therapy: A Systematic Review and Meta-Analysis of Randomized and Non-Randomized Studies - The Cardiac Rehabilitation Outcome Study (CROS). Eur J Prev Cardiol. 2016;23(18):1914-39. doi: 10.1177/2047487316671181.

Septal Ablation with Radiofrequency Catheters Guided by Echocardiography for Treatment of Patients with Obstructive Hypertrophic Cardiomyopathy: Initial Experience

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Abstract

Background: **Hypertrophic cardiomyopathy (HCM) can cause obstruction in the left ventricular outflow tract (LVOT), and be responsible for the onset of limiting symptoms, such as tiredness. When such symptoms are refractory to pharmacological treatment, interventionist alternative therapies can be useful, such as septal ablation through the infusion of alcohol in the coronary artery or through myectomy. Recently, the use of a radiofrequency (RF) catheter for endocardial septal ablation guided by electroanatomic mapping has proven to be efficient, despite the high incidence of complete atrioventricular block. An alternative would be the application of RF at the beginning point of the septal gradient guided by the transesophageal echocardiography (TEE). The echocardiography is an imaging method with high accuracy to determine septal anatomy.**

Objective: **To assess the long term effect of septal ablation for the relief of ventricular-arterial gradient, using TEE to help place the catheter in the area of larger septal obstruction. Besides, to assess the effects of ablation on the functional class and echocardiographic parameters.**

Methods: **Twelve asymptomatic patients, with LVOT obstruction, refractory to pharmacological therapy, underwent endocardial septal ablation with 8mm-tip catheters, whose placement was oriented in the region of larger obstruction, assisted by the TEE. Temperature-controlled and staggered RF applications were performed. After each application, the gradient was reassessed and a new application was performed according to the clinical criterion. The effects of RF applications were assessed both for the gradient at rest and for that provoked by the Valsalva maneuver, and considering the gradient. The differences were significant when p-value was lower than or equal to 0.05.**

Results: **It was possible to observe that the mean reduction of the maximum gradients was from 96.8±34.7 mmHg to 62.7±25.4 mmHg three months after the procedure (p=0.0036). After one year, the mean of maximum gradient was 36.1±23.8 mmHg (p=0.0001). The procedure was well tolerated, without records of complete atrioventricular block nor severe complications.**

Conclusion: **The TEE-guided septal ablation was efficient and safe, and the results were maintained during the clinical follow-up period. It is a reasonable option for the interventionist treatment of LVOT obstruction in HCM.**

Keywords: **Hypertrophic cardiomyopathy; LVOT obstruction, RF ablation; Myectomy; alcohol septal ablation**

Introduction

Obstructive hypertrophic cardiomyopathy (OHCM) is a genetic condition that manifests itself through myocardial hypertrophy, besides fibrosis of variable extension. The obstruction of the left ventricular outflow tract (LVOT) is an anatomical condition with dynamic behavior, and can cause symptoms such as limitation to efforts, besides being responsible for cases of sudden death. The interventionist treatment proposed for this condition can be alcohol injection in the septal branches of the coronary artery or myectomy.[1] The results of these procedures are still varied in the literature, and little adopted in the clinical practice.[2,3] Recently, the RF applied locally through a catheter, and using the electroanatomic mapping for a better characterization of the interventricular septum, has proven to be efficient due to the better control of the lesion extension and the more accurate placement of the catheter in the thicker region of the interventricular septum. This approach seems to be safer, especially regarding the impact on the conduction system of the septum.[4-6]

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Septal ablation by radiofrequency catheter

Myectomy has considerable morbidity and mortality rates, especially in scenarios in which there is no reference, experienced center that includes at least more than ten surgeries a year. This motivated the development of less invasive alternatives, such as septal alcoholization.[7]

Despite the lower postoperative morbidity and the need for postoperative units with less structure, advocates of alcoholization are also faced with significant limitations. The need for a favorable coronary anatomy (which cannot be found in up to 20% of the candidates to alcoholization) and the unpredictability of the extension of myocardial damage reduce the chances of applying this technique as a routine.

Recent studies show that the RF applied locally through a catheter has been efficient due to the better control of the injury extension and to the more precise placement of the catheter in the thicker region of the interventricular septum. These catheters were the same ones used in invasive electrophysiology for the treatment of ventricular and atrial arrhythmia. The researchers used intracavitary electroanatomic mapping to establish the septal region to be approached, besides the position of the catheter, respectively, aiming at reducing the risk of affecting the conduction system.[8-10] The ablation was performed in an electrophysiology or hemodynamic room, with access to the interventricular septum through retrograde aortic or transseptal path (rarely with an approach associated with the right septum). The catheters used in previous studies were irrigated, or had an 8mm-tip in adults. The results ranged, especially because of the techniques used to approach the gradient.[9-11]

We found only one study about RF catheter ablation in the pediatric population, using the electroanatomic mapping associated with transesophageal echocardiography.[12]

The RF catheter ablation allows the easy access of therapy to gradients located in the basal portions of the left ventricle, as well as to intraventricular gradients; therefore, it is not limited by coronary anatomy. The use of a transesophageal echocardiography (TEE) allows the real time location of the point of obstruction in real time during the procedure.

Hypothesis

Catheter ablation using electrophysiology techniques, by placing the therapeutic 8mm-tip catheter with the help of the TEE, is a simple method that allows the precise localization of the critical septal area to establish the ventricular-aortic gradient. These premises should make this technique simpler, more efficient and safer for the reduction of the LVOT obstruction.

Objectives

Primary Objective

To assess the safety and efficacy of RF application in the interventricular septum of patients with OHCM through 8mm-tip catheters whose placement on the target area was guided by TEE, aiming at reducing the gradient in LVOF.

Secondary Objective

To evaluate the repercussion of ventricular septal ablation on symptomatology, based on the functional class, besides the effects on electrocardiography and on the transthoracic echocardiogram before and three months and one year after the procedure.

Materials and methods

As proof of concept, we chose to conduct a pilot procedure in a symptomatic 63-year old patient, who had contraindication for an approach by hemodynamics and high surgical risk. The patient (not included in this series) presented mean post-myectomy residual ventricular gradient. The individual underwent a successful catheter ablation in the target area, with reduction of the initial gradient from 100 mmHg to less than 25 mmHg, and this result was maintained after 24 months of follow-up. The transseptal approach was used at first, but the access path was changed to the retrograde aortic path due to the instability of the catheter and the difficulty to access the proposed site for ablation. A magnetic resonance for control three months after the intervention identified the RF injury, caused by the use of catheters, adjacent to the lesion caused during the surgery.[13]

Patient selection

Twelve patients with OHCM were selected from the Cardiomyopathy Section of Instituto Dante Pazzanese de Cardiologia, with refractory symptoms to the pharmacological treatment. The 12 patients were selected for being in accordance with the inclusion and exclusion criteria, and for being interested in participating in the study, as well as being available to attend appointments and subsequent examinations of the protocol. They were all submitted to the following examinations: electrocardiography (EKG), transthoracic echocardiogram with doppler, besides blood profile including blood count, fasting glycemia, urea, creatinine, coagulogram.

The inclusion criteria were: individuals with symptomatic OHCM, whose gradient is provoked by a Valsalva maneuver higher than or equal to 50 mmHG, despite the treatment (or patients whose gradient is higher than 30 mmHg, with the need for the concomitant use of vasodilators); medical contraindication for myectomy (high surgical risk established by the cardiology staff or by patient's choice); or contraindication for septal alcoholization due to technical parameters. The excluded participants were: those with a definitive pacemaker or implantable cardioverter defibrillator, since they influence the mode of stimulation and the parameters in the ventricular gradient. It also would make it difficult to measure the effects of ablation in the heart conduction system, masking late atrioventricular blocks. Besides, we excluded individuals with atrial fibrillation, since the measurement of the gradient becomes little reproducible due to the irregularity of the heart rate (HR). Since the measurements would be necessary for the decision of interrupting ablation or continuing to apply it, the choice was to remove this variable in the initial stage of the protocol. Patients with ongoing infections and history of complex ventricular arrhythmia, or with a history

of sudden death recovered due to the probable indication of an implantable cardioverter defibrillator during follow-up, were also excluded. The transthoracic echocardiography at rest was performed in the morning, and patients were on their usual medications.

The Valsalva maneuver was performed by an experienced examiner, who explained its execution to the patients in detail. The echocardiographic records were obtained throughout the effort and relaxation stages, and were considered as the highest gradient values. The proper execution of the maneuver was defined by the evaluator, through the pre-load reduction, defined by the reduction of the mitral flow E-wave in the first attempt. Only when the patient was executing the maneuver properly, at another time, the gradients were recorded in the outflow. There was no control using barometers/flow meters.

The protocol and consent forms were approved by the Research Ethics Committee and are available in Plataforma Brasil (CAAE: 72754617.0.0000.5462; protocol number – CEP 4769/2017).

Ablation

The procedures were performed in a dedicated electrophysiology room, by electrophysiologists and cardiologists working with echocardiography, and with the supervision of the anesthesiology staff.

The strategies used by other researchers were based on the premise that the thicker point of the septum was the same where the gradient began. The gradient, in turn, is composed of the systolic anterior movement of the anterior leaflet of the mitral valve, movement of the papillary movement and septum. These anatomic data, point in which the gradient begins, can be observed with more accuracy by the echocardiogram during the ablation.

All of the procedures were performed under general anesthesia. A right femoral artery puncture was performed with an 8F guiding catheter to access the septal region of the left ventricle via retrograde aorta; two right femoral vein punctures with a 6F guiding catheter were performed to place the quadripolar catheter in the right septum; and we identified the His axis electrogram, besides another quadripolar catheter tip in the right ventricle. Then we measured the ventricular-aortic gradient and located the point of highest acceleration of the flow with the transesophageal echocardiography, characterizing the area of larger obstruction. The transesophageal echocardiography was performed under general anesthesia, and the images were initially obtained in the esophageal position. When necessary, with the evaluation of the short axis position, the probe was moved to the transgastric position. The examination was performed according to the protocol of the American Society of Echocardiography,[14] by observing the cavities in several angles (0, 30º, 45º, 60º, 90º) for the anatomical evaluation. The echocardiographic image allowed to identify the tip of the therapeutic catheter, which was overlapped to the septal region by the electrophysiologist, when it was possible to identify the aliasing. The echocardiography was then used to observe the distance between the anterior leaflet of the mitral valve and the stability of the contact with the region of interest.

With the help of fluoroscopy and the record of intracavitary electrical potentials with a TEB (Tecnologia Eletrônica Brasileira, São Paulo, Brazil) or EPtracer (Cardiotek, Netherlands) polygraph, the deflectable quadripolar catheter was placed in the His axis region; likewise, a quadripolar catheter was placed on the apical region of the right ventricle, and a bidirectional 8F therapeutic catheter with an 8mm-tip was placed in the left ventricle through the retroaortic course. The therapeutic catheter was impacted on the septal region of the LF (as previously described), in the point of the highest acceleration of the blood flow, where the RF was applied for 120 seconds (80W, 60ºC), followed by a new measurement of the gradient through a hemodynamic catheter, besides the assistance of the echocardiogram. To each application that resulted in the reduction of at least 25% of the initial gradient, four new applications were added to adjacent regions, observing the distance of at least 1 cm of the His axis electrogram (Figure 1).

When the maximum gradient reached a reduction of at least 25% of the initial value, the procedure was interrupted and new measures were taken in 10 and 20 minutes. At the end of the examination, the intraventricular gradient and the mitral reflux were reassessed, besides ruling out post-procedure complications.

After removing the introducers, the patients remained in the intensive care unit (ICU) for 24 hours, and were referred to the nursery for 3 to 5 days, with an assessment of troponin in the first 48 hours. Then, an echocardiography was performed 24 hours and six days after the procedure (to identify pericardial effusion or post-procedure thrombosis). After six weeks, three months, six months and 12 months, the patients were clinically reassessed. The transthoracic echocardiogram was repeated on the third and on the 12nd month.

Statistical analysis

The distribution of the continuous variables was assessed by the Shapiro-Wilk normality test for the comparative analyses of periods (pre-ablation, after three months, and pre-ablation, after 12 months). For the variables with normal distribution, the paired Student's t-test was used and the results were presented as mean and standard deviation. For those with non-normal distribution, the paired Wilcoxon test was used, and the results were presented as median and interquartile range. Thus, only the septal thickness analysis after 12 months was carried out with the Wilcoxon test. The other variables were analyzed using the Mann-Whitney test. In all of the conclusions obtained through the inferential analysis, the considered significance level was $\alpha = 5\%$. The functional class was the only analyzed categorical variable, and we did not use a statistical test for the pre and post-procedure comparison, considering that all individuals improved. The software used for statistical analyses was the R[r] (Viena, Austria).

Results

Eighteen patients were pre-selected. One of them was excluded for being less than 18 year of age; two for reporting paroxysmal atrial fibrillation or at the time of the procedure; two others, for having symptoms that were possibly related

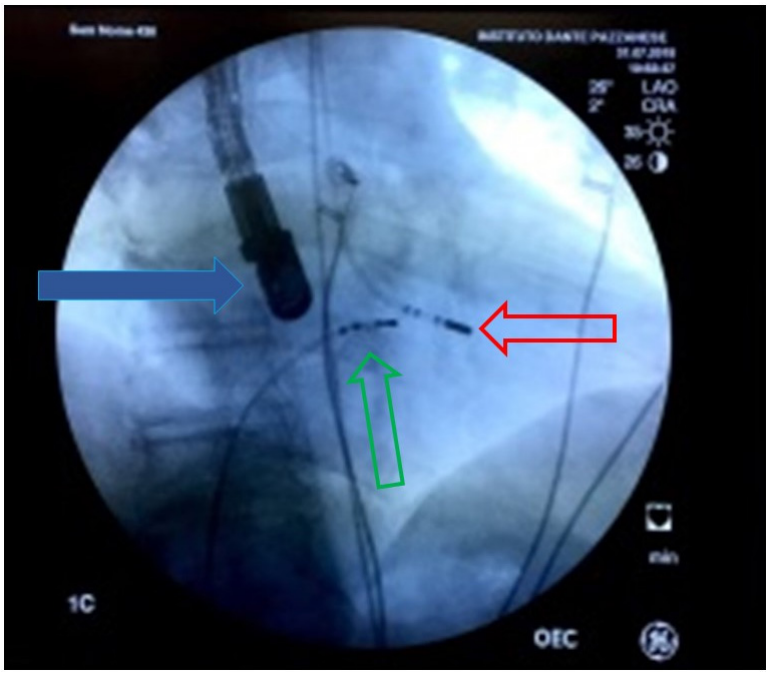

Figure 1 – *Fluoroscopy in a 30º right anterior oblique position, in which it is possible to observe the TEE probe (blue arrow), besides the catheters in the His axis region (green arrow) and the RF catheter (therapeutic). para Fluoroscopy in a 30º right anterior oblique position, in which it is possible to observe the TEE probe (blue arrow), besides the catheters in the His axis region (green arrow) and the RF catheter (therapeutic) - red arrow*

to other causes other than the gradient; and one individual was excluded due to a diagnosis of amyloidosis (Figure 2).

The 12 included patients corresponded to nine women and three men. The clinical and echocardiographic characteristics of this population are presented in Table 1. Clinically, the patients' symptoms were related to a high gradient.

Ablation

The mean duration of the procedures was three hours. The placement of the therapeutic catheter indicated by the echocardiography professional corresponded to the region with the highest gradient, as demonstrated in Figure 3.

The mean of initial maximum gradients measured during the procedure was 89 mmHg (±25,45). At the end, this mean decreased to 36.9 mmHg (±15.29). There were three cases of left bundle branch block related to the procedure, without the increment of the HV interval (all patients presented HV interval lower than or equal to 60 ms). There were no transient atrioventricular block nor prolongation of the PR interval in any of the cases. Likewise, there were no pericardial effusion nor clinical embolic brain events. One patient presented with arteriovenous fistula in the right inguinal region, which had to be surgically corrected. During hospitalization, all patients received an increased serum dose of troponin. The maximum value was reached in the first 12 hours, and was, in average, 7.15 ng/dL (±4.36). The mean time of hospitalization was 5.8 days (±2.7), per protocol. One patient was hospitalized for 13 days for the assessment of a hematoma in the left inguinal region, which was then diagnosed and treated as arteriovenous fistula (Table 2).

Table 2. Clinical and echocardiographic characteristics of patients before and after ablation. The described gradient was the maximum obtained even after being provoked.

Follow-up

There was a reduction of the provoked and at rest gradients in all persistent patients during follow-up. The data regarding the reduction of provoked and at rest gradients are presented in Figures 4 and 5. According to institutional protocol, the patients continued to receive the maximum dose of tolerated medication until their HRs were equal to or lower than 60 bpm (suggesting an efficient betablock).

It was observed that the reduction of the mean of maximum gradients was from 96.8±34.7 mmHg to 62.7±25.4 mmHg three months after the procedure (p=0.0036). Após um ano, a média dos gradientes máximos obtidos foi de 36,1±23,8 mmHg (p=0,0001).

Overall, 75% of the patients declared being in NYHA functional classification III, and 25% reported functional classification IV before the ablation procedure. One year after the procedure, 66.7% were in functional classification I, and 33.3%, II (Figure 6).

Regarding electrocardiographic changes, there were none that could justify a different treatment, such as atrioventricular blocks or ST segment depression. The three patients that presented with changes had left bundle branch block during

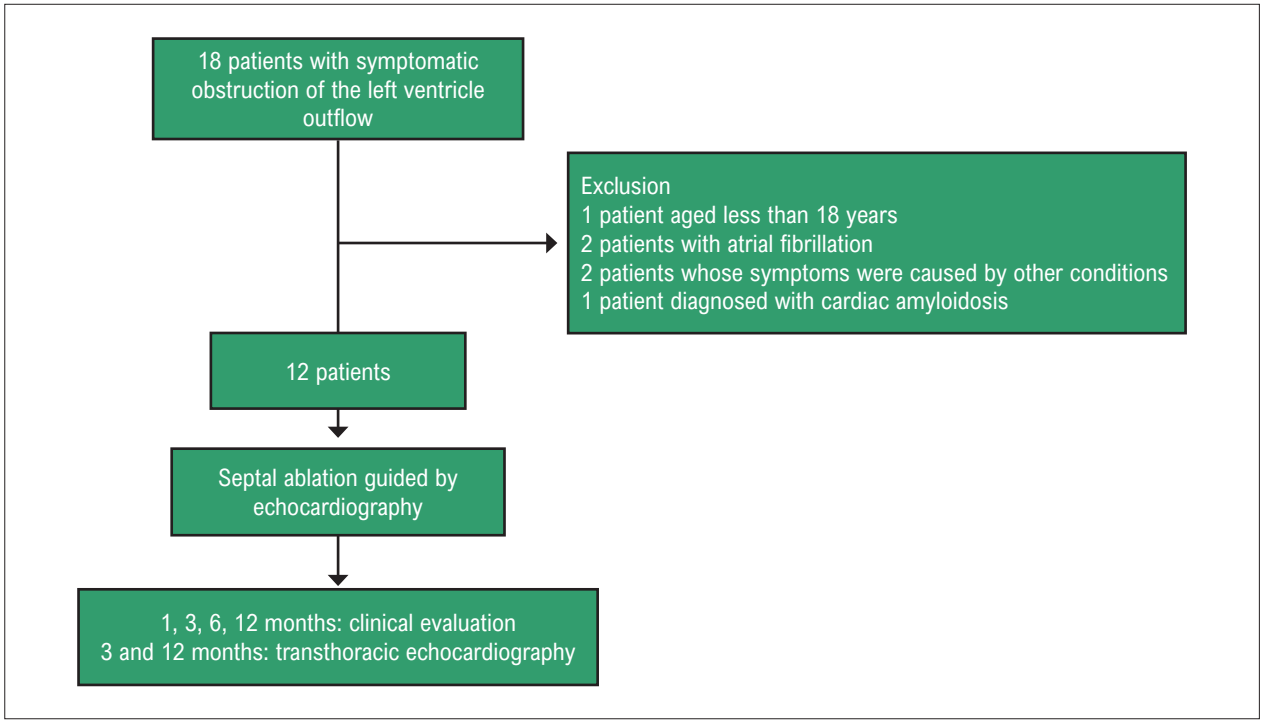

Figure 2 – *Flowchart showing patient selection and follow-up.*

Table 1 – Clinical and echocardiographic characteristics of the assessed population

Age	57.3 ± 3 years
Height	1.65 m ± 3.3
Weight	87 kg ± 15
Female gender	75%
SAH	75%
Diabetes mellitus	8%
Initial gradient at rest - mmHg	73.6 ± 38.1
Initial provoked gradient - mmHg	96.8 ± 23.8
Functional class III or IV	100%
Mean LVEF	67.0 ± 4
Septal thickness (mm)	21 ± 6.4
Left atrium (ml)	65.4± 29.7
Use of betablockers	100%
Calcium channel blockers	33%
HR at hospital admission	59.88 ± 4.19 bpm

SAH: systemic arterial hypertension; LVEF: left ventricular ejection fraction; HR: heart rate.

the procedure, which persisted throughout the one-year follow-up period (identified in Table 3). Except for the final diastolic diameter of the LV at the end of three months, but not one year of follow-up (which we consider as an isolated event), there was no significant change in the other echocardiographic parameters assessed in the three periods (preoperative, after three months and after one year). The mean of the parameters and the statistical significance are available in Table 3.

Discussion

This study shows that TEE-guided ventricular septal ablation is feasible, with favorable results in the significant reduction of the ventricular gradient, with low complication rates. All of the assessed patients benefitted from the procedure, as demonstrated by the improved functional classification.

Myectomy has been a reality for fifty years,[7] and it is still the most widely accepted intervention to relieve the

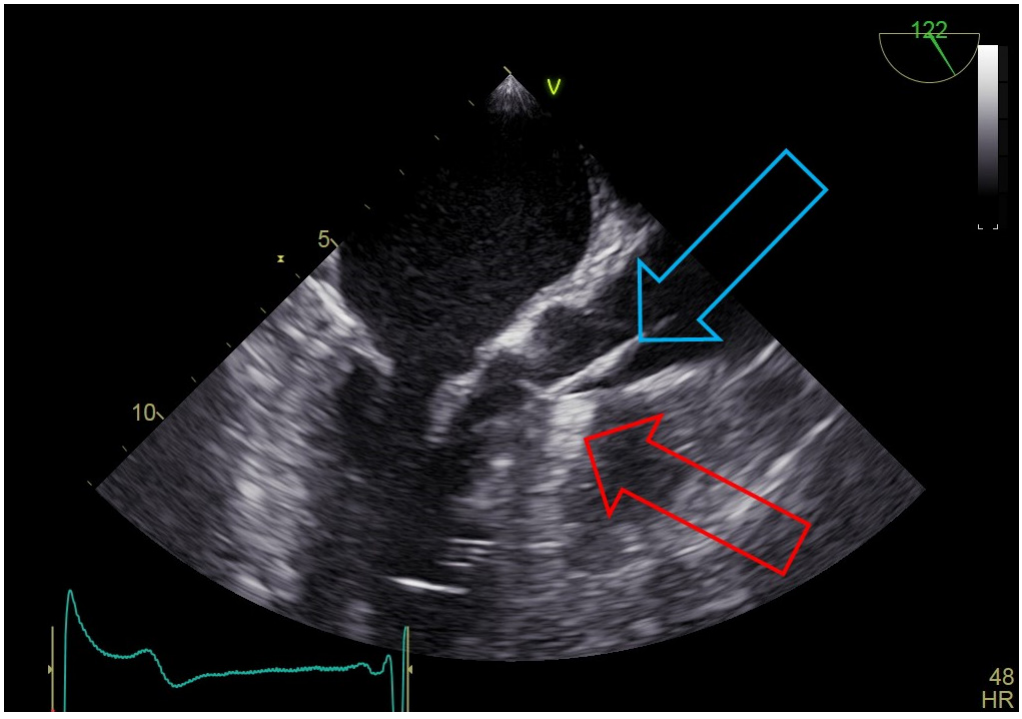

Figure 3 – *Perioperative transesophageal echocardiography, which shows the refringent interventricular septum (red arrow) and the radiofrequency (RF) therapeutic catheter, which, after surpassing the aortic valve, is impacted on the septum (blue arrow). This region is defined by the echocardiography professional as the one with the highest gradient. At this point, RF is applied and, if the gradient is reduced in at least 25%, new applications are repeated around the first application, thus extending the lesion area.*

obstruction of the LVOF. It is necessary, but a less invasive alternative has appeared, but has not been widely adopted by cardiologists: septal ablation with ethanol, which is a technique performed in the catheterization laboratory and can be a reasonable alternative to myectomy. The results of both techniques to reduce the gradient are still controversial regarding the change in prognosis.

The obstruction of the left ventricular ejection is quantified in mmHg, often through the transthoracic echocardiography. The difference of pressures observed before and after the point of obstruction is called a gradient, and the same occurs in up to one third of the patients with hypertrophic cardiomyopathy.[1] The maximum gradient obtained through the pulse and the continuous Doppler in the LVOF (at rest and after the Valsalva maneuver) is used as a marker for risk of sudden death in calculators of prognosis, such as the model proposed in 2014 by Elliot et al. in the guidelines of the European Society of Cardiology.[15] The model was validated and then presented at a congress of the same society, in 2017.[16]

The most used form of echocardiographic evaluation is the measurement of the gradient during the Valsalva maneuver. Less used alternatives are abdominal compression by the echocardiography physician, evaluation during an exercise stress test and pharmacological induction.[17,18] The use of a provocative maneuver allows to estimate the proper reproducibility of maximum gradients obtained at physical effort, as well as to minimize the impact of the daily variation of the gradient in situations such as dehydration and sedation.[19]

The pharmacological treatment with betablockers and calcium channel blockers is the initial therapy to control symptoms in people with symptomatic obstruction. The later are usually indicated for patients who are refractory to betablockers, or in association, when the target HR is not reached. It is important to be careful about the association of bradycardizing drugs in patients with hypertrophic cardiomyopathy, especially those whose gradients at rest are higher than 80 mmHg, with signs of heart failure.[20] Therefore, two thirds of our patients did not use the association of these pharmacological classes, since they reached the target HR and due to the inherent risk of using them. As shown, the sample of this study was only submitted to drug association when the target HR was above 60 bpm, and when there was clinical tolerance towards the associated treatment, which occurred in about one third of the sample. Therefore, there was no significant reduction of medication doses used after the conclusion of the one-year follow-up period.

The use of RF ablation was reported in 2011,[4] in a study that made way to a few others since then. The high morbidity and mortality surgical rates established the procedure of TEE-guided RF as a minimally invasive intervention. Besides, this technique can be used in younger patients (<35 years), and such a restriction is related to the septal alcoholization.

Table 2 – Individual characteristics of the patients

Patient	Age	Sex	Medications pré	Medications 12m	Maximum gradient pré	Maximum gradient 3m	Maximum gradient 12m	Functional class pré	Functional class 12m	Complications
1	60	F	Atenolol 100mg/day	Atenolol 100mg dia, verapamil 80mg/day	126	61	47	III	II	Femoral arteriovenous fistula. Vascular surgery. New LBBB
2	51	F	Propranolol 240mg/day	Propranolol 240mg/day	83	75	32	III	I	
3	71	M	Atenolol 100mg/day Disopiramida 250mg/day	Propranolol 120mg/day	100	53	99	III	II	
4	62	F	Propranolol 160mg/day	Propranolol 100mg/day	141	99	41	III	II	
5	58	F	Metoprolol 100mg/day verapamil 160mg/day	Metoprolol 150mg/day	152	55	25	IV	II	New LBBB
6	51	M	Atenolol 100mg/day diltiazem 180mg/day	Atenolol 50mg/day	88	95	17	III	I	
7	23	F	Propranolol 240mg/day not tolerated by hypotension	No medications	41	28	24	III	I	
8	73	F	Propranolol 240mg/day verapamil 360mg/day	Propranolol 240mg/day verapamil 360mg/day	135	89	56	III	I	
9	79	F	Ditiazem 120mg/day atenolol 360mg/day	Atenolol 100mg/day Ditiazem 120mg/day	70	70	18	IV	I	New LBBB
10	64	F	Atenolol 100mg/day	Atenolol 100mg/day	87	ND	17	III	I	
11	55	M	Metroprolol 75mg/day	Metroprolol 50mg/day	59	30	40	III	I	
12	41	F	Atenolol 200mg/day	Atenolol 50mg/day	80	35	17	III	I	

LBBB: left bundle branch block. NA: not available.

The RF procedure is not dependent on the position of septal coronary branches, and makes the extension of the post-ablation lesion predictable. On the other hand, it is estimated that the rate of reintervention after septal alcoholization is close to 12% due to the persistence of the symptomatic residual gradient.[19] The results obtained with the RF catheter ablation in our sample are similar to those of previous studies, which used the same technique as to the reduction of the LVOF gradient. The reduction ranged from 59% to 85% in some of them.[4,5,8,9]

The ablation protocol in our study was intentionally minimalist. We used ablation only on the left side, through the retrograde aortic approach, guided by TEE. Therefore, it would be easily reproducible in many laboratories. We chose to guide the ablation using echocardiography with fluoroscopy, because the maximum gradient is not only owed to the thicker septum. Other structures participate in the obstruction, such as the anterior movement of the mitral valve and papillary muscles. TEE was also useful to identify the mitral valve strand, thus preventing its lesion and failure.

The initial studies that used RF to reduce the gradient in OHCM used irrigated catheters. This type of catheter requires a continuous infusion of physiological serum

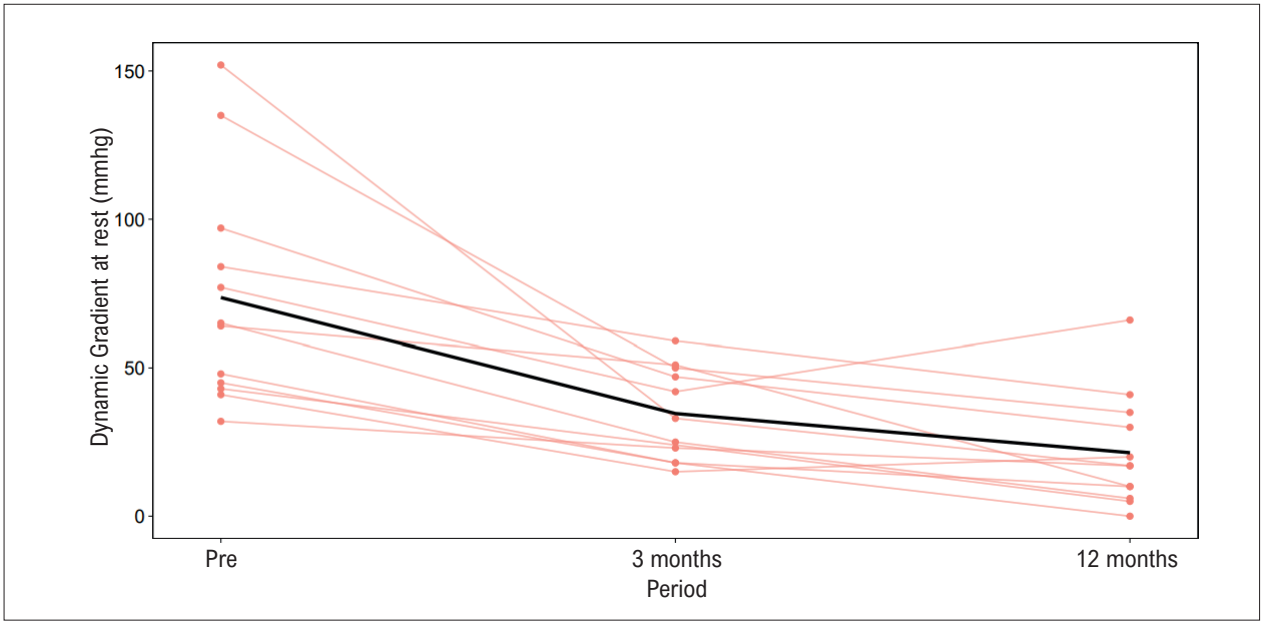

Figure 4 – *Variation of maximum gradients at rest and pre-procedure, after three and 12 months, for each patient. It is possible to observe the significant reduction of the gradient after ablation, and this result was maintained until the 12 months of observation.*

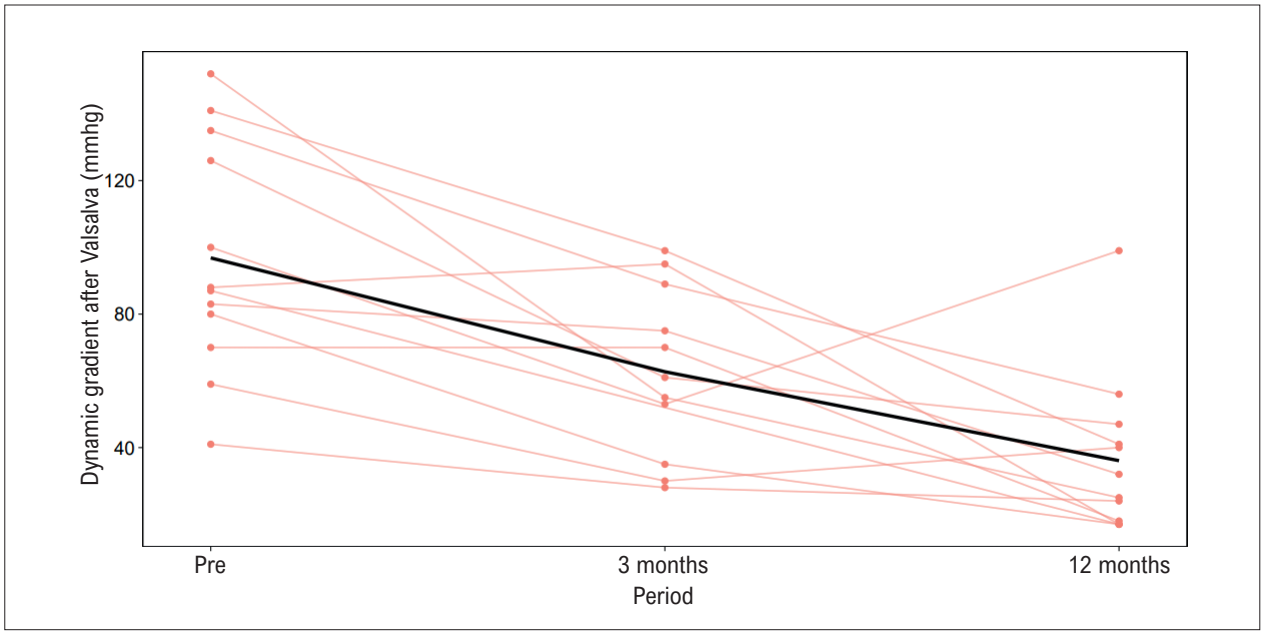

Figure 5 – *Variation of maximum pre-procedure gradients provoked by the Valsalva maneuver after three and 12 months, for each patient. Likewise, as observed in the at rest gradient, there was significant reduction of the gradient after ablation, and this result was maintained until the 12 months of observation.*

pumped by a specific infusion pump, and approximate flow of 1,000 ml/h during the application. The infusion flow is reduced during mapping (moment when the catheter is inside the heart, but the radiofrequency energy is not released), but even in this moment the patient receives 120 ml/h. In a review article, three patients presented with pulmonary edema or congestion after the procedure.[8] The therapeutic catheters with 8-mm tips used in our study do not require irrigation for functioning properly. Besides, even if it was not our intention, the use of a non-irrigated catheter can improve the cost-benefit relationship when compared to the irrigated one, so it can be a viable option for laboratories that do not have electroanatomic mapping promptly available.

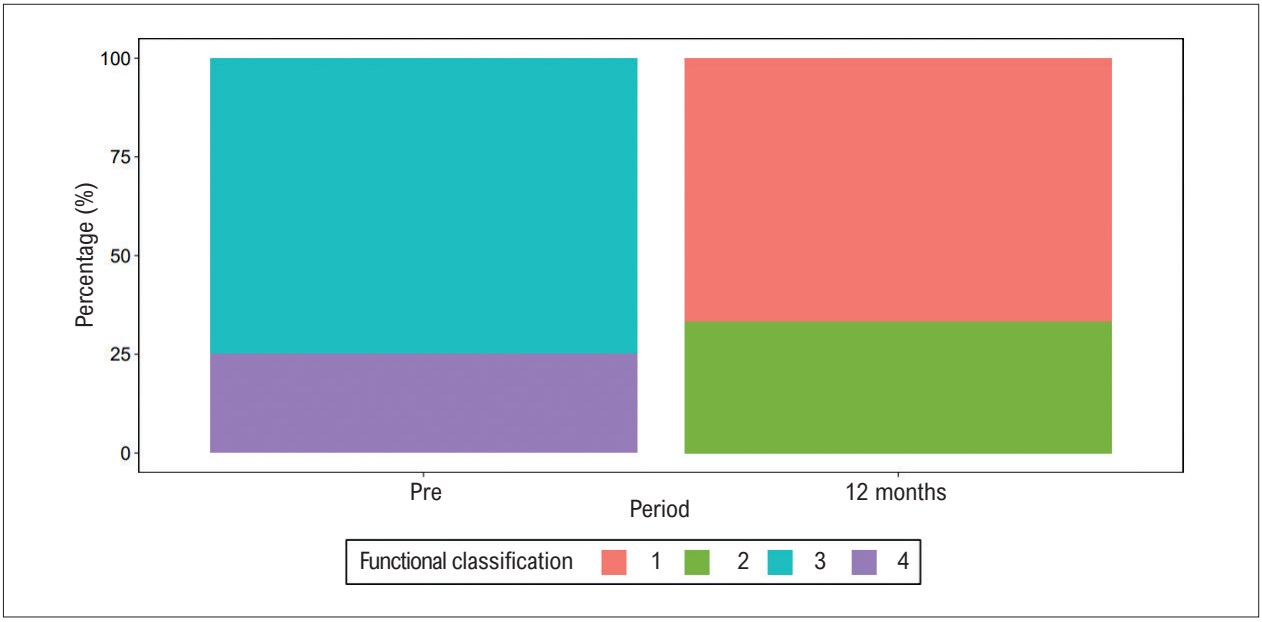

Figure 6 – *Variation of functional classification before and after the one-year follow-up.*

Table 3 – Echocardiographic characteristics before the procedure, after three and 12 months. Mean and standard deviation

	Before the procedure	3 months	p (3 months)	12 months	p 12 months
Aortic root	32.2 +/- 2.5	31.9 +/- 2.5	0.6618	32.4 +/- 2.7	0.3251
Left atrium (mm)	47.2 +/- 6.8	47.9 +/- 8.6	0.8100	46.8 +/- 6.5	0.3803
Indexed volume of the LA (ml)	65.4 +/- 29.7	60.1 +/- 15.1	0.0777	53.1 +/- 12.8	0.1144
Final diastolic diameter of the LV (mm)	42.4 +/- 4.3	44.1 +/- 3.4	0.0390	45.1 +/- 4.1	0.0692
Final systolic diameter of the LV (mm)	25.9 +/- 3.6	27.3 +/- 2.9	0.1946	27.3 +/- 2.7	0.8182
LV septum (mm)	21 +/- 6.4	20.9 +/- 4.5	0.4332	17.8 +/- 3.4	0.3017[a]
LV mass(g)	372.2 +/- 136.3	384.3 +/- 119.3	0.2644	358.6 +/- 86.9	0.8208
LVEF (SIMPSON - %)	68.7 +/- 5.4	68.1 +/- 4.1	0.4053	69.6 +/- 5.6	0.9642

LVDD: left ventricle diastolic diameter; LVSD: left ventricle systolic diameter; LVEF: left ventricular ejection fraction; LV: left ventricle. [a] : paired Wilcoxon test. The other p-values are from the paired Student's t-test.

The reduction of the NYHA functional classification was the main benefit resulting from the reduction of the ventricular-arterial gradient. After one year, all patients who referred having symptoms compatible with NYHA functional classifications III or IV reported improvement in the performance of activities of daily living, and similar results were found in other studies. The improvement of the functional classification during the observation period of this study (until the end of the first year) suggests a permanent modification of the functional status of the left ventricular septum. Since the reduction of the septal thickness was not significant, we believe that the healing of the left septal endocardium may inhibit its bulging towards the LVOF. We believe that the healing of the septum submitted to the RF lesion has inhibited the systolic bulging towards the LVOF, thus reducing the gradient. This mechanism would be different from the endocardial, transmural damage, which occurs when the alcoholic septal ablation[10] or the needle percutaneous intramyocardial septal RF ablation are performed.[11]

As to the safety of the technique used here, there were no cases of atrioventricular block. The HV interval was not prolonged for more than 60 ms, even in the three patients that presented damage in the left branch of the His axis. On the other hand, with the endocardial ablation by RF guided by electroanatomic mapping, there were no reports of atrioventricular block in a case series[8] and in up to 21% of the cases in the series by Lawentz et al.[4] In a study, the support of the acute pacemaker was necessary in 17% of the patients after the procedure, but the real number can be underestimated, once the study protocol required an implantable cardioverter defibrillator (ICD) in all patients

due to the extensive ablation in both sides of the septum.[5] We believe that the less aggressive protocol, with a lower threshold for interrupting the application of RF energy on the septum (reduction of 25% from the initial gradient), associated with TEE-guided ablation, may have played an important role in the matter of safety. A study with children with the diagnosis used perioperative echocardiography to locate the site with larger septal bulge to apply the RF, using therapeutic catheters with irrigated 4mm-tips associated with electroanatomic mapping,[12] whereas another analysis used an intracardiac echocardiography image integration technology associated with electroanatomic mapping (CARTOSOUND, Biosense Webstser, CA, USA).[21] Due to the heterogeneity of techniques, it is not possible to compare the complications of the TEE-guided procedures, those guided only by electroanatomic mapping, or by a combination of both. The meta-analysis by Poon et al. was not able to establish a correlation between the use of echocardiography and the rates of success or complications. However, it suggested a potential benefit of the use of intracardiac echocardiography associated with electroanatomic mapping in the localization of the target of the ablation.[21] This observation was based on the experience obtained in the study by Cooper et al., who was also a co-author of the meta-analysis.[21] Even if we can observe a maximum residual provoked gradient higher than 50 mmHg in two cases of the series, we consider that the initial protocol should be improved, in search of better success predictors that can be observed still in surgery. The small number of cases in this initial series also aimed at improving the symptoms and preserving the integrity of the electric conduction, with precise ablation. Maybe, in future analyses, a more extensive ablation can provide the same safety and lead to a higher reduction of gradients in the long term. Still, the criterion for reintervention would only be reached in one of the patients (symptomatic gradients higher than 50 mmHg, despite clinical treatment).

There are no studies comparing septal alcoholization and RF ablation. Some records suggest that the incidence of complete atrioventricular block is estimated in 10-15% of the patients who undergo septal alcoholization, especially those with left bundle branch block before the procedure. Besides, some level of transient atrioventricular block was observed in about 50% of the patients during or one week after the procedure.[16,17] Septal alcoholization was also related to the larger area of fibrosis if compared to myectomy, and high changes of ventricular arrhythmias in the postoperative period.[19]

A recent meta-analysis that included 74 patients of six studies reported two cases of tamponade that required treatment.[22] There were no major complications in our group. One patient presented with arteriovenous fistula, which required surgical correction in the two weeks after the procedure.

Limitations

Even though the results are encouraging, this is an observational study, whose follow-up time is relatively short. We believe that a comparison between methods (septal ablation with ethanol, endocardial RF or myectomy) would be ideal, but the number of patients submitted to both procedures should be higher, ideally randomized and, as a consequence, involving multiple research centers. An option would be to start a randomized prospective study and compare a group with intervention and another one without intervention (sham study), once the relief of symptoms is the final objective of the treatment. A placebo effect cannot be ruled out in a case series study such as this one. Due to the limited number of cases, it was not possible to quantify the probability of complex ventricular arrhythmias in the long term (even if none of the patients has presented a justification for an implantable cardioverter defibrillator or definitive pacemaker in a one-year period).

Conclusion

TEE-guided RF endocardial ablation is an efficient procedure, safe in the long term, which reduces the gradient of LVOF and improves the functional level of patients with severe obstruction.

Author Contributions

Conception and design of the research, Acquisition of data, Analysis and interpretation of the data, Statistical analysis, Obtaining financing, Writing of the manuscript, Critical revision of the manuscript for intellectual content: Valdigem BP, Correia EB, Moreira DAR, Le Bihan DCS, Pinto IM, Abizaid AA, Andalaft RB, Paladino Filho AT, Silva HAGP, Viesi JHZ.

Potential Conflict of Interest

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

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Study Association

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Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Instituto Dante Pazzanese de Cardiologia under the protocol number 727 54617.0.0000.5462. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

References

1. Gersh BJ, Maron BJ, Bonow RO, Dearani JA, Fifer MA, Link MS, et al. 2011 ACCF/AHA Guideline for the Diagnosis and Treatment of Hypertrophic Cardiomyopathy: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2011;124(24):783-831. doi: 10.1161/CIR.0b013e318223e2bd.
2. Maron BJ, Yacoub M, Dearani JA. Controversies in Cardiovascular Medicine. Benefits of Surgery in Obstructive Hypertrophic Cardiomyopathy: Bring Septal Myectomy Back for European Patients. Eur Heart J. 2011;32(9):1055-8. doi: 10.1093/eurheartj/ehr006.
3. Gietzen FH, Leuner CJ, Raute-Kreinsen U, Dellmann A, Hegselmann J, Strunk-Mueller C, et al. Acute and Long-term Results After Transcoronary Ablation of Septal Hypertrophy (TASH). Catheter Interventional Treatment for Hypertrophic Obstructive Cardiomyopathy. Eur Heart J. 1999;20(18):1342-54. doi: 10.1053/euhj.1999.1520.
4. Lawrenz T, Borchert B, Leuner C, Bartelsmeier M, Reinhardt J, Strunk-Mueller C, et al. Endocardial Radiofrequency Ablation for Hypertrophic Obstructive Cardiomyopathy: Acute Results and 6 Months' Follow-up in 19 Patients. J Am Coll Cardiol. 2011;57(5):572-6. doi: 10.1016/j.jacc.2010.07.055.
5. Crossen K, Jones M, Erikson C. Radiofrequency Septal Reduction in Symptomatic Hypertrophic Obstructive Cardiomyopathy. Heart Rhythm. 2016;13(9):1885-90. doi: 10.1016/j.hrthm.2016.04.018.
6. Hagège AA, Desnos M. New Trends in Treatment of Hypertrophic Cardiomyopathy. Arch Cardiovasc Dis. 2009;102(5):441-7. doi: 10.1016/j.acvd.2009.03.008.
7. Morrow AG, Reitz BA, Epstein SE, Henry WL, Conkle DM, Itscoitz SB, et al. Operative Treatment in Hypertrophic Subaortic Stenosis. Techniques, and the Results of Pre and Postoperative Assessments in 83 Patients. Circulation. 1975;52(1):88-102. doi: 10.1161/01.cir.52.1.88.
8. Lawrenz T, Borchert B, Leuner C, Bartelsmeier M, Reinhardt J, Strunk-Mueller C, et al. Endocardial Radiofrequency Ablation for Hypertrophic Obstructive Cardiomyopathy: Acute Results and 6 Months' Follow-up in 19 Patients. J Am Coll Cardiol. 2011;57(5):572-6. doi: 10.1016/j.jacc.2010.07.055.
9. Shelke AB, Menon R, Kapadiya A, Yalagudri S, Saggu D, Nair S, et al. A Novel Approach in the use of Radiofrequency Catheter Ablation of Septal Hypertrophy in Hypertrophic Obstructive Cardiomyopathy. Indian Heart J. 2016;68(5):618-23. doi: 10.1016/j.ihj.2016.02.007.
10. Aksu T, Guler T, Yalin K, Golcuk SE, Ozcan K. Septal Ablation for Hypertrophic Obstructive Cardiomyopathy: Transcoronary and Endocardial Approach. Am J Med Sci. 2016;352(5):466-71. doi: 10.1016/j.amjms.2016.08.025.
11. Liu L, Li J, Zuo L, Zhang J, Zhou M, Xu B, et al. Percutaneous Intramyocardial Septal Radiofrequency Ablation for Hypertrophic Obstructive Cardiomyopathy. J Am Coll Cardiol. 2018;72(16):1898-909. doi: 10.1016/j.jacc.2018.07.080.
12. Sreeram N, Emmel M, Giovanni JV. Percutaneous Radiofrequency Septal Reduction for Hypertrophic Obstructive Cardiomyopathy in Children. J Am Coll Cardiol. 2011;58(24):2501-10. doi: 10.1016/j.jacc.2011.09.020.
13. Valdigem BP, Correia EB, Moreira DAR, Le Bihan DCS, Pinto Filho IM, Paladino Filho AT, et al. Focused Endocardial Septal Ablation: A New Technique to Treat Post Myectomy Recurrent Gradient. Ann Thorac Surg. 2021:S0003-4975(21)00145-4. doi: 10.1016/j.athoracsur.2021.01.029.
14. Mitchell C, Rahko PS, Blauwet LA, Canaday B, Finstuen JA, Foster MC, et al. Guidelines for Performing a Comprehensive Transthoracic Echocardiographic Examination in Adults: Recommendations from the American Society of Echocardiography. J Am Soc Echocardiogr. 2019;32(1):1-64. doi: 10.1016/j.echo.2018.06.004.
15. Elliott PM, Anastasakis A, Borger MA, Borggrefe M, Cecchi F, Charron P, et al. 2014 ESC Guidelines on Diagnosis and Management of Hypertrophic Cardiomyopathy: The Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). Eur Heart J. 2014;35(39):2733-79. doi: 10.1093/eurheartj/ehu284.
16. European Society of Cardiology. Preventing Sudden Death in Hypertrophic Cardiomyopathy: New Backing for ESC Guidelines (HCM-EVIDENCE) [Internet]. Brussels: European Society of Cardiology; c2021 [cited 2021 Aug 26]. Available from: https://www.escardio.org/The-ESC/Press-Office/Press-releases/preventing-sudden-death-in-hypertrophic-cardiomyopathy-new-backing-for-esc-guidelines-hcm-evidence.
17. Agarwal S, Tuzcu EM, Desai MY, Smedira N, Lever HM, Lytle BW, et al. Updated Meta-Analysis of Septal Alcohol Ablation Versus Myectomy for Hypertrophic Cardiomyopathy. J Am Coll Cardiol. 2010;55(8):823-34. doi: 10.1016/j.jacc.2009.09.047.
18. Maron BJ, Nishimura RA. Surgical Septal Myectomy Versus Alcohol Septal Ablation: Assessing the Status of the Controversy in 2014. Circulation. 2014;130(18):1617-24. doi: 10.1161/CIRCULATIONAHA.114.011580.
19. Noseworthy PA, Rosenberg MA, Fifer MA, Palacios IF, Lowry PA, Ruskin JN, et al. Ventricular Arrhythmia Following Alcohol Septal Ablation for Obstructive Hypertrophic Cardiomyopathy. Am J Cardiol. 2009;104(1):128-32. doi: 10.1016/j.amjcard.2009.02.056.
20. Ommen SR, Mital S, Burke MA, Day SM, Deswal A, Elliott P, et al. 2020 AHA/ACC Guideline for the Diagnosis and Treatment of Patients with Hypertrophic Cardiomyopathy: Executive Summary: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2020;142(25):533-57. doi: 10.1161/CIR.0000000000000938.
21. Cooper RM, Shahzad A, Hasleton J, Digiovanni J, Hall MC, Todd DM, et al. Radiofrequency Ablation of the Interventricular Septum to Treat Outflow Tract Gradients in Hypertrophic Obstructive Cardiomyopathy: A Novel Use of CARTOSound® Technology to Guide Ablation. Europace. 2016;18(1):113-20. doi: 10.1093/europace/euv302.
22. Poon SS, Cooper RM, Gupta D. Endocardial Radiofrequency Septal Ablation - A New Option for Non-Surgical Septal Reduction in Patients with Hypertrophic Obstructive Cardiomyopathy (HOCM)?: A Systematic Review of Clinical Studies. Int J Cardiol. 2016;222:772-4. doi: 10.1016/j.ijcard.2016.08.123.

Echocardiography Guiding Percutaneous Treatment of Obstructive Hypertrophic Cardiomyopathy: Navigating (In Known Waters) Is Necessary

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Short Editorial related to the article: Septal Ablation with Catheters and Radiofrequency Guided by Echocardiography for Treating Patients with Obstructive Hypertrophic Cardiomyopathy: Initial Experience

Obstructive hypertrophic cardiomyopathy (HOCM) is the most common cardiac genetic disease and, besides the risk of malignant arrhythmias, it is responsible for symptoms such as palpitations, syncope, or presyncope, exertional dyspnea, and angina pectoris. Ten percent of patients are refractory to clinical treatment with beta-blockers or calcium channel blockers. Treatment alternatives such as surgical myectomy (SM) or non-invasive methods to reduce left ventricle outflow obstruction may be considered in this population.[1,2]

Although surgical myectomy is considered safe and the procedure of choice in experienced centers, it still has a percentage of post-procedure complications such as tamponade, interventricular septal communication, cerebrovascular accident dissection of coronary arteries, and non-fatal cardiac arrest. Controversy still exists about non-surgical hemodynamic treatment options, and the Heart Team's expertise is an important factor regarding decisions.[3]

Alcohol septal ablation (ASA), developed in 1995, has been the most frequently used non-surgical procedure, considered safe.[4] ASA feasibility is related to coronary septal anatomy and is reported to be responsible for relatively big areas of myocardium damage and carries a risk of bundle branch block, atrioventricular block, and pacemaker dependency. Also, gradient reductions after ASA used to be less impressive than surgical ones. Other options of septal occlusion as coiling septal arteries have also been described, although with other related complications.[5] Radiofrequency ablation (RFA) is another option for treating HOCM and was mostly applied to children based on this population's higher risk of arrhythmias when submitted to alcoholization.

Keywords

Cardiomyopathy, Hypertrophic/genetics; Ablation Techniques/methods; Alcohol Septal Ablation/methods; Miectomy; Gradient

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In this volume of ABC, Valdigen et al.[6] reported a case series of 12 adult patients treated with RFA guided with transesophageal echocardiography. This imaging modality can accurately visualize the catheter location in LV and help position it after evaluating the most obstructive portion of the LV septum. Results were good, with a significant reduction of LVOT obstruction from 3 months of follow-up. Two patients developed LVBBB without any interventional need. No major complications occurred.[6]

Intraprocedural echocardiography can also guide septal alcoholization using transthoracic or transesophageal views. Recently, echocardiographic enhanced contrast agents, based on microbubbles, has been used as a tool to study and quantify myocardium perfused areas related to septal coronaries. A small amount of contrast agents is infused on isolated septal coronaries, and perfusion myocardium images can be generated from bidimensional or even tridimensional techniques. With this tool, deciding the best coronary to approach (Figure 1) or even to decline proceeding is easier.[7] The use of three-dimensional echocardiography seems to be more accurate than conventional bidimensional to target safe and long-term effective septal reduction with ASA in obstructive HCM,[7] and its use should be preferred when available.[1] Echocardiographic contrasting of the myocardium can also be evaluated to guide surgical myectomy (SM).

In a recent meta-analysis of non-randomized studies, Bytyci, et al.[8] conclude that ASA and SM treatment of HOCM carry a similar mortality risk. Peri-procedural complications are less in alcohol ablation, but re-intervention and pacemaker implantations are more common.[8] There is still no significant data comparing non-surgical options to SM after using advanced echocardiographic techniques with or without perfusion agents.

Once no randomized trial data compares the efficacy of techniques in this scenario, although SM is preferred in experienced centers, treatment choices will still be chosen based on center expertise and heart team considerations about individual risk and benefits. The use of imaging techniques such as echocardiography, which can help guide the best anatomical septum target, maybe is the missing piece for success.

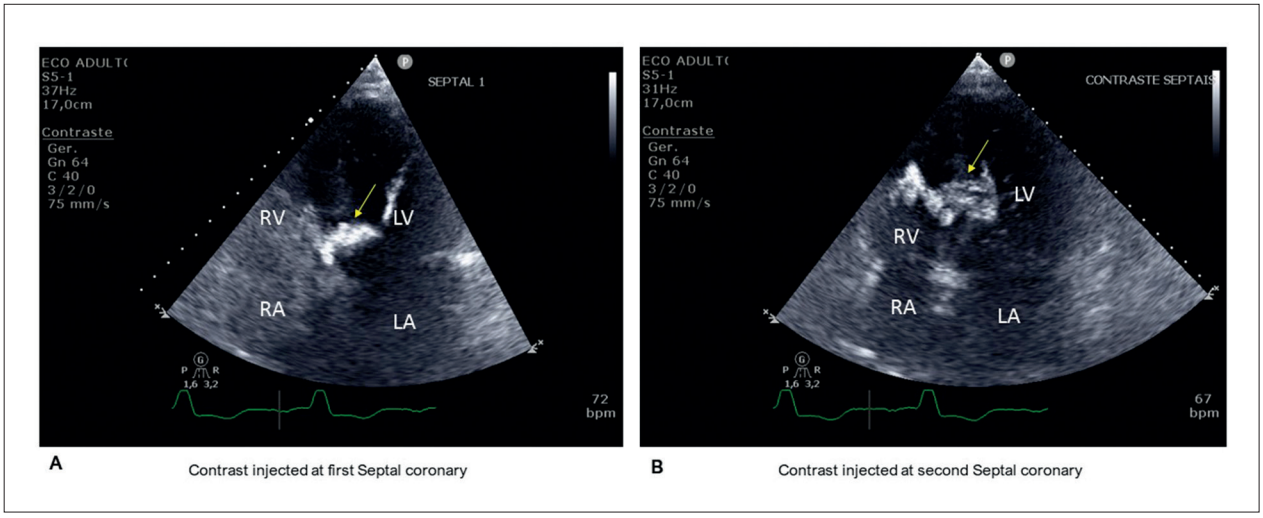

Figure 1 – *Images using echocardiography enhanced agent (SonoVue) injected at first septal coronary (Panel A) and second septal coronary (Panel B). Once the perfused myocardial area from the second septal coronary was larger and involved the RV's moderator band, the decision to occlude the first septal coronary was taken. RA: right atria; LA: left atria; RV: right ventricle; LV: left ventricle.*

References

1. Liebregts M, Vriesendorp PA, Ten Berg JM. Alcohol Septal Ablation for Obstructive Hypertrophic Cardiomyopathy: A Word of Endorsement. J Am Coll Cardiol. 2017;70(4):481-8. doi: 10.1016/j.jacc.2017.02.080.
2. Bazan SGZ, Oliveira GO, Silveira C, Reis FM, Malagutte K, Tinasi LSN, et al. Hypertrophic Cardiomyopathy: A Review. Arq Bras Cardiol. 2020;115(5):927-35. doi: 10.36660/abc.20190802.
3. Moya Mur JL, Salido Tahoces L, Mestre Barcelo JL, Fernandez Golfin C, Zamorano Gomez JL. Three-dimensional contrast echocardiography-guided alcohol septal ablation in hypertrophic obstructive cardiomyopathy. Eur Heart J Cardiovasc Imaging. 2014;15(2):226. doi: 10.1093/ehjci/jet152.
4. Rigopoulos AG, Seggewiss H. Twenty Years of Alcohol Septal Ablation in Hypertrophic Obstructive Cardiomyopathy. Curr Cardiol Rev. 2016;12(4):285-96. doi: 10.2174/1573403x11666150107160344.
5. Togni M, Billinger M, Cook S, Hess OM. Septal myectomy: cut, coil, or boil? Eur Heart J. 2008;29(3):296-8. doi: 10.1093/eurheartj/ehm561.
6. Valdigem BP, Correia EB, Moreira DAR, Bihan DL, Pinto IMF, Abizaid AAC, et al. Septal Ablation with Radiofrequency Catheters Guided by Echocardiography for Treatment of Patients with Obstructive Hypertrophic Cardiomyopathy: Initial Experience. Arq Bras Cardiol. 2022. Feb 7;S0066-782X2022005001201. doi: 10.36660/abc.20200732. Online ahead of print.
7. La Canna G, Scarfo I, Arendar I, Colombo A, Torracca L, Margonato D, et al. Targeting Alcohol Septal Ablation in Patients with Obstructive Hypertrophic Cardiomyopathy Candidates for Surgical Myectomy: Added Value of Three-Dimensional Intracoronary Myocardial Contrast Echocardiography. J Clin Med. 2021;10(10): :2166. doi: 10.3390/jcm10102166.
8. Bytyci I, Nistri S, Morner S, Henein MY. Alcohol Septal Ablation versus Septal Myectomy Treatment of Obstructive Hypertrophic Cardiomyopathy: A Systematic Review and Meta-Analysis. J Clin Med. 2020;9(10)):3062. doi: 10.3390/jcm9103062.

Original Article

Comparison between the Effects of Hymalaian Salt and Common Salt Intake on Urinary Sodium and Blood Pressure in Hypertensive Individuals

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Abstract

Background: **The Himalayan salt (HS) has become a popular alternative for the traditional table salt (TS) due to its health benefit claims, particularly for individuals with arterial hypertension. However, despite the increase in HS consumption, there is still a lack of clinical evidence to support a recommendation for its consumption by health professionals.**

Objective: **This cross-over study aimed to compare the impact of HS and TS intake on systolic blood pressure (SBP) and diastolic blood pressure (DBP), and urinary sodium concentration in individuals with arterial hypertension.**

Methods: **This study recruited 17 female patients with arterial hypertension who ate out no more than once a week. Participants were randomized into two groups, to receive and consume either HS or TS. Before and after each intervention, participants had their blood pressure measured and urine collected for mineral analysis. A p-value < 0.05 was considered statistically significant.**

Results: **There were no statistically significant differences before and after the HS intervention for DBP (70mmHg vs. 68.5mmHg; p=0.977), SBP (118.5 mmHg vs. 117.5 mmHg; p= 0.932) and sodium urinary concentration (151 mEq/24h vs. 159 mEq/24; p=0.875). Moreover, the between-group analysis showed no significant differences after the intervention regarding SBP (117mmHg vs 119 mmHg; p=0.908), DBP (68.5 mmHg vs. 71mmHg; p= 0,645) or sodium urinary concentration (159 mEq/24h vs. 155 mEq/24h; p=0.734).**

Conclusion: **This study suggests that there are no significant differences on the impact of HS consumption compared to TS on blood pressure and sodium urinary concentration in individuals with arterial hypertension.**

Keywords: **Blood Pressure; Hypertension; Cardiovascular Diseases; Risk Factors; Sodium Chloride; Sodium Chloride,Dietary; Urinalysis.**

Introduction

Hypertension (HTN) is one of the main risk factors for cardiovascular disease (CVD), and affects more than 35% of the Brazilian population over 40 years old.[1] It is well established that treating HTN may reduce the risk of cardiovascular events; therefore, this is considered to be one of the primary public health strategies for tackling CVDs.

Sodium intake is a key modifiable risk factors for HTN. [2] Studies show that high sodium intake is associated with higher blood pressure, while a low or moderate intake can have the opposite effect.[2–4] The World Health Organization (WHO) currently recommends a sodium intake of 2 g per day;[5] yet, in many countries salt consumption is actually more than double.[6] In Brazil, for instance, the average sodium consumption is 4.7 grams per day, mostly from table salt (TS) and seasonings (74.4%). [7]

Within this context, the Himalayan salt (HS) has become a popular alternative for the traditional TS, particularly for hypertensive individuals. Social media has become part of the public health scene and has been used to access, share, and spread medical information, being responsible for recent changes in health behavior.[8] In this context of excessive media consumption, boosted by the increase of food advertisements by social media, many health benefits have been attributed to the HS, without robust scientific evidence, contributing to the HS hype.

Those who advocate for the consumption of HS to control HTN base themselves on the beneficial effects of its unrefined characteristic. The rationale is that, unlike traditional salt, HS would retain a higher concentration of minerals such as iron,

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magnesium, calcium, zinc, and potassium, which are inversely associated with blood pressure values.[9–11]

Despite the increase in HS consumption and its health claims, there is still a lack of scientific evidence to support clinical recommendations by health professionals. Therefore, this study aimed to compare the impact of HS and TS consumption on blood pressure, and calcium, sodium, and potassium urine concentrations in individuals with arterial hypertension.

Methods

Study design

This was a randomized crossover trial that compared the effects of HS and TS intake on urinary sodium values and blood pressure of hypertensive individuals. Women with HTN aged between 40 and 65 years old were recruited for this study from a multidisciplinary care clinic for HTN. Inclusion criteria included: residing in the metropolitan region of a Brazilian city, with no changes in antihypertensive medication for at least 60 days.

The calculations were made based on previous data on the effects of reductions in sodium intake on blood pressure.[3] Sample size was calculated for comparison of means, considering an effect size of 1.56,[3] an alpha of 0.05 and test power (1-β) of 90%, and the result was 10 participants in each group.

Patients with heart failure, stroke in the last six months, acute myocardium infarction in the previous three months, uncontrolled diabetes (glycated hemoglobin above 8%), liver disease, hypothyroidism, chronic kidney disease, unstable psychiatric disorders, illicit drug users, and alcoholics were excluded, as were those who had their meals prepared with a salt different from the one provided by this study more than once per week.

This study was approved by the Research Ethics Committee of General Hospital of a Brazilian University (069428/2017) and all patients signed an informed consent form. The study was conducted under the Federal Resolution 446/2012.[12]

Before and after each intervention (HS and TS), participants attended two visits, with a 3 or 4 day-interval between them, conducted by the same researcher. Before the commencement of the intervention, biochemical tests were requested for participants who did not have recent tests recorded, and anthropometric measures (weight, height, and waist circumference) and demographic characteristics of all participants included in the study were collected. At their first visit, participants were randomly assigned to use either HS or TS (Figure 1). After four weeks of intervention and an additional two-weeks of washout, participants were crossed over to the alternative salt for another four weeks of intervention. During the washout period, participants were instructed to maintain their usual diet and consume the salt they were used to.

Additionally, before and after each intervention, a blood pressure device and a urine container were provided to each participant to perform blood pressure measurements and to collect a 24-hour urine sample, respectively. After three to four days, participants returned to the research center with the blood pressure device and the urine collected.

Salt Composition

We analyzed nine HS samples and three TS obtained from food markets in a metropolitan region in Brazil, to verify iodization and minerals' concentration. All samples of both salts were iodine fortified.

The HS brand whose sodium content was the closest to the mean of all HS samples was chosen for the intervention (intervention HS: 371.92 mg of sodium/g, 1.8 mg of potassium/g, 1.7 of magnesium/g, and 25.1 mcg of iodine/g), and the TS brand chosen was the most popular and commonly consumed by the Brazilian population (Intervention TS: 435.93 mg of sodium/g, 0.37 mg of potassium/g, 1.42 of magnesium/g and 150 mcg of iodine/g).

Food composition

Dietary intake was evaluated using a three-day food record applied during both intervention phases, to analyze the consumption of minerals that could affect blood pressure, such as calcium, magnesium, potassium, and sodium. Data were analyzed using the Dietbox™ software, based on IBGE[13] and Tucunduva food composition tables,[14] the latter being used only in the absence of a specific food in the IBGE tables.[13]

Urine analysis

Each participant received a 2.0-L urine jug and was instructed, orally and in writing, to collect a 24-hour urine sample. The first urine voided in the morning was discarded, and all other urine samples throughout the day were collected until and including the first urine void of the following morning, approximately at the same time of the first urine of the previous day. Urine was analyzed at the laboratory of the Federal University of Goias using the ion-selective membrane technique.[15]

Blood Pressure Analysis

Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP) measurements were obtained using a semi-automatic digital device (OMRON 705 CPINT, Illinois, USA) following the 7th Brazilian Guideline of Arterial Hypertension.[1] All patients undertook Home Blood Pressure Monitoring (HBPM), following the IV Brazilian Guidelines for HBPM.[16] Participants were instructed to perform 24 measurements, three in the morning and three in the afternoon for four days. Tests were considered valid if at least 15 effective measures were performed during the period.

Salt dispensing

Participants received one to two kilograms (depending on monthly average family consumption) of HS or TS, according to their allocation group. After the washout period, participants received the same amount of the other salt.

Participants were instructed to use only the salt provided during the intervention and to return the remaining salt back to the research center after the intervention period, for estimation of the mean consumption per person.

Statistical analysis

Statistical analyses were performed using the SPSS statistical program for Windows version 20. Normality of data distribution

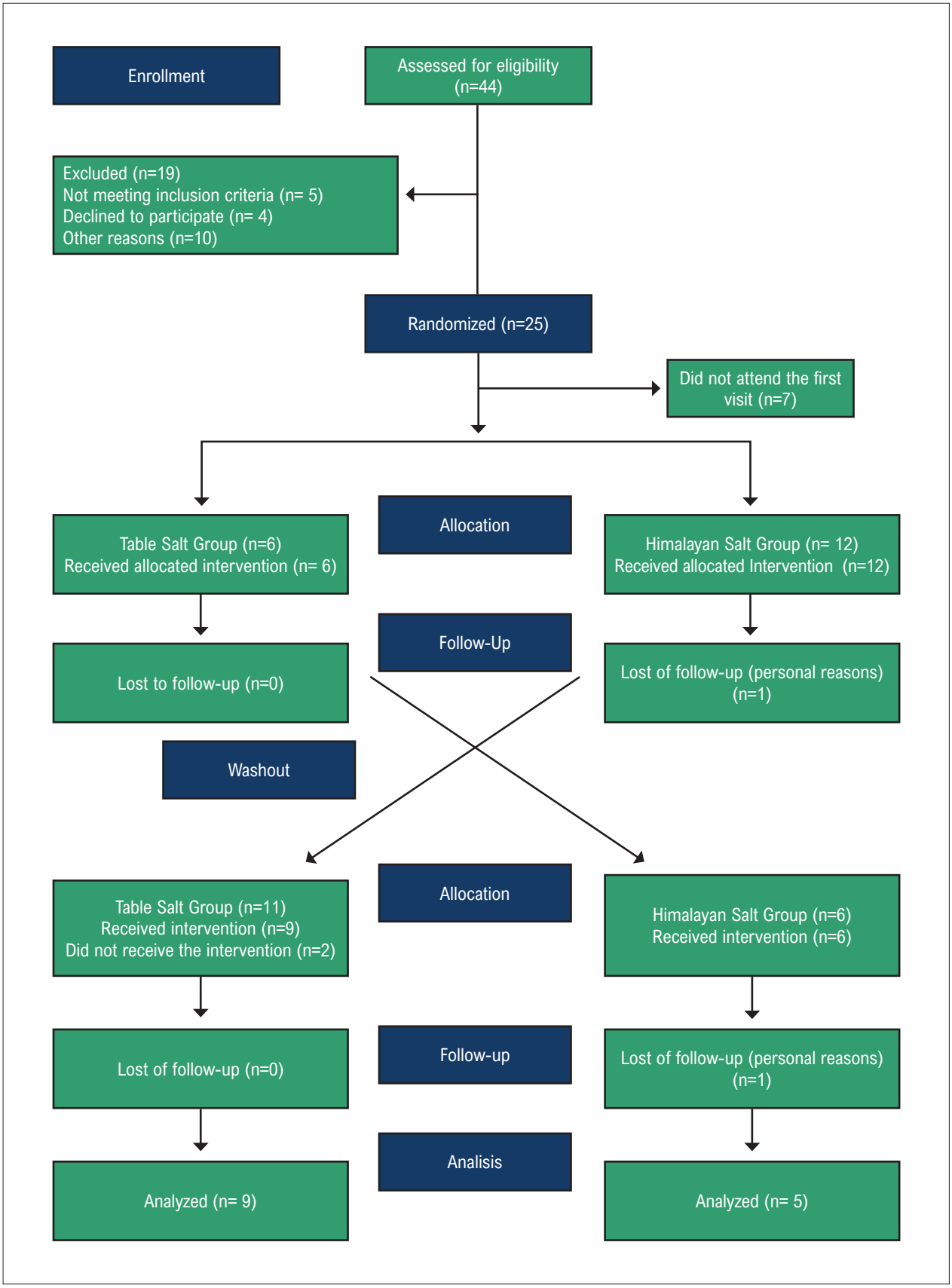

Figure 1 – *Flow diagram of patients' randomization.*

was tested using the Kolmogorov-Smirnov test, which showed that the data were not normally distributed. Differences between baseline and post intervention in each group were determined using the Wilcoxon test for the nonparametric variables. Analysis between groups was performed using the Mann-Whitney test for nonparametric variables. Sodium intake was also divided by total nutrient density and differences in intake between groups were analyzed using the Mann-Whitney test. Descriptive statistics were used for all variables; continuous variables were presented as median and interquartile range, and categorial variables as frequency and percentage.

The difference between groups was tested by intention to treat (ITT) and per protocol (PP) analysis, and since there were no differences between the two analyses, only PP analysis is shown in this study. A p-value < 0.05 was considered statistically significant.

Results

Of 44 eligible patients, 25 agreed to participate; seven of them did not attend the first visit, thus 18 participants entered the study. Due to personal reasons, two participants withdrew before the start of the study, and 17 participants completed at least one of the two intervention arms. Of the 17 participants analyzed, 14 participants underwent both intervention arms, one only the TS intervention and 2 only HS intervention, due to personal reasons (Figure. 1). We analyzed 14 participants since there were no difference between ITT and PP analysis.

Anthropometric measurements and demographic characteristics are described in Table 1.

The median of salt intake per person during HS and TS intervention was 6.37 grams and 5.98 grams, respectively, with no significant difference (p=0.808). Median duration of the intervention was 35 days in both groups.

Blood pressure values and urine mineral concentrations after both interventions were not significantly different compared with pre-intervention (Tables 2 and 3).

The analysis of food records showed no significant difference in sodium (total amount p=0.222 or nutrient density, p=0.195), calcium, magnesium and potassium intake between TS and HS interventions (Table 4). Moreover, the intergroup analysis showed no significant differences in blood pressure and mineral concentration between HS and TS before and after intervention (Figures 2 and 3).

Discussion

To our knowledge, this is the first study to investigate the effects of HS consumption on human blood pressure and urine mineral concentrations. The results suggested no significant differences within or between groups before and after interventions.

In our study, after both interventions, there was no change on blood pressure values. The HS given to participants had 64.01 mg less sodium per gram of salt than the TS provided. Considering the average salt consumption in each group, mean sodium intake from HS and TS was 2268 mg and 2506 mg per day, respectively. Therefore, the average difference in sodium intake was 238 mg daily, a minor reduction that may explain the lack of significance. Drake et al.[17] also analyzed the composition of Himalayan and table salt and did not find significant difference in sodium concentration (3.68×10^5 and 3.81×10^5 ppm, respectively).[17]

Barros et al.[18] found significant differences in blood pressure values after the replacement of traditional salt with light salt. However, light salt has 260 mg less sodium per gram of salt, hence resulting in a greater reduction in sodium intake as compared to the HS.[18] In contrast, Arantes et al.[19] analyzed the effect of salt intake reduction (6g-4g) on blood pressure and urinary sodium concentration in hypertensive individuals. Their results were in line with ours; reductions of salt intake were not associated with significant changes in blood pressure.[19]

According to the WHO[5] and He et al.,[20] there is a decrease in SBP and DBP after a reduction in salt intake from the amount usually consumed by the population, 11 grams daily, to the recommended value, 5 to 6 grams daily.[5,20] The estimated sodium intake using the 24-hour urine collection method sample was 3.47g after HS and 3.65g after TS intervention. Therefore, regardless of the type of salt used, consumption was higher than the recommended by OMS.[5] Although the study design did not allow us to follow each participant to guarantee the correct use of the salt, the average amount of salt used per person could not explain the sodium concentration observed in the urine. We hypothesize that the excess sodium intake may be due to the consumption of ultra-processed foods that were not accounted in this analysis. Arantes et al.[19] also suggest that the lack of control over the consumption of processed foods and out-of-home meals probably interferes on urinary sodium excretion and blood pressure results.[19]

Moreover, the increased sodium intake observed may be related to the characteristics of the sample, i.e., individuals with HTN, who may prefer and consume more salt than normotensive population.[21]

Despite the higher content of potassium in HS, the HS intervention group did not show higher urinary potassium concentrations or significant decrease in blood pressure. This result corroborates the study of Barros et al.,[16] which demonstrated no influence of the light salt potassium content on blood pressure reduction amongst people with arterial hypertension. One possible reason for this controversy could be that the recommendation of potassium intake to improve blood pressure is 4700 mg, a value higher than the one found in the HS.[22] Therefore, potassium intake should be encouraged by food sources such as vegetables and fruits.

In addition to the observed lack of significant differences in clinical parameters between TS and HS consumption, it is important to note that HS costs up to 30 times more than TS.

This study has some limitations such as the small sample size and the impossibility to control participants' food intake during the study. Moreover, individual salt intake may have been overestimated or underestimated by the method used. In addition, the variability in individual sensitivity to sodium was not measured and therefore could be a limitation. Nevertheless, our findings highlight the need of evidence-

Table 1 – Anthropometric characteristics of study participants (n=17)

Baseline characteristics		N=17
Age (years)		58 (54; 60.5)
BMI (kg/m²)		29.20 (27.55;35.33)
Waist circumference (cm)		98 (93.50;104.75)
Average number of people eating at home		3 (2;3.37)
Smoking	Yes	1(5.9%)
	No	16 (94.1%)
Race	Black	4 (23,53%)
	White	7 (41,18%)
	Mixed race	6 (35.29%)
Alcoholism	No	17 (100%)
Education Level		
Elementary School		3 (17.6%)
Middle School	Complete	2 (11.8%)
	Incomplete	1 (5.9%)
High School	Complete	5 (29.4%)
	Incomplete	2 (11.8%)
Technical Degree		4 (23.5%)
Family income		
None		1(5.9%)
≤ US$473		9 (52.9%)
US$473 - US$945		6 (35.3%)
> US$945		1 (5.9%)
Regular physical activity	Yes	11 (64.7%)
	No	6 (35.3%)

BMI: Body mass index.

Table 2 – Blood pressure values and sodium, potassium and calcium urine concentrations before and after the Himalayan salt intervention (n=15)

	Before	After	p[1]
SBD (mmHg)	118.5 (111.0,130.5)	117.5 (114.0,133.5)	0.932
DBP (mmHg)	70 (65.0,76.0)	68.5 (66.0,79.0)	0.977
Sodium (mEq/L)	151.5 (111.00,194.75)	159 (134.00, 192.00)	0.875
Potassium(mEq/L)	57.5 (43.50,70.75)	55 (40.00,74.50)	0.362
Calcium(mEq/L)	107.5 (73.75,175.25)	96 (57.47,145.50)	0.423

Values are shown as median (25th,75th). 1Wilcoxon test for non-parametric measures; HS: Himalayan Salt; SBD: systolic blood pressure; DBP: diastolic blood pressure.

Table 3 – Blood pressure values and sodium, potassium and calcium urine concentrations before and after the table salt intervention (n=16)

	Before	After	p[1]
SBD (mmHg)	121 (111,133.00)	118 (109,141)	0.463
DBP (mmHg)	74 (70.00, 78.00)	70 (67.00, 81.00)	0.329
Sodium(mEq/L)	158 (92.00,191.00)	151 (116.00,195.00)	0.345
Potassium(mEq/L)	54 (48.00, 65.00)	48 (37.00,64.00)	0.173
Calcium(mEq/L)	113.90 (65.70, 188.10)	84.20 (72.00, 118.50)	0.433

Values are shown as median (25^{th},75^{th}). [1] Wilcoxon test for non-parametric measures; HS: Himalayan salt TS: table salt; SBD: systolic blood pressure; DBP: diastolic blood pressure.

Table 4 – Comparison of median intake of sodium, potassium, magnesium and calcium of participants undergoing the Himalayan salt and the table salt intervention (n=14)

	Himalayan salt	Table salt	p[1]
Na (mg)	1054.07 (727.71,1607.69)	848.3 (567.52, 1390.33)	0.222
K (mg)	1652.2 (1340.41,1848.70)	1639.87 (1318.44, 2367.36)	0.485
Ca (mg)	329.11 (247.03,466.73)	363.93 (245.30, 522.66)	0.474
Mg (mg)	151.71 (125.22,178.07)	158.61 (119.00,187.52)	0.643

Values are shown as median (25th,75th). [1]Mann- Whitney Test; Na: sodium; K: potassium; Ca: calcium; Mg: magnesium.

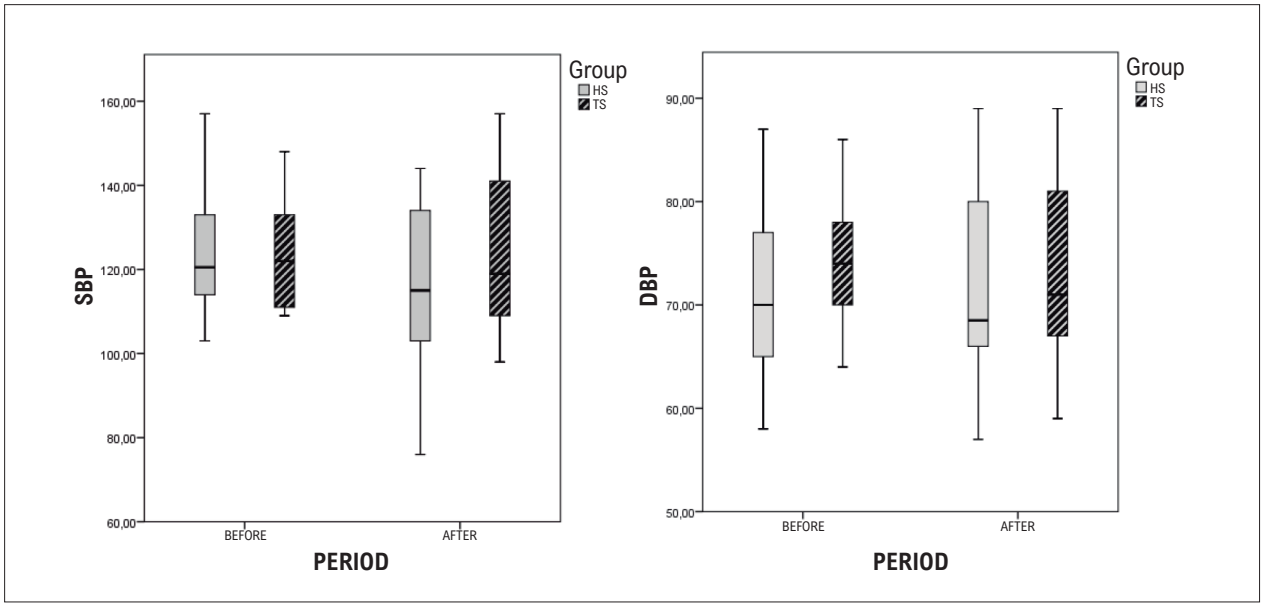

Figure 2 – *Comparison of systolic blood pressure (SBP) and diastolic blood pressure (DBP) values between pre-and post-interventions (Himalayan salt [HS] and the table salt [TS] interventions)[1] (n=14)*

based practices by health professionals, as not all claimed benefits on labels have been scientifically proven. Further studies are required to confirm our findings.

Conclusion

There were no significant differences between pre- and post-interventions or between HS and TS groups in blood pressure and urinary sodium excretion. Therefore, the replacement of TS with HS was shown to be an ineffective measure to improve blood pressure parameters. Lifestyle modifications, such as reduction in salt intake along with regular exercise, remain the best strategy in arterial hypertension control. There is a clear need for more randomized controlled studies, especially with a larger sample size, to investigate the impact of HS consumption on health.

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Author Contributions

Conception and design of the research: Loyola IP, Sousa MF, Jardim PCBV; Acquisition of data: Loyola IP; Analysis and interpretation of the data and Critical revision of the manuscript for intellectual content: Loyola IP, Sousa MF, Jardim TV, Mendes MM, Jardim PCBV; Statistical analysis: Loyola IP, Sousa MF, Jardim TV, Mendes MM; Obtaining financing: Loyola IP, Jardim PCBV; Writing of the manuscript: Loyola IP, Jardim TV, Mendes MM, Jardim PCBV.

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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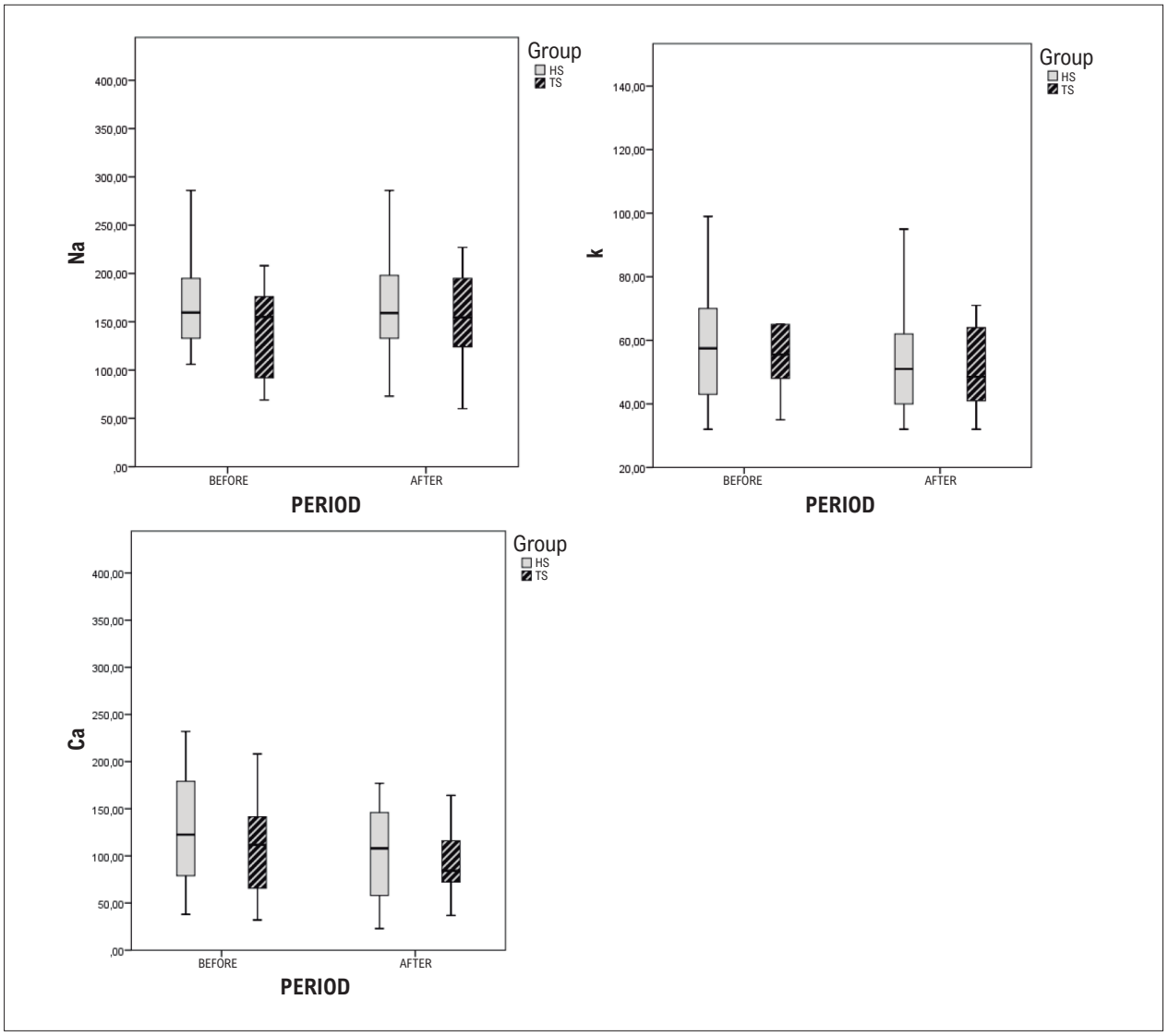

Figure 3 - *Comparison of urinary sodium (Na), calcium (Ca) and potassium (K) values between Himalayan salt (HS) and table salt (TS) groups before and after intervention (n=14); Mann- Whitney Test.*

References

1. Malachias M, Souza W, Plavnik F, Rodrigues C, Brandão A, Neves M, et al. 7ª Diretriz Brasileira de Hipertensão Arterial (SBC, SBH, SBN, 2016). Arq Bras Cardiol. 2016;107(3):1–103.
2. Sacks F, Svetkey L, Vollmer W, Appel L, Bray G, Harsha D, et al. Effects On Blood Pressure Of Reduced Dietary Sodium And The Dietary Approaches To Stop Hypertension (DASH) diet. J cardiopulm Rehab. 2001;21(3):176.
3. Pimenta E, Gaddam KK, Oparil S, Aban I, Husain S, Dell'Italia LJ, et al. Effects of dietary sodium reduction on blood pressure in subjects with resistant hypertension: Results from a randomized trial. Hypertension. 2009;54(3):475–81.
4. Graudal N, Hubeck-Graudal T, Jurgens G. Effects of low sodium diet versus high sodium diet on blood pressure , renin , aldosterone , catecholamines , cholesterol , and triglyceride (Review) Summsry revire for main comparison. Cochrane Database of Systematic Review. 2017;(4):1–25.
5. World Health Organization.WHO. Guideline : Sodium intake for adults and children. World Health Organization (WHO), Geneva; 2012.
6. Poirier P, Ph D, Wielgosz A, Ph D, Morrison H, Ph D, et al. Association of Urinary Sodium and Potassium Excretion with Blood Pressure. N Engl J Med. 2014;371(7):601–11.
7. Instituto Brasileiro de Geografia e Estatistica (IBGE) Pesquisa de Orçamento Familiar 2008-2009. Rio de Janeiro; 2011.
8. Centola D. Social Media and the Science of Health Behavior. Circulation. 2013;127(21):2136-44.
9. Aburto NJ, Hanson S, Gutierrez H, Hooper L, Elliott P, Cappuccio FP. Effect of increased potassium intake on cardiovascular risk factors and disease: Systematic review and meta-analyses. BMJ (Online). 2013;346(7903):1–19.
10. Kolte D, Vijayaraghavan K, Khera S, Sica DA, Frishman WH. Role of Magnesium in Cardiovascular Diseases. Cardiol Rev. 2014;22(4):182–92.

11. Livingstone KM, Lovegrove JA, Cockcroft JR, Elwood PC, Janet E, Givens DI, et al. Evidence from the Caerphilly Prospective Study. Hypertension. 2013; 61:42-7.

12. Brasil.Ministério da Saúde, Conselho Nacional de Saúde. Resolução nº 466, de 12 de dezembro de 2012, que trata sobre as diretrizes e normas regulamentadoras de pesquisas envolvendo seres humanos. Diário Oficial da União [Internet]. 2012 [cited 2016 Nov 21];12:59. Available from: http://conselho.saude.gov.br/resolucoes/2012/Reso466.pdf

13. Instituto Brasileiro de Geografia e Estatística (IBGE). Pesquisa de orçamentos familiares 2008-2009 : tabelas de composição nutricional dos alimentos consumidos no Brasil / Rio de Janeiro; 2011.

14. Philippi ST. Tabela de composição de alimentos: suporte para decisão nutricional. 6a ed. Barueri (SP);Manole; 2017.

15. Oesch U, Ammann D, Simon W. Ion-Selective Membrane Electrodesfor Clinical Use. Clin Chem.1986;1459(8):1448–59.

16. Sociedade Brasileira de Cardiologia V diretrizes de monitorização ambulatorial da pressão arterial (mapa) e III diretrizes de monitorização residencial da pressão arterial (mrpa). Arq Bras Cardiol. 2011;97(3):1-23.

17. Drake SL, Drake MA. Comparison of salty taste and time intensity of sea and land salts from around the world. J Sensory Stud. 2011;26(1):25–34.

18. de Almeida Barros CL, Sousa ALL, Chinem BM, Rodrigues RB, Jardim TSV, Carneiro SB, et al. Impacto da substituição de sal comum por sal light sobre a pressão arterial de pacientes hipertensos. Arq Bras Cardiol. 2014;104(2):128–35.

19. Arantes AC, Ana Luiza Lima Sousa PV de OV, Jardim PCBV, Jardim T de SV, Rezende JM, Lelis E de S, et al. Effects of added salt reduction on central and peripheral blood pressure. Arq Bras Cardiol. 2020;114(3):554–61.

20. He F, Li J, Macgregor G. Effect of longer term modest salt reduction on blood pressure : Cochrane systematic review and meta-analysis of randomised trials. BMJ (Online). 2013;1325(April):1–15.

21. Villela PTM, De-Oliveira EB, Villela PTM, Bonardi JM, Moriguti JC, Ferriolli E, et al. A Preferência ao Sal está Relacionada à Hipertensão e não ao Envelhecimento. Arq Bras Cardiol. 2019;113(3):392-9.

22. World Health Organization. WHO. Guideline: Potassium intake for adults and children. Geneva; 2012.

Himalayan Salt and Table Salt Intake among Hypertensive Individuals

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Short Editorial related to the article: Comparison between the Effects of Hymalaian Salt and Common Salt Intake on Urinary Sodium and Blood Pressure in Hypertensive Individuals

With the involvement of approximately 30% of the Brazilian population, arterial hypertension is listed as one of the main causes of cardiovascular disease.[1] The current WHO recommendation for sodium intake is < 2g/person/day, or 5g salt/person/day. However, it is already known that the salt intake pattern of the Brazilian population reaches up to 12g/day. Although the increase in blood pressure has a multifactorial etiology, excessive sodium intake is among the main causes.[2,3]

This element has important physiological functions such as regulation of extracellular volume, nerve conduction and muscle function.[4] There is little disagreement in the literature about the benefits of reducing sodium intake for the hypertensive population. A strategy widely addressed by social media and in print was the adoption of Himalayan Salt for being rich in iron, zinc, calcium, magnesium and potassium and its supposed benefits over table salt in pressure control on hypertensive patients.[4-9] In this context, Loyola IP et al.[10] evaluated the impact of table salt and Himalayan salt intake on blood pressure parameters and urinary sodium concentration in hypertensive individuals.[10]

In this publication, the authors performed a randomized, crossover study in which women aged between 40 and 65 years were recruited. The sample was then divided into 2 groups: Himalayan salt and table salt. The intervention period was 4 weeks for each type of treatment, and after 2 weeks of washout, there was an alternation of salt type for another 4 weeks. Salt samples were evaluated and fortified with iodine, and guidance was given on diet and the use of types of salt.[10]

In the end, 18 women were considered eligible for the study. The median duration of the intervention was 35 days, and the mean salt intake was 6.37g and 5.98g of Himalayan salt and table salt, respectively. Despite the lack of statistical difference between the groups regarding blood pressure parameters and urinary sodium concentration, this work magnifies the importance of controlled and randomized clinical trials on the subject. The commercialization and use of Himalayan salt have gained a lot of media attention, especially for its supposed antihypertensive effects, and this work scientifically strengthens the orientation on the intake of this element by the hyper and normotensive population. It is important to emphasize the fundamental role of lifestyle changes and regular physical activity as treatment strategies for arterial hypertension.

Keywords

Hypertension; Sodium Chloride, Dietary; Risk Factors; Salt Intake; Urinalysis/methods; Life Style; Physical Activity

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References

1. Malachias M, Souza W, Plavnik F, Rodrigues C, Brandão A, Neves M, et al. 7a Diretriz Brasileira de Hipertensão Arterial (SBC, SBH, SBN, 2016). Arq Bras Cardiol. 2016;107(3):1–103. doi: 10.5935/abc.20160151.
2. World Health Organization (WHO). Guideline sodium intake for adults and children. (approved by the Guidelines Review Committee). Geneva; 2012.
3. Arantes AC, Souza ALL, Vitorino PVO, Jardim PCBC, Jardim TSV, Rezende JM, et al. Efeito da redução de sal de adição sobre a pressão arterial central e periférica. Arq Bras Cardiol. 2020;114(3):554-61. doi: 10.36660/abc.20180426.
4. Moore-Fayet F, Wibisono C, Carr P, Duve E, Petocz P, Lancaster G, et al. An analysis of the mineral composition of Pink Salt available in Australia. Foods.2020; 9(10):1-15. doi: 10.36660/abc.20180426
5. Centola D. Social Media and the Science of Health Behavior. Circulation. 2013;127(21):2136-44. doi: 10.1161/CIRCULATIONAHA.112.101816.
6. Aburto NJ, Hanson S, Gutierrez H, Hooper L, Elliott P, Cappuccio FP. Effect of increased potassium intake on cardiovascular risk factors and disease: Systematic review and meta-analyses. BMJ. 2013;346:f1378. doi: 10.1136/bmj.f1378. doi: 10.1136/bmj.f1378.
7. Kolte D, Vijayaraghavan K, Khera S, Sica DA, Frishman WH. Role of Magnesium in Cardiovascular Diseases. Cardiol Rev. 2014;22(4):182–92.
8. Livingstone KM, Lovegrove JA, Cockcroft JR, Elwood PC, Janet E, Givens DI, et al. Evidence from the Caerphilly Prospective Study. Hypertension. 2013;61(1):42-7. doi: 10.1161/HYPERTENSIONAHA.111.00026.
9. Poirier P, Ph D, Wielgosz A, Ph D, Morrison H, Ph D, et al. Association of urinary sodium and potassium excretion with blood pressure. N Engl J Med. 2014;371(7):601–11. doi: 10.1056/NEJMoa1311989.
10. Loyola IP, Sousa MF, Jardim TV, Mendes MM, Kunz W, Barroso S, et al. Comparação entre os efeitos da ingestão de sal do Himalaia e de sal comum sobre os valores de sódio urinário e pressão arterial em indivíduos hipertensos. Arq Bras Cardiol. 2022; Feb 7;S0066-782X2022005001217. doi: 10.36660/abc.20210069.

Schistosomiasis & Heart - On Behalf of the Neglected Tropical Diseases and other Infectious Diseases affecting the Heart (the NET-Heart Project)

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Abstract

Background: Schistosomiasis is a Neglected Tropical Disease which may lead to cardiovascular (CV) complications. However, the CV involvement in schistosomiasis has yet to be fully elucidated due to the limited number of cases and lack of reliable evidence, as schistosomiasis typically occurs in locations without adequate infrastructure for robust data collection.

Objective: This systematic review aims to assess cardiovascular implications of schistosomiasis, including in the diagnosis and treatment, and propose an algorithm for screening of CV manifestations.

Methods: A systematic review was performed in the MEDLINE/PubMed and LILACS databases of articles on the CV involvement in schistosomiasis.

Results: Thirty-three records were considered for this review: six review articles, one systematic review, one clinical trial, 14 observational studies, seven case reports, and four cases series. CV involvement includes a wide spectrum of clinical conditions, such as myocardial ischemia, ventricular dysfunction, myocarditis, pulmonary arterial hypertension, and pericarditis.

Conclusions: Cardiac complications of schistosomiasis may cause long-term disability and death. Clinical monitoring, physical examination, early electrocardiogram, and echocardiogram should be considered as key measures to detect CV involvement. Due to the lack of effective treatment of complications, sanitation and education in endemic areas are necessary for the elimination of this global health problem.

Keywords: Schistosomiasis; Cardiovascular Diseases; Tropical Medicine.

Introduction

Schistosomiasis is a Neglected Tropical Disease (NTD) caused by blood flukes, which are trematode worms of the genus *Schistosoma*. It is endemic to rural regions with weak health infrastructure and limited access to potable water or water sanitation methods. Accordingly, schistosomiasis was added to the World Health Organization´s (WHO) 2008-2015 Global Plan to Combat NTD.[1]

According to the WHO, approximately 240 million people are affected by schistosomiasis globally, with more than 90% of cases occurring in Africa.[1] Schistosomiasis is transmitted through penetration of Schistosoma cercariae, which are found in fresh water, into the skin. Once the larvae penetrate the skin, they invade the venous system and spread to organs such as the heart, lungs, liver, and intestines. *Schistosoma mansoni* is the main specie that infects humans and may lead to potentially life-threatening cardiovascular (CV) events. In published case reports, myocarditis, pericarditis, and myocardial ischemia have been documented in the acute phase of the disease.[2,3] These CV outcomes are poorly understood due to a limited number of cases and lack of reporting.[4] Patients with acute CV complications may also be asymptomatic at presentation, contributing to deficiencies in data collection. The most relevant CV complication of schistosomiasis is pulmonary arterial hypertension (PAH).[5-7] Signs and symptoms of patients with schistosomiasis-associated PAH do not differ from those documented from other etiologies.

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Schistosomiasis is estimated to be the main cause of PAH in endemic countries. Despite this, diagnosis is limited to regions with access to adequate medical equipment, and there are currently no specific medications for PAH associated with schistosomiasis. The most used pharmacologic agent is praziquantel (PZQ), which presumably prevents further progression of the disease by reversing vascular remodeling.

This systematic review is part of the "NET-Heart Project" (Neglected Tropical Diseases and Other Infectious Diseases Affecting the Heart), an initiative of the "Emerging Leaders" section of the Interamerican Society of Cardiology (IASC).[8-10] The purpose of this study was to expand the knowledge on the impact of NTD on CV health. The aim of this review was to provide an overview of the CV involvement in schistosomiasis and to propose an algorithm for diagnosis.

Methods

A systematic review of the literature was conducted following the design of the NET-Heart Project.[8,11] MEDLINE/PubMed and LILACS were searched using any association of schistosomiasis with CV involvement, with no date restrictions. Only human studies, available in English were used. Papers were excluded if the full text was not available. The keywords used according to the MESH terminology were: "schistosomiasis", "heart", "cardiac", "pericardium", "pericarditis", and "cardiovascular disease". Articles were screened by two independent investigators (ELPM and LGGB). Interobserver agreement, assessed by Kappa statistics, was 0.93. Discrepancies were solved by consensus. An additional search was manually conducted from the reference lists of the selected articles.

The search yielded 110 articles, of which 33 articles were included in this systematic review: six review articles, one systematic review, one clinical trial, 14 observational studies, seven case reports, and four cases series (Figure 1). Table 1 (supplementary material) summarizes the studies considered for this review.

Results

Epidemiology

Schistosomiasis is a chronic parasitic disease caused by blood flukes of the genus Schistosoma. Among those infected with schistosomes, approximately 120 million are symptomatic and 20 million have severe forms of the disease including the hepatosplenic and urinary forms.[12]

Schistosomiasis is considered endemic to South America, the Caribbean, Southeast Asia, and Africa (Figure 2). Africa is the most affected area, with more than 90% of the 41,000 deaths and 1.7 million disability-adjusted life years attributed to this disease annually. Moreover, the growth of international tourism to endemic countries has resulted in increasing number of infections in travelers. In terms of CV involvement, schistosomiasis is one of the most common causes of PAH worldwide, accounting for 30.8% of all cases of PAH in endemic areas.[13]

Pathophysiology and Cardiovascular Involvement

There are five major *Schistosoma* species which infect humans. *S. mansoni*, *S. haematobium,* and *S. japonicum* cause most human infections.[13] The *life cycle of Schistosoma* is shown in Figure 3.

PAH due to schistosomiasis is particularly associated with the hepatosplenic form of *S. mansoni* infection.[14] Schistosomiasis eggs may bypass the liver through portosystemic collateral vessels and be deposited into the lungs. The eggs cause T-helper type-2 cell-predominant immune response resulting in granuloma formation. It has been demonstrated that interleukins (IL-4 and IL-3) stimulate the release of transforming growth factor-β leading to remodeling and angiomatous and plexiform lesions.[13] Alternatively, species whose eggs are in vesical plexus can reach the lungs directly.[15-17]

The pathophysiology of schistosomiasis-associated PAH can be summarized as the following: mechanical obstruction of the pulmonary circulation by worm eggs; inflammation leading to endothelial cell dysfunction; and portal hypertension due to liver periportal fibrosis leading to pulmonary overflow and then endothelial cell dysfunction.[5]

Acute schistosomiasis, known as Katayama fever, may have CV effects, causing myocarditis, asymptomatic myocardial ischemia, and pericarditis.[2,18] The species identified to have cardiac involvement in the acute phase are *S. haematobium*, *S. mansoni,* and *S. japonjicum*. Myocarditis and pericarditis during acute schistosomiasis may be related to an allergic response induced by Schistosoma, where eosinophils play an essential role.[19-21] The mechanism of myocardial ischemia as a consequence of schistosomiasis has not been described, and is rarely reported.[2,3] It may occur secondary to compression of the left main coronary artery due to pulmonary artery dilatation. Severe dilatation of the pulmonary artery can also result in rupture, causing cardiac tamponade.[17]

Symptoms

PAH induced by schistosomiasis may be asymptomatic. However, in later stages of the disease, patients can present symptoms of right heart failure such as shortness of breath, bilateral edema in the lower extremities, and tachycardia. Signs and symptoms of PAH in schistosomiasis are described in Table 1.

Symptoms are non-specific, and mainly associated to right ventricular dysfunction. At onset, patients may report that their symptoms are exercise-induced. As the disease progresses, patients may develop advanced right heart failure with symptoms of systemic venous congestion.[17,22] A hoarse voice has been noted, which is caused by compression of the recurrent laryngeal nerve. Angina has been reported in cases that have progressed to myocardial ischemia.[17] Other clinical signs of schistosomiasis-associated PAH include hepatomegaly, ascites, peripheral edema, and elevated jugular venous pressure.[17]

In acute schistosomiasis involving the heart, patients with myocarditis may exhibit chest pain. These patients may be asymptomatic, with diagnosis made based on laboratory tests. Also, there is a report of a patient who had delayed myocardial perfusion of the septum with subendocardial enhancement two months after the acute phase, without clinical signs of ischemia.[2]

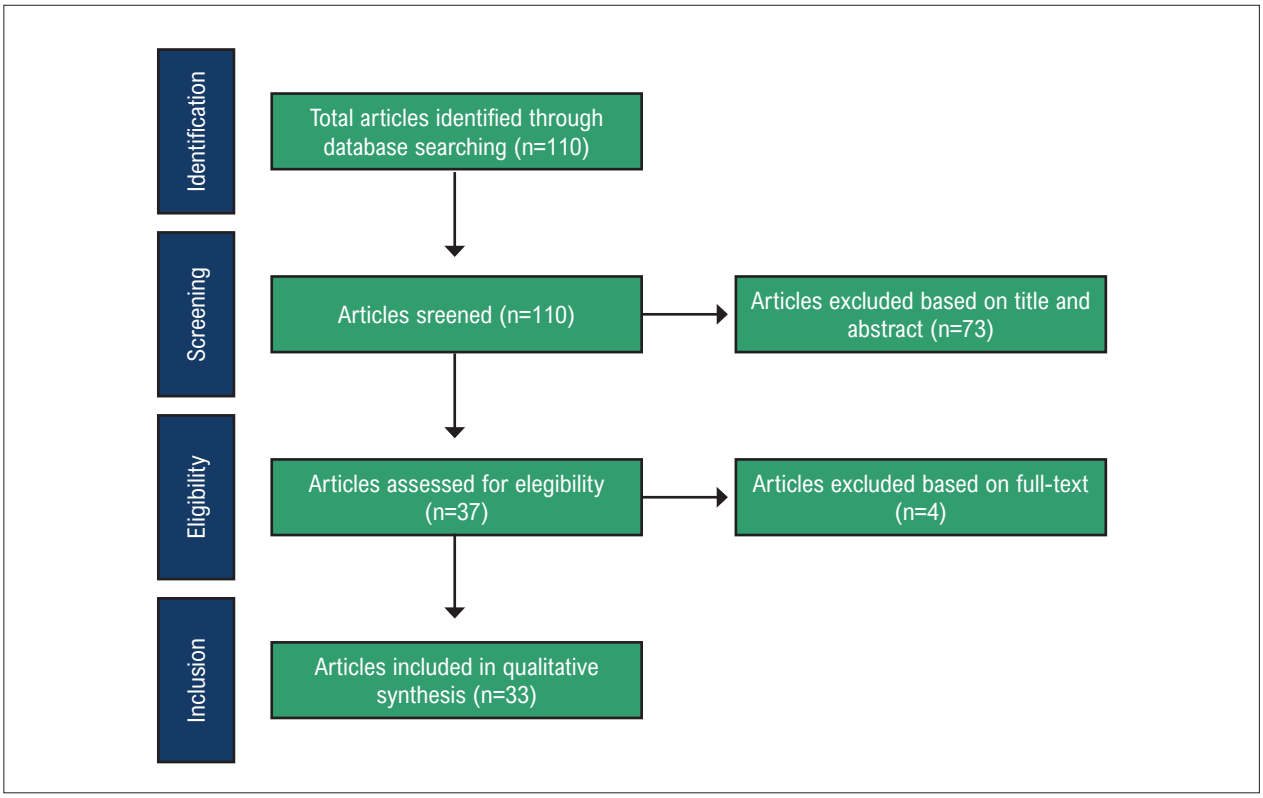

Figure 1 – *Flowchart of PRISMA Methodology.*

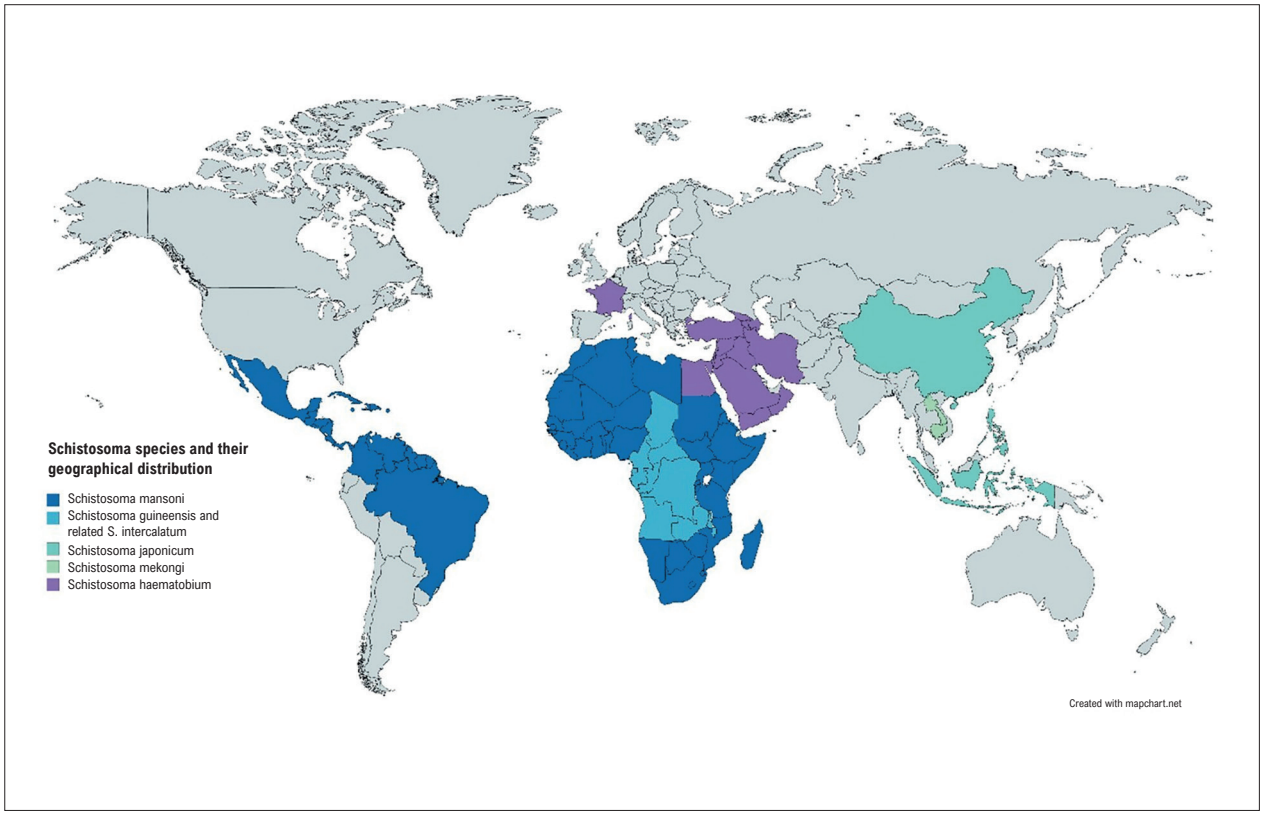

Figure 2 – *Geographical distribution of Schistosoma species; image adapted from World Health Organization*[1]

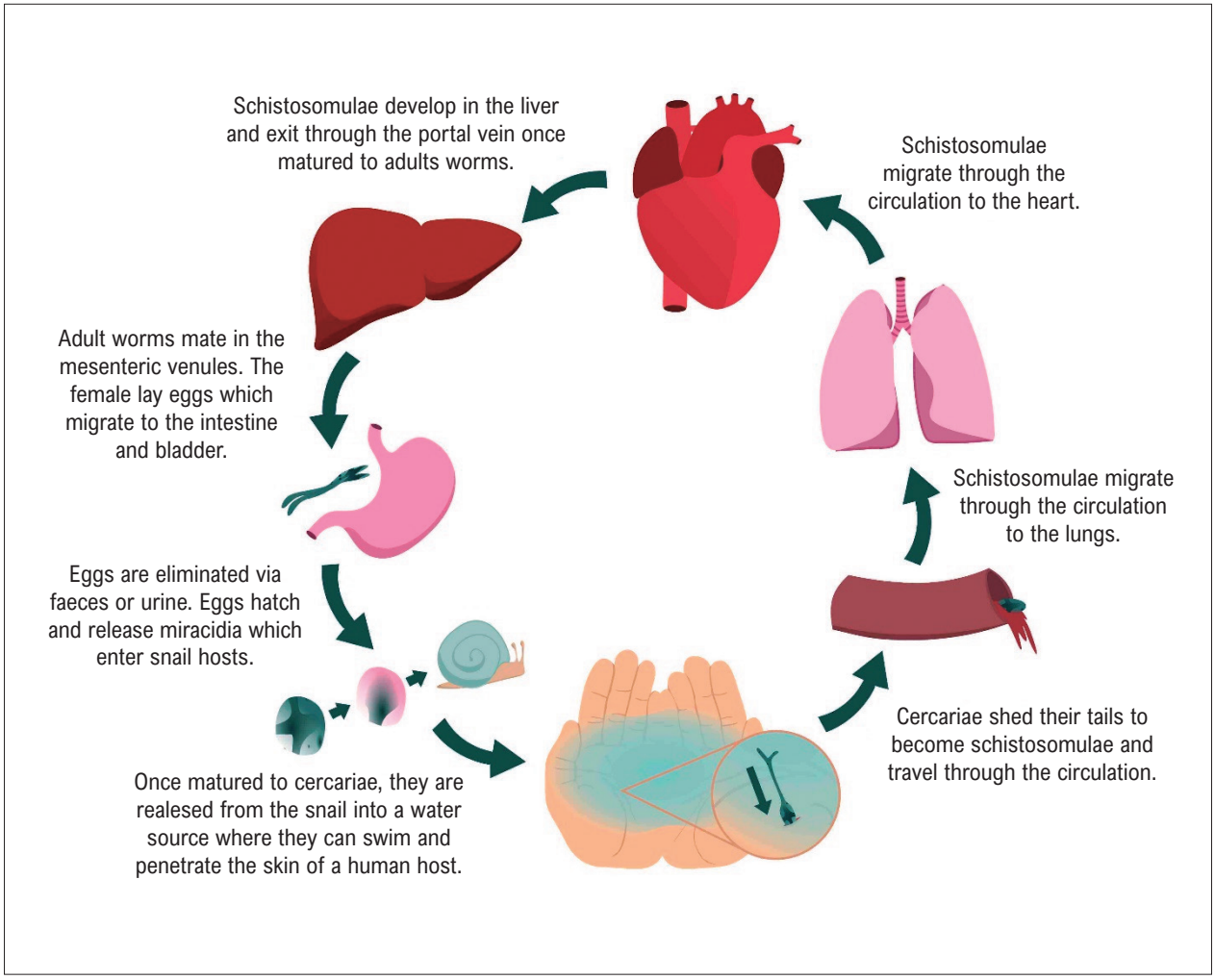

Figure 3 – *Life cycle of Schistosoma.*

Table 1 – Symptoms and signs of schistosomiasis-associated pulmonary arterial hypertension

Symptoms	Signs
Pulmonary Arterial Hypertension	
Shortness of breath	Hoarseness
Weakness	Hemoptysis
Angina	Left parasternal lift
Syncope	Accentuated pulmonary component of the second heart sound
Cough	Right ventricular third heart sound
Nausea and vomiting	Parasternal systolic murmur of tricuspid regurgitation
	Diastolic murmur of pulmonary regurgitation
Right Heart Failure	
Dyspnea	Jugular plethora
Abdominal pain	Ascites
Limb edema	Hepatomegaly
Fatigue	Peripheral edema

Data adapted from Galie et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS). Eur Heart J. 2016;37(1):67-119.

Diagnostic Tests

The diagnosis of schistosomiasis requires an accurate and guided anamnesis, physical examination, laboratory tests, and imaging studies. In endemic areas, schistosomiasis must be highly suspected in patients with manifestations of PAH. In non-endemic countries, a recent trip to endemic areas should be considered if CV symptoms occur.

The identification of the parasite is an important part of diagnosis; however, the microscopic examination of eggs in urine (*S. haematobium*) or faeces (*S. japonicum, S. Mansoni*) is not always possible if the parasite is in the prepatent period.[23] Additionally, available serological tests are limited, as they do not discriminate between active infection and past exposure.[12,24] Finally, PCR-based assays have been developed for the detection of Schistosome DNA in feces, sera, and plasma during all phases of the disease.[25]

Regarding cardiac involvement, patients with PAH may show right atrial enlargement, right ventricular hypertrophy, and right bundle branch block on electrocardiogram (ECG).[19,26] Additionally, X-ray typically shows prominent left and right pulmonary arteries. The echocardiogram is a key tool in the evaluation of these patients.[27]

In acute schistosomiasis, the echocardiogram helps to identify myocarditis, pericarditis, or myocardial ischemia.[2,28,29] In patients with PAH, it may reveal right ventricular enlargement with septal bowing, tricuspid regurgitation, hypertrophy of the right ventricular free wall, and an increased right ventricular pressure. In addition, the echocardiogram allows to evaluate different parameters of the right ventricular function, such tricuspid annular plane systolic excursion or fractional area change. There is no pathognomonic sign of schistosomiasis-induced PAH, so the differential diagnosis should include all other causes of pulmonary hypertension.[5]

In patients with acute myocarditis, the ECG show mainly repolarization abnormalities.[30] In a study with 1,500 American soldiers who contracted acute schistosomiasis during World War II, the anomalies of T-waves (99%) and ST segments (52%) were the most common abnormalities. However, these changes were attributed to the side-effects of anti-schistosomiasis drugs used at that moment. ECG changes including widespread ST elevation and PR depression has been demonstrated in the acute phase of up to 60% of cases.[31,32]

The echocardiogram is the first line image method for the evaluation of the cardiac function. In patients with myocarditis, it could show systolic dysfunction of the left ventricle with high filling pressures.[33] Pericardial effusion can be present in up to 60% cases with pericarditis and wall motion abnormalities at rest may be present in myocardial ischemia.[31,34] Cardiac magnetic resonance (CMR) is the gold standard for the evaluation of ventricular function and volume, and allows a unique tissue characterization; therefore, CMR should be consider as an useful tool in patients with myocardial injury or pericardium involvement.[35]

A diagnostic algorithm for early detection of cardiovascular involvement as a complication of schistosomiasis can be seen in Figure 4.

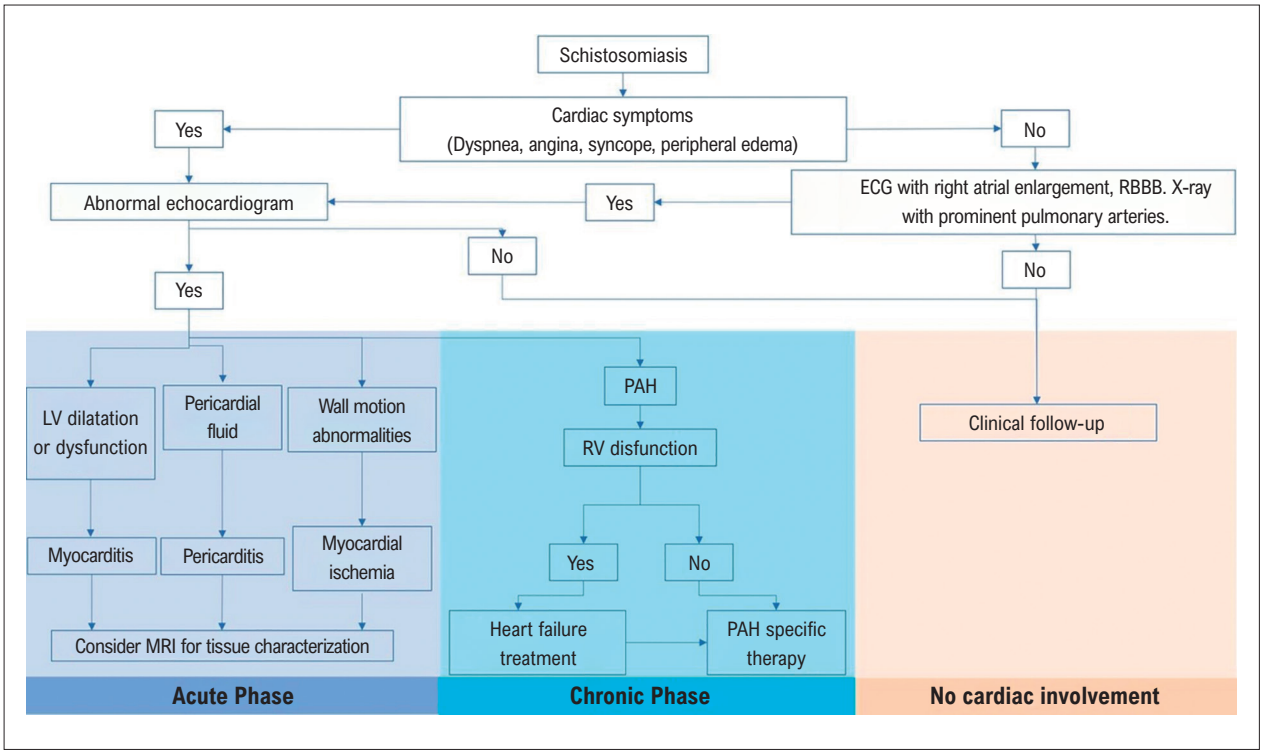

Figure 4 – *Diagnostic algorithm proposed for diagnosis of cardiac involvement in Schistosomiasis; LV: left ventricular; MRI: magnetic resonance imaging; ECG: electrocardiogram; RBBB: right bundle branch block; PAH: pulmonary arterial hypertension; RV: right ventricular.*

Treatment

Table 2 describes the principal agents used in the management of schistosomiasis. The drug of choice for schistosomiasis is PZQ, a derivative of pyrazinoisoquinoline, with good efficacy against all species of human pathogenic schistosomes and a cure rate of 80%.[36] The main drawback is that PZQ cannot be used for chemoprophylaxis as it is only effective against mature worms.[17,37] It should be noted that when prescribed during the acute phase of the disease, PZQ generally does not prevent the advancement to chronic phase. It is also associated with exacerbation of signs and symptoms in approximately 50% of cases, by inducing a type of allergic response to parasitic destruction. In some cases, this exacerbation of symptoms can be life-threatening causing encephalitis, myocarditis, and pulmonary events secondary to vasculitis.[17,38]

The mainstay treatment during the acute phase of the disease is based on corticosteroids, which attenuate the cardiac toxicity of eosinophils, immune complexes, hypersensitivity reactions to parasite toxins, and surface antigens. If myocarditis is suspected, the use of PZQ should be postponed until cardiac recovery and management will vary according to patient's clinical and hemodynamic data.[17] In two cases of myocarditis secondary to schistosomiasis, angiotensin-converting enzyme (ACE) inhibitors and beta-blockers were effective for cardiac recovery.[2] In patients whose condition deteriorates despite optimal medical management, mechanical circulatory support, ventricular assist devices, or extracorporeal membrane oxygenation as a bridge to transplantation or recovery may be required. Similarly, in cases of pericardial disease, treatment should consist of steroidal therapy to suppress inflammation secondary to the infection.[3]

Antischistosomal chemotherapy has cure rates ranging from 40 to 80% and is especially dependent on the specific chemotherapeutic agent, species of parasite, and nutritional status of the host.[17,39]

Data on the efficacy of PAH treatment in schistosomiasis are scarce. Experimental studies showed that antischistosomal therapy reduces pulmonary vascular remodeling and, consequently, pulmonary hypertension. However, it may not be beneficial in chronic pulmonary hypertension, where studies suggest that pulmonary remodeling and PAH may persist even after complete deworming and disappearance of the eggs.[5]

In a small cohort of 12 patients with PAH secondary to schistosomiasis, improvements in functional class, cardiac output, and distance in the six-minute walk test were demonstrated using phosphodiesterase-5 inhibitors or endothelin receptor 1 antagonists.[40] On the other hand, surgical management of oesophageal varices, like the transjugular intrahepatic portosystemic shunt, can increase the load on the right ventricle, increasing the risk of more shunting of eggs from the portal system.[5]

Despite the similarities with idiopathic PAH, studies support that patients with PAH secondary to schistosomiasis have a less severe hemodynamic profile and significantly better survival rates.[41-43]

Discussion

Schistosomiasis is one of the most prevalent NTD, that disproportionately impacts marginalized individuals in endemic regions. Increased prevalence has been partially attributed to increase in tourism and visits to the affected regions. Schistosomiasis is a global public health issue, that requires improved detection and management.

Table 2 – Treatment for schistosomiasis

Specific treatment of Schistosomiasis			
Drug	**Dose**	**Special considerations**	**Phase of the disease**
Corticosteroids* (prednisone)	Adult: 1.5-2.0 mg/kg per day by mouth for 3 weeks. Pediatric: 0.05-2.0 mg/kg per day, three doses a day by mouth	Decreases plasma levels of PZQ by 50%. Ruling out bacterial infection and strongyloidiaisis	Use within the first two months after contact with water.
Praziquantel	*S haematobium*, *S mansoni*, 40 mg/kg per day, one or two doses a day by mouth; *S japonicum*, 60 mg/kg per day, two or three doses a day by mouth.	Requires an effective host-specific response against the schistosome. Caution when performing tasks that require alertness on the first two days of treatment	Throughout the course of the disease
Oxamniquine	*S mansoni* only, 20 mg/kg per day, for two to three days by mouth.	It is effective against schistosomula and prevents the chronic phase	Early phase of the disease
Artemether	*S haematobium, S mansoni, S japonicum*, prophylaxis: 6 mg/kg every 2-4 weeks by mouth.	It is effective against invasive cercariae, mature schistosomula, and mature adult worms	It can be used as a chemoprophylactic in endemic areas for people at high risk of infection
Treatment of Schistosomiasis-associated pulmonary arterial hypertension			
Phosphodiesterase-5 inhibitors		Sildenafil, tadalafil, vardenafil	
Endothelin receptor 1 antagonists		Ambrisentan, bosentan, macitentan	

** Associated treatment to avoid or treat acute complications.*

CV involvement of schistosomiasis depends on the phase of the disease. It has been reported that in acute schistosomiasis, patient may present myocarditis, pericarditis, or silent myocardial ischemia accompanying a classic hypersensitivity reaction. PAH is the most relevant complication of chronic schistosomiasis and, interestingly, the histopathological findings reported in the pulmonary vasculature in schistosomiasis-related PAH are similar to idiopathic PAH. However, a recent meta-analysis showed significantly better hemodynamic profile and five-year survival rates in schistosomiasis-related PAH patients compared to idiopathic PAH.[41,43]

There is a considerable gap in terms of diagnosis and treatment of schistosomiasis as there is no gold standard test.[12,24] History of living in or having traveled to an endemic area should trigger a clinical suspicion.

In the acute scenario, diagnosing cardiac involvement is a challenge due to its heterogenous presentation. Myocarditis can be present without chest pain and only with unspecific repolarization abnormalities in the ECG and high troponin levels. Similarly, pericarditis and myocardial ischemia may be completely asymptomatic and detected only by abnormal ECG findings. In the diagnostic algorithm, echocardiogram is suggested as a key tool in the course of these patients. CMR is proposed as a complementary tool as it provides tissue characterization and is accurate for quantification of ventricular function (Figure 4). However, CMR maybe not available in endemic areas where the health resources are limited.

In all patients with PAH, background exposure should be investigated, and microscopic examination of eggs in urine and feces, serological test, or PCR assay should be performed to establish the diagnosis of patients at risk for schistosomiasis.[44] An echocardiogram is essential for diagnosis and follow-up in these patients.

Treatment is dependent on CV involvement and disease phase of the patient. Cardiac involvement in acute disease should be treated with corticosteroids to attenuate inflammatory response. The use of cardiac medications, such as ACE inhibitors and beta blockers is empiric. There is a lack of scientific evidence guiding definitive treatment of these patients. In PAH, there is no specific treatment for schistosomiasis; currently the options are limited to medications for idiopathic PAH.

Conclusions

CV complications of schistosomiasis predominantly impacts those with limited access to healthcare. Treatment is variable, and depends on CV involvement, species of Schistosoma, and disease phase. The most effective way of reducing the global impact of the disease is by prevention, focusing on identifying groups at risk, and improving access to drinking and sanitation in endemic areas.

Author Contributions

Conception and design of the research and Critical revision of the manuscript for intellectual content: Posada-Martínez EL, Gonzalez-Barrera LG, Liblik K, Gomez-Mesa JE, Saldarriaga C, Farina JM, Parodi J, Zhou Z, Martinez-Selles M, Baranchuk A; Acquisition of data and Writing of the manuscript: Posada-Martínez EL, Gonzalez-Barrera LG, Baranchuk A; Analysis and interpretation of the data: Posada-Martínez EL, Gonzalez-Barrera LG, Gomez-Mesa JE, Saldarriaga C, Farina JM, Parodi J, Zhou Z, Martinez-Selles M, Baranchuk A.

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

References

1. World Health Organization. [Internet]. Geneva: World Health Organization; 2021 [cited 2021 Jul 20]. Available from: https://www.who.int/features/factfiles/schistosomiasis/en/.
2. Epelboin L, Jauréguiberry S, Estève JB, Danis M, Komajda M, Bricaire F, et al. Myocarditis During Acute Schistosomiasis in Two Travelers. Am J Trop Med Hyg. 2010;82(3):365-7. doi: 10.4269/ajtmh.2010.09-0084.
3. Jesus AR, Silva A, Santana LB, Magalhães A, Jesus AA, Almeida RP, et al. Clinical and Immunologic Evaluation of 31 Patients with Acute Schistosomiasis Mansoni. J Infect Dis. 2002;185(1):98-105. doi: 10.1086/324668.
4. van der Horst R. Schistosomiasis of the Pericardium. Trans R Soc Trop Med Hyg. 1979;73(2):243-4. doi: 10.1016/0035-9203(79)90227-x.
5. Gavilanes F, Fernandes CJ, Souza R. Pulmonary Arterial Hypertension in Schistosomiasis. Curr Opin Pulm Med. 2016;22(5):408-14. doi: 10.1097/MCP.0000000000000300.
6. Ferreira RC, Domingues AL, Bandeira AP, Markman Filho B, Albuqerque Filho ES, Araújo ACC, et al. Prevalence of Pulmonary Hypertension in Patients with Schistosomal Liver Fibrosis. Ann Trop Med Parasitol. 2009;103(2):129-43. doi: 10.1179/136485909X398168.
7. Wünschmann D, Ribas E. Chronic cor pulmonale due to granulomatous and obliterating pulmonary arteritis caused by schistosomiasis. Zentralbl Allg Pathol. 1989;135(3):241-7.
8. Burgos LM, Farina J, Liendro MC, Saldarriaga C, Liprandi AS, Wyss F, et al. Neglected Tropical Diseases and Other Infectious Diseases Affecting the Heart. The NET-Heart Project: Rationale and Design. Glob Heart. 2020;15(1):60. doi: 10.5334/gh.867.
9. Ortiz HIA, Farina JM, Saldarriaga C, Mendoza I, Liprandi AS, Wyss F, et al. Human African Trypanosomiasis & Heart. Expert Rev Cardiovasc Ther. 2020;18(12):859-65. doi: 10.1080/14779072.2020.1828066.

10. Zhou Z, Lopez HIAO, Pérez GE, Burgos LM, Farina JM, Saldarriaga C, et al. Toxoplasmosis and the Heart. Curr Probl Cardiol. 2021;46(3):100741. doi: 10.1016/j.cpcardiol.2020.100741.

11. Scatularo CE, Ballesteros OA, Saldarriaga C, Mendoza I, Wyss F, Liprandi AS, et al. Zika & Heart: A Systematic Review. Trends Cardiovasc Med. 2020:1050-1738(20)30147. doi: 10.1016/j.tcm.2020.11.003.

12. Colley DG, Bustinduy AL, Secor WE, King CH. Human Schistosomiasis. Lancet. 2014;383(9936):2253-64. doi: 10.1016/S0140-6736(13)61949-2.

13. Nunes MC, Guimarães MH Jr, Diamantino AC, Gelape CL, Ferrari TC. Cardiac Manifestations of Parasitic Diseases. Heart. 2017;103(9):651-8. doi: 10.1136/heartjnl-2016-309870.

14. Andrade ZA, Andrade SG, Susin M. Pathological Changes Due to Massive Schistosomal Infection in Man (A Case Presentation). Rev Inst Med Trop Sao Paulo. 1974;16(3):171-7.

15. Franco-Paredes C, Rouphael N, Méndez J, Folch E, Rodríguez-Morales AJ, Santos JI, et al. Cardiac Manifestations of Parasitic Infections Part 3: Pericardial and Miscellaneous Cardiopulmonary Manifestations. Clin Cardiol. 2007;30(6):277-80. doi: 10.1002/clc.20092.

16. Lapa M, Dias B, Jardim C, Fernandes CJ, Dourado PM, Figueiredo M, et al. Cardiopulmonary Manifestations of Hepatosplenic Schistosomiasis. Circulation. 2009;119(11):1518-23. doi: 10.1161/CIRCULATIONAHA.108.803221.

17. Galiè N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, et al. 2015 ESC/ERS Guidelines for the Diagnosis and Treatment of Pulmonary Hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Heart J. 2016;37(1):67-119. doi: 10.1093/eurheartj/ehv317.

18. Badr MH, Abdel-Aziz O. Assessment of Left Ventricular Function in Schistosomiasis. Egypt J Bilharz. 1976;3(1):79-88.

19. Nyman R, von Sinner W, Mygind T, Kagevi I. Paraesophageal Varices Presenting as a Retrocardiac Mediastinal Mass. A Case Report. Acta Radiol. 1994;35(3):255-7.

20. Omer HO, Wahab SMA. Secondary Amyloidosis Due to Schistosoma Mansoni Infection. Br Med J. 1976;1(6006):375-7. doi: 10.1136/bmj.1.6006.375.

21. Sarazin M, Caumes E, Cohen A, Amarenco P. Multiple Microembolic Borderzone Brain Infarctions and Endomyocardial Fibrosis in Idiopathic Hypereosinophilic Syndrome and in Schistosoma Mansoni Infestation. J Neurol Neurosurg Psychiatry. 2004;75(2):305-7.

22. Butrous G. Schistosome Infection and its Effect on Pulmonary Circulation. Glob Cardiol Sci Pract. 2019;2019(1):5. doi: 10.21542/gcsp.2019.5.

23. Gelfand M, Alves W, Woods RW. The Frequency of Schistosomal Ovideposition in the Heart. Trans R Soc Trop Med Hyg. 1959;53(3):282-4. doi: 10.1016/0035-9203(59)90009-4.

24. Gray DJ, Ross AG, Li YS, McManus DP. Diagnosis and Management of Schistosomiasis. BMJ. 2011;342:2651. doi: 10.1136/bmj.d2651.

25. Oliveira LM, Santos HL, Gonçalves MM, Barreto MG, Peralta JM. Evaluation of Polymerase Chain Reaction as an Additional Tool for the Diagnosis of Low-Intensity Schistosoma Mansoni Infection. Diagn Microbiol Infect Dis. 2010;68(4):416-21. doi: 10.1016/j.diagmicrobio.2010.07.016.

26. Badawi H, Nomeir AM. Electrocardiograms of right ventricular hypertrophy in bilharzial cor pulmonale. Br Heart J. 1965;27(3):355-64. doi: 10.1136/hrt.27.3.355.

27. Mocumbi AO, Gonçalves C, Damasceno A, Carrilho C. Active Schistosomiasis, Severe Hypereosinophilia and Rapid Progression of Chronic Endomyocardial Fibrosis. Cardiovasc J Afr. 2016;27(5):4-6. doi: 10.5830/CVJA-2016-030.

28. Lorbeau BM, Petit G. The Electrocardiogram During Bilharziosis Caused by Schistosoma Mansoni. Arch Mal Coeur Vaiss. 1978;71(1):95-103.

29. Kamo E, Iijima T, Iuchi M, Ishizaki T. The Influence on the Heart by Schistosomiasis Japonica. Electrocardiographic Analysis in an Endemic area in Yamanashi Prefecture. Jpn Circ J. 1970;34(8):673-8. doi: 10.1253/jcj.34.673.

30. Waye JD, Donoso E, Spingarn CL, Edelman MH. Cardiotoxic Effects of Antimony Dimercaptosuccinate in Schistosomiasis with Special Reference to Coexistent Hepatic Dysfunction. Am J Cardiol. 1962;10:829-35. doi: 10.1016/0002-9149(62)90178-9.

31. Adler Y, Charron P, Imazio M, Badano L, Barón-Esquivias G, Bogaert J, et al. 2015 ESC Guidelines for the Diagnosis and Management of Pericardial Diseases: The Task Force for the Diagnosis and Management of Pericardial Diseases of the European Society of Cardiology (ESC)Endorsed by: The European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J. 2015;36(42):2921-64. doi: 10.1093/eurheartj/ehv318.

32. Sapire DW, Silverman NH. Myocardial Involvement in Antimonial Therapy: A Case Report of Acute Antimony Poisoning with Serial ECG Changes. S Afr Med J. 1970;44(33):948-50.

33. Caforio AL, Pankuweit S, Arbustini E, Basso C, Gimeno-Blanes J, Felix SB, et al. Current State of Knowledge on Aetiology, Diagnosis, Management, and Therapy of Myocarditis: A Position Statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. Eur Heart J. 2013;34(33):2636-48. doi: 10.1093/eurheartj/eht210.

34. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for Cardiac Chamber Quantification by Echocardiography in Adults: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2015;28(1):1-39. doi: 10.1016/j.echo.2014.10.003.

35. Arnold JR, McCann GP. Cardiovascular Magnetic Resonance: Applications and Practical Considerations for the General Cardiologist. Heart. 2020;106(3):174-81. doi: 10.1136/heartjnl-2019-314856.

36. Grandière-Pérez L, Ansart S, Paris L, Faussart A, Jaureguiberry S, Grivois JP, et al. Efficacy of Praziquantel During the Incubation and Invasive Phase of Schistosoma Haematobium Schistosomiasis in 18 Travelers. Am J Trop Med Hyg. 2006;74(5):814-8.

37. Tarr L. Effect of the Antimony Compounds, Fuadin and Tartar Emetic, on the Electrocardiogram of Man; A Study of the Changes Encountered in 141 Patients Treated for Schistosomiasis. Ann Intern Med. 1947;27(6):970-88. doi: 10.7326/0003-4819-27-6-970.

38. Suarez RM, Santiago-Stevenson D, Hernandez-Morales F. Electrocardiographic Changes During Anthiomaline Treatment of Schistosomiasis. Am Heart J. 1948;36(6):923-33. doi: 10.1016/0002-8703(48)90286-5.

39. Coutinho A, Lima CA, Alves C. A Clinical Trial of Ciba 32644-Ba in Patients with S. Mansoni Bilharziasis. Acta Trop Suppl. 1966;9:187-95.

40. Fernandes CJCS, Dias BA, Jardim CVP, Hovnanian A, Hoette S, Morinaga LK, et al. The Role of Target Therapies in Schistosomiasis-Associated Pulmonary Arterial Hypertension. Chest. 2012;141(4):923-8. doi: 10.1378/chest.11-0483.

41. Fernandes CJS, Jardim CV, Hovnanian A, Hoette S, Dias BA, Souza S, et al. Survival in Schistosomiasis-Associated Pulmonary Arterial Hypertension. J Am Coll Cardiol. 2010;56(9):715-20. doi: 10.1016/j.jacc.2010.03.065.

42. Fernandes CJC, Piloto B, Castro M, Oleas FG, Alves JL Jr, Prada LFL, et al. Survival of Patients with Schistosomiasis-Associated Pulmonary Arterial Hypertension in the Modern Management Era. Eur Respir J. 2018;51(6):1800307. doi: 10.1183/13993003.00307-2018.

43. Knafl D, Gerges C, King CH, Humbert M, Bustinduy AL. Schistosomiasis-Associated Pulmonary Arterial Hypertension: A Systematic Review. Eur Respir Rev. 2020;29(155):190089. doi: 10.1183/16000617.0089-2019.

44. Saad MAH, Watany MM. Schistosoma Mansoni and Endocarditis: From Egg to Free DNA Detection in Egyptian Patients and Infected BALB/c Mice. J Helminthol. 2019;93(2):139-48. doi: 10.1017/S0022149X17001183.

*Supplemental Materials

For additional information, please click here.

Diagnostic Performance of Coronary Tomography Angiography and Serial Measurements of Sensitive Cardiac Troponin in Patients With Chest Pain and Intermediate Risk for Cardiovascular Events

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Abstract

Background: Coronary tomography angiography (CTA) has been mainly used for chest pain evaluation in low-risk patients, and few data exist regarding patients at intermediate risk.

Objective: To evaluate the performance of serial measures of sensitive troponin and CTA in intermediate-risk patients.

Methods: A total of 100 patients with chest pain, TIMI risk scores of 3 or 4, and negative troponin were prospectively included. All patients underwent CTA and those with coronary stenosis ≥ 50% were referred to invasive coronary angiography. Patients with coronary lesions <50% were discharged and contacted 30 days later by a telephone call to assess clinical outcomes. Outcomes were hospitalization, death, and myocardial infarction at 30 days. The comparison between methods was performed by Kappa agreement test. The performance of troponin measures and CTA for detecting significant coronary lesions and clinical outcomes was calculated. Results were considered statistically significant when $p < 0.05$.

Results: Coronary stenosis ≥ 50% on CTA was found in 38% of patients and significant coronary lesions on coronary angiography were found in 31 patients. Two clinical events were observed. Kappa agreement analysis showed low agreement between troponin measures and CTA in the detection of significant coronary lesions (kappa = 0.022, p = 0.78). The performance of CTA for detecting significant coronary lesions on coronary angiography or for predicting clinical events at 30 days was better than sensitive troponin measures (accuracy of 91% versus 60%).

Conclusion: CTA performed better than sensitive troponin measures in the detection of significant coronary disease in patients with chest pain and intermediate risk for cardiovascular events.

Keywords: Cardiovascular Diseases; Risk Factors; Risk Management; Chest Pain; Tomography, X-Ray Computed/methods; Troponin T; Troponin I; Angiotomography Coronary/methods.

Introduction

Chest pain is one of the most common complaints in emergency rooms worldwide. Great advances in clinical practice have been achieved with the use of coronary tomography angiography (CTA) and high-sensitivity troponin in the diagnosis of acute coronary syndrome (ACS).[1-4]

Sensitive and high-sensitivity troponin T and I assays have detection thresholds for myocardial injury 10 to 100 times lower than conventional troponins. These assays have better accuracy for the diagnosis of ACS, particularly in patients with short-term chest pain. Most studies evaluating the accuracy of repeated troponin measures in ruling out ACS included patients with low risk for cardiovascular events as assessed by the TIMI (thrombolysis in myocardial infarction), HEART or GRACE risk scores.[5,6]

The anatomic evaluation of the coronary tree using CTA has a special role in the exclusion of ACS in patients at low-to-intermediate risk for coronary artery disease. CTA findings correlated well with invasive coronary angiography in a study that included 230 patients with chest pain. High sensitivity and specificity, and negative predictive values were seen when lesions greater than 50% were found in CTA. In the ROMICAT-II trial, the CTA strategy was as safe as the usual care strategy with respect to major cardiovascular events at 28 days. Therefore, CTA is an accurate non-invasive method for detecting ACS in patients with acute chest pain. However, its validation was mainly done in patients with low-risk profiles.[7] The present study aims to evaluate the performance of sensitive troponin assays and CTA in the detection of significant coronary lesions on coronary angiography and clinical events in patients with chest pain and intermediate risk for cardiovascular events.

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Methods

Study Patients

The study design is presented in Figure 1. We prospectively included a total of 100 patients presenting with chest pain at the Emergency Department of the Heart Institute, InCor, University of Sao Paulo Medical School, Sao Paulo, Brazil. To be included, patients had to be aged between 40 and 75 years old, present with chest pain for at least two hours before arrival and have a TIMI risk score of 3 or 4. Additionally, a new or probable new deviation of ST of at least 0.5 mV and/or T wave inversion of at least 0.2 mV should not be present on the electrocardiogram, and their first measure of sensitive troponin should be < 99 percentile for trial inclusion. Exclusion criteria comprised: pregnancy, hemodynamic instability, serum creatinine > 1.5 mg/dL, intolerance to beta-blockers, allergy to iodine contrast, asthma, thoracic trauma in the previous 30 days, body mass index > 40 kg/m2, previous coronary artery bypass graft surgery, and known coronary lesion $\geq$ 50%. Our Institutional Review Board for human subject studies approved this study, and all participants provided written informed consent prior to enrolment. There is no conflict of interest of any author.

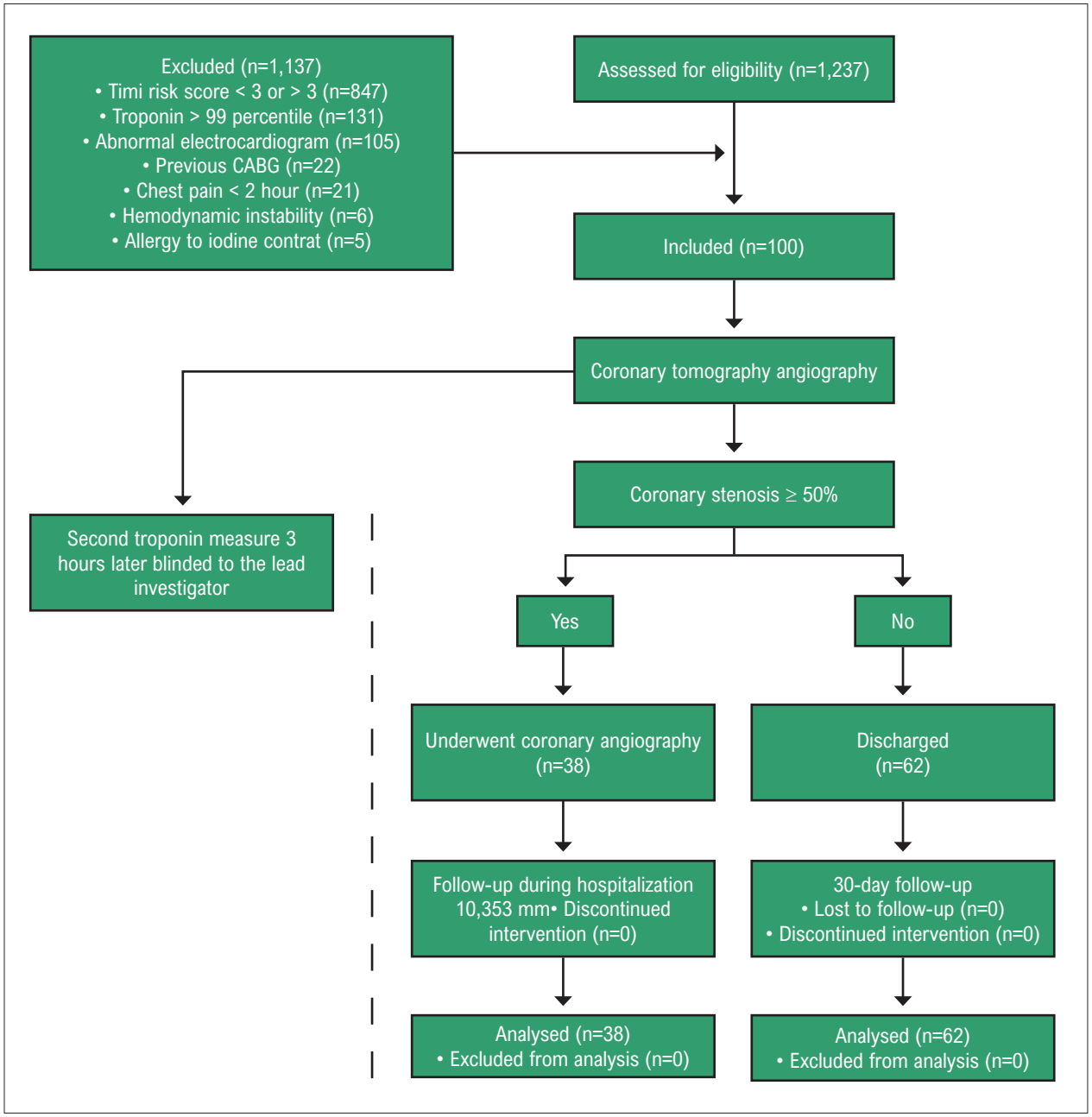

Figure 1 – *Study design and flowchart; CABG: coronary artery bypass grafting.*

Sensitive troponin assay

Blood samples were drawn for sensitive troponin I measurement at two time points: at presentation and three hours later. The investigators were blinded to the second measurement until the end of the study period. Quantitative determination of troponin I was made by a sandwich-type immunoassay performed in three stages that uses direct chemiluminescence technology and constant quantities of two monoclonal antibodies. A reagent was added for detection of non-specific bindings. The commercial kit ADVIA Centaur® TnI-Ultra (Siemens Healthcare Diagnostics, Tarrytown, NY, USA) was used for this in an automated equipment of the same brand. The 99th percentile value was 0.04 ng/ml. Sensitive troponin assays was donated by Siemens Healthcare Diagnostics.

Coronary tomography angiography

After trial inclusion, all patients underwent CTA. CTA images were acquired using a 320 detector-row scanner (Aquilion ONE, Canon Medical Systems, Japan) and a standard scanning protocol. To reach a heart rate lower than 65 bpm during acquisition, patients received oral metoprolol (50-100 mg).

Study outcomes

Two subgroups were studied: a) patients who underwent coronary angiography when CTA showed coronary stenosis ≥ 50%; and b) patients whose CTA showed no lesions or lesions < 50% and were discharged and contacted 30 days later by a telephone call to assess clinical outcomes. Coronary lesions ≥ 70% at coronary angiography were considered significant. Clinical outcomes of interest were hospitalization, death and myocardial infarction.

Statistical analysis

Data were analyzed with the SAS Statview 5.0 software. Descriptive analysis of baseline characteristics was performed using means and standard deviations when a normal distribution of data was assumed, and median and interquartile intervals were used in non-normal distribution. The Kolmogorov-Smirnov test was used to assess the normality of distribution of continuous variables. Comparison of the time from patient arrival to the second troponin test *versus* time from patient arrival to CTA was made using the unpaired T-test.

The comparison between diagnostic methods was performed through Kappa agreement analysis. We compared the agreement between troponin measures and significant coronary lesions on coronary angiography or clinical outcomes. The results were considered statistically significant when $p < 0.05$. We calculated the sensitivity, specificity, positive predictive values, negative predictive values and accuracy of sensitive troponin or CTA in the detection of significant coronary lesions in coronary angiography or clinical events in the whole population (N=100). We also calculated the performance of troponin measures in the detection of significant coronary lesions in the subpopulation who underwent coronary angiography (N=38). Performance was calculated using as positivity a second troponin result above the 99th percentile and the percentage variation of the method in relation to the first measurement, identifying the best cutoff point by the ROC curve. Complementary analysis was made by calculating the area under the ROC curve and the cut-off score of troponin percentage increase and significant coronary lesions determined by coronary angiography and clinical events or by coronary angiography alone.

Based on an alpha error of 0.05 and using a power of 0.8 for primary outcomes, the number of individuals needed for this study was at least 71 according to previous studies, considering the incidence of coronary lesions with stenosis greater than or equal to 50% in patients at intermediate risk (TIMI risk), use of CTA in around 24% of patients,[8] and diagnosis of ACS by the use of sensitive troponin in 11.4% of patients undergoing chest pain protocols.[6] These data were used to evaluate the hypothesis of an existing difference in performance between these methods.

Results

Study population

A total of 100 patients with acute chest pain and TIMI risk scores of 3 or 4 were consecutively included. Clinical characteristics are presented in Table 1. Inclusion and follow-up of patients were performed between April 2016 and March 2019 when the previously estimated sample size was reached. Overall, mean age was 62.9 ± 10.5 years and 58% were female. Most of the study population (81%) had a TIMI risk score of 3. Sensitive troponin variations of 20% were observed in 29 patients. Coronary stenosis ≥ 50% on CTA was found in 38% of patients (≥ 70% in 25 patients), and all of them underwent coronary angiography. Significant coronary lesions at coronary angiography were found in 31 patients.

Clinical Events

All patients were alive at 30 days. In patients discharged without coronary angiography, two new hospitalizations were observed at 30 days. There were no observed deaths or myocardial infarctions in the follow-up.

Agreement analysis in the overall population

Agreement between sensitive troponin and CTA findings

This analysis included all patients of the study (N=100). The kappa agreement test showed a slight agreement between the second measure of positive troponin and CTA in the detection of significant coronary lesions (kappa = 0.022, p = 0.78). The time between patient arrival and the result of the second troponin was 312.08 ± 82.39 minutes versus 256.70 ± 83.91 minutes between patient arrival and CTA (p < 0.0001). The mean time between CTA to discharge was 6,837.10 ± 8,068.17 minutes, and all patients were submitted to coronary angiography in the first 24 hours of admission. Five patients showed a positive troponin result in the second measurement but were discharged as they did not present significant lesions on CTA.

Table 1 – Baseline characteristics of study patients (n=100)

Demographic characteristics	
Age (years)	62.9 (± 10.5)
Male sex	42 (42%)
Comorbidities/risk factors	
Hypertension	87 (87%)
Diabetes	49 (49%)
Dyslipidemia	79 (79%)
Previous stroke/TIA	5 (5%)
Previous acute MI	18 (18%)
Previous PCI	16 (16%)
Smoking (current or previous)	52 (52%)
Family history of CAD	44 (44%)
Clinical presentation	
Systolic blood pressure (mmHg)	144.9 (± 23.7)
Heart rate (bpm)	71.9 (± 13.0)
TIMI risk 3	81 (81%)
TIMI risk 4	19 (19%)
Laboratory results	
Hemoglobin (g/dL)	13.8 (± 1.5)
Creatinine (mg/dL)	0.92 (± 0.3)

CAD: coronary artery disease; MI: myocardial infarction; PCI: percutaneous coronary intervention; SD: standard deviation; TIA: transient ischemic attack; TIMI: thrombolysis in myocardial infarction.

Agreement between sensitive troponin variations and the presence of significant coronary lesions at coronary angiography or the occurrence of clinical events

Using the presence of significant coronary lesions at coronary angiography or the occurrence of clinical events at 30 days as the gold standard, the Kappa agreement test with a positive troponin result in the second measurement showed a slight agreement (kappa = 0.002, p = 0.979). The best cut-off for troponin variation from baseline to the second measure regarding the presence of significant coronary lesions on coronary angiography or the occurrence of clinical events at 30 days was 20%. The area under the ROC curve for the 20% variation in sensitive troponin was 0.508 (CI 95%: 0.386 – 0.629) (Figure 2).

Performance of sensitive troponin measures or coronary lesions ≥ 50% on CTA in the detection of significant coronary lesions on coronary angiography or the occurrence of clinical events

The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of a) a positive troponin result in the second measure; b) troponin variations of 20%; and c) coronary lesions ≥ 50% on CTA for detection of lesions ≥ 70% on coronary angiography or for prediction of clinical events at 30 days are presented in Table 2. The overall performance of CTA for detecting the composed outcome was better than troponin measures.

Agreement analysis in patients who underwent coronary angiography

Agreement between sensitive troponin variations and the presence of significant coronary lesions on coronary angiography

This analysis included only patients who underwent coronary angiography (N=38). Using the presence of significant coronary lesions on coronary angiography as the gold standard, the Kappa agreement test with a positive troponin result in the second measure showed slight agreement (kappa = 0.006, p = 0.922). The best cut-off for troponin variation regarding the presence of significant coronary lesions on coronary angiography was 20%. Area under ROC curve for the 20% variation in sensitive troponin was 0.465 (CI 95%: 0.230 – 0.701) (Figure 2).

Performance of sensitive troponin measures in the detection of significant coronary lesions on coronary angiography

The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of a) a positive troponin result in the second measure, and b) troponin variations of 20% in the detection of lesions ≥ 70% at coronary angiography are presented in Table 3.z Significant coronary lesions were detected by coronary angiography in 81.6% of patients with lesions ≥ 50% on CTA. This proportion was higher than the one for positive troponin in the second measure or its variations. High specificities were found

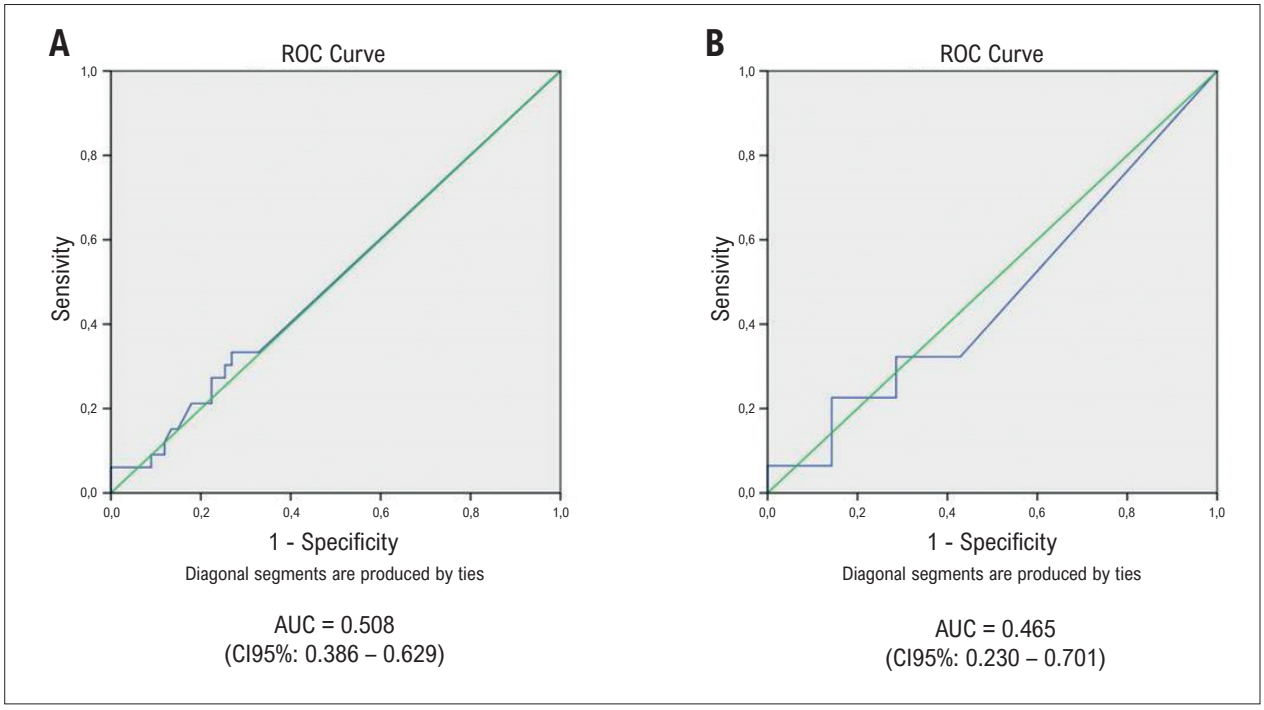

Figure 2 – *ROC curve for 20% variation in sensitive troponin and detection of (A) significant coronary lesions at coronary angiography and the occurrence of clinical events and (B) significant coronary lesions at coronary angiography only. AUC: area under curve; CI: confidence interval*

Table 2 – Performance of the second measure of positive troponin, troponin variation of 20%, and coronary lesions ≥ 50% at computed tomography angiography in detecting lesions ≥ 70% at coronary angiography or to predict clinical events at 30 days

	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Accuracy
Second positive troponin result	12.1%	88.1%%	33.3%	67.0%	63.0%
Troponin variation ≥ 20%	33.3%	73.1%	37.9%	69.0%	60.0%
Coronary lesions ≥ 50% at CTA	93.9%	89.6%	81.6%	96.8%	91.0%

CTA: computed tomography angiography.

Table 3 – Performance of the second positive troponin result or troponin variation of 20% in detecting lesions ≥ 70% on coronary angiography

	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Accuracy
Second measure of positive troponin	12.9%	85.7%%	80%	18.2%	26.3%
Troponin variation ≥ 20%	32.3%	71.4%	83.3%	19.2%	39.5%

for a positive troponin result in the second measure and troponin variations of 20% - 85.7% and 71.4%, respectively.

Discussion

Our study presents the performance of sensitive troponin measures or CTA in the detection of significant coronary lesions on coronary angiography and/or clinical events in patients with chest pain and intermediate risk for cardiovascular events. Sensitive troponin measures agreed poorly with the detection of significant coronary lesions on CTA or coronary angiography and with the occurrence of clinical events. CTA was superior to the measure of serial troponin, with better sensitivity and negative predictive value in the detection of coronary artery disease. In clinical practice, patients with acute chest pain are often discharged from the hospital according to chest pain protocols based only on the serial measurement of troponins. Our findings suggest that intermediate risk patients without ischemic alterations on the electrocardiogram should preferably be stratified at admission by CTA. This strategy may reduce

the chance of erroneous hospital discharge in these situations. We emphasize the fact that the assessment of clinical events becomes secondary in this context due to the sample size, and hence the agreement with the diagnosis of coronary heart disease was the most relevant finding.

It is not uncommon that patients with chest pain are released from emergency rooms after initial evaluation and develop ischemic events in the following hours. These individuals do not receive an adequate treatment at the appropriate time.[3,9] It is estimated that one in eight patients with unstable angina will suffer an acute myocardial infarction (AMI) in the next two weeks. Mortality in patients with AMI admitted or mistakenly released from the emergence departments ranges from 6% to 25%,[3] which leads to lawsuits related to medical malpractice.[4] The incidence of adverse outcomes in patients with TIMI risk score of 3 and 4 can reach up to 11.1%.[10,11] However, studies exploring diagnostic strategies for chest pain evaluation in this specific population are scarce and come mostly from secondary analyses.

In 2006, Morris et al.[8] conducted a study including 1,000 consecutive patients with acute chest pain to explore whether the use of TIMI risk score could help predict combined events at 30 days in this population. The AUC was 0.79 (CI 95%: 0.75 - 0.84), which showed a good applicability of the score. Since then, studies have suggested that patients with intermediate scores (3 and 4) should have troponin measured and a provocative ischemic test performed, when possible.[8,12] Our findings also suggest that it is important to better evaluate the presence of coronary heart disease in this population using a non-invasive test in addition to troponin measures.

Using two serial measurements of sensitive troponin with short time intervals is a good approach to rule out acute coronary syndromes in low-risk patients, which allows the implementation of rapid chest pain assessment protocols.[5,6,13,14-31] A study on patients with suspected ACS showed that a 20% increase in high-sensitivity troponin levels were associated with greater probability of ACS, with an area under the ROC curve of 0.785. Other studies observed that variations in high-sensitivity troponin T over a few hours also had high negative predictive values.[32] However, it is worth noting that the population included in most studies that showed a very high accuracy of ultrasensitive troponin had a low risk. The negative predictive value of a 20% variation in sensitive troponin in our study was 69%, an index below what the literature has shown, which may be justified by the inclusion of patients at intermediate risk.

In ROMICAT study, the use of CTA in addition to the TIMI risk score increased the accuracy for event prediction.[33] The ROMICAT-II study included 1000 patients with chest pain and first negative troponin result, who were randomized to perform CTA or follow the usual chest pain protocol.[34] During the 2-year follow-up including 333 patients, it was observed that CTA had high predictive power with an AUC of 0.61 for combined cardiovascular events. When associated with the TIMI score, the AUC reached 0.84. In this study, only 5.4% of patients had TIMI risk between 3 and 4.[35,36] We believe our findings add to these results as we showed that, in intermediate risk patients, CTA performed better than serial measures of sensitive troponin.

When compared to traditional chest pain protocols, CTA does not alter outcomes such as death or AMI, however it reduces length of hospital stay and the number of unnecessary hospital admissions.[5,7,37-56] Litt et al.[7] showed that the use of CTA, compared with the traditional chest pain evaluation protocol, had an excellent safety profile in low-risk patients, as no death or AMI occurred at 30 days. Additionally, CTA promoted a higher number of hospital discharges (49.6% vs. 22.7%) and shorter hospital stay (18 hours vs. 24.8 hours, $p < 0.001$). The agreement between CTA and cardiac catheterization findings also seems to be strong.[44,45] In ROMICAT-II, hospital stay was 7.6 hours shorter in the CTA group compared to the usual care group. In our study, we also observed that the time interval between patient arrival and CTA was approximately one hour shorter than the time between patient arrival and the result of the second troponin.

Our results should be interpreted in light of some limitations. This was a single center study, with a relatively small sample size, and the number of clinical events was low. Therefore, larger studies should be performed to validate our findings. Intermediate risk patients were rarely represented in previous studies investigating strategies for chest pain evaluation. We believe our findings add to the existing literature and suggest that CTA may have an important role in ruling out acute coronary syndromes in this population.

Conclusions

CTA performed better than sensitive troponin measures in the detection of significant coronary disease in patients with chest pain and intermediate risk for cardiovascular events.

Registration

NCT02772991 – CONECTTIN trial

Author Contributions

Conception and design of the research and Analysis and interpretation of the data: Soeiro AM; Acquisition of data: Soeiro AM, Biselli B, Leal TCAT, Jallad S, Goldstein PG, Nomura CH, Nakamura D; Statistical analysis: Soeiro AM, Bossa AS, Guimarães PO, César MC; Obtaining financing: Soeiro AM, Nomura CH, Nakamura D, Rochitte CE; Writing of the manuscript: Soeiro AM, Bossa AS, Guimarães PO, Rochitte CE; Critical revision of the manuscript for intellectual content: Serrano Jr CV, Soares PR, Oliveira Jr. MT.

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.

References

1. Czarnecki A, Chong A, Lee DS, Schull MJ, Tu JV, Lau C, et al. Association between physician follow-up and outcomes of care after chet pain assesment in high-risk patient. Circulation. 2013;127:1386-94.
2. Cannon CP. Acute coronary syndromes: risk stratification and initial management. Cardiol Clin. 2005;23(4):401-9.
3. Herren KR, Mackway-Jones K. Emergency management of cardiac chest pain: a review. Emerg Med J. 2001;18(1):6-10.
4. Haasenritter J, Aerts M, Bosner S, Buntinx F, Burnand B, Herzig L, et al. Coronary heart disease in primary care: accuracy of medical history and physical findings in patients with chest pain – a study protocol for a systematic review with individual patient data. BMC Family Practice. 2012 Ago 9;13:81.
5. Hamm CW, Bassand J, Agewall S, Bax J, Boersma E, Bueno H, et al. ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. The Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J.2011;32(23):2999–3054.
6. Jaffe AS. Use of biomarkers in the emergency department and chest pain unit. Cardiol Clin.2005;23(4):453-65.
7. Litt HI, Gatsonis C, Snyder B, Singh H, Miller CD, Entrikin DW, et al. CT angiography for safe discharge of patients with possible acute coronary syndromes. N Engl J Med.2012;366(15):1393-403.
8. Conway Morris A, Caesar D, Gray S, Gray A. TIMI risk score accurately risk stratifies patients with undifferentiated chest pain presenting to an emergency department. Heart. 2006 Sep;92(9):1333-4.
9. Fernandez JB, Ezquerra EA, Genover XB, O'Callaghan AC, Gárriz II, Jimenez JJ, et al. Chest pain units. Organization and protocol for the diagnosis of acute coronary syndromes. Rev Esp Cardiol. 2002;55(2):143-54.
10. Holly J, Fuller M, Hamilton D, Mallin M, Black K, Robbins R, et al. Prospective evaluation of the use of the thrombolysis in myocardial infarction score as a risk stratification tool for chest pain patients admitted to an ED observation unit. Am J Emerg Med. 2013 Jan;31(1):185-9.
11. Alderwish E , Schultz E, Kassam Z, Poon M, Coplan N. Evaluation of Acute Chest Pain: Evolving Paradigm of Coronary Risk Scores and Imaging. Rev Cardiovasc Med. 2019 Dec 30;20(4):231-44. doi: 10.31083/j.rcm.2019.04.589.
12. Levsky JM, Haramati LB, Spevack DM, Menegus MA, Chen T, Mizrachi S, et al. Coronary Computed Tomography Angiography Versus Stress Echocardiography in Acute Chest Pain: A Randomized Controlled Trial. JACC Cardiovasc Imaging. 2018 Sep;11(9):1288-97. doi: 10.1016/j.jcmg.2018.03.024. Epub 2018 Jun 13.
13. Cullen L, Mueller C, Parsonage WA, Wildi K, Greenslade JH, Twerenbold R, et al. Validation of high-sensitivity troponin I in a 2-hour diagnostic strategy to assess 30-day outcomes in emergency department patients with possible acute coronary syndrome. J Am Coll Cardiol. 2013 Oct 1;62(14):1242-9.
14. Januzzi JL, Bamberg F, Lee H, Truong QA, Nichols JH, Karakas M, et al. High-sensitivity troponin T concentrations in acute chest pain patients evaluated with cardiac computed tomography. Circulation.2010;121(10):1227-34.
15. Lippi G. Biomarkers of myocardial ischemia in the emergency room: cardiospecific troponin and beyond. Eur J of Intern Med.2013;24(2):97-9.
16. Thygesen K, Mair J, Giannitsis E, Mueller C, Lindahl B, Blankenberg S, et al. How to use high-sensitivity cardiac troponins in acute cardiac care. Eur Heart J.2012;21(18):1-7.
17. Sonel A, Sasseen BM, Fineberg N, Bang N, Wilensky RL. Prospective study correlating fibrinopeptide A, troponin I, myoglobin and myosin light chain levels with early and late ischemic events in consecutive patients presenting to the emergency department with chest pain. Circulation.2000;102(10):1107-13.
18. Dadkhah S, Sharain K, Sharain R, Kiabayan H, Foschi A, Zonta C, et al. The value of bedside cardiac multibiomarker assay in rapid and accurate diagnosis of acute coronay syndromes. Crit Pathways Cardiol.2007;6(2):76-84.
19. Chan D, Ng LL. Biomarkers in acute myocardial infarction. BMC Med.2010;8:34.
20. Gravning J[1], Smedsrud MK, Omland T, Eek C, Skulstad H, Aaberge L, et al. Sensitive troponin assays and N-terminal pro-B-type natriuretic peptide in acute coronary syndrome: prediction of significant coronary lesions and long-term prognosis. Am Heart J. 2013 May;165(5):716-24.
21. Mohammed AA, Januzzi JL Jr. Clinical applications of highly sensitive troponin assays. Cardiol Rev. 2010 Jan-Feb;18(1):12-9.
22. Omland T. Sensitive cardiac troponin assays: sense and sensibility. Eur Heart J. 2012 Apr;33(8):944-6.
23. Meune C, Reichlin T, Irfan A, Schaub N, Twerenbold R, Meissner J, et al. How safe is the outpatient management of patients with acute chest pain and mildly increased cardiac troponin concentrations? Clin Chem. 2012 May;58(5):916-24.
24. Bohula May EA, Bonaca MP, Jarolim P, Antman EM, Braunwald E, Giugliano RP, et al. Prognostic performance of a high-sensitivity cardiac troponin I assay in patients with non-ST-elevation acute coronary syndrome. Clin Chem. 2014 Jan;60(1):158-64.
25. Correia LC, Sodré FL, Lima JC, Sabino M, Brito M, Garcia G, et al. Prognostic value of high-sensitivity troponin I versus troponin T in acute coronary syndromes. Arq Bras Cardiol. 2012 May;98(5):406-12.
26. Wu AH, Jaffe AS. The clinical need for high-sensitivity cardiac troponin assays for acute coronary syndromes and the role for serial testing. Am Heart J. 2008 Feb;155(2):208-14.
27. Than M, Aldous S, Lord SJ, Goodacre S, Frampton CM, Troughton R, et al. A 2-hour diagnostic protocol for possible cardiac chest pain in the emergency department: a randomized clinical trial. JAMA Intern Med. 2014 Jan;174(1):51-8.
28. Tanindi A, Cemri M. Troponin elevation in conditions other than acute coronary syndromes. Vasc Health Risk Manag.2011;7:597-603.
29. Than M, Cullen L, Reid CM, Lim SH, Aldous S, Ardagh MW, et al. A 2-h diagnostic protocol to assess patients with chest pain symptoms in the Asia-Pacific region (ASPECT): a prospective observational validation study. Lancet. 2011 Mar 26;377(9771):1077-84.
30. Than M, Cullen L, Aldous S, Parsonage WA, Reid CM, Greenslade J, et al. 2-Hour accelerated diagnostic protocol to assess patients with chest pain symptoms using contemporary troponins as the only biomarker: the ADAPT trial. J Am Coll Cardiol. 2012 Jun 5;59(23):2091-8.
31. Reiter M, Twerenbold R, Reichlin T, Benz B, Haaf P, Meissner J, et al. Early diagnosis of acute myocardial infarction in patients with pre-existing coronary artery disease using more sensitive cardiac troponin assays. Eur Heart J. 2012 Apr;33(8):988-97.
32. Biener M, Mueller M, Vafaie M, Jaffe AS, Widera C, Katus HA, et al. Diagnostic performance of rising, falling, or rising and falling kinetic changes of high-sensitivity cardiac troponin T in an unselected emergency department population. Eur Heart J Acute Cardiovasc Care. 2013 Dec;2(4):314-22.
33. Ferencik M, Schlett CL, Bamberg F, Truong QA, Nichols JH, Pena AJ, et al. Comparison of traditional cardiovascular risk models and coronary atherosclerotic plaque as detected by computed tomography for prediction of acute coronary syndrome in patients with acute chest pain. Acad Emerg Med. 2012 Aug;19(8):934-42.
34. Hoffmann U, Truong QA, Schoenfeld DA, Chou ET, Woodard PK, Nagurney JT, et al. Coronary CT angiography versus standard evaluation in acute chest pain. N Engl J Med. 2012 Jul 26;367(4):299-308.
35. Singer AJ, Domingo A, Thode HC Jr, Daubert M, Vainrib AF, Ferraro S, et al. Utilization of coronary computed tomography angiography for exclusion of

coronary artery disease in ED patients with low- to intermediate-risk chest pain: a 1-year experience. Am J Emerg Med. 2012 Nov;30(9):1706-11.

36. Schlett CL, Banerji D, Siegel E, Bamberg F, Lehman SJ, Ferencik M, et al. Prognostic value of CT angiography for major adverse cardiac events in patients with acute chest pain from the emergency department: 2-year outcomes of the ROMICAT trial. JACC Cardiovasc Imaging. 2011 May;4(5):481-91.

37. Amsterdam EA, Kirk JD, Bluemke DA, Diercks D, Farkouh ME, Garvey JL, et al. Testing of low-risk patients presenting to the emergency department with chest pain: a scientific statement from the American Heart Association. Circulation. 2010 Oct 26;122(17):1756-76.

38. Pferfeman E, Forlenza LMA. Estrutura da unidade de dor torácica. In:Serrano Jr. CV, Timerman A, Stefanini E. Tratado de cardiologia SOCESP – 2° ed – Barueri – SP: Manole,2009: 844-60.

39. Lau J, Ioannidis JP, Balk EM, Milch C, Terrin N, Chew PW, et al. Diagnosing acute cardiac ischemia in the emergency department: a systematic review of the accuracy and clinical effect of current technologies. Ann Emerg Med.2001;37:453-60.

40. Cury RC, Feutchner G, Pena CS, Janowitz WR, Katzen BT, Ziffer JA. Acute chest pain imaging in the emergency department with cardiac computed tomography angiography. J Nucl Cardiol.2008;15(4):564-75.

41. Limkakeng AT, Halpern E, Takakuwa KM. Sixty-four-slice multidetector computed tomography: the future of ED cardiac care. Am J Emerg Med.2007;25(4):450-8.

42. Poon M, Cortegiano M, Abramowicz AJ, Hines M, Singer AJ, Henry MC, et al. Associations between routine coronary computed tomography angiography and reduced unnecessary hospital admissions, length of stay, recidivism rates, and invasive coronary angigraphy in the emergency department triage of chest pain. J Am Coll Cardiol.2013;62(6):543-52.

43. Truong QA, Hayden D, Woodard PK, Kirby R, Chou ET, Nagurney JT, et al. Sex differences in the effectiveness of early coronary computed tomography angiographiy compared with standard emergency department evaluation for acute chest pain: the rule-out myocardial infarction with computer-assisted tomography (ROMICAT)-II Trial. Circulation.2013;127(25):2494-502.

44. Budoff MJ, Dowe D, Jollis JG, Gitter M, Sutherland J, Halamert E, et al. Diagnostic performance of 64-multidetector row coronary computed tomographic angiography for evaluation of coronary artery stenosis in individuals without known coronary artery disease: results from the prospective multicenter ACCURACY (Assessment by Coronary Computed Tomographic Angiography of Individuals Undergoing Invasive Coronary Angiography) trial. J Am Coll Cardiol. 2008 Nov 18;52(21):1724-32.

45. Petcherski O, Gaspar T, Halon DA, Peled N, Jaffe R, Molnar R, et al. Diagnostic accuracy of 256-row computed tomographic angiography for detection of obstructive coronary artery disease using invasive quantitative coronary angiography as reference standard. Am J Cardiol. 2013 Feb 15;111(4):510-5.

46. Goldstein JA, Chinnaiyan KM, Abidov A, Achenbach S, Berman DS, Hayes SW, et al. The CT-STAT (Coronary Computed Tomographic Angiography for Systematic Triage of Acute Chest Pain Patients to Treatment) trial. J Am Coll Cardiol. 2011 Sep 27;58(14):1414-22.

47. Puchner SB, Liu T, Mayrhofer T, Truong QA, Lee H, Fleg JL, et al. High-risk plaque detected on coronary CT angiography predicts acute coronary syndromes independent of significant stenosis in acute chest pain: results from the ROMICAT-II trial. J Am Coll Cardiol. 2014 Aug 19;64(7):684-92.

48. Hulten E, Goehler A, Bittencourt MS, Bamberg F, Schlett CL, Truong QA, et al. Cost and resource utilization associated with use of computed tomography to evaluate chest pain in the emergency department: the Rule Out Myocardial Infarction using Computer Assisted Tomography (ROMICAT) study. Circ Cardiovasc Qual Outcomes. 2013 Sep 1;6(5):514-24.

49. Blankstein R, Ahmed W, Bamberg F, Rogers IS, Schlett CL, Nasir K, et al. Comparison of exercise treadmill testing with cardiac computed tomography angiography among patients presenting to the emergency room with chest pain: the Rule Out Myocardial Infarction Using Computer-Assisted Tomography (ROMICAT) study. Circ Cardiovasc Imaging. 2012 Mar;5(2):233-42.

50. Hoffmann U, Truong QA, Fleg JL, Goehler A, Gazelle S, Wiviott S, et al. Design of the Rule Out Myocardial Ischemia/Infarction Using Computer Assisted Tomography: a multicenter randomized comparative effectiveness trial of cardiac computed tomography versus alternative triage strategies in patients with acute chest pain in the emergency department. Am Heart J. 2012 Mar;163(3):330-8, 338.e1.

51. Staniak HL, Bittencourt MS, Sharovsky R, Benseñor I, Olmos RD, Lotufo PA. Calcium score to evaluate chest pain in the emergency room. Arq Bras Cardiol. 2013 Jan;100(1):90-3.

52. Rubinshtein R, Halon DA, Gaspar T, Jaffe R, Karkabi B, Flugelman MY, et al. Usefulness of 64-slice cardiac computed tomographic angiography for diagnosing acute coronary syndromes and predicting clinical outcome in emergency department patients with chest pain of uncertain origin. Circulation. 2007 Apr 3;115(13):1762-8.

53. Cury RC, Budoff M, Taylor AJ. Coronary CT angiography versus standard of care for assessment of chest pain in the emergency department. J Cardiovasc Comput Tomogr. 2013 Mar-Apr;7(2):79-82.

54. Nasis A, Meredith IT, Nerlekar N, Cameron JD, Antonis PR, Mottram PM, et al. Acute chest pain investigation: utility of cardiac CT angiography in guiding troponin measurement. Radiology. 2011 Aug;260(2):381-9.

55. Kargoli F, Levsky J, Bulcha N, Mustehsan MH, Brown-Manhertz D, Furlani A, et al. Comparison Between Anatomical and Functional Imaging Modalities for Evaluation of Chest Pain in the Emergency Department. Am J Cardiol. 2020 Apr 4;S0002-9149(20)30273-3.doi: 10.1016/j.amjcard.2020.03.024.

56. Yang S, Manjunath L, Willemink MJ, Nieman K. The role of coronary CT angiography for acute chest pain in the era of high-sensitivity troponins. J Cardiovasc Comput Tomogr. 2019 Sep-Oct;13(5):267-73. doi: 10.1016/j.jcct.2019.05.007. Epub 2019 Jun 15.

Role of Computed Tomography in Excluding Acute Coronary Syndrome: is Anatomy the Way?

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Short Editorial related to the article: Diagnostic Performance of Coronary Tomography Angiography and Serial measurements of Sensitive Cardiac Troponin in Patients With Chest Pain and Intermediate Risk for Cardiovascular Events

Chest pain is one of the most common reasons for admission to the emergency room (ER). Although only a small minority of these correspond to an acute coronary syndrome (ACS), the potential severity of a misdiagnosis or a non-diagnosis implies using systematic protocols to confirm or exclude coronary artery disease (CAD) as a cause of symptoms. In recent years, the sequential blood testing of high-sensitive troponin (cTnI-hs) levels has become a safe and effective method in this context and is commonly applied worldwide.[1-3] However, this approach is associated with prolonged times in the ER and is not error-free, as some patients with unstable angina may not be correctly identified.

New approaches using imaging methods to exclude CAD gained relevance and have generated interest from the scientific community. Cardiac CT angiography (CTA), due to its high diagnostic performance, is assumed to be the main candidate to change the *status-quo* of the current approach based on serial blood testing. It is a simple, fast and robust test with a high negative predictive value – which makes it particularly suitable in ER, where it is essential to quickly and effectively exclude the presence of CAD. The ROMICAT studies were among the first to document the advantages of CTA in this context and to emphasize its additive prognostic value concerning the TIMI risk score (TIMI RS). However, like the vast majority of studies that used CTA in the context of hospital ER, their results mostly apply to low-risk populations.[4,5]

In this issue of the journal, Matos Soeiro et al.[6] publish an interesting study that compares the performance of CTA against the serial assessment of cTnI-hs in 100 patients with chest pain referred to the ER, initially negatives ECG and cTnI-hs and an intermediate TIMI RS.[6] Unsurprisingly, CTA performed better than cTnI-hs measurements in detecting important CAD, with the time interval between patient arrival and CTA being approximately one hour shorter than the interval between patient arrival and the result of the second troponin measurement. The study also attempted to assess the clinical impact of hospitalization, death, and acute myocardial infarction at 30 days through telephone follow-up. However, the small sample size and low event rate (2%) made detecting any potential differences between the two approaches impossible. Even so, based on these results, the authors suggest that patients at intermediate risk without ischemic changes on the electrocardiogram should preferably be stratified at admission by CTA, as it is more efficient in identifying CAD.

This study adds information to previous scientific knowledge as it applies to intermediate-risk populations, but its results should be interpreted cautiously. More important than documenting the low agreement between troponin measurements and the presence of coronary lesions is finding the most cost-effective strategy for excluding an ACS in the context of ER admissions due to chest pain – which is sometimes impossible using only anatomical tests such as CTA. Just as we mentioned the probability of false negatives with the use of a strategy based on serial blood-testing, the documentation of anatomically relevant CAD (defined by the presence of coronary stenosis ≥50%) does not guarantee that it is responsible for the symptoms and that we are facing an ACS. In intermediate-risk populations such as the one studied, the presence of stable and asymptomatic CAD is not rare, and it may be an innocent bystander without any functional and clinical impact. Therefore, in light of the current evidence, we must be cautious in systematically adopting this strategy to avoid overdiagnosis and "overtreatment" with inadequate revascularizations – which have been proven to have deleterious effects in the context of stable coronary disease. Based on this single-center study, with a small sample size and a very small number of clinical events, it is impossible to affirm the efficacy and adequacy of systematically testing with CTA all the patients coming to the ER due to chest pain and an intermediate risk of events. This work is yet another important contribution to highlighting the role that CTA can play in the management of these patients. It adds to the long evidence that documents the benefits of this technique in different scenarios and the imperative need to make this technology available in the national health services of the 21st century.[7-10]

Keywords

Cardiovascular Diseases; Risk Factors; Chest Pain; Diagnostic.Imaging; Tomography,X-Ray Computed/methods.

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References

1. Correia LC, Sodré FL, Lima JC, Sabino M, Brito M, Garcia G, et al. Prognostic value of high-sensitivity troponin I versus troponin T in acute coronary syndromes. Arq Bras Cardiol. 2012 May;98(5):406-12. doi:10.1590/s0066-782X2012005000034
2. Nicolau JC, Feitosa Filho GS, Petriz J, Furtado RH, Précoma DB, Lemke W, et al. Brazilian Society of Cardiology Guidelines on Unstable Angina and Acute Myocardial Infarction without ST-Segment Elevation – 202. Arq Bras Cardiol. 2021 Jul;117(1):181-264. doi: 10.36660/abc.20210180.
3, Domingues C, Ferreira MJV, Ferreira JM, Marinho AV, Alves PM, Ferreira C, et al. Prognostic Value of Isolated Elevated Troponin I Levels in Patients without Acute Coronary Syndrome Admitted to the Emergency Department. Arq Bras Cardiol. 2021 May;116(5):928-37. doi: 10.36660/abc.20190356.
4. Litt HI, Gatsonis C, Snyder B, Singh H, Miller CD, Entrikin DW, et al. CT angiography for safe discharge of patients with possible acute coronary syndromes. N Engl J Med.2012;366(15):1393-403. doi:10.1590/s0066-782X2012005000034.
5. Hoffmann U, Truong QA, Schoenfeld DA, Chou ET, Woodard PK, Nagurney JT, et al. Coronary CT angiography versus standard evaluation in acute chest pain. N Engl J Med. 2012 Jul 26;367(4):299-308. doi:1056/NEJMoa1201163.
6. Matos Soeiro AA, Biselli B, Leal TCAT et al. Desempenho Diagnóstico da Angiotomografia Computadorizada e da avaliação seriada de troponina cardíaca sensível em pacientes com dor torácica e risco Intermediário para eventos cardiovasculares. Arq Bras Cardiol. 2022 Feb 7;S00-66-782X2022005001216. doi: 10.36660/abc.20210006.
7. Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C, et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. Eur Heart J. 2020;41(3):407-77. doi: 10.1093/eurheartj/ehz425.
8. Bettencourt N, Mendes L, Fontes JP et al. Consensus document on chronic coronary syndrome assessment and risk stratification in Portugal: A position paper statement from the [Portuguese Society of Cardiology's] Working Groups on Nuclear Cardiology, Magnetic Resonance and Cardiac Computed Tomography, Echocardiography, and Exercise Physiology and Cardiac Rehabilitation. Rev Port Cardiol (Engl Ed). 2020 Dec 18:S0870-2551(20)30467-4. doi: 10.1016/j.repc.2020.10.009
9. Carmo PB, Magliano CAS, Rey HCV, Camargo GC, Trocado LFL, Gottlieb I. Análise da Custo-Efetividade da Angiotomografia Coronariana no SUS, em Comparação com Outros Métodos Não Invasivos na Suspeita de DAC Estável. Arq Bras Cardiol. 2022; 118(3):578-585. doi:10.36660/abc.20201050.
10. Poppi NT. It is Time for Coronary Computed Tomography Angiography to be Incorporated into the SUS. Arq Bras Cardiol. 2022 Mar;118(3):586-7. doi:36660/abc.20220033.

Original Article

Hormone therapy and Hypertension in Postmenopausal Women: Results from the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil)

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Abstract

Background: Hypertension is a major risk factor for cardiovascular morbidity and mortality in post-menopausal women. Although menopausal hormone therapy (MHT) is a very effective treatment for vasomotor symptoms during this period, the influence of this therapy on blood pressure is not yet clear.

Objective: To evaluate the relationship between the use of MHT and hypertension in participants of the ELSA-Brasil.

Methods: A cross-sectional study using the baseline ELSA-Brasil data in a cohort of 2,138 women who had experienced natural menopause. This study analyzed hypertension, defined as arterial pressure ≥140/90 mmHg or previous antihypertensive use, and use of MHT, with participants being classified into never, past, and current users. Associations were assessed using an adjusted logistic regression model, with statistical significance set at p<0.05.

Results: Overall, 1,492 women (69.8%) had never used MHT, 457 (21.4%) had used it in the past, and 189 (8.8%) were current users. The use of MHT was more common in women who had a body mass index (BMI) <25 kg/m² and triglyceride levels <150 mg/dl, and who were physically less inactive, non-smokers, and non-diabetics. Current MHT users were less likely to have hypertension (OR=0.59; 95% CI: 0.41-0.85) compared to those who had never used MHT. In most cases, MHT was started at or before 59 years of age, within 10 years of becoming menopausal, and its use lasted for up to five years.

Conclusion: Current MHT use was not related to hypertension, particularly in healthy women and in those under 60 years of age.

Keywords: Postmenopause; Hormone Replacement Therapy.

Introduction

Hypertension is a major risk factor for cardiovascular morbidity and mortality in post-menopausal women.[1] The menopausal transition accounts for changes that can increase the likelihood of hypertension and other cardiovascular risk factors. Indeed, changes in the endogenous sex hormones and in the physiology of aging itself may affect the cardiac function, cause arterial stiffness and insulin resistance, alter one's lipid profile, and increase one's bodyweight and central adiposity.[1,2]

Although menopausal hormone therapy (MHT) is the most effective treatment for vasomotor symptoms and for the genitourinary syndrome of menopause, and is a very effective treatment for the prevention of bone loss and fractures,[3] other effects are also involved, and this treatment may be associated with cardiovascular risk markers.[4,5] The risks and benefits of MHT use seem to depend on the type of hormone prescribed, the dose and the duration of use, the route of administration, and the moment at which treatment is begun.[3]

Findings regarding the effect of MHT on arterial blood pressure in women have been conflicting, with clinical trials reporting either a neutral effect[6,7] or a protective effect with a reduction in blood pressure,[8,9] while others with the same design have suggested a harmful effect with an increase in blood pressure levels.[10,11]

Because most of the studies dealing with this subject were performed with samples of North American and European women, there is a need to evaluate the effect of MHT on blood pressure in Brazilian women. Based on the hypothesis

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that MHT affects blood pressure levels, this study aimed to evaluate the relationship between MHT use and hypertension in women participating in the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil).

Materials and Methods

Study design and population

This study analyzed baseline data from the ELSA-Brasil (2008-2010), a multicenter cohort that consisted of 15,105 civil servants working at public higher education and scientific research institutes in six Brazilian cities. Of these, 8,218 were women. Details on the study have already been published elsewhere.[12]

For the present analysis, 2,138 women who had experienced natural menopause and were normotensive, or who had received a diagnosis of hypertension after menopause, were evaluated. Conversely, a further 1,453 participants were excluded because they had undergone surgical or treatment-induced menopause, had a history of premature ovarian failure, had used MHT, or had received a diagnosis of hypertension prior to reaching menopausal age. In the analyses specifically related to the time of use or the date of starting MHT use, some participants were excluded due to missing data.

Data collection

A trained team, certified to carry out each procedure, performed the data collection. A rigorous system of quality control was implemented.[13] Face-to-face interviews were conducted using standardized questionnaires, and clinical and laboratory tests were conducted at the research centers.[12]

Menopause and MHT

The participants who replied "no" to the following question: "Do you still menstruate?", and those who also reported not having menstruated for over a year were considered menopausal.[14] The type of menopause was investigated from the participant's answer to the question: "Why do you no longer menstruate?" Age at menopause was determined from answers to the question: "How old were you when you menstruated for the last time?"

In relation to MHT use, the participants were asked: "Do you use or have you ever used drugs containing female hormones to relieve menopausal symptoms?" and "Are you currently using drugs containing female hormones to relieve menopausal symptoms?" These two questions were combined to obtain the exposure variable. The pattern of MHT use was evaluated categorically, with participants being classified into never, past, or current users, and the women who had never used MHT constituting the reference category.

To identify the time at which MHT use was begun in relation to he menopause, a variable was created by subtracting the age at which menopause occurred from the woman's age upon beginning use of MHT. The time of menopause at the beginning of treatment was dichotomized into <10 and ≥10 years, and the time of MHT use into <5 and ≥5 years, in accordance with current consensuses on the risks and benefits of MHT to one's health.[3]

Current MHT users were asked the generic or brand name of the hormone they were using. Based on this information, the variables "type of hormone" and "route of administration" were created. The type of hormone was classified as: estrogen + progestogen; estrogen; progestogen; estrogen + testosterone; tibolone; and others. The variable "route of administration" was dichotomized into "oral" and "non-oral". To ensure that only systemic MHT was included in the analysis, participants reporting using only vaginal MHT formulations were excluded from the study.

Arterial blood pressure and hypertension

Blood pressure was measured using an Omron HEM 705CPINT blood pressure monitor following a 5-minute resting period, with the participant seated, her feet resting on the ground, and after emptying her bladder. The cuff was chosen as a function of the participant's arm circumference, with the left arm being selected for this measurement. Three measurements were taken in a quiet environment with controlled temperature conditions (20-24ºC) and at intervals of one minute.[15] The mean of the two last measurements was used for the analysis of blood pressure levels, presented here as systolic and diastolic blood pressure.

Participants whose mean systolic pressure was ≥140 mmHg and/or whose mean diastolic pressure was ≥90 mmHg, in accordance with the guidelines of the European and the Brazilian Societies of Cardiology,[16,17] or who reported having used antihypertensive drugs in the preceding two weeks, were considered hypertensive.

Co-variables

Participants who had received a diagnosis of diabetes or were under treatment with insulin or oral hypoglycemic drugs were defined as having diabetes. In addition, a diagnosis of diabetes was made in the presence of fasting glucose levels ≥126 mg/dl, or 2-hour levels in a glucose tolerance test≥200 mg/dl or a glycosylated hemoglobin ≥6.5%.[18]

Samples for laboratory tests were collected following 12-hour overnight fasting. The oral glucose tolerance test was performed by administering 75 grams of adextrose solution. Glucose was measured by the hexokinase method using the ADVIA Chemistry® system, and glycosylated hemoglobin was measured by high performance liquid chromatography. Triglyceride and high-density lipoprotein (HDL)-cholesterol levels were determined by an enzymatic colorimetric method using the ADVIA Chemistry® system, while low-density lipoprotein (LDL)-cholesterol levels were estimated by the Friedewald equation. The lipid profile was classified based on the desirable levels of HDL-cholesterol (>40 mg/dl) and triglycerides (<150 mg/dl), and the upper limit for LDL-cholesterol (<130 md/dl).[19]

Physical activity was evaluated from the leisure time and displacement domains of the International Physical Activity Questionnaire, an instrument that has been validated for use with adult Brazilians.[20] The participants were classified as "active" (vigorous physical activity >60 minutes/week or

moderate physical activity ≥150 minutes/week) or "inactive" (vigorous activity <60 minutes/week and other less intense activities <150 minutes/week).[21]

Toledo® scales and Seca® stadiometers were used to measure weight and height respectively,[15] with the participants using standardized study clothing during measurements. Body mass index (BMI) as calculated using the formula *weight/height*^{2} and classified as underweight/normal weight (BMI <25 kg/m^2), overweight (25-29.9 kg/m^2), or obesity (≥30 kg/m^2). Alcohol consumption was classified as excessive (≥140 grams of alcohol/week) or not excessive (<140 grams of alcohol/week).[22]

The variable *age* was analyzed as a continuous and categorical variable. The variable race/ethnicity was obtained by asking the following question: "*The Brazilian census (IBGE) uses the categories 'black, brown, white, Asian, or indigenous' to classify a person's color or ethnicity. If you had to answer the Brazilian census today, how would you describe your color or ethnicity?*" Participants who self-identified as "indigenous" (n =21) or "Asian" (n = 72) were excluded from the analysis due to the low number of subjects.

Data analysis

The characteristics of the sample are described as absolute frequencies and proportions. For the quantitative variables, medians and interquartile ranges were used, since the distribution of the data was not normal, as indicated by the Shapiro-Wilk test of normality. Pearson's chi-square test was used to evaluate the association between health-related aspects and sociodemographic variables as a function of being a never, past, or current MHT user. Fisher's exact test was used to compare the type of hormone according to the presence of hypertension. Median systolic and diastolic pressure was compared using the Kruskal-Wallis test, followed by Dunn's post hoc test.

The association between the independent variable (MHT) and the dependent variable (hypertension) was tested using multivariate logistic regression. Effect modification was analyzed using product terms; however, none of the co-variables was found to be an effect modifier. Potential confounding variables were evaluated by comparing the odds ratios (OR) of the crude association with the OR, following adjustment for the possible confounding variables of *age* and *BMI*, with the parameter being a difference of at least 10% between the associations. Only the variable BMI was identified as a confounding factor in the analysis; however, based on the established literature and on its clinical relevance, it was decided to also take age into consideration. The significance level adopted was 5% and the Stata 12 software program was used throughout the statistical analysis.

Ethical aspects

The internal review boards of all the institutes involved in the ELSA-Brasil approved the study protocol, as did the National Committee for Ethics in Research. All the participants signed an informed consent form. Participants who had clinical alterations detected by the study were referred to the referral health services.

Results

The median age of the 2,138 women participating in the study was 57 years (IQR 53-62). According to self-reports, 1,492 (69.8%) were never users of MHT, while 457 (21.4%) were past users and 189 (8.8%) were current users.

MHT use was more common in women with a BMI <25 kg/m^2 and triglyceride levels <150 mg/dl, and in less physically inactive women, non-smokers and non-diabetics. Of the past users, 59.7% were ≥60 years of age, while 54.5% of the current users were 50-59 years of age (Table 1).

The prevalence of hypertension was 40.2%. Of the hypertensive women, 71.3% had never used MHT, while 5.8% were current MHT users. Of the normotensive women, 68.8% had never used MHT, while 10.9% were current users.

Table 2 shows the crude and the age- and BMI-adjusted associations between MHT use and the presence of hypertension. Current MHT users were significantly less likely to have hypertension (OR=0.59; 95% CI: 0.41-0.85) when compared to never users. This adjusted inverse association persisted even after making further adjustment for the route of administration (data not presented in tables).

In the comparative analysis of blood pressure levels according to exposure to MHT, considering hypertensive (using or not antihypertensive) and normotensive, results showed that current MHT users had the lowest median systolic blood pressure of 113mmHg, as compared to never users at 118.5mmHg, and to past users at 120mmHg (p=0.001). Furthermore, the upper limit was notably lower (Figure 1). Statistically significant differences were found only between never/current use (p=0.00) and between current use/past use (p=0.00).

Of the current and past users of MHT, the majority had begun treatment at or before 59 years of age, within 10 years of experiencing menopause, and the duration of therapy was up to 5 years, regardless of hypertension. Nevertheless, the proportion of hypertensive women was greatest among those who began MHT after 60 years of age and/or 10 years or more after menopause (Table 3).

In the group of current users who had hypertension, the most common MHT type consisted of combined estrogen-progestogen formulations followed by estrogen alone. However, in normotensive users of MHT, tibolone was also widely used, as well as the combined estrogen-progestogen formulations. All the different types of MHT were more common in the normotensive women compared to the hypertensive women. The majority of the women (80.3%) were found to use the oral route of administration; nevertheless, there was no statistically significant association between the route of administration and the presence of hypertension (Table 4).

Discussion

The results indicate that the use of MHT is not related to arterial hypertension. MHT users were less likely to have hypertension compared to past or never users, regardless of age or BMI. Nevertheless, these findings must be analyzed with caution.

Table 1 – Sociodemographic characteristics, lifestyle, and health status of the women who experienced natural menopause, according to the use of menopausal hormone therapy. ELSA-Brasil, 2008-2010

Characteristics	Never Users n (%)	Past Users n (%)	Current Users n (%)	p-value
Age				0.000
40-49 years	140 (9.4)	16 (3.5)	20 (10.5)	
50-59 years	900 (60.3)	168 (36.8)	103 (54.5)	
≥60 years	452 (30.3)	273 (59.7)	66 (35.0)	
Ethnicity/skin color				0.000
Black	272 (19.4)	54 (12.6)	17 (9.1)	
Brown	384 (27.4)	114 (26.6)	45 (24.2)	
White	747 (53.2)	260 (60.8)	124 (66.7)	
Schooling				0.000
High school	805 (54.0)	192 (42.0)	50 (26.5)	
University degree	687 (46.0)	265 (58.0)	139 (73.5)	
*** Excessive alcohol consumption**				0.243
No	1.436 (96.5)	444 (97.4)	179 (94.7)	
Yes	52 (3.5)	12 (2.6)	10 (5.3)	
Smoking				0.000
Never smoked	821 (55.0)	289 (63.2)	106 (56.1)	
Former smoker	427 (28.6)	120 (26.3)	68 (36.0)	
Smoker	244 (16.4)	48 (10.5)	15 (7.9)	
Physical activity				0.001
Inactive	1.204 (81.6)	337 (74.6)	138 (73.4)	
Active	271 (18.4)	115 (25.4)	50 (26.6)	
Body mass index				0.000
≤ 24.9 kg/m²	502 (33.6)	185 (40.5)	99 (52.4)	
25.0 - 29.9 kg/m²	517 (34.7)	183 (40.0)	71 (37.6)	
≥ 30.0 kg/m²	473 (31.7)	89 (19.5)	19 (10.0)	
Diabetes				0.007
No	1.128 (75.7)	365 (79.9)	160 (84.7)	
Yes	363 (24.3)	92 (20.1)	29 (15.3)	
Arterial hypertension				0.000
No	880 (59.0)	260 (57.0)	139 (73.5)	
Yes	612 (41.0)	197 (43.0)	50 (26.5)	
Cardiovascular disease				0.581
No	1.412 (94.8)	431 (94.3)	182 (96.3)	
Yes	78 (5.2)	26 (5.7)	7 (3.7)	
LDL-cholesterol				0.396
<130 mg/dL	648 (43.4)	215 (47.0)	84 (44.4)	
≥130 mg/dL	844 (56.6)	242 (53.0)	105 (55.6)	
HDL–cholesterol				0.041
>40 mg/dL	1.452 (97.3)	446 (97.6)	178 (94.2)	
≤40 mg/dL	40 (2.7)	11 (2.4)	11 (5.8)	
Triglycerides				0.000
<150 mg/dL	1.044 (70.0)	351 (76.8)	158 (84.0)	
≥150 mg/dL	448 (30.0)	106 (23.2)	31 (16.0)	

**Excessive alcohol consumption: ≥140grams of alcohol/week; HDL: high- density lipoprotein; LDL: low-density lipoprotein.*

Table 2 – Association between the use of menopausal hormone therapy and hypertension. ELSA-Brasil, 2008-2010

	Never user n=1492	Past user n=457	Current user n=189
Arterial hypertension n (%)			
No	880 (68.8)	260 (20.3)	139 (10.9)
Yes	612 (71.3)	197 (22.9)	50 (5.8)
OR (95%CI)			
Crude	1	1.08 (0.88-1.34)	0.51 (0.36-0.72)
Adjusted*	1	0.89 (0.71-1.13)	0.59 (0.41- 0.85)

*OR: Odds Ratio; *Adjusted for age and body mass index.*

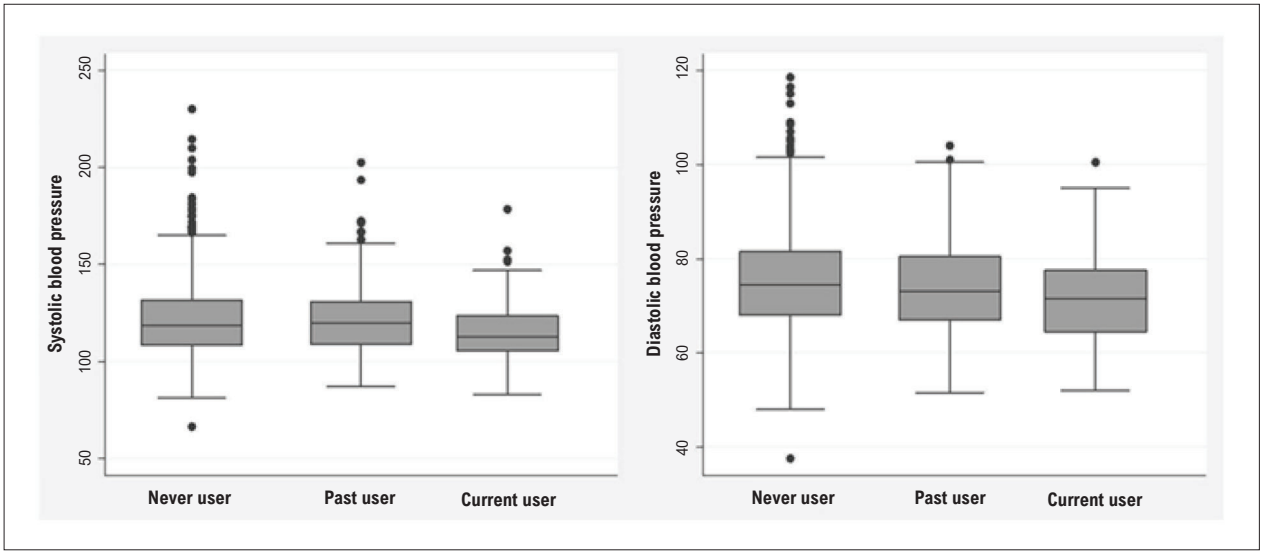

Figure 1 – *Median systolic and diastolic blood pressure according to the pattern of use of menopausal hormone therapy.*

Table 3 – Age at beginning of menopausal hormone therapy, time since menopause, and duration of menopausal hormone therapy use according to whether or not hypertension was present in past and urrent users. ELSA-Brasil, 2008-2010

Characteristics	Normotensive women n (%)	Hypertensive women n (%)	p-value
Age at beginning of MHT [a]			0.034
<60 years	377(63.3)	219(36.7)	
≥60 years	9(40.9)	13(59.1)	
Duration of menopause at beginning of MHT			0.000
<10 years	378 (63.7)	215 (36.3)	
≥10 years	3 (17.6)	14 (82.4)	
Duration of MHT			0.927
<5 years	252(62.4)	152(37.6)	
≥5 years	142(62.0)	87(38.0)	

a Menopausal hormone therapy. NB: Specifically for this analysis, exclusions of some observations were necessary due to missing data and for this reason, the sum may vary for the different variables.

Table 4 – Type of menopausal hormone therapy and the route of administration of current regimen, according to the presence of hypertension. ELSA-Brasil, 2008-2010

Characteristics	Normotensive women (n=138)	Hypertensive women (n=50)	p-value
	n (%)	n (%)	
Type of hormone			0.024*
Estrogen + progestogen	65 (47.1)	18 (36.0)	
Estrogens	28 (20.3)	16 (32.0)	
Progestogens	3 (2.2)	-	
Estrogens + testosterone	5 (3.6)	3 (6.0)	
Tibolone	35 (25.4)	8 (16.0)	
Others	2 (1.4)	5 (10.0)	
Route of administration			0.190
Oral	114 (82.6)	37 (74.0)	
Non-oral	24 (17.4)	26.0)	

** Fisher's exact test. NB: One participant was excluded due to missing data.*

The possibility of women with health problems being less likely to be prescribed hormones, cannot be ruled out. MHT users had a more favorable health profile, being healthier in almost all the parameters evaluated here. A study conducted within the ELSA-Brasil showed that women with at least one clinical contraindication to MHT were less likely to be exposed to this type of medication.[23] Therefore, the prescription of MHT may have been more restricted in the case of women with hypertension, since, although hypertension alone is not a formal contraindication, it is frequently associated with diseases for which hormone use would be contraindicated. Nonetheless, the present results are in agreement with the findings of the Rancho Bernardo Study conducted in California with 1,044 women, in which the blood pressure levels of participants in current use of MHT were lower than those of a control group.[24]

The Baltimore study, with a 10-year follow-up time, found that although systolic blood pressure levels increased in both the users and non-users of MHT, the increase was less expressive in the users.[25] In the present study, differences in median blood pressure levels were also found between users and non-users of MHT, particularly in relation to systolic blood pressure, with a difference of 5.5 mmHg between current and never users. However, in a randomized clinical trial in which variations in blood pressure were determined by ambulatory blood pressure monitoring (ABPM), a decrease was found both in systolic and diastolic blood pressure in MHT users.[8]

A study conducted in Finland evaluated the effect of the different routes of administration of MHT. Although both the oral and transdermal routes of administration resulted in a decrease in daytime systolic blood pressure, this reduction was maintained for longer (6 months) with the oral route. However, that study only analyzed the short-term effect.[9] In the present sample, although most of the MHT users used the oral route of administration, no significant differences were found between the hypertensive and normotensive women as a function of the route of administration.

Endogenous estrogen is believed to act through a physiological mechanism that can promote a reduction in arterial blood pressure via a vasodilatory effect, such as an increase in nitric oxide, inhibition of the renin-angiotensin system, a reduction in the transcription of angiotensin-converting enzyme, and the regulation of vasoconstrictors, such as endothelin.[2,26] Nevertheless, despite this apparent benefit of endogenous sex hormones on women's cardiac health, studies on the effect of the exogenous use of these substances on blood pressure levels have generated conflicting results.

A cross-sectional Australian study that included women of 45-75 years of age found that hormone use was associated with a significantly greater likelihood of having hypertension.[27] Furthermore, the Women's Health Initiative (WHI) clinical trial, which evaluated women of 50-79 years of age, found that MHT led to a small increase in systolic blood pressure over a follow-up period of approximately 5.2 years.[10] Conversely, neither the Postmenopausal Estrogen/Progestin Intervention (PEPI), which followed women of 45-64 years of age over a three-year period,[28] nor a study conducted in Denmark[6] with women of the same age group, found any effect of MHT on arterial blood pressure.

The differences found in the previous studies could be explained first by the variations in the populations, whose ages ranged from 45 to 79 years. Secondly, the regimens, dosages, and hormonal formulations differed, and follow-up times ranged from 6 months to 10 years.[6,8-10] Finally, the definitions of hypertension and methods of blood pressure measurement varied, with home monitoring,[10,25,28] ABPM,[8,9] and self-reporting[27] being used.

In those clinical trials that reported an association between MHT and a reduction in blood pressure or a

neutral effect, sample sizes were small, the women enrolled were younger, and participants were followed up for a maximum period of one year.[7,8] Conversely, in those in which an increase in blood pressure was reported, studies tended to have larger sample sizes, involve longer periods of follow-up (up to five years), and be conducted in older women[10] or in women with prior coronary heart disease.[11]

In addition to the association found in the present study between MHT and a lesser likelihood of hypertension, the low prevalence of MHT is noteworthy. Only 8.8% of the women were current users, a finding that was expected when bearing in mind that the data from this study were generated some years after the publication of the Heart and Estrogen/Progestin Replacement Study (HERS) and the WHI study. Those publications emphasized the risks of MHT and contributed to a considerable reduction in its use, with restrictions for the prescription of MHT and the establishment of criteria for treatment.[10,11]

The pattern of MHT use seen here is in agreement with current recommendations, since most users were under 60 years of age, when the risk-benefit ratio of MHT appears to be more favorable, had initiated therapy within 10 years of the menopause, and had used the treatment for periods of up to 5 years.[3,4,29] In the women who initiated hormone use later, the frequency of hypertension was found to be greater; however, those women constituted a minority in this sample. The fact that the recommended time limits are being respected probably offers some protection to MHT users.

The MHT users in the present study had better health conditions, a healthier lifestyle and a better education level. A similar profile was found in a study conducted in Pennsylvania.[30] Bearing in mind the pattern of health indicators among the users of MHT, the possibility has to be taken into account that the association between hormone use and a lesser likelihood of hypertension could have been affected by the health profile of these women and not only by the effect of MHT.

Despite the apparent benefit of MHT found here, it is important to emphasize that in accordance with current recommendations, MHT is only indicated for the treatment of the vasomotor symptoms of menopause and not as a strategy to prevent cardiovascular diseases and their risk factors.[3,4]

One of the strengths of the present study is its substantial sample size and the fact that the sample consisted of women from three large geographic regions of the country. Nevertheless, caution is required when making generalizations, since the ELSA-Brasil, despite its robust sample and the known similarities between the results of this study and those of population-based surveys conducted in Brazil, consists of civil servants who are not representative of the general public insofar as their sociodemographic characteristics are concerned.

Other limitations include the methodological impossibility of evaluating reverse causality in the associations observed here, as well as a possible memory bias with respect to the data concerning menopause and the beginning of MHT use, which were obtained using questionnaires. Nevertheless, any bias that may have occurred would be minimal, since the menopause is an important event in women's lives. In addition, some factors not evaluated, such as sodium intake, kidney function, and the dose used in the hormone regimens, could have led to residual confounding.

Conclusion

These results suggest that current MHT use is not related to hypertension, particularly in women with a healthy lifestyle and those under 60 years of age; however, future studies may clarify the effect of MHT on arterial blood pressure. Despite the ethical issues surrounding studies on MHT due to the delicate risk/benefit balance, longitudinal studies may be more appropriate to evaluate this association and may also include the possibility of identifying long-term effects following the end of MHT use.

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Author Contributions

Conception and design of the research and Obtaining financing: Aquino EML, Griep RH; Acquisition of data: Gabrielli L, Almeida MCC, Aquino EML, Matos SMA, Griep RH; Analysis and interpretation of the data: Ferreira-Campos L, Gabrielli L, Almeida MCC, Aquino EML, Matos SMA, Aras R; Statistical analysis and Writing of the manuscript: Ferreira-Campos L, Gabrielli L, Almeida MCC, Aras R; Critical revision of the manuscript for intellectual content: Ferreira-Campos L, Gabrielli L, Almeida MCC, Aquino EML, Matos SMA, Griep RH, Aras R.

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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References

1. Barton M, Meyer MR. Postmenopausal hypertension: mechanisms and therapy. Hypertension. 2009;54(1):11-8. doi: 10.1161/HYPERTENSIONAHA.108.120022.

2. Zhao D, Guallar E, Ouyang P,Subramanya V, Vaidya D, Nolumele CE, et al. et al. Endogenous Sex Hormones and Incident Cardiovascular Disease in Post-Menopausal Women. J Am Coll Cardiol. 2018;71(22):2555-66. doi: 10.1161/HYPERTENSIONAHA.108.120022.

3. The 2017 hormone therapy position statement of The North American Menopause Society. Menopause. 2017;24(7):728-53. DOI: 10.1097/GME.0000000000000921

4. Fernandes C, Pinho Neto J, Gebara O,Andrade J, Pinto Neto A, Luna de Athayde AV, et al.Sociedadi Brasileira de Cardiologia, Sociedade e Assov]ciação Brasileira do Climatério (SOBRAC). Iº Diretriz brasileira sobre prevenção de doenças cardiovasculares em mulheres climatéricas e a influência da terapia de reposição hormonal (TRH) da Sociedade Brasileira de Cardiologia (SBC) e da Associação Brasileira do Climatério (SOBRAC), Arq Bras Cardiol.2008;91(supl 1):1-23.

5. Khalil RA. Estrogen, vascular estrogen receptor and hormone therapy in postmenopausal vascular disease. Biochem Pharmacol. 2013;86(12):1627-42. DOI: 10.1016/j.bcp.2013.09.024

6. Skouby SO, Sidelmann JJ, Nilas L, Gram J, Jespersen J. The effect of continuous combined conjugated equine estrogen plus medroxyprogesterone acetate and tibolone on cardiovascular metabolic risk factors. Climacteric. 2008;11(6):489-97. doi: 10.1080/13697130802455150.

7. Gambacciani M, G Rosano, B Cappagli, A Pepe, C Vitale, A R Genazzani. Clinical and metabolic effects of drospirenone–estradiol inmenopausal women: a prospective study.Climateric.2008;11(1):18-24. doi: 10.3109/13697137.2010.520099.

8. Van Ittersum FJ, van Baal WM, Kenemans P, Mijatovic V, Donker AJ, van der Mooren MJ, et al. Ambulatory--not office--blood pressures decline during hormone replacement therapy in healthy postmenopausal women. Am J Hypertens. 1998;11(10):1147-52. doi: 10.1016/s0895-7061(98)00165-4.

9. Cacciatore B, Paakkari I, Hasselblatt R, Nieminen MS, Toivoonen J, Tekkanen MI, et al. Randomized comparison between orally and transdermally administered hormone replacement therapy regimens of long-term effects on 24-hour ambulatory blood pressure in postmenopausal women. Am J Obstet Gynecol. 2001;184(5):904-9. DOI: 10.1067/mob.2001.111246

10. Rossouw JE, Anderson GL, Prentice RL,LaCroix AZ, Kooperberg C, Stefanick ML, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. JAMA. 2002;288(3):321-33. doi: 10.1001/jama.288.3.321.

11. Hulley S, Grady D, Bush T, Furberg C, Herrington D, Riggs R, et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and Estrogen/progestin Replacement Study (HERS) Research Group. JAMA. 1998;280(7):605-13. doi: 10.1001/jama.280.7.605.

12. Aquino EM, Barreto SM, Bensenor IM, Carvalho MS, Chor D, Duncan BB, et al. Brazilian Longitudinal Study of Adult Health (ELSA-Brasil): objectives and design. Am J Epidemiol. 2012;175(4):315-24DOI: 10.1001/jama.280.7.605 .

13. Schmidt MI, Griep RH, Passos VM, Lught VC, Goulart AC, Menezes GM, et al. Estratégias e desenvolvimento de garantia e controle de qualidade no ELSA-Brasil [Strategies and development of quality assurance and control in the ELSA-Brasil]. Rev Saude Publica. 2013;47(Suppl 2):105-12. doi: 10.1590/s0034-8910.2013047003889.

14. World Health Organization (WHO). Research on the menopause in the 1990s. Report of a WHO Scientific Group. World Health Organ Tech Rep Ser. 1996;866:1-107. PMID: 8942292.

15. Mill JG, Pinto K, Griep RH,Goulart A, Foppa M, Lotufo PA< et al. Aferições e exames clínicos realizados nos participantes do ELSA-Brasil [Medical assessments and measurements in ELSA-Brasil]. Rev Saude Publica. 2013;47(Suppl2):54-62. doi: 10.1590/s0034-8910.2013047003851.

16. Williams B, Mancia G, Spiering W,Agabiti Rosei E, Azizi M, Burnier M, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. Eur Heart J. 2018;39(33):3021-104. doi: 10.1093/eurheartj/ehy339.

17. Malachias MVB, Gomes MAM, Nobre F, Alessi A, Feitosa AD, Coelho EB. 7th Brazilian Guideline of Arterial Hypertension: Chapter 2 - Diagnosis and Classification. 7ª Diretriz Brasileira de Hipertensão Arterial: Capítulo 2 - Diagnóstico e Classificação. Arq Bras Cardiol. 2016;107(3 Suppl 3):7-13. doi: 10.5935/abc.20160152.

18. American Diabetes Associatio. Standards of Medical Care in Diabetes -2014, Diabetes Care. 2014;37(Suppl 1):S14-90. doi: 10.2337/dc14-S014.

19. Catapano AL, Graham I, De Backer G,Wiklund O, Chapman MI, Drexel H, et al. 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias. Eur Heart J. 2016;37(39):2999-3058. doi: 10.1093/eurheartj/ehw272

20. Matsubo G, Araujo S, Matsubo T, et al. Questionário Internacional De Atividade Física (Ipaq): Estudo de validade e reprodutibilidade no Brasil. Rev Bras Atividade Física Saúde.2012;6:5-18.

21. World Health Organization (WHO), Global Recommendations on Physical Activity for Health . [Cited in 2019 Aug 08] Available from:WHO. http://www.who.int/dietphysicalactivity/publications/9789241599979/en/

22. Fuchs FD, Chambless LE, Whelton PK, Nieto FJ, Heiss G. Alcohol consumption and the incidence of hypertension: The Atherosclerosis Risk in Communities Study. Hypertension. 2001;37(5):1242-50. doi: 10.1161/01.hyp.37.5.1242.

23. Aquino EM, Almeida MD, Menezes GM, de Figueiredo RC, Bensinor IM, Mengue SS, et al Postmenopausal hormone therapy in the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil): who still uses it?. Pharmacoepidemiol Drug Saf. 2016;25(6):609-17. doi: 10.1002/pds.3992.

24. Fung MM, Poddar S, Bettencourt R, Jassal SK, Barrett-Connor E. A cross-sectional and 10-year prospective study of postmenopausal estrogen therapy and blood pressure, renal function, and albuminuria: the Rancho Bernardo Study. Menopause. 2011;18(6):629-37. doi: 10.1097/gme.0b013e3181fca9c4.

25. Scuteri A, Bos AJ, Brant LJ, Talbot L, Lakatta EG, Fleg JL. Hormone replacement therapy and longitudinal changes in blood pressure in postmenopausal women. Ann Intern Med.2001;135(4):229-38.. doi: 10.7326/0003-4819-135-4-200108210-00007.

26. Miller VM, Duckles SP. Vascular actions of estrogens: functional implications. Pharmacol Rev. 2008;60(2):210-41. doi: 10.1124/pr.107.08002.

27. Chiu CL, Lujic S, Thornton C, O,Louglin A, Makris A, Hennessy A, et al. Menopausal hormone therapy is associated with having high blood pressure in postmenopausal women: observational cohort study. PLoS One. 2012;7(7):e40260. doi: 10.1371/journal.pone.0040260.

28. Effects of estrogen or estrogen/progestin regimens on heart disease risk factors in postmenopausal women. The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial. The Writing Group for the PEPI Trial. JAMA. 1995;273(3):199-208. Erratum in :JAMA.1995;274(21):1676 PMID 7807658.

29. Baber RJ, Panay N, Fenton A; IMS Writing Group. 2016 IMS Recommendations on women's midlife health and menopause hormone therapy. Climacteric. 2016;19;2(2):109-50. doi: 10.3109/13697137.2015.1129166.

30. Matthews KA, Kuller LH, Wing RR, Meilahn EN, Plantinga P. Prior to use of estrogen replacement therapy, are users healthier than nonusers?. Am J Epidemiol. 1996;143(10):971-8. doi: 10.1093/oxfordjournals.aje.a008678.

Overcoming Women's Lifelong Hormonal Rollercoaster: A Turning Point for Cardiovascular Prevention

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Short Editorial related to the article: Hormone therapy and Hypertension in Postmenopausal Women: Results from the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil)

Although cardiovascular diseases (CVD), especially coronary artery disease and stroke, are the leading cause of death and disability in Brazil, both in women and men,[1,2] addressing cardiovascular (CV) prevention implies a comprehensive approach to the inherent differences related to sex. In this sense, understanding, for instance, the role of hypertension, a major risk factor for coronary artery disease and stroke in Brazilian women,[3] in the context of this population's specificities is key.[1]

Hypertensive disorders, including pregnancy-induced hypertension (occurring in 6-7% of pregnancies) and preeclampsia/eclampsia (occurring in up to 10% of pregnancies), are important CV risk factors[4,5] that should be accounted for when assessing women's CV risk.[1]

As women age and estrogen levels decline, risks increase for osteoporosis and cardiovascular disease.[6] Vasomotor symptoms (hot flashes and night sweats), prevalent among late perimenopausal and recently menopausal women, are linked to an increased risk of cardiovascular disease and cognitive changes.[7,8] Although menopausal hormone therapy (MHT) remains the most effective treatment for vasomotor symptoms of menopause,[8] its association with hypertension remains unclear.[9-13] Observational studies have previously suggested reduced risks of cardiovascular disease and dementia with postmenopausal hormone therapy,[9] but the initial publication in 2002 of findings from a randomized, controlled trial conducted by the Women's Health Initiative (WHI) reported increased risks of cardiovascular disease, venous thromboembolism (VTE), and breast cancer.[10] Treatment of both groups in the WHI trial was stopped early to prevent possible harm. Compared with placebo, combination therapy (0.625 mg of conjugated equine estrogens [CEE] plus 2.5 mg of medroxyprogesterone acetate) increased the annual risk of CVD by 0.6 per one thousand women and of stroke and breast cancer by 0.9 per one thousand women. Subsequent post hoc analyses conducted according to age and time from the onset of menopause (with menopause defined as 12 months without a menstrual period) suggested increased risks of coronary heart disease and stroke among WHI participants who started hormone therapy after the age of 60 years, thus supporting the "timing hypothesis".[10] In the Etude *Épidémiologique de femmes de la Mutuelle Générale de l'Education* (E3N) cohort, MHT was associated with a modest but significant increased risk of incident hypertension, especially when using oral estrogen in combination with a progestogen such as pregnane and norpregnane derivatives.[14]

In a cross-sectional study from the baseline assessment of the ELSA-Brazil study, including 2.138 women that have undergone natural menopause, Ferreira-Campos et al.[15] assessed the relation between MHT and hypertension (defined as BP ≥140/90 mmHg or previous use of any antihypertensive drugs). The authors have found that 1.492 women (69.8%) have never used MHT, 457 (21.4%) were previous users, and 189 (8.8%) were current users. In this study, current MHT users were less likely to present hypertension than women who have never used MHT (Odds Ratio [OR]=0.59; CI 95% 0.41-0.85). Additionally, current MTH users presented lower median systolic blood pressure than women who have never used MTH and previous users (113 mmHg,118,5 mmHg and 120 mmHg, respectively, (p=0.001).[15] This study's conclusions, while cautious, contrast with recent larger longitudinal assessments from cohort studies and clinical trials. In this case, the study's cross-sectional nature may represent a limitation. The "timing hypothesis" not possible to assess in this study design could be determinant for a different outcome. While cross-sectional analyses constitute a substantial body of evidence generators, longitudinal assessments and the "magic of randomization" may be informative for certain research questions.

Keywords

Estrogen Replacement Therapy/adverse effects; Women; Menopause; Progestins/adverse effects; Prevention and Control; Risk Factors

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References

1. Oliveira GMMD, Wenger NK. Considerações Especiais na Prevenção de Doenças Cardiovasculares nas Mulheres. Arquivos brasileiros de cardiologia 2022;118(2):374-7. doi: 10.36660/abc.20220028.
2. Oliveira GMM, Brant LCC, Polanczyk CA, Biolo A, Nascimento BR, Malta DC, et al. Cardiovascular Statistics - Brazil 2020. Arq Bras Cardiol. 2020;115(3):308-439. doi: 10.36660/abc.20200812.
3. Brant LCC, Nascimento BR, Veloso GA, Gomes CS, Polanczyk C, Oliveira GMM, et al. Burden of Cardiovascular diseases attributable to risk factors in Brazil: data from the "Global Burden of Disease 2019" study. Rev Soc Bras Med Trop 2022;55(suppl 1):e0263. doi: 10.1590/0037-8682-0263-2021.
4. Perak AM, Ning H, Khan SS, Van Horn LV, Grobman WA, Lloyd-Jones DM. Cardiovascular Health Among Pregnant Women, Aged 20 to 44 Years, in the United States. J Am Heart Assoc. 2020;9(4):e015123. doi: 10.1161/JAHA.119.015123.
5. Cho L, Davis M, Elgendy I, Epps K, Lindley KJ, Mehta PK, et al. Summary of Updated Recommendations for Primary Prevention of Cardiovascular Disease in Women: JACC State-of-the-Art Review. J Am Coll Cardiol. 2020;75(20):2602-18. doi: 10.1016/j.jacc.2020.03.060.
6. Freedman RR. Menopausal hot flashes: Mechanisms, endocrinology, treatment. The Journal of Steroid Biochemistry and Molecular Biology 2014;142:115-20. doi: 10.1016/j.jsbmb.2013.08.010.
7. Thurston RC. Vasomotor symptoms: natural history, physiology, and links with cardiovascular health. Climacteric. 2018;21(2):96-100. doi: 10.1080/13697137.2018.1430131.
8. Pinkerton JV. Hormone Therapy for Postmenopausal Women. N Engl J Med. 2020;382(5):446-55. doi: 10.1056/NEJMcp1714787.
9. Lobo RA. Hormone-replacement therapy: current thinking. Nat Rev Endocrinol. 2017;13(4):220-31. doi: 101038/nrendo.2016.164. doi: 10.1038/nrendo.2016.164.
10. Writing Group For The Women SHII. Risks and Benefits of Estrogen Plus Progestin in Healthy Postmenopausal Women: Principal Results From the Women's Health Initiative Randomized Controlled Trial. JAMA: 2002;288(3):321-33. doi: 10.1001/jama.288.3.321.
11. Guthrie KA, Lacroix AZ, Ensrud KE, Joffe H, Newton KM, Reed SD, et al. Pooled Analysis of Six Pharmacologic and Nonpharmacologic Interventions for Vasomotor Symptoms. Obstetrics & Gynecology 2015;126(2):413-22. doi: 10.1097/AOG.0000000000000927.
12. Kaunitz AM. Extended duration use of menopausal hormone therapy. Menopause. 2014;21(6):679-81. doi: 10.1097/GME.0000000000000175.
13. Johnson A, Roberts L, Elkins G. Complementary and Alternative Medicine for Menopause. JeVID Based Integr Med. 2019;24: 2515690X19829380. doi: 10.1177/2515690X19829380
14. Madika A-L, MacDonald CJ, Fournier A, Mounier-Vehier C, Béraud G, Boutron-Ruault M-C. Menopausal hormone therapy and risk of incident hypertension: role of the route of estrogen administration and progestogens in the E3N cohort. Menopause 2021;28(111204-1208. doi: 10.1097/GME.0000000000001839.).
15. ABC-2021-0218. ABC-2021-0218. Ferreira-Campos et al Terapia hormonal e hipertensão em mulheres na pós-menopausa:resultados do estudo longitudinal de saúde do adulto. Arq Bras Cardiol.2022.

Simple Echocardiographic Parameters are Strong Predictors of the Cardiovascular Risk in Asymptomatic Individuals: Elsa-Brasil Cohort

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Abstract

Background: Several studies have evaluated echocardiographic abnormalities as predictors of cardiovascular risk; however, none have associated the global cardiovascular risk with echocardiographic abnormalities in the Brazilian population.

Objective: This study evaluates the association between the global cardiovascular risk (ASCVD score) and three echocardiographic abnormalities: left ventricular hypertrophy (LVH), left ventricular diastolic dysfunction (LVDD), and increased left atrium (LA) volume.

Methods: The study population was composed of participants from ELSA-Brasil who underwent echocardiography between 2008 and 2010 (n = 2973). They were asymptomatic and had no history of cardiovascular disease. The ASCVD score was calculated in two periods: 2008-2010 and 2012-2014. Prevalence ratios (PR) were estimated with 95% confidence intervals (CI).

Results: There is an association between echocardiographic abnormalities and high global cardiovascular risk (ASCVD score ≥ 7.5) in both study periods, separately. The combined global risk (low risk in the first period and high risk in the second period) was significantly associated only with LVDD (PR = 3.68, CI 95% 2.63–5.15) and LVH (PR = 2.20, 95% CI 1.62–3.00).

Conclusion: Echocardiographic abnormalities (LVDD, LVH, and increased LA volume) are independent predictors of cardiovascular risk in Brazilian adults.

Keywords: Cardiovascular Diseases; Risk Factors; Left Ventricular Diastolic Dysfunction; Left Atrial Volume; Diagnostic, Imaging; Echocardiography/methods; Atherosclerosis; Sedentarism.

Introduction

Cardiovascular diseases (CVD) are a global public health problem and a research priority in many countries.[1] In Brazil, the Longitudinal Study of Adult Health (ELSA-Brasil) aims to investigate the prevalence of chronic non-communicable diseases, especially CVD, and their risk factors in the adult population.[2] In this context, the identification of CV risk predictors merits investigation.

The most universally used CV risk score is the Atherosclerotic Cardiovascular Disease (ASCVD) score, whose parameters were defined by studies conducted in the United States of America.[3] Other studies have assessed the predictive ability of echocardiographic abnormalities.[4,5] However, no study has investigated the association of the ASCVD score with echocardiographic abnormalities in the Brazilian population.

Thus, considering the ASCVD score as an intermediate CV outcome, this study assessed the association of echocardiographic abnormalities with ASCVD in asymptomatic individuals without previous CVD involved in two periods of the ELSA-Brasil study: baseline (period 1) and 4 years later (period 2).

Methods

Population

The population was composed of ELSA-Brasil participants who underwent echocardiography between 2008 and 2010. These individuals were part of two samples, one random,

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composed of 10% of the cohort (n = 15,105) and the other, composed of individuals older than 60 years not included in the random sample. At the baseline, those who reported CVD were excluded (left ventricular dysfunction, myocardial infarction, stroke, atrial fibrillation or flutter, and moderate or severe valve disease).

To calculate the ASCVD score, data produced in 2008–2010 and 2012–2014 by ELSA-Brasil were extracted, as described elsewhere.[6] Echocardiography was performed only in the first period.

As a multicenter study, the research protocol was approved by the ethics committee of each institution and by the National Research Ethics Commission.

Echocardiography

Echocardiography was performed by trained and certified professionals using a device of the same model (Aplio XG; Toshiba Corporation, Tokyo, Japan) at all six ELSA-Brasil centers, following a standardized technique. Real-time and static images were selected and sent in DICOM (Digital Imaging Communications in Medicine) format to the reading center, where the measurements of the examinations were performed.[6]

We analyzed three echocardiographic parameters: left ventricular hypertrophy (LVH), left ventricular diastolic dysfunction (LVDD) and increased left atrium (LA) volume. LVH was defined according to two criteria: mass index and relative wall thickness (RWT). The mass index was calculated by indexing the LV mass to the body surface area (BSA) or height ^{2,7}.[7] The LV mass measurements were done by 2D echocardiography (linear method)[8] at the reading center,[9] and the LV mass (in grams) was calculated using the formula 0.80 (1.04 [interventricular septum + LV internal dimension + posterior wall]^3 - [LV internal dimension]^3) + 0.6, according to Devereux et al.[10] RWT was calculated using the formula (2 × posterior wall thickness) / (LV inner diameter at the end of diastole).[8] Using these two criteria, the LV geometry was classified as normal, concentric remodeling, concentric hypertrophy, or eccentric hypertrophy.[11] The cutoff point for the mass indexed to the BSA was 95 g/m^2 for women and 115 g/m^2 for men.[8] With the mass indexed to height,^{2,7} the cutoff point was 44 g/height^{2,7} for women and 48 g/height^{2,7} for men.[12] The cutoff point for the RWT for both sexes was 0.42, considering the two mass index criteria.[8]

Assessment of LV diastolic function was based on the American Society of Echocardiography recommendations published in 2009.[13] The following measures were used to classify the diastolic function: E/A ratio (ratio of E and A velocities of mitral influx), the velocity of medial and lateral e' waves (assessed with tissue Doppler), E/e' ratio, and indexed LA volume. The cutoff points for classifying diastolic dysfunction were as follows: E/A (≤ 0.8, between 0.8 and 2.0, and ≥ 2.0), medial e' (< 8), lateral e' (< 10), mean E/e' (≤ 8,>8 and <13, and ≥ 13), and indexed LA volume (> 34 mL/m^2). Based on these criteria, diastolic function was classified as normal, diastolic dysfunction grade I or impaired relaxation (normal LA pressure), diastolic dysfunction grade II or pseudonormal (signs of elevated LA pressure), diastolic dysfunction grade III or restrictive filling (significantly elevated LA pressure).

LA volume indexed to the BSA for men and women was categorized as normal (up to 34 mL/m^2), mildly enlarged (between 35 and 41 mL/m^2), moderately enlarged (between 42 and 48 mL/m^2), and severely enlarged (> 48 mL/m^2).[8]

To jointly analyze the three echocardiographic abnormalities (LVDD, LVH, and increased LA volume), the variable "Echocardio parameter" was created. It was normal when none of the three abnormalities were present and abnormal when at least one of the abnormalities was present.

Global CV risk score

The global CV risk (ASCVD score) was calculated based on age, sex, race (white, African-American, and others), total cholesterol, high-density lipoprotein (HDL)-cholesterol, systolic blood pressure, treatment for hypertension, presence of diabetes mellitus, and smoking. This score calculates the risk of experiencing a cardiovascular fatal or non-fatal event in 10 years (low < 7.5% and high ≥ 7.5%).[3] The global risk for each participant in the two study periods was calculated. The combined risk, defined as low risk in the first period and high risk in the second period, was also analyzed.

Other CV risk factors

In addition to the three echocardiographic abnormalities, we also assessed physical activity, alcohol consumption, serum triglyceride level, body mass index (BMI), and educational level. Concerning physical activity, participants were categorized as sedentary/not very active (< 150 min/week of moderate physical activity) or physically active/very active (at least 150 min/week of moderate physical activity).[14] Concerning alcohol consumption, the categories were excessive or non-excessive drinking (> 210 or < 210 g of alcohol per week for men and > 140 or < 140 g of alcohol per week for women). Concerning serum triglyceride level, the categories were < 150 or ≥ 150 mg/dL. With respect to BMI, the participants were classified as obese (≥ 30 kg/m^2), overweight (≥ 25and < 30 kg/m^2), or eutrophic (< 25 kg/m^2).[15] Finally, two categories of educational level were considered: up to complete high school and university degree.

Statistical analysis

Initially, a descriptive analysis of the participants' sociodemographic, clinical, and echocardiographic profiles was performed, considering absolute and relative frequencies. Subsequently, a bivariate logistic regression analysis was performed to verify the association between the echocardiographic, clinical, and sociodemographic characteristics and the global CV risk in each study period and the combined risk. Prevalence ratios (PRs) were estimated with 95% confidence intervals (CIs), using the CS command of the STATA version 12 software. The prLogistic package of R version 3.5.1 software was used for the multivariate logistic regression analysis to estimate PRs using logistic models and CIs using the delta and bootstrap methods.[16] Effect modification was evaluated for the following

covariates: education, physical activity, excessive alcohol consumption, triglyceride level, and BMI. The likelihood ratio test was used in the multivariate logistic regression model, incorporating product terms (interaction) between the main association and each covariate. A p-value of < 5% in the likelihood ratio test was indicative of an effect change.

Results

Sociodemographic and clinical characteristics of the study population at baseline

After excluding individuals who reported having a CV disease, the final study sample comprised 2973 participants, with an average age of 60.26 ± 8.89 years, mainly white and black (56.4% and 39.9%), and most with a university degree (56.7%). Sociodemographic and clinical characteristics of the participants at the baseline of the study are shown in table 1. Clinical characteristics of the participants in period 2 of the study are shown in table S1.

Global CV risk (ASCVD score)

The ASCVD score was assessed as an intermediate clinical outcome in the two study periods. Association of global risk with separate and grouped echocardiographic parameters was analyzed using sociodemographic (educational level) and clinical (physical activity, alcohol intake, hypertriglyceridemia, and BMI) factors. As age, sex, race/color, total cholesterol, HDL-cholesterol, hypertension, diabetes mellitus, and smoking are part of the construction of this risk score, the association with these variables was not evaluated.

The global risk was < 7.5% (low) in 1398 participants (47%) in the first period and 1034 participants (38.3%) in the second period, and ≥ 7.5% (high) in 1575 participants (53%) in the first period and 1665 participants (61.7%) in the second period. The combined risk (low risk in the first period and high risk in the second period) was present in 312 participants (23.7%).

Echocardiographic characteristics

In 50.8% of the participants' diastolic function was considered normal, and in 41.8% as abnormal (of these, 31.2% were grade I). In 7.4% of the participants, the diastolic function or the degree of diastolic dysfunction could not be determined.

The LA volume was increased in 15.6% of 2438 participants.

LVH was classified based on two types of mass indexing: BSA (in 2670 participants) and height$^{2.7}$ (in 2651 participants). The proportion of participants with LVH was higher when indexing by height was used (18.5% versus 10.6%), mainly at the expense of concentric hypertrophy (11.1% versus 6.4%).

In the simultaneous analysis of the three parameters, 65.8% of the participants presented at least one and 34.2% had none of the three abnormalities. (Table 2)

Bivariate regression analysis of the association of echocardiographic, clinical, and sociodemographic abnormalities with global risk

Among the echocardiographic abnormalities, LVDD had the strongest association with global risk (≥7.5) in the first and second) study periods. LVDD was also the abnormality that was most associated with the combined risk.

The association between LVH and global risk was similar for both mass indices (indexed to BSA and indexed to height$^{2.7}$). LVH was associated with global risk in both periods, with the strongest association being with the combined global risk.

Increased LA volume was the variable with the lowest association with global risk and without association with the combined risk.

When the three parameters were analyzed together (variable Echocardio parameter), the association with global risk was greater in the first study period.

No association was observed between physical activity and global risk concerning the other risk factors. On the contrary, excessive drinking, high triglycerides, BMI, and educational level (university degree as a reference) were associated with risk in both study periods. The Association of these variables with the combined risk was not statistically significant. (Table 3)

Multivariate logistic regression analysis of the association between echocardiographic abnormalities and global risk

The association between echocardiographic abnormalities and global risk was adjusted for some clinical and sociodemographic variables that were not part of the outcome (global risk). The dysfunction was stratified using this variable because of the effect interaction between LVDD and educational level in the first multivariate regression model using the risk in the first period. However, when LVDD was assessed as the main variable, it was not adjusted for education.

In the first multivariate logistic regression model (echocardiographic variables and global risk in the first period), we observed that the strongest association occurred between global risk and the Echocardio parameter. The second strongest association occurred between global risk and LVDD in the participants with an education level of up to complete high school.

Likewise, the strongest association was observed in the second multivariate logistic regression model between global risk and the Echocardio parameter. The second strongest association was observed between global risk and LVDD (in this model, there was no interaction with educational level).

In the third multivariate logistic regression model (echocardiographic variables and combined global risk), LVDD was the variable with the strongest association with combined global risk. In this model, the association between combined global risk and LA dilation was not significant. (Table 4). The final regression model is shown in table S2.

In 2016, after completing this study, the new recommendations for the evaluation of LV diastolic function were published.[17] It was possible to determine LVDD applying these criteria in 1434 individuals (48%). Diastolic function was normal in 829 (57.8%)

Table 1 – Clinical and sociodemographic characteristics of the participants, n=2973, at the baseline of the study

Clinical and sociodemographic characteristics	n	%
Sex		
Men	1358	45.7
Women	1615	54.3
Ages (years)		
35- 44	220	7.4
45- 54	487	16.4
55- 64	1240	41.7
65- 74	1025	34.5
Race		
White	1658	56.4
Black	1174	39.9
Others	109	3.7
Educational level		
University degree	1686	56.7
Up to complete high school	1287	43.3
Hypertension		
Yes	1440	48.5
BMI		
Overweight	1262	42.4
Obesity	659	22.2
Fasting blood glucose		
(≥126 mg/dl)	367	12.3
Glycated hemoglobin		
(≥6.5)	323	10.9
Total cholesterol		
(> 200 mg/dl)	1847	62.2
Low HDL		
Yes	509	17.1
High triglycerides		
Yes	940	31.6
Excessive drinker		
Yes	223	7.5
Smoking		
Ex-smoker	1047	35.2
Smoker	296	10.0
Physical activity		
Sedentary	1262	42.8

BMI: body mass index; HDL: high-density lipoprotein.

participants, and among those who had diastolic dysfunction: 165 (11.5%) were classified as type I, 18 (1.3%) as type II and 3 (0.2%) as type III. In 419 (29.2%) participants, the diastolic function or the degree of diastolic dysfunction could not be determined (data not shown). The obtained results were very similar to the original: LVDD persisted with the strongest association with global risk in the first and second study periods (PR= 3.38, 95% CI 2.53; 4.52 and 2.91, 95% CI 2.40; 3.52, respectively) as well as with the combined global risk (PR = 3.24, 95 % CI 2.17; 4.84).

Table 2 – Echocardiographic characteristics of the participants in period 1, n = 2973

Characteristic	n	%
Diastolic function (n=1384)		
No dysfunction	703	50.8
Type I dysfunction	432	31.2
Type II dysfunction	147	10.6
Indeterminate	102	7.4
LA volume (n=2438)		
Normal	2058	84.4
Mildly enlarged	281	11.5
Moderately enlarged	73	3.0
Severely enlarged	26	1.1
LV geometry (mass/BSA) (n=2670)		
Normal	1449	54.3
Concentric remodeling	940	35.2
Concentric hypertrophy	170	6.4
Eccentric hypertrophy	111	4.2
LV geometry (mass/height$^{2.7}$) (n=2651)		
Normal	1344	50.7
Concentric remodeling	815	30.7
Concentric hypertrophy	295	11.1
Eccentric hypertrophy	197	7.4
Echocardio Parameter (n=1419)		
Normal	486	34.2
Abnormal	933	65.8

LA: left atrium; LV: left ventricle; BSA: body surface area.

Discussion

We observed an association between echocardiographic abnormalities and high global CV risk (ASCVD score ≥ 7.5) in the two study periods.

Of the three echocardiographic abnormalities analyzed individually, LVDD had the strongest association with global risk in the bivariate and multivariate logistic regression analyses.

Despite being a cohort of asymptomatic individuals without previous CVD, our data reveal that 41.8% of the participants had LVDD. Of these, the majority were grade I or impaired relaxation. However, in the case of a cohort of older people (mean age 60.2 ± 8.8 years), a higher prevalence of LVDD grade I was expected because normal aging is associated with a decrease in LV relaxation, leading to diastolic dysfunction.[18] It is worth mentioning that Huttin et al.[19] showed a much lower prevalence of LVDD in individuals aged > 60 years when they used the 2016 recommendations concerning previous recommendations for classifying LVDD. Likewise, Almeida et al.[20] observed that the prevalence of LVDD in individuals older than 45 years was much lower when using the 2016 recommendations[17] than when using the 2009 recommendations.[13] These authors found a prevalence of LVDD of 1.4% and 38.1% when they used the 2016 and 2009 recommendations, respectively. Similarly, in our study, we observed a prevalence of LVDD of 13% and 41.8% when using the recommendations of 2016 and 2009, respectively.

In the bivariate logistic regression analysis of the association between echocardiographic abnormalities and the global risk in periods 1 and 2or the combined risk, all three abnormalities were associated with the ASCVD score. LVDD showed the strongest association with the CV risk among the three abnormalities. Tsang et al.[21] also concluded that LVDD was a stronger risk predictor than LA dilation and LV mass. Likewise, Kardys et al.[22] observed that LVDD was a stronger predictor of CV risk than LVH. These authors found no association between LA dilation and mortality from all causes.

When multivariate logistic regression was performed, LVDD remained the echocardiographic parameter with the greatest association with global risk. The other echocardiographic parameters analyzed (LVH and LA dilation) maintained associations with the global risk in both study periods; however, LA dilation did not present a statistically significant association with the combined risk. In the Strong Heart Study,[23] it was observed that LVDD was associated with CV mortality regardless

Table 3 – Bivariate association between global cardiovascular risk (in both periods and combined risk) and echocardiographic and clinical characteristics in period 1 (2008 - 2010), n = 2973

Variable	Global risk (period 1)		Global risk (period 2)		Combined risk (low-risk period 1 and high-risk period 2)	
	PR	CI 95%	PR	CI 95%	PR	CI 95%
Echocardio Parameter						
Abnormal	3.26	2.72; 3.91	2.59	2.23; 3.01	2.74	2.00; 3.76
Diastolic function						
With dysfunction	2.87	2.49; 3.30	2.55	2.26; 2.89	3.48	2.55; 4.74
LV geometry (mass/BSA)						
With hypertrophy	1.54	1.42; 1.67	1.45	1.36; 1.56	2.10	1.59; 2.77
LV geometry (mass/ height$^{2.7}$)						
With hypertrophy	1.48	1.37; 1.60	1.44	1.35; 1.53	1.95	1.56; 2.45
LA volume						
Increased	1.24	1.14; 1.36	1.16	1.07; 1.26	1.16	0.87; 1.55
Leisure-time physical activity						
Sedentary	1.00	0.94; 1.08	1.02	0.96; 1.08	0.98	0.81; 1.20
Excessive drinker						
Yes	1.34	1.22; 1.47	1.24	1.14; 1.35	1.04	0.67; 1.61
High triglycerides						
Yes	1.30	1.22; 1.39	1.20	1.13; 1.27	1.09	0.90; 1.36
BMI						
Overweight	1.27	1.17; 1.38	1.19	1.11; 1.28	1.09	0.88; 1.36
Obesity	1.30	1.19; 1.43	1.22	1.13; 1.33	1.27	0.99; 1.64
Educational level						
Up to complete high school	1.11	1.04; 1.19	1.08	1.02; 1.15	1.13	0.93; 1.37

LA: left atrium; LV: left ventricle; BSA: body surface area; BMI: body mass index.

Table 4 – Multivariate logistic regression* of echocardiographic variables in relation to the global risk, considering prevalence ratios (PR) and respective 95% confidence intervals (95% CI), n = 2973

Variables	Global risk Period 1 (model 1)		Global risk Period 2 (model 2)		Combined global risk Periods 1 and 2 (model 3)	
	PR	CI 95%	PR	CI 95%	PR	CI 95%
Echocardio parameter						
Abnormal	4.01	3.20; 5.03	3.04	2.49; 3.70	2.80	2.02; 3.88
Diastolic dysfunction						
Presence (all)	-	-	2.95	2.46; 3.54	3.68	2.63; 5.15
Presence (University degree **)	2.91	2.31; 3.67	-	-	-	-
Presence (Up to complete high school**)	3.88	2.87; 5.26	-	-	-	-
LV hypertrophy						
Presence	1.72	1.52; 1.94	1.63	1.47; 1.81	2.20	1.62; 3.00
LA dilation						
Presence	1.31	1.15; 1.49	1.20	1.07; 1.34	1.16	0.86; 1.57

**adjusted for: high triglycerides, BMI, physical activity, educational level and excessive drinker. **stratified by educational level and adjusted for: high triglycerides, BMI, physical activity and excessive drinker. LA: left atrium; LV: left ventricle.*

of the other echocardiographic abnormalities, similar to the result of our study. Likewise, Redfield et al.[24] observed that LVDD was strongly associated with mortality from all causes, thus proving to be a predictor of CV risk.

The Framingham Heart Study[25] showed that LVH is a predictor of death from CVD and all causes. Recently, Desai et al.[26] and Lind et al.[27] described a risk association between LVH and CV events, similar to what was found in this study. Unlike the current study, however, those previous studies evaluated clinical outcomes (coronary heart disease, cerebrovascular disease, and heart failure) and not an intermediate outcome such as the ASCVD score.

Increased LA volume was associated with global risk (ASCVD score ≥ 7.5) in both periods of the current study, both in the bivariate and multivariate logistic regression analyses. However, we did not find a significant association with the combined risk. Similarly, Laukkanen et al.[28] observed an association between LA dilation and mortality; however, when adjusted for LVH, this association was not significant. In another study, Gardin et al.[29] observed an association of LA dilation only with heart failure but not with ischemic heart disease. Bombelli et al.[30] concluded that LA dilation is a predictor of CV events.

This study demonstrated that echocardiographic abnormalities are associated with a high-risk score (≥ 7.5), whereas the absence of these abnormalities is associated with a low-risk score (< 7.5). Thus, these echocardiographic parameters can be adopted as risk markers, expanding the range of diagnostic findings that allow the early estimation of CV risk in patients. Echocardiographic findings are influenced by some risk factors part of the ASCVD score, mainly blood pressure and diabetes. They may also reflect subclinical changes such as coronary atherosclerosis and myocardial hypertrophy, among others, that are not part of the score. We chose to use the ASCVD score in our study because it is the 10-year CV risk prediction score most widely used internationally.

Study limitations and future perspectives

Our study had some limitations. As the ELSA-Brasil cohort comprises civil servants, the possibility of generalizing our results to the Brazilian adult population is limited. However, the generalization of the results is partly supported by the similarities in the prevalence of behavioral risk factors and chronic conditions identified in two studies: ELSA-Brasil[15] and VIGITEL,[31] which produced representative data for Brazilian adults. Another limitation of the study is the failure to use the most current classification of LVDD because the data were collected between 2008 and 2010. However, as we described in Results, applying the 2016 recommendations to our data, we observed essentially the same findings, reinforcing the importance of the LVDD parameter for the global cardiovascular risk. New cohort studies in the Brazilian population should be carried out to identify whether these echocardiographic abnormalities can add incremental prognostic information to ASCVD.

Conclusion

Our study showed that echocardiographic abnormalities (LVDD, LVH, and increased LA volume) are associated with a high global CV risk (ASCVD score ≥ 7.5) in asymptomatic Brazilian adults without previous CVD. Of the three echocardiographic abnormalities, LVDD showed the strongest association with the global risk. More studies are needed to assess the cost-effectiveness ratio to justify the incorporation of these variables in the CV risk estimation routine and the adoption of prevention measures at the population level.

Author Contributions

Conception and design of the research: Fernandes LP, Aras Junior R; Acquisition of data: Fernandes LP, Almeida MCC; Analysis and interpretation of the data: Fernandes LP, Almeida MCC, Campos ACP, Câmara EN, Foppa M, Aras Junior R; Statistical analysis: Fernandes LP, Campos ACP; Writing of the manuscript: Fernandes LP; Critical revision of the manuscript for intellectual content: Almeida MCC, Matos SA, Câmara EN, Foppa M, Ribeiro AL, Barreto SM, Aras Junior R.

Potential Conflict of Interest

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

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Study Association

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Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Instituto de Saúde Coletiva/UFBA under the protocol number 027-06. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

References

1. World Health Organization (WHO). World health statistics 2018: monitoring health for the SDGs, sustainable development goals. Geneva: 2018. p.1–86
2. Brasil. Ministério da Saúde. Departamento de Ciência e Tecnologia, Secretaria de Ciência, Tecnologia e Insumos Estratégicos [ELSA Brasil: the greatest epidemiological study in Latin America]. Rev Saude Publica. 2009 Feb;43(1). doi:S0034-89102009000100028
3. Goff DC, Lloyd-Jones DM, Bennett G, Coady S, D'Agostino RB, Gibbons R et al. 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk. J Am Coll Cardiol. 2014 Jul 1;63(25):2935–59. doi: 10.1016/j.jacc.2013.11.005. Epub 2013 Nov 12.
4. Armstrong AC, Jacobs DR, Gidding SS, Colangelo LA, Gjesdal O, Lewis CE et al. Framingham score and LV mass predict events in young adults: CARDIA study. Int J Cardiol. 2014 Mar 15;172(2):350–5. doi: 10.1016/j.ijcard.2014.01.00

5. Nayor M, Cooper LL, Enserro DM, Xanthakis V, Larson MG, Benjamin EJ et al. Left ventricular diastolic dysfunction in the community: Impact of diagnostic criteria on the burden, correlates, and prognosis. J Am Heart Assoc. 2018;7(11):e008291. doi: 10.1161/JAHA.117.008291.

6. Aquino EML, Barreto SM, Bensenor IM, Carvalho MS, Chor D, Duncan BB et al. Brazilian Longitudinal Study of Adult Health (ELSA-Brasil): Objectives and Design. Am J Epidemiol. 2012 Feb 15;175(4):315–24. doi: 10.1161/JAHA.117.008291.

7. Cuspidi C, Meani S, Negri F, Giudici V, Valerio C, Sala C et al. Indexation of left ventricular mass to body surface area and height to allometric power of 2.7: Is the difference limited to obese hypertensives? J Hum Hypertens. 2009 Nov;23(11):728–34. doi: 10.1038/jhh.2009.16.

8. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L et al. Recommendations for Cardiac Chamber Quantification by Echocardiography in Adults: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging. 2015 Mar;16(3):233–71. doi: 10.1093/ehjci/jev014.

9. Tognon AP, Foppa M, Luft VC, Chambless LE, Lotufo P, El Aouar LMM et al. Reproducibility of Left ventricular Mass by Echocardiogram in the ELSA-Brasil. Arq Bras Cardiol. 2015 Feb; 104(2): 104- 11. doi: 10.5935/abc.20140183. Epub 2014 Nov 28.

10. Devereux RB, Alonso DR, Lutas EM, Gottlieb GJ, Campo E, Sachs I et al. Echocardiographic assessment of left ventricular hypertrophy: Comparison to necropsy findings. Am J Cardiol. 1986 Feb 15;57(6):450–8. doi: 10.1016/0002-9149(86)90771-x.

11. Foppa M, Duncan BB, Rohde LEP. Echocardiography-based left ventricular mass estimation. How should we define hypertrophy? Cardiovasc Ultrasound. 2005 Jun 17;3:17. doi: 10.1186/1476-7120-3-17.

12. Marwick TH, Gillebert TC, Aurigemma G, Chirinos J, Derumeaux G, Galderisi M, et al. Recommendations on the Use of Echocardiography in Adult Hypertension: A Report from the European Association of Cardiovascular Imaging (EACVI) and the American Society of Echocardiography (ASE). J Am Soc Echocardiogr. 2015 Jul 1;28(7):727–54. doi: 10.1016/j.echo.2015.05.002.

13. Nagueh SF, Appleton CP, Gillebert TC, Marino PN, Oh JK, Smiseth OA et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. Eur J Echocardiogr.2009;10(2):165-93, doi: 10.1093/ejechocard/jep007.

14. Pitanga FJG, Matos SMA, Almeida M da C, Barreto SM, Aquino EML. Leisure-time physical activity, but not commuting physical activity, is associated with cardiovascular risk among ELSA-Brasil participants. Arq Bras Cardiol. 2018;110(1):36–43. doi: 10.5935/abc.20170178.

15. Schmidt MI, Duncan BB, Mill JG, Lotufo PA, Chor D, Barreto SM, et al. Cohort Profile: Longitudinal Study of Adult Health (ELSA-Brasil). Int J Epidemiol. 2015 Feb 1;44(1):68–75. doi: 10.1093/ije/dyu027. Epub 2014 Feb 27.

16. Ospina R, Amorim LD. Estimation of prevalence ratios using logistic models and confidence intervals with delta and brootstrap methods. 2019. [Internet] [Cited in 2021 May 10] Available from: http://www2.uaem.mx/r-mirror/web/packages/prLogist.

17. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF, Dokainish H, Edvardsen T et al. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging. 2016 Dec;17(12):1321–60 doi: 10.1093/ehjci/jew082.

18. Schirmer H, Lunde P, Rasmussen K. Mitral flow derived Doppler indices of left ventricular diastolic function in a general population. The Tromso study. Eur Heart J. 2000;21(16):1376–86. doi: 10.1053/euhj.1999.2036.

19. Huttin O, Fraser AG, Coiro S, Bozec E, Selton-Suty C, Lamiral Z et al. Impact of Changes in Consensus Diagnostic Recommendations on the Echocardiographic Prevalence of Diastolic Dysfunction. J Am Coll Cardiol. 2017 Jun 27;69(25):3119–21. doi: 10.1016/j.jacc.2017.04.039.

20. Almeida JG, Fontes-Carvalho R, Sampaio F, Ribeiro J, Bettencourt P, Flachskampf FA et al. Impact of the 2016 ASE/EACVI recommendations on the prevalence of diastolic dysfunction in the general population. Eur Heart J Cardiovasc Imaging. 2018;19(4):380–6. doi: 10.1093/ehjci/jex252.

21. Tsang TSM, Barnes ME, Gersh BJ, Takemoto Y, Rosales AG, Bailey KR et al. Prediction of risk for first age-related cardiovascular events in an elderly population: The incremental value of echocardiography. J Am Coll Cardiol. 2003;42(7):1199–205. doi: 10.1016/s0735-1097(03)00943-4. DOI: 10.1016/j.ijcard.2007.12.031

22. Kardys I, Deckers JW, Stricker BHC, Vletter WB, Hofman A, Witteman JCM. Echocardiographic parameters and all-cause mortality: The Rotterdam Study. Int J Cardiol. 2009;133(2):198–204. doi: 10.1016/j.ijcard.2007.12.031.

23. Bella JN, Palmieri V, Roman MJ, Liu JE, Welty TK, Lee ET et al. Mitral ratio of peak early to late diastolic filling velocity as a predictor of mortality in middle-aged and elderly adults: The strong heart study. Circulation. 2002 Apr 23;105(16):1928–33. doi: 10.1161/01.cir.0000015076.37047.d9.

24. Redfield MM, Jacobsen SJ, Burnett JC, Mahoney DW, Bailey KR, Rodeheffer RJ. Burden of systolic and diastolic ventricular dysfunction in the community: Appreciating the scope of the heart failure epidemic. J Am Med Assoc. 2003 Jan 8;289(2):194–202. doi: 10.1001/jama.289.2.194.

25. Levy D, Garrison RJ, Savage DD, Kannel WB, Castelli WP. Prognostic Implications of Echocardiographically Determined Left Ventricular Mass in the Framingham Heart Study. N Engl J Med 1990;322(22):1561–6. doi: 10.1056/NEJM199005313222203.

26. Desai CS, Bartz TM, Gottdiener JS, Lloyd-Jones DM, Gardin JM. Usefulness of Left Ventricular Mass and Geometry for Determining 10-Year Prediction of Cardiovascular Disease in Adults Aged >65 Years (from the Cardiovascular Health Study). Am J Cardiol. 2016;118(5):684–90. doi: 10.1016/j.amjcard.2016.06.016.

27. Lind L, Sundström J. Change in left ventricular geometry over 10 years in the elderly and risk of incident cardiovascular disease. J Hypertens. 2019;37(2):325–30. doi: 10.1097/HJH.0000000000001897.

28. Laukkanen JA, Kurl S, Eränen J, Huttunen M, Salonen JT. Left atrium size and the risk of cardiovascular death in middle-aged men. Arch Intern Med. 2005;165(15):1788–93. doi: 10.1097/HJH.0000000000001897.

29. Gardin JM, McClelland R, Kitzman D, Lima JAC, Bommer W, Klopfenstein HS et al . M-Mode echocardiographic predictors of six- to seven-year incidence of coronary heart disease, stroke, congestive heart failure, and mortality in an elderly cohort (The Cardiovascular Health Study). Am J Cardiol. 2001;87(9):1051–7. doi: 10.1016/s0002-9149(01)01460-6.

30. Bombelli M, Facchetti R, Cuspidi C, Villa P, Dozio D, Brambilla G et al. Prognostic significance of left atrial enlargement in a general population results of the PAMELA study. Hypertension. 2014;64(6):1205–11. doi: 10.1161/HYPERTENSIONAHA.114.03975.

31. Brasil.Ministério da Saúde. Departamento de Análise de Situação de Saúde. Vigilância de Fatores de Risco e Proteção para Doenças Crônicas por Inquérito Telefônico, Vigitel - 2010. Brasília;2011.

*Supplemental Materials

For additional information of table S1, please click here.

For additional information of table S2, please click here.

Can Simple Echocardiographic Parameters Replace The ASCVD Probabilistic Model Calculation?

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Short Editorial related to the article: Simple Echocardiographic Parameters are Strong Predictors of the Cardiovascular Risk in Asymptomatic Individuals: Elsa-Brasil Cohort

The study by Fernandes et al.[1] used data from the ELSA-BRASIL Cohort.[2,3] It showed that in asymptomatic patients with no history of cardiovascular disease, echocardiographic measurements that are part of the daily routine of any echocardiography service are independently associated with the ASCVD predictor model. A total of 2,973 Brazilian participants without cardiovascular disease were evaluated between 2008 and 2010. The ASCVD score calculation used data produced in 2008-2010 and 2012-2014; echocardiography was performed exclusively at the initial moment (period 1). After multivariate logistic regression analysis, the echocardiographic parameters with statistical significance (controlled for body mass index, hypertriglyceridemia, physical activity, educational level and excessive alcohol consumption) were diastolic dysfunction, left ventricular hypertrophy, and left atrial volume indexed by body surface area. Left ventricular diastolic dysfunction was the strongest predictor of association with a high risk of cardiovascular events (ASCVD > 7.5%).[1]

Diastolic dysfunction is a marker of cardiovascular events, including total mortality and hospitalizations for HF.[4] In the ischemic cascade, diastolic dysfunction, symptomatic or not, is one of the earliest manifestations. It is also useful in identifying those patients with stage B heart failure.[4] Echocardiography is the non-invasive, available and low-cost tool most used to evaluate this alteration. The major obstacle is that ventricular diastole mechanisms are complex, multifactorial, age-related, and subject to both acute and chronic hemodynamic and coronary flow changes.[4-6]

Expressing what we have just described, the international guidelines focused on this topic have reduced the number of variables analyzed with significant changes in the search for greater practicality and diagnostic accuracy.[5,6] Despite the modifications already incorporated, its diagnosis is sometimes difficult, laborious and still with "indeterminate" results.[4-6] The most relevant echocardiographic parameter found in this publication, from the point of view of the association with ASCVD, is perhaps the echocardiographic finding most subject to criticism. There are up to fifteen variables that can be interpreted in verifying LV diastole, all with their respective limitations.[4-7] This somehow impairs its reliability, reproducibility and, consequently, its external validity.

Left ventricular hypertrophy is a known marker of cardiovascular events, including total mortality,[8,9] but without a defined association with intermediate outcomes (score), as demonstrated in this study.

Despite being a marker of diastolic function, the left atrial volume has a weak relationship with it and with LV filling pressures,[4] especially in this specific profile of analyzed participants. Larger atrial volumes are related to higher pressures in this cavity. However, this volumetric increase can occur due to other situations not directly linked to atherosclerotic disease. This increase may result from rheumatic mitral disease, atrial arrhythmias, and even physiological changes in healthy athletes.[4]

The study by Fernandes et al.[1] is relevant as it exclusively analyzed the Brazilian population and demonstrated an association between echocardiogram data and the ASVCD probabilistic score. So, can echocardiographic parameters of diastolic function replace the calculation of this predictive score? Although there is an independent association between them, biological systems are complex, and other variables that may confuse are not fully addressed. Another issue to consider is that these three parameters are subject to different quantification techniques and may suffer different influences and an inter- and intra-observer variability beyond acceptable. However, we believe that the study by Fernandes et al.[1] opens the possibility for future studies aiming to assess whether these parameters described above can add value to ASCVD, refining its prediction probability and risk stratification.

Keywords

Cardiovascular Diseases; Hypertrophy, Left Ventricular; Diastolic, Dysfunction; Echocardiography/methods; Risk, Stratification; Hospitalization; Mortality.

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References

1. Fernandes LP, Almeida MCC, Matos SA, et al. Parâmetros Ecocardiográficos Simples são Fortes Preditores de Risco Cardiovascular em Indivíduos Assintomáticos: Coorte Elsa-Brasil. Arq Bras Cardiol. 2021; (online).ahead print
2. Brasil. Ministério da Saúde. Departamento de Ciência e Tecnologia, Secretaria de Ciência, Tecnologia e Insumos Estratégicos [ELSA Brasil: the greatest epidemiological study in Latin America]. Rev Saude Publica. 2009 Feb;43(1). doi:S0034-89102009000100028
3. Aquino EML, Barreto SM, Bensenor IM, Carvalho MS, Chor D, Duncan BB et al. Brazilian Longitudinal Study of Adult Health (ELSA-Brasil): Objectives and Design. Am J Epidemiol. 2012 Feb 15;175(4):315–24. doi: 10.1161/JAHA.117.008291.
4. Nagueh SF. Left Ventricular Diastolic Function: Understanding Pathophysiology, Diagnosis, and Prognosis With Echocardiography. JACC Cardiovasc Imaging. 2020 Jan;13(1 Pt 2):228-244. doi: 10.1016/j.jcmg.2018.10.038.
5. Nagueh SF, Appleton CP, Gillebert TC, Marino PN, Oh JK, Smiseth OA, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. J Am Soc Echocardiogr. 2009;22(2):107-33. doi:10.1016/j.echo.2008.11.023
6. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF, Dokainish H, Edvardsen T, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2016;29(4):277-314. doi: 10.1016/j.echo.2016.01.011.
7. Castillo JM, Albuquerque ES, Silveira CAM,Lamprea DP, Sena DM. Avaliação da função diastólica utilizando ecocardiografia Doppler e strain bidimensional. Arq Bras Cardiol: Imagem cardiovasc. 2017;30(2):46-53. ID: biblio-833518
8. Levy D, Garrison RJ, Savage DD, Kannel WB, Castelli WP. Prognostic Implications of Echocardiographically Determined Left Ventricular Mass in the Framingham Heart Study. N Engl J Med 1990;322(22):1561–6. doi: 10.1056/NEJM199005313222203.
9. Kardys I, Deckers JW, Stricker BHC, Vletter WB, Hofman A, Witteman JCM. Echocardiographic parameters and all-cause mortality: The Rotterdam Study. Int J Cardiol. 2009;133(2):198–204. doi: 10.1016/j. ijcard.2007.12.031.

Impact of High Cardiovascular Risk on Hospital Mortality in Intensive Care Patients Hospitalized for COVID-19

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Abstract

Background: **Some studies have shown a higher prevalence of deaths in patients with cardiovascular risk factors (CRF) during hospitalization for COVID-19.**

Objectives: **To assess the impact of high cardiovascular risk in patients hospitalized in intensive care for COVID-19**

Methods: **Retrospective study with patients admitted to an intensive care unit, with a diagnosis of COVID-19 confirmed by RT-PCR, and with at least one troponin measurement during hospitalization. The criteria for defining high cardiovascular risk (HCR) patients were: history of established cardiovascular disease (myocardial infarction, stroke, or peripheral arterial disease), diabetes, chronic kidney disease with clearance < 60ml/min, or presence of 3 CRFs (hypertension, smoking, dyslipidemia, or age > 65 years). The primary outcome of this study is all-cause in-hospital mortality. P<0.05 was considered significant.**

Results: **This study included 236 patients, mean age = 61.14±16.2 years, with 63.1% men, 55.5% hypertensive, and 33.1% diabetic; 47.4% of the patients also presented HCR. A significant increase in mortality was observed as the number of risk factors increased (0 FRC: 5.9%; 1 FRC: 17.5%; 2 FRC: 32.2% and ≥3 FRC: 41.2%; p=0.001). In the logistic regression adjusted for severity (SAPS3 score), the HCR and myocardial injury group had a higher occurrence of in-hospital mortality (OR 40.38; 95% CI 11.78-138.39). Patients without HCR but with myocardial injury also exhibited a significant association with the primary outcome (OR 16.7; 95% CI 4.45-62.74).**

Conclusion: **In patients hospitalized in intensive care for COVID-19, HCR impacts in-hospital mortality only in patients with myocardial injury.**

Keywords: **Cardiovascular Diseases/complications; COVID-19; Intensive Care; Ultrasensitivity Troponin; Myocardial Injury; Cardiovascular Risk; Inpatients.**

Introduction

Since December 2019, we have observed a significant rise in the number of cases of disease caused by the new coronavirus (COVID-19), which led to the declaration of a pandemic in March 2020. To date, more than 100 million people have been infected, causing more than 2 million deaths worldwide.[1]

Initial studies that evaluated patients hospitalized for COVID-19 identified greater vulnerability of patients with cardiovascular risk factors.[2,3] In this population, myocardial injury documented by troponin increase, which proved to be an independent marker of death, is more prevalent.[4] In patients admitted to the intensive care unit, this mortality is even higher.[5]

By contrast, most studies published on this topic were carried out in developed countries, where we found a higher prevalence of these risk factors.[6] Therefore, data on the outcome of these patients in developing countries are needed.

The aim of this study is to assess hospital mortality in intensive care patients hospitalized for COVID-19 according to cardiovascular risk.

Methods

Study population

This work was a retrospective study including patients admitted to the intensive care unit of a tertiary hospital for

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COVID-19, with a serological confirmation by means of RT-PCR and with at least one ultrasensitive troponin measurement during hospitalization (convenience sample). The study period was from March/2020 to May/2020. Patients with dementia, advanced/terminal illnesses, patients undergoing palliative care, and those with a hospital stay of fewer than two days were excluded.

Data were obtained by consulting hospital electronic medical records. The data collected were: age, gender, admission and peak of ultrasensitive troponin, admission and peak d-dimer, obesity (BMI ≥ 30kg/m^2), previous heart failure (report of previous signs and symptoms compatible with heart failure or echocardiogram with reduced ejection fraction or use of medications to treat heart failure), renal failure (creatinine clearance < 60ml/min), previous acute myocardial infarction (AMI), previous stroke, peripheral arterial disease, smoking, and dyslipidemia.

The criteria for defining high cardiovascular risk (HRC) patients were: history of established cardiovascular disease (infarction, stroke, or peripheral arterial disease), diabetes, chronic kidney disease with clearance < 60ml/min, or presence of three risk factors (hypertension, smoking, dyslipidemia, or age > 65 years).

The ultrasensitive troponin kit used in the study was provided by VITROS® Ortho Clinical Diagnostics, with a cutoff point of 9ng/L (99th percentile). Above this value, we considered myocardial injury.

The primary outcome of this study is all-cause in-hospital mortality, while the secondary outcome is composite of in-hospital mortality, myocardial injury, and need for mechanical ventilation support.

Statistical analysis

Continuous variables were presented as mean and standard deviation (when there is a normal distribution) or median and interquartile range (not normally distributed). The normality test used was the Kolmogorov-Smirnov. Categorical variables were displayed as a percentage. Clinical and laboratory variables were compared according to primary and secondary outcomes in univariate analysis using the chi-square test (categorical variables) and unpaired Student's t-test or non-parametric Mann-Whitney test (continuous variables). Outcomes were also assessed according to the number of cardiovascular risk factors and were divided into four subgroups: (HCR with myocardial injury, HCR without myocardial injury, non-HCR with myocardial injury, and non-HCR without myocardial injury). These subgroups were also evaluated using binomial logistic regression adjusted by severity (using SAPS3 score) for the primary outcome. Finally, all variables studied were included in the classification tree,[7] a machine learning method, aiming to identify predictive variables of the primary outcome. $P<0.05$ was considered significant. For statistical analysis, the SPSS, version 26, was used.

Ethical aspects

This study was approved by the ethics committee of Instituto D'Or de Ensino e Pesquisa and is registered on the Brasil platform under number 33206620.00.0000.5249. As it is a retrospective study, the informed consent form was waived by the ethics committee.

Results

The flow chart of the inclusion of patients in the study is shown in Figure 1. After evaluating 271 admissions, 236 patients were included for analysis.

The characteristics of this population are shown in Table 1.

There was a high prevalence of arterial hypertension (55.5%) and diabetes (33.1%). The other risk factors were less prevalent. In the analysis of mortality according to the number of risk factors, we found a higher occurrence of the primary and secondary outcomes in patients with more cardiovascular risk factors (Figure 2).

Table 2 shows the univariate analysis of clinical variables and risk factors according to the occurrence of the primary outcome.

In univariate analysis, several clinical characteristics were significantly associated with a higher prevalence of the primary outcome. Table 3 shows the univariate analysis related to the secondary outcome.

Similar to the primary outcome, several characteristics were associated with the secondary outcome. In the analysis by risk group (HCR with myocardial injury, HCR without myocardial injury, non-HCR with myocardial injury, and non-HCR without myocardial injury), it was observed that the HCR with myocardial injury group had a higher mortality (57.9%), significantly higher than the groups without myocardial injury, but with no statistical difference compared to the non-HCR with myocardial injury group (Figure 3).

In the logistic regression adjusted for severity (SAPS3 score), the group of patients with HCR and myocardial injury had the highest risk of mortality, followed by the non-HCR group with myocardial injury (Table 4).

In the classification tree, for the primary outcome, myocardial injury was found to be the first classifying characteristic, followed by arterial hypertension. This classification model had an accuracy of 85.2% (Figure 4).

Discussion

This study evaluated the impact of high cardiovascular risk in patients admitted to intensive care for COVID-19. This approach allowed for the inclusion of patients with a higher severity profile and a higher prevalence of cardiovascular risk factors. In this population, more than half of the patients had arterial hypertension and a third had diabetes. The high proportion of patients over 65 years of age (45.3%) is also noteworthy. The main finding of this study was the observation that patients with HCR had a significantly higher mortality only when associated with myocardial injury.

Most published studies only assessed the impact of cardiovascular risk factors on mortality from COVID-19, generating conflicting results. Di Castelnuovo et al.[8] studied almost 4000 patients in an Italian multicenter study, using statistical analysis techniques based on machine learning[8]. This study included older patients (54.8% over 65 years), but

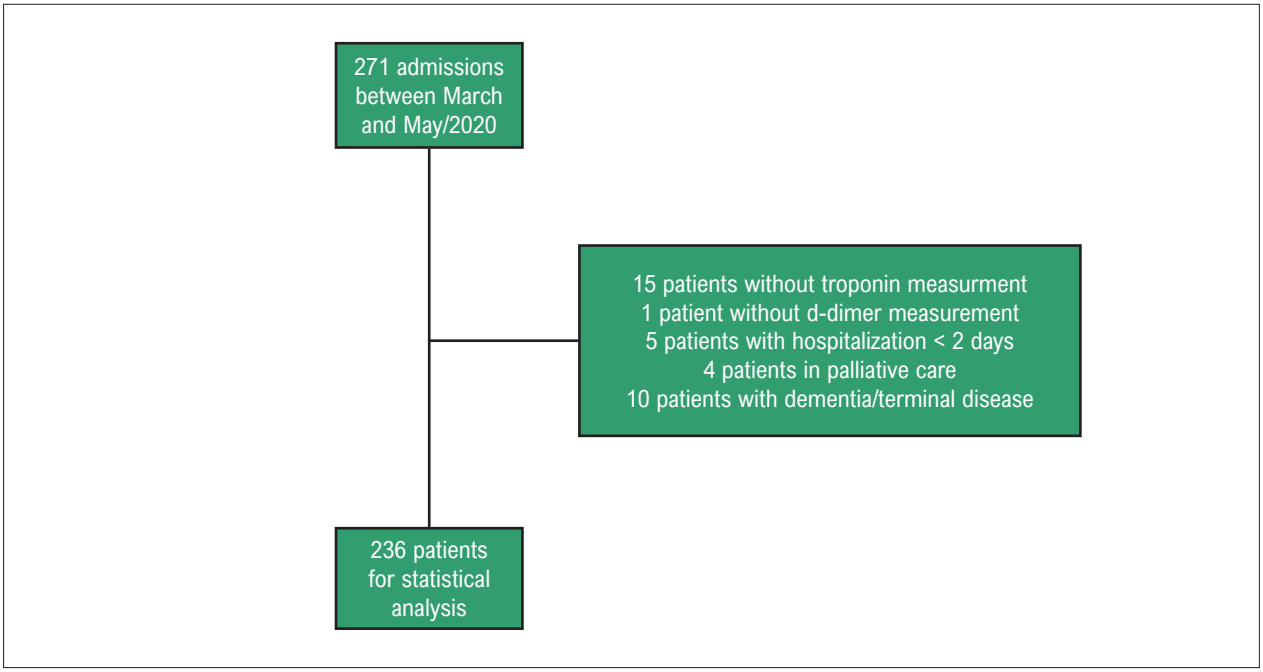

Figure 1 – *Flow chart of inclusion of patients in the study.*

Table 1 – General characteristics of the studied sample

Variables	N=236
Age (years) - mean ± SD	61.14 ± 16.2
Age ≥ 65 years (%)	45.3
Male sex (%)	63.1
Obesity (%)	20.3
Previous HF (%)	4.2
CKD (%)	5.1
SAH (%)	55.5
Diabetes (%)	33.1
Previous AMI (%)	5.9
PAD (%)	8.9
AF (%)	3.0
Previous stroke (%)	3.4
Tobacco use (%)	4.7
Dyslipidemia (%)	13.6
Mechanical ventilation (%)	30.4
Vasopressor use (%)	25.0
Renal replacement therapy (%)	10.7
Myocardial injury (%)	29.7
SAPS3 – median (IQR)	42.0 (34.5 – 50.0)
Hospitalization duration (days) – median (IQR)	7 (4 - 14)
Primary outcome (%)	24.2
Secondary outcome (%)	38.6

SD: standard deviation; HF: heart failure; CKD: chronic kidney disease; SAH: systemic arterial hypertension; AMI: acute myocardial infarction; PAD: Peripheral Artery Disease; AF: atrial fibrillation; IQR: interquartile range.

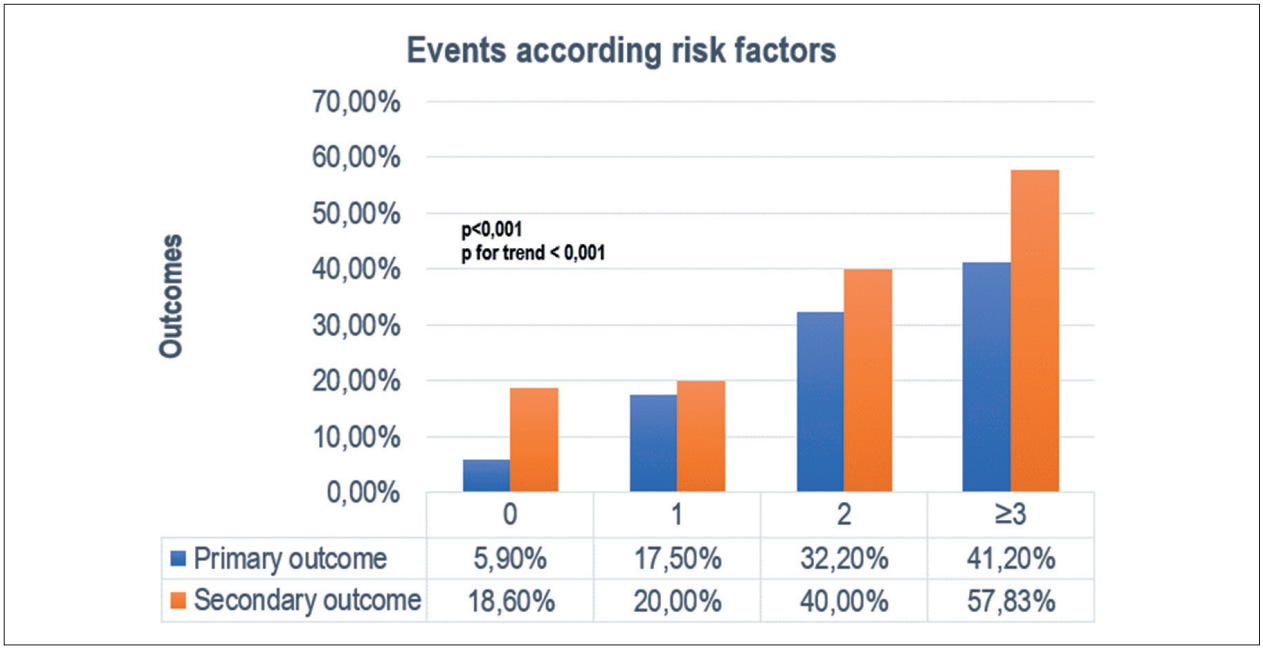

Figure 2 – *Evolution of the primary and secondary outcome according to the number of risk factors, performed using the chi-square test.*

Table 2 – Univariate analysis of characteristics according to the primary outcome

Variables	Primary outcome		p
	Yes (n=57)	No (n=179)	
Age (years) - mean ± SD	71.3±13.5	59.2±15.9	<0.001
Age ≥ 65 years (%)	75.4	35.8	<0.001
Obesity (%)	28.1	17.9	0.072
Previous HF (%)	10.5	2.2	0.015
CKD (%)	12.3	2.8	0.010
SAH (%)	68.4	51.4	0.017
Diabetes (%)	49.1	27.9	0.003
Previous AMI (%)	7.0	5.6	0.450
PAD (%)	10.5	8.4	0.396
AF (%)	8.8	1.1	0.010
Previous stroke (%)	8.8	1.7	0.022
Tobacco use (%)	7.0	3.9	0.260
Dyslipidemia (%)	15.8	12.8	0.357
Mechanical ventilation (%)	87.0	12.4	<0.001
Vasopressor use (%)	70.4	10.6	<0.001
Renal replacement therapy (%)	35.2	2.9	<0.001
Myocardial injury (%)	80.7	13.4	<0.001
Troponin peak (ng/L) - median (IQR)	58 (13-276)	7 (4 – 10)	<0.001
D-dimer peak (ng/mL) - median (IQR)	7857 (4124-24121)	1327 (754-3087)	<0.001
SAPS3 - median (IQR)	52 (44 - 61)	39 (34 - 46)	<0.001
High cardiovascular risk (%)	70.2	40.2	<0.001

Comparison of clinical and laboratory characteristics according to the primary outcome (in-hospital death). SD: standard deviation; HF: heart failure; CKD: chronic kidney disease; SAH: systemic arterial hypertension; AMI: acute myocardial infarction; PAD: Peripheral Artery Disease; AF: atrial fibrillation; IQR: interquartile range.

Table 3 – Univariate analysis of characteristics according to secondary outcome

Variables	Secondary outcome		p
	Yes (n=86)	No (n=138)	
Age (years) - mean ± DP	69.0±15.5	57.8±15.1	<0.001
Age ≥ 65 years (%)	67.0	31.7	<0.001
Obesity (%)	23.1	18.6	0.253
Previous HF (%)	7.7	2.1	0.041
CKD (%)	9.9	2.1	0.010
SAH (%)	69.2	46.9	0.001
Diabetes (%)	40.7	28.3	0.034
Previous AMI (%)	8.8	4.1	0.118
PAD (%)	12.1	6.9	0.130
AF (%)	5.5	1.4	0.080
Previous stroke (%)	6.6	1.4	0.039
Tobacco use (%)	5.5	4.1	0.427
Dyslipidemia (%)	14.3	13.1	0.471
Vasopressor use (%)	62.8	1.4	<0.001
Renal replacement therapy (%)	27.9	0.0	<0.001
D-dimer peak (ng/mL) - median (IQR)	6118 (3365-18433)	1030 (613-1880)	<0.001
SAPS3 - median (IQR)	37 (29-43)	50 (43-60)	<0.001
High cardiovascular risk (%)	62.6	37.9	<0.001

Comparison of clinical and laboratory characteristics according to secondary outcome (composed of hospital death, myocardial injury, and need for mechanical ventilation). SD: standard deviation; HF: heart failure; CKD: chronic kidney disease; SAH: systemic arterial hypertension; AMI: acute myocardial infarction; PAD: Peripheral Artery Disease; AF: atrial fibrillation; IQR: interquartile range.

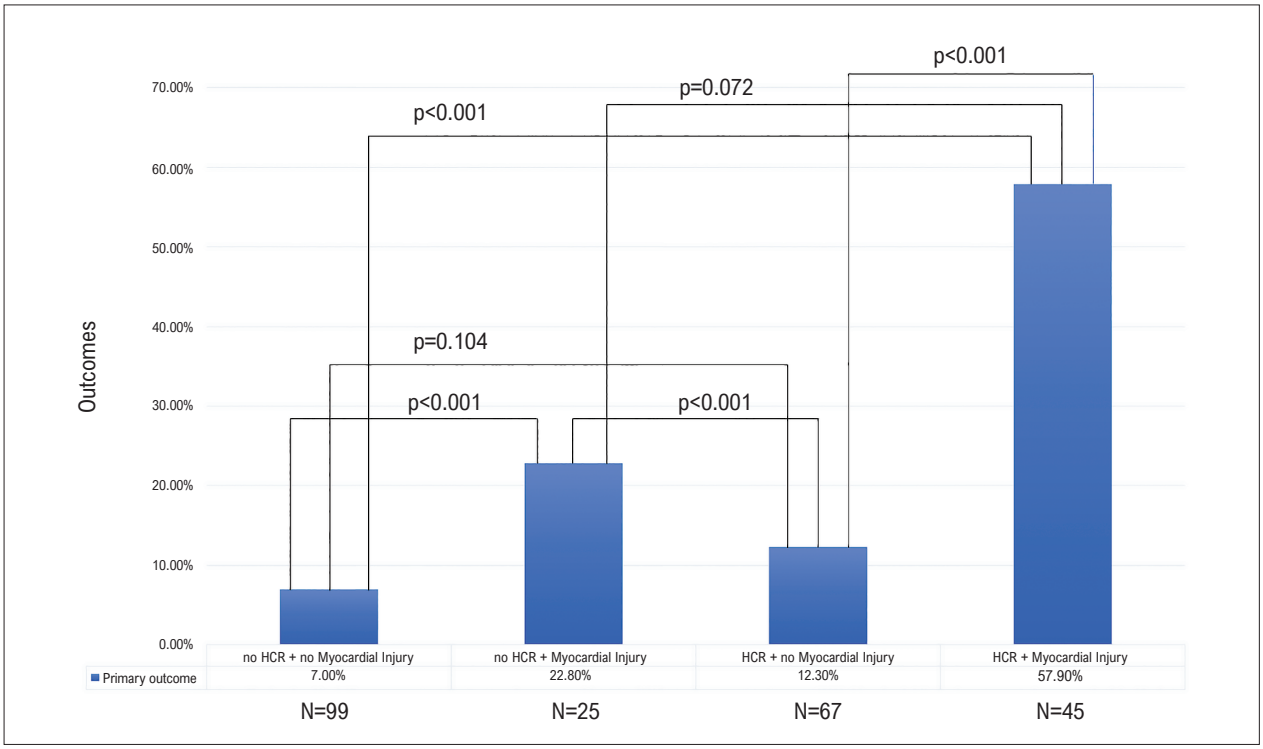

Figure 3 – *Occurrence of the primary outcome in the subgroups determined according to cardiovascular risk and troponin elevation. Comparison between groups performed with the chi-square test. HRC: high cardiovascular risk.*

Table 4 – Binomial logistic regression for the primary outcome.

Variable	OR	CI 95%	p
No HCR + no myocardial injury	Reference		
No HCR + myocardial injury	16.70	4.45-62.74	<0.001
HCR + no myocardial injury	2.06	0.56-7.56	0.2745
HCR + myocardial injury	40.38	11.78-138.39	<0.001
SAPS3	1.05	1.02-1.09	0.0023

HRC: high cardiovascular risk.

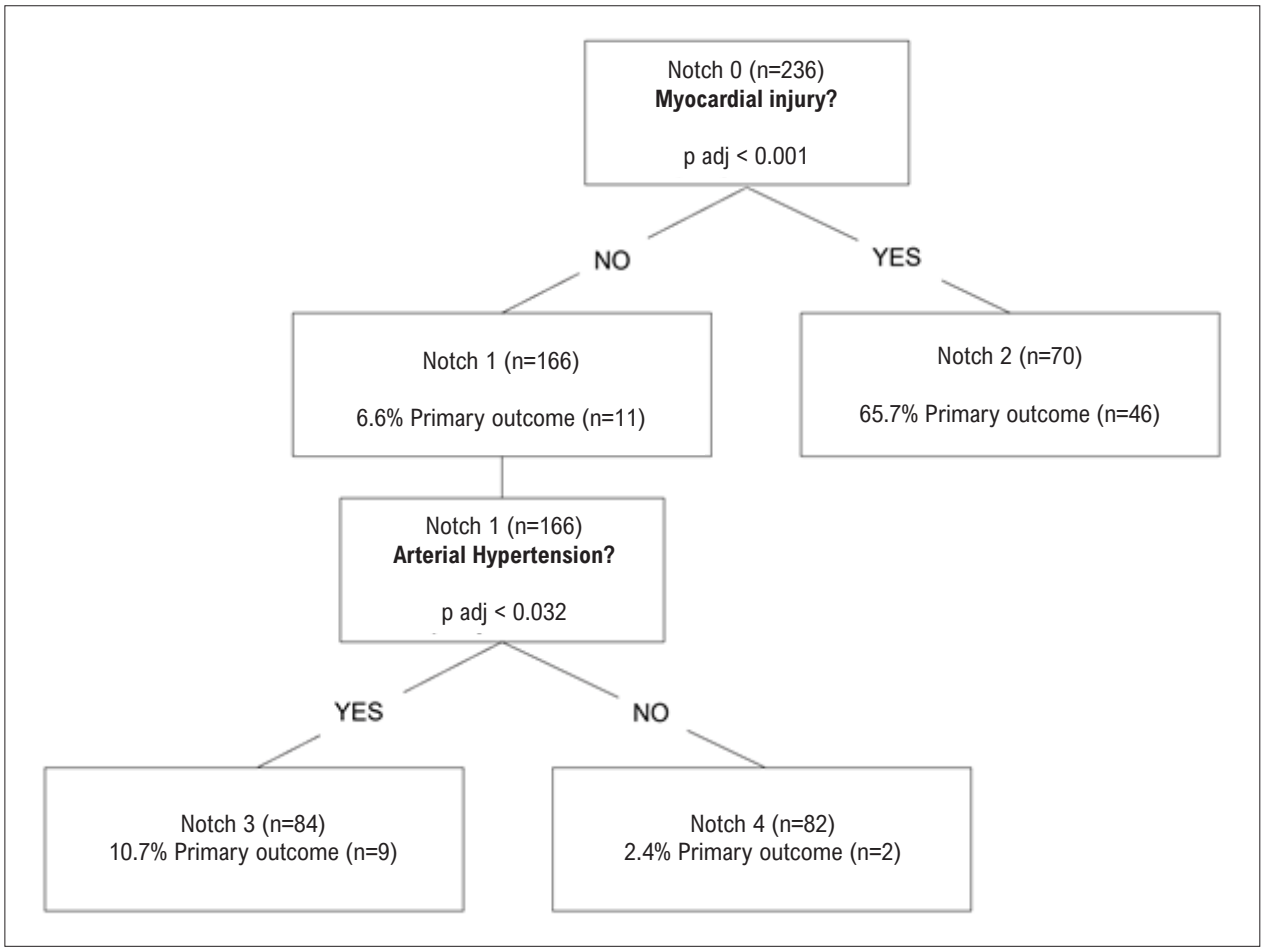

Figure 4 – *Classification tree for the primary outcome.*

with a similar prevalence of arterial hypertension (48.8%) and a lower prevalence of diabetes (19%). The main predictors of in-hospital death were renal dysfunction, high CRP levels, and advanced age. No association was found with obesity, smoking, cardiovascular disease, and related comorbidities.

Collard et al.[9] analyzed data from eight hospitals participating in the CovidPredict cohort in Germany.[9] For the analysis of cardiovascular risk factors, they evaluated the use of antihypertensive, antidiabetic, and lipid-lowering drugs. The study included 1,604 patients with a mean age of 66 years; 46% were hypertensive and 25.7% diabetic. It was observed that patients with more than one cardiovascular risk factor had a 52% higher 3-week mortality, regardless of gender and age. Furthermore, the use of two or more antihypertensive or antidiabetic, or lipid-lowering drugs was associated with a worse prognosis in patients with COVID-19. Our study found a similar result, demonstrating a progressive increase in hospital mortality as the number of risk factors increases.

Silverio et al.[10] performed a meta-analysis that included 18,300 patients.[10] In the univariate analysis, an association between in-hospital death and age, diabetes, and hypertension was observed. However, in multivariate regression, only diabetes and older age were associated with hospital death.

Only one study used a data analysis strategy similar to the present study. Guo et al.[11] analyzed 187 patients in Wuhan (origin of the pandemic), aiming to assess the association of underlying cardiovascular disease and myocardial injury with fatal outcomes in patients with COVID-19.[11] This population was younger (mean age=58.5 years), with a lower prevalence of hypertension (32.6%) and diabetes (15.0%). In the statistical analysis of this study, data related to cardiovascular risk were not evaluated, but regarding established cardiovascular disease, which was defined by the presence of hypertension, coronary artery disease and, cardiomyopathy. Patients with established cardiovascular disease and myocardial injury had a mortality of 69.44%, while patients without cardiovascular disease but with myocardial injury had a mortality of 37.5%. These results are similar to those described in this article, although different classification criteria and statistical techniques were used.

Thus, we observed that no study published so far aimed to study patients characterized as having high cardiovascular risk, which represented 47.4% of this sample. Troponin, a marker of myocardial injury, demonstrated its prognostic importance in previous studies[4,11] and, in this study, in the classification tree, it was the first prognostic marker of in-hospital mortality. In the subgroup of patients who did not present myocardial injury, arterial hypertension was the comorbidity significantly associated with in-hospital death.

In logistic regression, the SAPS3 score, a severity score in intensive care performed on admission,[12] was used to adjust for potential confounders in the analysis of subgroups according to cardiovascular risk and myocardial injury. After adjustment, it was observed that patients with high cardiovascular risk and myocardial injury had a 40-fold higher risk of in-hospital death when compared to patients without high risk and normal troponin, regardless of the severity presented upon admission. In patients with myocardial injury, but without high cardiovascular risk, a high risk of mortality was observed (OR 16.70; 95% CI 4.45-62.74), but with a lower magnitude when compared to patients with a high cardiovascular risk and myocardial injury. By contrast, in patients without myocardial injury, the high cardiovascular risk did not significantly impact in-hospital death.

This study has some limitations that are inherent to a retrospective study. All data were evaluated through the verification of electronic medical records, and it was not possible to confirm data or additional questions to the patient or family members. In addition, not all patients underwent echocardiography or BNP measurements, which are important information in a study that assesses the cardiovascular impact of COVID-19. Furthermore, the small number of patients in the study limits the statistical analysis and conclusions drawn from these results.

Despite the limitations, this is the first study that specifically analyzes the population at high cardiovascular risk in patients admitted to the intensive care unit for COVID-19.

Conclusions

In patients hospitalized in intensive care for COVID19, the presence of high cardiovascular risk impacts in-hospital mortality only in patients with elevated troponin levels.

Author Contributions

Conception and design of the research: Gomes BFO, Petriz JLF, Carmo Junior PR, Pereira BB, Oliveira GMM; Acquisition of data: Gomes BFO, Menezes IRR, Azevedo AS, Silva TMB, Silva VL, Peres LS, Pereira DFP, Dutra GP, Paula SAM, Mendes BFS; Analysis and interpretation of the data: Gomes BFO, Petriz JLF, Dutra GP, Carmo Junior PR, Pereira BB, Oliveira GMM; Statistical analysis: Gomes BFO, Pereira BB, Oliveira GMM; Writing of the manuscript and Critical revision of the manuscript for intellectual contente: Gomes BFO, Petriz JLF, Menezes IRR, Azevedo AS, Silva TMB, Silva VL, Peres LS, Pereira DFP, Dutra GP, Paula SAM, Mendes BFS, Carmo Junior PR, Pereira BB, Oliveira GMM.

Potential Conflict of Interest

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

Sources of Funding

There were no external funding sources for this study.

Study Association

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

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Instituto D'Or de Ensino e Pesquisa under the protocol number 33206620.0.0000.5249. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

References

1. COVID-19 CORONAVIRUS PANDEMIC. Worldometers, 2021. [Internet]. [Cited in 2021 Feb 15]. Available from:https://www.worldometers.info/coronavirus/
2. Guan WJ, Ni ZY, Hu Y,Liang WA, Ou CH, He JX, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med. 2020;382(18):1708-20 doi: 10.1056/NEJMoa2002032.
3. Wang D, Hu B, Hu C, Zhu F, Zhang J, Wang B, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. JAMA 2020;323:1061-9. doi: 10.1001/jama.2020.1585.
4. Shi S, Qin M, Shen B, Cai Y, Liu T, Yang F, et al. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. JAMA Cardiol. 2020; 5(7):802-10. doi: 10.1001/jamacardio.2020.0950.

5. Sabatino J, De Rosa S, Di Salvo G, Indolfi C. Impact of cardiovascular risk profile on COVID-19 outcome. A meta-analysis. PLoS ONE. 2020;15(8):e0237131. https://doi.org/10.1371/journal.pone.0237131

6. Tzoulaki I, Elliott P, Kontis V, Ezzati M. Worldwide Exposures to Cardiovascular Risk Factors and Associated Health Effects: Current Knowledge and Data Gaps. Circulation. 2016 Jun 7;133(23):2314-33. doi: 10.1161/CIRCULATIONAHA.115.008718.

7. Hothorn T, Zeileis A. A Modular Toolkit for Recursive Partytioning in R. Journal of Machine Learning Research,2015 16, 3905-3909. URL http://jmlr.org/papers/v16/hothorn15a.html.

8. Di Castelnuovo A, Bonaccio M, Costanzo S, Gialluisi A, Antinori A, Berselli N, et al. Common cardiovascular risk factors and in-hospital mortality in 3,894 patients with COVID-19: survival analysis and machine learning-based findings from the multicentre Italian CORIST Study. Nutr Metab Cardiovasc Dis. 2020;;30(11):1899-913. doi: 10.1016/j.numecd.2020.07.031.

9. Collard D, Nurmohamed NS, Kaiser Y, Reeskamp LF, Dormans T, Moeniralam H, et al. Cardiovascular risk factors and COVID-19 outcomes in hospitalised patients: a prospective cohort study. BMJ Open. 2021;11(2):e045482. doi: 10.1136/bmjopen-2020-045482.

10. Silverio A, Di Maio M, Citro R, Esposito L, Iuliano G, Bellino M, et al. Cardiovascular risk factors and mortality in hospitalized patients with COVID-19: systematic review and meta-analysis of 45 studies and 18,300 patients. BMC Cardiovasc Disord. 2021; 21(1):23. doi: 10.1186/s12872-020-01816-3.

11. Guo T, Fan Y, Chen M, Wu X, Zhang L, He T, et al. Cardiovascular Implications of Fatal Outcomes of Patients With Coronavirus Disease 2019 (COVID-19). JAMA Cardiol. 2020;;5(7):811-8. doi: 10.1001/jamacardio.2020.1017. Erratum in: JAMA Cardiol. 2020;5(7):848. PMID: 32219356; PMCID: PMC7101506.

12. Metnitz PG, Moreno RP, Almeida E, Jordan B, Bauer P, Campos RA, et al. SAPS 3 – from evaluation of the patient to evaluation of the intensive care unit. Part 1:objectives, methods and cohort description. Intensive Care Med. 2005; 31(10): 1336–44. DOI: 10.1007/s00134-005-2762-6

How Can the Presence of Cardiovascular Diseases Impact Morbidity and Mortality in Patients with COVID-19?

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Short Editorial related to the article: Impact of High Cardiovascular Risk on Hospital Mortality in Intensive Care Patients Hospitalized for COVID-19

Since the pandemic's beginning, the disease caused by the SARS-CoV-2 virus, called COVID-19, has shown itself to be a wide-spectrum and unpredictable condition, with patients being practically asymptomatic. In contrast, others had severe pulmonary involvement, the major cause of morbidity and mortality associated with the disease.[1-3]

At an early stage, COVID-19 was shown to have a broad and potentially alarming link to the cardiovascular system. Angiotensin-2-converting enzyme receptors have been shown to directly interface with viral pathogenesis and maybe the cellular gateway for type 2 pneumocytes, macrophages and cardiomyocytes.[1] Thus, patients with cardiovascular diseases were more susceptible to severe forms of the disease. Hypertension, arrhythmias, cardiomyopathies and coronary artery disease were among the main comorbidities in critically ill patients with COVID-19. Patients with cardiovascular diseases (particularly those with hypertension) have a morbidity rate of up to 10.5% after infection with COVID-19.[2] In the present study, we can observe a similar relationship. It was clear in this Brazilian series how the presence of atherosclerotic disease and traditional risk factors alone or together were capable of impacting mortality and prognosis. Although the study has a limited series, it includes only high-risk patients with a high rate of outcomes, allowing the evaluation of results to be consistent and following exactly the same line as the international literature.[4]

Likewise, the myocardial injury proved to be a potential marker of mortality in COVID-19. Even after more than two years of illness, the proposed mechanisms of cardiovascular injury are not yet fully established. However, it is suggested that they would be direct damage to cardiomyocytes, systemic inflammation, myocardial interstitial fibrosis, interferon-mediated immune response, exaggerated cytokine response by T cells, endothelial dysfunction, in addition to coronary plaque destabilization and hypoxia.[1-3]

Troponin elevations were significantly related to increased mortality and cardiac arrhythmias. Marker enhancement occurs more often in people with chronic cardiovascular disease than previously healthy individuals. The increase in prothrombotic and inflammatory activity and hypoxia contribute to myocardial injury. However, myocarditis, stress-induced cardiomyopathy, acute heart failure, and direct cardiomyocyte injury also contribute to its occurrence. Even conditions not directly related to the heart but common in COVID-19, such as pulmonary embolism, sepsis, and critical condition of the patient, lead to increased troponin.[5,6] Also, in the study presented, the myocardial injury may be the main prognostic marker and the most relevant finding in this series. Looking at the results, it is possible to see how troponin significantly and independently impacted mortality more than any other score, comorbidity or risk factor. Thus, it presented itself as the main prognostic marker independently, even predicting high mortality in patients without previous cardiovascular diseases or accumulated risk factors.[4]

In patients who require admission to intensive care units, COVID-19 has shown that the occurrence of cardiovascular manifestations is even greater. Cardiac arrhythmias were observed in 16.7% of hospitalized patients, 7% of patients who did not require observation in intensive care and 44% of those admitted to the ICU. Metabolic dysfunctions, inflammation, and activation of the sympathetic nervous system would be the main predisposing factors for changes in heart rhythm.[2] Such findings are consistent with the study presented, in which the mortality of patients considered critical reached 24%, and the combined outcome of death, mechanical ventilation and myocardial injury in 38% of the population evaluated.[4]

We now have a better understanding of COVID-19 and its cardiovascular manifestations. It is clear how much cardiovascular comorbidities and the cardiological manifestations of COVID can worsen the prognosis, especially in critically ill patients. Troponin is increasingly established as one of the major independent prognostic markers of the disease. Several gaps in pathophysiology and treatment remain unclarified, being targets of future clinical studies.

Keywords

Cardiovascular Diseases/complications; Covid-19; SARS-CoV-2; Risk Factors; Pulmonary Heart Disease/mortality; Hospital Mortality/trends; Troponin/adverse effects

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References

1. Babapoor-Farrokhran S, Gill D, Walker J, Rasekhi RT, Bozorgnia T, Amanullah A. Myocardial injury and COVID-19: Possible mechanisms. Life Sci. 2020 Jul 15;253:117723. doi: 10.1016/j.lfs.2020.117723.
2. Guzik TJ , Mohiddin SA , Dimarco A, Patel V, Savvatis K, Marelli-Berg FM, et al. COVID-19 and the cardiovascular system: implications for risk assessment, diagnosis, and treatment options. Cardiovasc Res. 2020 Aug 1;116(10):1666-87. doi: 10.1093/cvr/cvaa106
3. Askin L, Tanrıverdi O, Askin HS. The effect of coronavirus disease 2019 on cardiovascular diseases. Arq Bras Cardiol.2020 Jun 1;114(5):817-22. doi: 10.36660/abc.20200273.
4. Impacto do alto risco cardiovascular na mortalidade hospitalar em pacientes internados em terapia intensiva por COVID-19
5. Sandoval Y, Januzzi Jr JL, Jaffe AS. Cardiac troponin for assessment of myocardial injury in COVID-19: JACC Review Topic of the Week. J Am Coll Cardiol. 2020;76(10):1244-58. doi: 10.1016/j.jacc.2020.06.068
6. Siripanthong B, Nazarian S, Muser D, Deo R, Santangeli P, Khanji MY, et al. Recognizing COVID-19–related myocarditis: The possible pathophysiology and proposed guideline for diagnosis and management. Heart Rhythm. 2020;17(9):1463-71. doi: 10.1016/j.jacc.2020.06.068

Signs of Cardiac Injury in Critically Ill Paediatric Patients with COVID-19: a Single-Center Experience in Brazil

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Abstract

Background: **Some patients with COVID-19 present myocardial injury.**

Objective: **To detect myocardial injury in critically ill paediatric patients, and to compare cardiac involvement between children with severe acute respiratory syndrome (SARS) and children with multisystemic inflammatory syndrome (MIS-C).**

Methods: **All COVID-19 children admitted to a referral intensive care unit were prospectively enrolled and had a two-dimensional echocardiogram (2D-TTE) and a cardiac troponin I (cTnI) assay within the first 72 hours. For statistical analysis, two-sided $p < 0.05$ was considered significant.**

Results: **Thirty-three patients were included, of which 51.5% presented elevated cTnI and/or abnormal 2D-TTE and 36.4% needed cardiovascular support, which was more frequent in patients with both raised cTnI and 2D-TTE abnormalities than in patients with normal exams (83.3% and 33.3%, respectively; p 0.006, 95% CI = 0.15-0.73). The most common 2D-TTE findings were pericardial effusion (15.2%) and mitral/tricuspid regurgitation (15.2%). Signs of cardiac involvement were more common in MIS-C than in SARS. MIS-C patients also presented a higher rate of the need for cardiovascular support (66.7% vs 25%, p 0.03, 95% CI = -0.7 to -0.04) and a more frequent rate of raised cTnI (77.8% vs 20.8%; p 0.002, 95% CI = 0.19 to 0.79). The negative predictive values of cTnI for the detection of 2D-TTE abnormalities were 100% for MIS-C patients and 73.7% for SARS patients.**

Conclusion: **signs of cardiac injury were common, mainly in MIS-C patients. 2D-TTE abnormalities were subtle. To perform a cTnI assay upon admission might help providers to discriminate those patients with a more urgent need for a 2D-TTE.**

Keywords: **COVID-19; Heart; Child.**

Introduction

Until early February 2021, the number of cases of COVID-19 in the world had already reached more than 105 million people, including nearly 9.5 million in Brazil, of whom 231,000 died.[1] As for viral tropism, lungs are not the only COVID-19 target. Cardiovascular compromise in COVID-19 infected patients has been well described worldwide. SARS-COV2 infection has been linked to acute myocardial injury, myocarditis, arrhythmias, and venous thromboembolism. These conditions predispose patients to severe disease and death, mainly those with pre-existing cardiovascular diseases.[2,3]

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Children have been reported as a small fraction of confirmed COVID-19 patients, representing around 2% of the number of hospitalized patients with SARS (severe acute respiratory syndrome) and around 0.5% of the number of deaths in Brazil and other countries.[1,4] At the beginning of the pandemic, most of the children infected by the new coronavirus SARS-COV2 were asymptomatic or presented mild symptoms. Later, an increasing number of children admitted to paediatric intensive care units (PICU´s) was observed worldwide, with shock in the presence of SARS-CoV-2 infection.[5-9] They presented with a hyperinflammatory syndrome with manifestations similar to Kawasaki's disease, toxic shock syndrome or secondary hemophagocytic lymphohistiocytosis. This condition was named "Multisystemic Inflammatory Syndrome in Children" (MIS-C), and has been commonly associated with cardiac dysfunction, hypotension, arrhythmias and coronary artery dilatation.[10-13]

The main objectives of this study were to detect signs of myocardial injury in critically ill paediatric patients with COVID-19 admitted to a referral PICU in Brazil, through cardiac troponin I (cTnI) assay and two-dimensional transthoracic echocardiogram (2D-TTE), and to compare cardiac involvement between children with SARS and children with MIS.

Methods

This was an observational single-center cohort study performed at a tertiary children´s hospital, elected as the only referral center for critically ill paediatric COVID-19 patients in Distrito Federal, Brazil, an area with an estimated population of 3.5 million. This study was approved by the local Research Ethic Committee, which waived the need for consent (protocol CAAE 34511120.0.0000.8927). The project was designed in May 2020, before the first admission of a paediatric patient at our PICU. All children with confirmed COVID-19 admitted in the PICU between May 28th and August 27th, 2020, presenting either with SARS or MIS-C, were prospectively included in the study. The confirmation of COVID-19 was made either by using real time polymerase chain reaction (RT-PCR) from samples of nasopharyngeal or oropharyngeal swabs, or by immunological testing for Immunoglobulin M or Immunoglobulin G to viral spike glycoprotein using an Enzyme-Linked Immunosorbent Assay (ELISA).

The study protocol determined that all COVID-19 patients admitted to the PICU underwent a 2D-TTE and a cTnI assay within 72 hours of hospital admission.

The 2D-TTE exams were carried out at bedside by three experienced paediatric cardiologists, following the guidelines of the American Society of Echocardiography, using a Toshiba Xario SSA 660-A (Toshiba Medical Systems Corporation, Japan).[14] The following 2D-TTE parameters and structures were assessed: left ventricular (LV) systolic function (using the Teichholz method), right ventricular (RV) systolic function (using eye-ball and tricuspid annular plane systolic excursion), wall motion, valvular function (using color Doppler), pericardium, coronary arteries (their diameters were indexed to body surface and plotted against Z-scores), and signs of pulmonary hypertension (RV systolic pressure > 40 mmHg or mean pulmonary artery pressure > 25 mmHg).[15,16] A LVEF < 55% was considered to be an LV systolic dysfunction. RV systolic dysfunction was considered when TAPSE Z-score was < -2 or by qualitative analysis.[17] Some patients underwent more than one 2D-TTE during their hospitalization, according to their clinical course and at the discretion of the assistant physician, but only the 2D-TTE performed upon admission was considered for analysis.

The measurement of cTnI was performed using the Elecsys Troponin I STAT kit (Roche Diagnostics), which had a cut-off value of 0.1 ng/ml.

The present study described the patient's demographic data, type of COVID-19 presentation, pre-existing conditions, length of ICU stay, length of hospital stay, type of respiratory support, length of respiratory support, need for vasoinotropic support, maximum vasoinotropic score (VIS), initial and peak cTnI and 2D-TTE abnormalities on the admission day. In some cases, pro-BNP (brain natriuretic peptide) and CKMB (creatine phosphokinase-MB) assays were ordered by the assistant physicians, for clinical judgment. These results were presented as well.

The definition of SARS was in accordance with the Center for Disease Control and Prevention (CDC), which defines it as a severe acute respiratory syndrome associated with the diagnosis of SARS-CoV-2 infection. The definition of MIS-C was also in accordance with the CDC, which defines it as a severe illness leading to hospitalization in patients under 21 years of age, with a fever for at least 24 hours, showing laboratory evidence of inflammation, with multisystemic (≥ 2) organ involvement, confirmed or presumed SARS-CoV-2 infection, and no alternative plausible diagnosis.[18]

Statistical analysis

For the assessment of data normality, the Kolmogorov-Smirnov test was performed to calculate the area under a normal curve, presumed as being when approximately 95% of the area was within 1.96 standard deviations of the mean. Continuous variables were expressed as mean ± standard deviation (SD) or median and interquartile range, according to the existence of normal data. Categorical variables were described as percentages. The Mann-Whitney test was used to compare continuous variables with skewed distribution. For the comparison of continuous variables with normal distribution, the unpaired student´s t test was used. The Kruskal-Wallis test, with the Conover-Iman method was used to compare VIS variances among patients with distinct combinations of findings on exams. The positive and negative predictive values of cTnI for the detection of 2D-TTE abnormalities were calculated. Two-sided $p < 0.05$ was considered statistically significant. All analyses were performed using StatsDirect, v. 3.3.4 2020 (Merseyside, UK).

Results

Thirty-three patients were included in the study, with an age range of 31 days to 17 years. When the last patient was included, our study population represented 3% of all children diagnosed with COVID-19 in our region, meaning that nearly all critically ill children in our area must have been included in the study.[19] The great majority (72.7%) presented a diagnosis of SARS. Three patients presented congenital heart diseases: one in status post-Senning operation (atrial baffle for D-transposition of the great arteries), another with a complete atrioventricular septal defect, and another one with an atrial septal defect, diagnosed during the study. There was one death due to a periorbital cellulitis complication in a patient with bone marrow aplasia. This patient had presented a diagnosis of SARS. Table 1 summarizes the general findings of our study.

Cardiac injury and cardiovascular compromise

Seventeen out of 33 patients (51.5%) presented with elevated cTnI and/or abnormal 2D-TTE. Five patients presented raised cTnI and abnormal 2D-TTE (15.2%); isolated raised cTnI was found in seven patients (21.2%); and an isolated abnormal 2D-TTE was found in five patients (15.2%).

Twelve patients (36.4%) needed cardiovascular support with inotropic or vasoactive drugs, chosen and titrated according to their clinical hemodynamic findings and at the discretion of the PICU team. Ten out of these 12 patients (83.3%) had abnormal cTnI and/or 2D-TTE, while among the 21 patients that did not need cardiovascular support, seven (33.3%) presented abnormal exams; this difference was statistically significant ($p = 0.006$, 95% CI = 0.15-0.73).

Among the five patients with both raised cTnI and abnormal 2D-TTE (a), 80% needed inotropic or vasoactive drugs (VIS 26 ± 24.8); among the patients with and isolated abnormal 2D-TTE (b), 60% needed these drugs (VIS 5 ± 5); among those with an isolated raised cTnI (c), 42.8% needed inotropic or vasoactive drugs (VIS 8.4 ± 13.4), whereas the use of these drugs was found in 12.5% of those patients with normal exams (d) (VIS 1.2 ± 3.6). Concerning VIS, a statistically significant difference was found only between patients "a" and "d" (p= 0.006); the difference between other pairwise comparisons were not significant (a vs b, p= 0.23; a vs c, p= 0.14; b vs c, p= 0.83; b vs d, p= 0.15; c vs d, p= 0.18). Table 2 summarizes the cardiovascular-related findings of our population.

2D-TTE abnormalities were found in 10 patients (30.3%). The most common findings were mild pericardial effusion (5 patients) and non-trivial mitral/tricuspid regurgitation (5 patients). Only two patients presented LV systolic dysfunction, who had fully recovered upon hospital discharge. One of the patients with LV systolic dysfunction also presented wall motion abnormality and a mild pericardial effusion. This patient had a cardiac magnetic resonance (CMR) performed 7 months later, and the pericardial effusion was still present, with no other CMR signs of myocarditis. No cases of coronary dilatation or pulmonary hypertension were found. Table 3 describes the main characteristics of the 10 patients that presented an abnormal 2D-TTE. Patient number 3, a boy in post-Senning operation status, presented SARS and atrial flutter. This patient had undergone a 2D-TTE at another institution 50 days ahead of the diagnosis of COVID-19. On that occasion, both tricuspid regurgitation and RV systolic dysfunction were considered mild, different from what was seen in this admission.

MIS-C vs SARS

The need for cardiovascular support was more frequent in patients presenting MIS-C than in those presenting SARS (66.7% and 25%, respectively, p 0.03, 95% CI = -0.7 to -0.04). Among those that needed cardiovascular support, the VIS score was higher in MIS-C patients than in SARS patients, but this finding was not statistically significant (28.2 ± 21.3 for MIS-C and 10.7 ± 5.7 for SARS, p= 0.1).

A raised cTnI was more frequently observed in patients with MIS-C than in patients with SARS (77.8% and 20.8%, respectively; p= 0.002, 95% CI = 0.19 to 0.79); however, the difference in peak cTnI was not statistically significant (p= 0.19). 2D-TTE abnormalities were found in 44.4% of the patients with MIS-C and in 25% of the patients with SARS (p= 0.28). The only statistically significant difference in the rate of 2D-TTE abnormalities were in the rate of LV systolic dysfunction, which was more common in MIS-C patients than in SARS patients (22.2% vs zero; p= 0.02, 95% CI = -0.06 to 0.55). No differences were found concerning length of ICU stay (p= 0.58), length of hospital stay (p= 0.86) and length of respiratory support (p= 0.61).

The positive predictive values of cTnI for the detection of 2D-TTE abnormalities were 70% for MIS-C patients

Table 1 – Demographic and general features of paediatric patients with COVID-19

Characteristics	All patients (33)	SARS (24)	MIS-C (9)	p	95% CI
Male	19 (57.6%)	15 (62.5%)	4 (44.4%)	0.35	
Age (years)	6.4 ± 5.6	5.7 ± 5.6	8.2 ± 5.5	0.2	
BMI (Kg/m2)	18.2 ± 6	17.9 ± 5.8	18.9 ± 6.7	0.79	
Chronic disorders	**18 (54.5%)**	**16 (66.7%)**	**2 (22.2%)**	**0.02**	**0.06 to 0.69**
Haematologic	6 (18.2%)	6 (25%)	0		
Cardiac	3 (9.1%)	2 (8.3%)	1 (11.1%)		
Neurologic	3 (9.1%)	2 (8.3%)	0		
Obesity	3 (9.1%)	2 (8.3%)	1 (11.1%)		
Nephrologic	2 (6.1%)	2 (8.3%)	0		
Pulmonary	2 (6.1%)	2 (8.3%)	0		
Diabetes	1 (3%)	1 (4.2%)	0		
Length of ICU stay (days)	**6 (3-12)**	**7 (3-12)**	**5 (3-7)**	**0.32**	
Length of hospital stay (days)	14 (10-19)	15.5 (12-21.2)	10 (7-14)	0.09	
Respiratory support	**27 (81.8%)**	**22 (91.7%)**	**5 (55.6%)**	**0.008**	**0.05 to 0.67**
Oxygen Only	14 (42.4%)	13 (54.2%)	1 (11.1%)		
CPAP	1 (3%)	1 (4.2%)	0		
Mechanical ventilation	12 (36.4%)	8 (33.3%)	4 (44.4%)		
Duration of respiratory support (days)	**5 (1-9)**	**6(2.5-10.5)**	**2 (0-5)**	**0.14**	

BMI: body mass index; ICU: intensive care unit; CPAP: continuous positive airway pressure.

and 20% for SARS patients. The negative predictive values were, respectively, 100% and 73.7%. Pro-BNP assay was not performed in all patients, since it was not part of the protocol, but an elevated pro-BNP was a common finding when performed (91.7%), regardless of the type of COVID presented by the patient. CKMB assay was not performed in all patients, since it was not part of the protocol, but it was elevated in 52.6% of the patients, with no significant difference according to COVID-19 presentation.

Discussion

This study was developed with the aim of detecting signs of myocardial injury in critically ill paediatric patients, and to compare cardiac involvement between children presenting SARS and children presenting MIS-C. The diagnostic methods chosen for this assessment were transthoracic echocardiography and cardiac troponin I assay. Our PICU was the only referral unit for paediatric cases offered by the Brazilian Unified Health System (SUS, in Portuguese), in our region. Since the study was designed before the admission of the first case, it was possible to include all critically ill children with COVID-19 in our geographic area during the first COVID-19 wave in Brazil in 2020. This is possibly the most important strength of our study.

Myocardial involvement in COVID-19 is common and appears histologically in different forms: myocarditis-like disease, myocardial inflammation, thromboembolic disease and infarction. These findings have been supported by CMR imaging studies of adult and paediatric patients and by pathological evidence.[8,20-24] However, these methods to diagnose myocarditis, myocardial edema or ischemic heart injury are not feasible in most of the children, due to the invasive nature of endomyocardial biopsy and to the difficulties in performing CMR imaging in acutely ill children, especially when there are constraints in using advanced imaging techniques during the COVID-19 pandemic.

cTnI is a cardiac-specific contractile protein found in cardiomyocytes and has a high sensitivity (95%) for the diagnosis of viral myocarditis in children.[25] However, it can also be released in cases of excessive wall stress, myocardial ischemia or increased myocardial oxygen demand, situations often found in patients with COVID-19, especially in those with chronic medical conditions.[26] One of the caveats about measuring cTnI in children is that the cut-off values are designed to diagnose infarctions in adults and these cut-offs may well be related to the amount of damaged tissue.[27] Therefore, it is reasonable to argue that, if we are using adult cut-off values, the detection of raised cardiac troponin in children might be revealing a more extensive damage to the heart. Even in adults with COVID-19, abnormal CMR studies have been found without a simultaneous elevation in cardiac troponin.[20] Nevertheless, some authors have reported their experience with MIS-C patients and have shown that troponin elevation is a common finding, and that it occurs in more than 70% of the cases.[6,7,28] In our study, approximately 50% of the

Table 2 – Cardiovascular support and cardiac findings of paediatric patients with COVID-19

Characteristics	All patients (33)	SARS (24)	MIS-C (9)	p	95% CI
Cardiovascular support	12 (36.4%)	6 (24%)	6 (66.7%)	0.03	-0.69 to -0.04
Maximum VIS *	19 ± 17	11 ± 6	28 ± 21	0.051	-37.6 to 2.6
Abnormal cTnI	**12 (36.4%)**	**5 (20.8%)**	**7 (77.8%)**	**0.002**	**-0.79 to -0.19**
Peak cTnI		0.41 ± 0.48	0.61 ± 0.61	0.56	
Abnormal Echo and cTnI		1/5 (20%)	4/7 (57.1%)	0.2	
High pro-BNP	22/25 (88%)	15/17 (88.2%)	7/8 (87.5%)	0.96	
High CKMB	10/19 (52.6%)	5/11 (45.4%)	5/8 (62.5%)	0.46	
Abnormal 2D-TTE	**8 (24.2%)**	**4 (16%)**	**4 (44.4%)**	**0.08**	
LV systolic dysfunction	2 (6.1%)	0	2 (22.2%)	0.1	
RV systolic dysfunction	1 (3%)	1 (4.2%)	0	0.28	
TR/MR	5 (15.2%)	2 (8.3%)	3 (33.3%)	0.47	
Pericardial effusion	5 (15.2%)	4 (16.7%)	1 (11.1%)	0.03	0.04 to 0.96
WMA	1 (3%)	0	1 (11.1%)	0.28	
Coronary abnormality	0	0	0		
MLCA Z-score	-0.23 ± 0.8	-0.23 ± 0.88	-0.23 ± 0.57	1	
RCA Z-score	0.16 ± 0.87	0.14 ± 0.88	0.22 ± 0.9	0.81	

*2D-TTE: two-dimensional transthoracic echocardiogram.; BNP: brain natriuretic peptide; CKMB: creatine phosphokinase-MB; cTnI: cardiac troponin I; VIS: vasoinotropic score; LV: left ventricular; MLCA: main left coronary artery; MR: mitral regurgitation; RCA: right coronary artery; RV: right ventricular; TR: tricuspid regurgitation; WMA: wall motion abnormality. *Of those who needed cardiovascular support.*

Table 3 – Clinical, laboratory and echocardiographic findings of the eight patients who presented an abnormal 2D-TTE upon admission

Patient number	1	2	3	4	5	6	7	8	9	10
Gender	M	M	M	F	F	F	M	F	F	F
Age	14 y	12 y	7 y	13 y	3 y	11 y	20 m	10 m	2 y	13 y
BSA	1.21	1.39	1.02	1.55	0.54	1.15	0.58	0.41	0.35	1.58
BMI	13.1	17.2	17.7	22.6	12.3	15.5	14.7	16.7	16.6	17.7
Comorbidity	SCD	-	CHD	-	BMA	-	-	-	CPD and CP	Diabetes
Presentation	SARS	MIS-C	SARS	MIS-C	SARS	MIS-C	MIS-C	SARS	SARS	SARS
Length of ICU stay W(days)	12	5	22	7	8	6	3	2	12	5
Length of hospital stay (days)	16	10	34	9	8	10	7	15	18	8
Respiratory support (days)	4	5	10	2	8	3	0	2	17	5
Mechanical ventilation (days)	0	3	2	0	1	2	0	0	0	2
Peak cTnI (cut-off 0.1 ng/ml)	< 0.1	0.27	< 0.1	1.91	< 0.1	0.58	0.22	0.13	< 0.1	< 0.1
cTnI normalization	-	3 days	-	4 days	-	5 days	1 day	1 day	-	-
Maximum VIS	0	50	5	15	10	55	10	0	10	0
Pro-BNP (cut-off 125 pg/ml)	NA	27183	5546	5341	988	22985	31188	1133	2445	NA
CKMB (cut-off 25 ng/ml)	NA	19.4	17.9	28.4	NA	41	23.6	24.4	NA	NA
Initial TTE	Minimum PE	Mild MR	Severe RV dysfunction, mild/moderate LV dysfunction, severe TR	Mild LV dysfunction, wall motion abnormality, mild PE	Mild PE	Moderate MR, mild LV dysfunction	Mild TR	Moderate PE	Mild PE	Mild MR
Discharge TTE	NA	normal	Severe RV dysfunction, mild LV dysfunction, moderate TR	Normal	Mild PE		Mild TR	Mild MR, minimum PE	NA	NA

BMA: bone marrow aplasia; BNP: brain natriuretic peptide; CHD: congenital heart disease; CKMB: creatine phosphokinase-MB; CP: cerebral palsy; CPD: chronic pulmonary disease; LV: left ventricular; MR: mitral regurgitation; NA: not available; PE: pericardial effusion; RV: right ventricular; SCD: sickle cell disease; VIS: vasoactive inotropic score.

patients presented raised cTnI and/or echocardiographic abnormalities, confirming the high rate of myocardial injury in this subset of patients.

A very relevant finding in our work was the fact that patients who had both raised cTnI and abnormal 2D-TTE needed more cardiovascular support than those with normal exams, which is in agreement with some studies in the adult population with COVID-19 and SARS. These studies describe that the clinical course is worse when there is a troponin leak and an abnormal 2D-TTE.[29-31] In our cohort, this was represented by a higher rate of patients in need of inotropic or vasoactive drugs, as well as in higher doses.

2D-TTE abnormalities were found in 30.3% of our population. The most common findings were mild pericardial effusion and mild mitral/tricuspid regurgitation. Only two patients presented LV systolic dysfunction, who fully recovered upon hospital discharge. The 2D-TTE abnormalities found in our study were mostly transitory and followed by a normalization of cTnI, revealing the dynamic course of the disease and, possibly, a healing process.

The two patients with LV systolic dysfunction represented only 16.7% of the patients who needed inotropes or vasopressors in our cohort, suggesting a major vasoplegic or inflammatory nature of this disease, as opposed to a state of low cardiac output syndrome. One of these patients with LV systolic dysfunction had the highest peak of cTnI in our cohort. Concerning LV systolic function, different findings have been described elsewhere: Grimaud and Ramcharam found a fall in LV ejection fraction in more than 80% of their MIS-C patients admitted to their PICUs presenting a shock.[6,32] These differences might be related to local policies of ICU admission; different timing of diagnosis; different patient characteristics (demographics, presence of comorbidities); different patient genetic backgrounds with different interactions with SARS-COV2 causing distinct immune responses; different virus strains causing varying degrees of cardiovascular compromise; and different study methodologies (timing of imaging assessment, choice of method to assess cardiac function, etc.).

Raised cTnI was found in approximately 80% of the MIS-C patients and approximately 20% of the SARS patients; however, a raised cTnI was neither associated with LV systolic dysfunction, nor with circulatory shock. Five of the seven patients (71.4%) with raised cTnI in the MIS-C subgroup had some 2D-TTE abnormality, while in the subgroup with SARS, this rate was 20% (1/5). It is important to note that, in our study population, a normal cTnI assay upon admission had a very high negative predictive value, suggesting that this assay could be used to rule-out cardiac injury, avoiding unnecessary cardiovascular imaging in selected patients. While the number of patients with elevated cTnI is small, it still seems that there is a potential benefit of the cTnI assay as a screening test for 2D-TTE abnormalities. Furthermore, it was found that cTnI elevation and abnormal findings in 2D-TTE were transitory, behaving clinically as a usual non-fulminant acute myocarditis. In this context, timing for diagnosis is crucial, although the clinical impact of this diagnosis remains unknown. As for typical myocarditis, the incidence of chronic cardiomyopathy in the future of these children is unknown.

None of our patients presented coronary abnormalities, which is in agreement with findings from Grimaud et al, in France.[32] Other studies also found a low rate of coronary abnormalities.[7,33] Other imaging findings of COVID-19 in children have also been described. In the study by Ramcharan et al., 67% of the patients presented transient valve regurgitation.[6] In the study by Grimaud et al., 65% of the patients presented non-trivial mitral or tricuspid regurgitation, and pericardial effusion was observed in 40% of their population.[32] Non-trivial mitral or tricuspid regurgitation was found in 15% of our cohort, the same rate of pericardial effusion, with no difference between SARS and MIS-C.

Some cohorts have also reported changes in the heart rhythm in patients with systemic manifestations of SARS-CoV2 infection. In a New York cohort, with 393 patients, it was observed that 17.7% of patients hospitalized with SARS-COV2 and under mechanical ventilation, had atrial arrhythmias, versus 1.9% of those who did not need mechanical ventilation.[34] In another cohort in China, with 187 patients, it was observed that 5.9% of the patients had tachyarrhythmias while they were hospitalized.[29] The only case of arrhythmia seen in our study was in a child in post Senning operation status, a situation where atrial arrhythmias are known as a late complication of the surgery. In this case, it is unclear if the arrhythmia was triggered by COVID-19. This patient presented a worsening in his RV systolic function, with a normal cTnI.

Study limitations

This study was designed in May, almost simultaneously with the announcement of the MIS-C phenotype of COVID-19. Therefore, we did not have enough information about MIS-C at that moment, and the design of the study did not include the assessment of inflammatory or coagulopathy markers, although some patients had done this type of blood work. The clinical haemodynamics (blood pressure, capillary refill time, heart rate, blood lactate) of the patients was not reviewed and the use of vasoactive or inotropic drugs was performed at the discretion of the assistant physicians. The present study opted to use the VIS score to represent the severity of the cardiovascular compromise in a standard fashion. Parameters of myocardial deformation were not evaluated, and we recognize that changes in strain may be present before the drop in the ejection fraction.

Conclusions

The prevalence of signs of myocardial injury in COVID-19 infected children in need of intensive care was high (50%), and this was not exclusive of MIS-C patients. MIS-C patients with both elevated cardiac troponin I and abnormal findings in the 2D-TTE very often present signs of shock. Markers of cardiac injury were transitory and early outcomes, in general, were favorable. Finally, considering the high number of infected patients recently admitted to PICUs around the world and that health resources may be limited, performing

a cTnI assay might help healthcare providers to discriminate those patients with a more urgent need for 2D-TTE.

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Author Contributions

Conception and design of the research, Statistical analysis and Analysis and interpretation of the data: Kozak MF; Acquisition of data: Kozak MF, Cabral MB, Diniz JD, Saliba A, Kawahara SH; Writing of the manuscript: Kozak MF, Pessoa YC, Silva LOC, Leite BCP, Saliba A; Critical revision of the manuscript for intellectual content: Kozak MF, Pessoa YC, Silva LOC, Leite BCP, Diniz JD, Saliba A, Kawahara SH.

Potential Conflict of Interest

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

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References

1. Brasil. Ministério da Saúde. Boletim Epidemiológico Especial: Doença pelo Coronavírus COVID-19. Semana epidemiológica 5/2021. Brasília (DF): Secretaria de Vigilância em Saúde; 2021.
2. Driggin E, Madhavan MV, Bikdeli B, Chuich T, Laracy J, Biondi-Zoccai G, et al. Cardiovascular Considerations for Patients, Health Care Workers, and Health Systems During the COVID-19 Pandemic. J Am Coll Cardiol. 2020;75(18):2352-71. doi: 10.1016/j.jacc.2020.03.031.
3. Edelson DP, Sasson C, Chan PS, Atkins DL, Aziz K, Becker LB, et al. Interim Guidance for Basic and Advanced Life Support in Adults, Children, and Neonates with Suspected or Confirmed COVID-19: From the Emergency Cardiovascular Care Committee and Get with The Guidelines-Resuscitation Adult and Pediatric Task Forces of the American Heart Association. Circulation. 2020;141(25):933-43. doi: 10.1161/CIRCULATIONAHA.120.047463.
4. Irfan O, Muttalib F, Tang K, Jiang L, Lassi ZS, Bhutta Z. Clinical Characteristics, Treatment and Outcomes of Paediatric COVID-19: A Systematic Review and Meta-Analysis. Arch Dis Child. 2021;106(5):440–8. doi: 10.1136/archdischild-2020-321385.
5. Shekerdemian LS, Mahmood NR, Wolfe KK, Riggs BJ, Ross CE, McKiernan CA, et al. Characteristics and Outcomes of Children with Coronavirus Disease 2019 (COVID-19) Infection Admitted to US and Canadian Pediatric Intensive Care Units. JAMA Pediatr. 2020;174(9):868-73. doi: 10.1001/jamapediatrics.2020.1948.
6. Ramcharan T, Nolan O, Lai CY, Prabhu N, Krishnamurthy R, Richter AG, et al. Paediatric Inflammatory Multisystem Syndrome: Temporally Associated with SARS-CoV-2 (PIMS-TS): Cardiac Features, Management and Short-Term Outcomes at a UK Tertiary Paediatric Hospital. Pediatr Cardiol. 2020;41(7):1391-401. doi: 10.1007/s00246-020-02391-2.
7. Whittaker E, Bamford A, Kenny J, Kaforou M, Jones CE, Shah P, et al. Clinical Characteristics of 58 Children with a Pediatric Inflammatory Multisystem Syndrome Temporally Associated with SARS-CoV-2. JAMA. 2020;324(3):259-69. doi: 10.1001/jama.2020.10369.
8. Dolhnikoff M, Ferranti JF, Monteiro RAA, Duarte-Neto AN, Gomes-Gouvêa MS, Degaspare NV, et al. SARS-CoV-2 in Cardiac Tissue of a Child with COVID-19-Related Multisystem Inflammatory Syndrome. Lancet Child Adolesc Health. 2020;4(10):790-94. doi: 10.1016/S2352-4642(20)30257-1.
9. Belhadjer Z, Méot M, Bajolle F, Khraiche D, Legendre A, Abakka S, et al. Acute Heart Failure in Multisystem Inflammatory Syndrome in Children in the Context of Global SARS-CoV-2 Pandemic. Circulation. 2020;142(5):429-36. doi: 10.1161/CIRCULATIONAHA.120.048360.
10. Jiang L, Tang K, Levin M, Irfan O, Morris SK, Wilson K, et al. COVID-19 and Multisystem Inflammatory Syndrome in Children and Adolescents. Lancet Infect Dis. 2020;20(11):276-88. doi: 10.1016/S1473-3099(20)30651-4.
11. Feldstein LR, Rose EB, Horwitz SM, Collins JP, Newhams MM, Son MBF, et al. Multisystem Inflammatory Syndrome in U.S. Children and Adolescents. N Engl J Med. 2020;383(4):334-46. doi: 10.1056/NEJMoa2021680.
12. Dufort EM, Koumans EH, Chow EJ, Rosenthal EM, Muse A, Rowlands J, et al. Multisystem Inflammatory Syndrome in Children in New York State. N Engl J Med. 2020 Jul 23;383(4):347-58. doi: 10.1056/NEJMoa2021756.
13. Sanna G, Serrau G, Bassareo PP, Neroni P, Fanos V, Marcialis MA. Children's Heart and COVID-19: Up-to-Date Evidence in the Form of a Systematic Review. Eur J Pediatr. 2020;179(7):1079-87. doi: 10.1007/s00431-020-03699-0.
14. Lopez L, Colan SD, Frommelt PC, Ensing GJ, Kendall K, Younoszai AK, et al. Recommendations for Quantification Methods During the Performance of a Pediatric Echocardiogram: A Report from the Pediatric Measurements Writing Group of the American Society of Echocardiography Pediatric and Congenital Heart Disease Council. J Am Soc Echocardiogr. 2010;23(5):465-95. doi: 10.1016/j.echo.2010.03.019.
15. Lopez L, Colan S, Stylianou M, Granger S, Trachtenberg F, Frommelt P, et al. Relationship of Echocardiographic Z Scores Adjusted for Body Surface Area to Age, Sex, Race, and Ethnicity: The Pediatric Heart Network Normal Echocardiogram Database. Circ Cardiovasc Imaging. 2017;10(11):e006979. doi: 10.1161/CIRCIMAGING.117.006979.
16. Galiè N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, et al. 2015 ESC/ERS Guidelines for the Diagnosis and Treatment of Pulmonary Hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Heart J. 2016;37(1):67-119. doi: 10.1093/eurheartj/ehv317.
17. Koestenberger M, Ravekes W, Everett AD, Stueger HP, Heinzl B, Gamillscheg A, et al. Right Ventricular Function in Infants, Children and Adolescents: Reference Values of the Tricuspid Annular Plane Systolic Excursion (TAPSE) in 640 Healthy Patients and Calculation of Z Score Values. J Am Soc Echocardiogr. 2009;22(6):715-9. doi: 10.1016/j.echo.2009.03.026.
18. CDC Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with Coronavirus Disease 2019 (COVID-19). Washington: Centers for Disease Control and Prevention. 2020 [cited 2021 Jul 8]. Available from: https://emergency.cdc.gov/han/2020/han00432.asp.
19. Estado do Distrito Federal. Boletim Epidemiológico N. 178: Emergência de Saúde Pública COVID-19 no âmbito do Distrito Federal. Brasília: Secretária do Estado do Distrito Federal; 2020.

20. Puntmann VO, Carerj ML, Wieters I, Fahim M, Arendt C, Hoffmann J, et al. Outcomes of Cardiovascular Magnetic Resonance Imaging in Patients Recently Recovered from Coronavirus Disease 2019 (COVID-19). JAMA Cardiol. 2020;5(11):1265-73. doi: 10.1001/jamacardio.2020.3557.

21. Clark DE, Parikh A, Dendy JM, Diamond AB, George-Durrett K, Fish FA, et al. COVID-19 Myocardial Pathology Evaluation in Athletes with Cardiac Magnetic Resonance (COMPETE CMR). Circulation. 2021;143(6):609-12. doi: 10.1161/CIRCULATIONAHA.120.052573.

22. Basso C, Leone O, Rizzo S, De Gaspari M, van der Wal AC, Aubry MC, et al. Pathological Features of COVID-19-Associated Myocardial Injury: A Multicentre Cardiovascular Pathology Study. Eur Heart J. 2020;41(39):3827-35. doi: 10.1093/eurheartj/ehaa664.

23. Lindner D, Fitzek A, Bräuninger H, Aleshcheva G, Edler C, Meissner K, et al. Association of Cardiac Infection With SARS-CoV-2 in Confirmed COVID-19 Autopsy Cases. JAMA Cardiol. 2020;5(11):1281-5. doi: 10.1001/jamacardio.2020.3551.

24. Theocharis P, Wong J, Pushparajah K, Mathur SK, Simpson JM, Pascall E, et al. Multimodality Cardiac Evaluation in Children and Young Adults with Multisystem Inflammation Associated with COVID-19. Eur Heart J Cardiovasc Imaging. 2021;22(8):896-903. doi: 10.1093/ehjci/jeaa212.

25. Wang D, Li T, Cui H, Zhang Y. Analysis of the Indicating Value of Cardiac Troponin I, Tumor Necrosis Factor-, Interleukin-18, Mir-1 and Mir-146b for Viral Myocarditis Among Children. Cell Physiol Biochem. 2016;40(6):1325-33. doi: 10.1159/000453185.

26. Park KC, Gaze DC, Collinson PO, Marber MS. Cardiac Troponins: From Myocardial Infarction to Chronic Disease. Cardiovasc Res. 2017;113(14):1708-18. doi: 10.1093/cvr/cvx183.

27. Arruda-Olson AM, Roger VL, Jaffe AS, Hodge DO, Gibbons RJ, Miller TD. Troponin T Levels and Infarct Size by SPECT Myocardial Perfusion Imaging. JACC Cardiovasc Imaging. 2011;4(5):523-33. doi: 10.1016/j.jcmg.2011.03.010.

28. World Health Organization. Multisystem Inflammatory Syndrome in Children and Adolescents with COVID-19. Geneva: WHO Library; 2020.

29. Guo T, Fan Y, Chen M, Wu X, Zhang L, He T, et al. Cardiovascular Implications of Fatal Outcomes of Patients with Coronavirus Disease 2019 (COVID-19). JAMA Cardiol. 2020;5(7):811-8. doi: 10.1001/jamacardio.2020.1017.

30. Nascimento JHP, Costa RLD, Simvoulidis LFN, Pinho JC, Pereira RS, Porto AD, et al. COVID-19 and Myocardial Injury in a Brazilian ICU: High Incidence and Higher Risk of In-Hospital Mortality. Arq Bras Cardiol. 2021;116(2):275-82. doi: 10.36660/abc.20200671.

31. Giustino G, Croft LB, Stefanini GG, Bragato R, Silbiger JJ, Vicenzi M, et al. Characterization of Myocardial Injury in Patients with COVID-19. J Am Coll Cardiol. 2020;76(18):2043-55. doi: 10.1016/j.jacc.2020.08.069.

32. Grimaud M, Starck J, Levy M, Marais C, Chareyre J, Khraiche D, et al. Acute Myocarditis and Multisystem Inflammatory Emerging Disease Following SARS-CoV-2 Infection in Critically Ill Children. Ann Intensive Care. 2020;10(1):69. doi: 10.1186/s13613-020-00690-8.

33. García-Salido A, Vicente JCC, Hofheinz SB, Ramírez JB, Barrio MS, Gordillo IL, et al. Severe Manifestations of SARS-CoV-2 in Children and Adolescents: From COVID-19 Pneumonia to Multisystem Inflammatory Syndrome: A Multicentre Study in Pediatric Intensive Care Units in Spain. Crit Care. 2020;24(1):666. doi: 10.1186/s13054-020-03332-4.

34. Goyal P, Choi JJ, Pinheiro LC, Schenck EJ, Chen R, Jabri A, et al. Clinical Characteristics of Covid-19 in New York City. N Engl J Med. 2020;382(24):2372-4. doi: 10.1056/NEJMc2010419.

How Should We Investigate Cardiovascular Injury In Critically Ill COVID-19 Pediatric Patients In A Scenario Of Socioeconomic Vulnerability?

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Short editorial related to the article: Signs of Cardiac Injury in Critically Ill Paediatric Patients with COVID-19: a Single-Center Experience in Brazil

Literature published worldwide has extensively documented cardiovascular injury among COVID-19 critically ill patients. Cardiac involvement appears to be a prominent feature of the disease in adults, occurring in 20% to 30% of hospitalized patients and contributing to 40% of deaths.[1] Children and adolescents are mostly spared by COVID-19, with few having severe symptoms and even fewer deaths. However, the description of the multisystem inflammatory syndrome in children (MIS-c) reinforced that, although rare, severe clinical presentation and death are possible in the pediatric population.[2] Cardiovascular compromise in MIS-c associated with COVID-19 is frequent and is one of the World Health Organization (WHO) diagnostic criteria for this pathologic condition (Figure 1).[3,4]

Feldstein et al. detected 80% of cardiac compromise in a group of 186 MIS-c patients from 26 American states. Of note, 91% of these patients had at least one echocardiogram performed during their hospital stay.[5] Recent national data documented 48% of echocardiographic abnormalities in a single-center cohort of hospitalized COVID-19 pediatric patients, associated with MIS-c, admission to the pediatric intensive care unit, multiple organ dysfunction, the need for ventilatory/vasoactive support, and death. In the same study, ventricular systolic dysfunction and coronary artery aneurysms detected by echocardiogram were associated with higher levels of troponin and d-dimer and inflammatory biomarkers.[6]

Due to COVID-19 in children, higher mortality rates have been recorded in Brazil compared with other countries (8.2% x 1%), mainly due to socioeconomic vulnerability and poor access to appropriate medical support. Since data on out-of-Hospital mortality is frequently missing, underestimating the pandemic effect on our pediatric population is expected.[7]

According to robust data collected from 5857 patients younger than 20 years old, all hospitalized with laboratory-confirmed COVID-19, ethnic, regional and socioeconomic conditions seem to shape the mortality of children with COVID-19 in Brazil. Compared with white children, indigenous and mixed-race children had significantly higher odds of mortality (OR 5.83, 95% CI 2.43 to 14.02; OR 1.93, 95% CI 1.48 to 2.51, respectively). The authors also found a regional influence (higher mortality in the North - OR 3.4, 95% CI 2.48 to 4.65) and a socioeconomic association (lower mortality among children from more socioeconomically developed municipalities - OR 0.26, 95% CI 0.17 to 0.38).[8]

Life-threatening cardiovascular complications in a resource-poor setting may be unrecognized, contributing to unfavorable outcomes in critically ill COVID-19 pediatric patients. High-cost imaging tools, such as Computed Tomography or Cardiac Magnetic Resonance, are usually unavailable. Even a bedside echocardiogram, suggested by most current MIS-c management guidelines, may not be accessible at admission.[9]

Identifying laboratory parameters at early presentation may trigger heightened suspicion of cardiovascular impairment and the need for intensive care management, particularly in the absence of imaging resources.

A multinational study of LATAM youth examined the distinguishing features of severe acute respiratory syndrome due to SARS-COV 2 infection and MIS-c, with versus without cardiac involvement. Ninety-eight patients from 32 centers in 10 countries of Central America, South America, and Mexico were included. The cardiac group was defined as diagnosed with arrhythmia, including premature atrial or ventricular contractions, sustained or non-sustained atrial or ventricular tachycardias, or atrioventricular block of any degree; dilation of any coronary artery segment (z-score > +2); left ventricle ejection fraction below 50%; dilated left ventricle (diastolic diameter z-score > +2); qualitative assessment of moderate or greater regurgitation of atrioventricular or semilunar valves; any pericardial effusion; clinical diagnosis of myocarditis by treating provider; clinical diagnosis of peripheral edema; or vascular thrombus/embolism.[9] Forty-eight patients showed cardiac involvement, and 50 did not. The cardiac group had higher frequency of ICU admission

Keywords

Children; COVID-19/complications; Cardiovascular Diseases/complications; Severe Acute Respiratory Syndrome; Inflammation; Hospitalization

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1. **Children and adolescents (0-19 years) with fever ≥ 3 days.**
2. **And at least two of the following:**
   a. Rash, bilateral non-purulent conjunctivitis, or mucous-cutaneous inflammation signs (oral, hands or feet).
   b. Hypotension or shock
   c. **Features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities (including echocardiographic findings or elevated cardiac enzymes).**
   d. Evidence of coagulopathy (by elevated d-dimers, prothrombin time, partial thrombopalstin time).
   e. Acute gastrointestinal problems (diarrhea, vomiting or abdominal pain).
3. **And:** elevated markers of inflammation such as erythrocyte sedimentation rate (ESR), C-reative protein (CRP) or procalcitonin.
4. **And:** no other source of microbial cause of inflammation.
5. **And:** severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) confirmed infection by real time-polymerase chain reaction (RT-PCR) and/or serology, or likely contact with patients with COVID-19.

Figure 1 – *World Health Organization (WHO) definition criteria for multisystem inflammatory syndrome in children (MIS-c), associated with COVID-19.*

(77% vs 54%, p = 0.02); invasive ventilation (23% vs 4%, p = 0.007) and vasoactive support (27% vs 4%, p = 0.002). Regarding laboratory profile, cardiac group had higher frequency of elevated troponin (33% vs 12%, p = 0.01), elevated alanine aminotransferase (33% vs 12%, p = 0.02) and thrombocytopenia (46% vs 22%, p = 0.02). Receiver operating curve analysis showed that abnormal laboratory profile (elevated troponin, elevated alanine aminotransferase or thrombocytopenia) had an area under the curve of 0.75, with 94% sensitivity and 98% negative predictive value on the need for intensive care unit.[9]

In a group of 33 critically ill COVID-19 pediatric patients admitted to a single center in Brazil, Kozak *et al*. detected a higher frequency of troponin elevation in MIS-c patients than in non-MIS-c patients (77.8% vs. 20.8%; p = 0.002). Moreover, the negative predictive value of elevated troponin at admission for detecting echocardiographic abnormalities was 100% in the MIS-C group and 73.7% in the non-MIS-c group. The authors suggest that troponin level at admission may be a valuable parameter to identify patients in more urgent need of an echocardiogram in an overwhelmed public health system.[10]

In conclusion, larger studies must be held in vulnerable socioeconomic scenarios to identify low-cost and widely available tools for detecting COVID-19 pediatric patients with cardiovascular involvement at admission. This is of uttermost importance for clinical decision-making in the face of limited pediatric intensive care unit resources.

References

1. Shi S, Qin M, Shen B, Cai Y, Liu T, Yang F, et al. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. *JAMA Cardiol*. 2020;5(7):802-10. doi: 10.1001/jamacardio.2020.0950.
2. Sanna G, Serrau G, Bassareo PP, Neroni P, Fanos V Marcialis MA. Children's heart and COVID-19: Up-to-date evidence in the form of a systematic review. Eur J Pediatr. 2020 Jul;179(7):1079-87. doi: 10.1007/s00431-020-03699-0.
3. Nakra NA, Blumberg DA, Herrera-Guerra A, Lakshminrusimha S. Multisystem inflammatory syndrome in children (MIS-C) following SARS-CoV-2 infection: review of clinical presentation, hypothetical pathogenesis, and proposed management. Children (Basel). 2020;7(7): 69. doi: 10.3390/children7070069.
4. World Health Organization. Multisystem inflammatory syndrome in children and adolescents temporally related to COVID-19 [Internet]. Geneva; 2020 [citado 9 dez. 2019]. Disponível em: https://www.who.int/news-room/commentaries/detail/multisystem-inflammatory-syndrome-in-childrenand-adolescents-with-covid-19.
5. Feldstein LR, Rose EB, Horwitz SM, Collins JP, Newhams MM, Son MBF, et al. Multisystem inflammatory syndrome in U.S. children and adolescents. N Engl J Med. 2020;383(4):334-46. doi: 10.1056/NEJMoa2021680
6. Diniz MFR, Cardoso MF, Sawamura KSS, Menezes CRB, Lianza AC, Pereira MFB, et al. The Heart of Pediatric Patients with COVID-19: New Insights from a Systematic Echocardiographic Study in a Tertiary Hospital in Brazil. Arq Bras Cardiol. July 18 2021.

7. Sáfadi MA, Kfouri RA. Dados epiidemiológicos de Covid-19 em pediatria. Nota Técnica. São Paulo: Sociedade Brasileira de Pediatria: Departamento Científico de Imunizações e Departamento Científico de Infectologia; 2021.

8. Sousa BLA, Brentani A, Ribeiro CCC, Dolhnikoff M, Grisi SJFE, Ferrer APS, Ferraro AA. Non-communicable diseases, sociodemographic vulnerability and the risk of mortality in hospitalized children and adolescents with COVID-19 in Brazil: a cross-sectional observational study. BMJ Open. 2021 Sep 6;11(9): e 050724. http://dx.doi.org/10.1136/bmjopen-2021-050724

9. Pignatelli R,Vazquez CA, Rivera IR, Zenteno PA, Acosta YT, Huertas-Quiñones M, *et al*. Pediatric multisystem SARS COV2 with versus without cardiac involvement: a multicenter study from Latin America. Eur J Pediatr.2021;180(9):2879-88. doi: 10.1007/s00431-021-04052-9.

10. Kozak MF, Pessoa YC, Silva LOC, Cabral MB, Leite BCP, Diniz JD, Saliba A, Kawahara SH. Sinais de injúria cardíaca em pacientes pediátricos com COVID-19 gravemente enfermos: uma experiência de centro único no Brasil. Arq Bras Cardiol. 2022, in press.

Original Article

Perceptions of Cardiac Rehabilitation Participants Regarding their Health Behaviors and Information Needs during the COVID-19 Pandemic in Brazil

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Abstract

Background: COVID-19 has impacted how people receive health care for many conditions, including cardiovascular diseases.

Objectives: To examine perceptions of cardiac rehabilitation (CR) participants regarding their health behaviors and information needs during the COVID-19 pandemic in Brazil.

Methods: In this cross-sectional study, a 27-item questionnaire, developed by the investigators, was administered online to participants from two CR programs. Questions included health literacy (HL; using the Brief Health Literacy Screening Tool), technology use, perceptions before and during the COVID-19 pandemic, and information needs. Pearson correlation coefficients, paired t-tests, and ANOVA were used as appropriate. $P < 0.05$ was considered statistically significant for all tests.

Results: Overall, 159 (25.5%) CR participants answered the questionnaire. Of these, 89.9% had limited or marginal HL and 96.2% reported having internet access at home. Patients are mainly concerned about their family's health and their own, as well as how the coronavirus is dangerous to their health and how it has changed their lifestyle. Participants perceived that the quality of their health behaviors significantly decreased during the pandemic. The pandemic also changed information needs of CR participants as new needs emerged, such as the control of anxiety levels, staying motivated to live healthily during a pandemic, and how COVID-19 can impact their health condition. Participants with adequate HL significantly perceived the severity of the disease and having access to information significantly more than those with limited HL.

Conclusions: Our results highlighted the impact of the pandemic on CR participants' perceptions regarding their health behaviors and information needs, which can be influenced by HL levels.

Keywords: Cardiac Rehabilitation; COVID-19; Health Literacy; Needs Assessment; Surveys and Questionnaires.

Introduction

SARS-CoV-2 is a novel coronavirus identified as the cause of the coronavirus disease 2019 (COVID-19), which began in Wuhan, China in late 2019 and spread worldwide.[1] More than one year after being declared a pandemic, the number of confirmed COVID-19 cases worldwide reached 147,000,000, with Brazil ranking third among the countries with the highest number of confirmed cases and second in number of deaths.[2]

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Due to its *highly contagious* pathogenic, people worldwide are trying to prevent the spread of infection by practicing social distancing,[3] which has impacted how they work, connect with others, and receive health care from many conditions, including cardiovascular diseases (CVDs).[4]

Cardiovascular diseases are among the leading burdens of disease and the leading cause of death worldwide, with more than 80% of these deaths occurring in low- and middle-income countries,[5] including Brazil.[6] Cardiac rehabilitation (CR) is an established model of secondary prevention that has not only proven clinical and cost-effectiveness, but can significantly reduce hospitalizations and mortality rates.[7-9] In general, CR is delivered in clinical settings with patients visiting hospitals or rehabilitation centers for weekly in-person exercise and education sessions.[10,11] Thus, the necessary measures to curb the widespread transmission of COVID-19 have affected the delivery of CR, with an estimation of approximately 4,400

programs worldwide closed due to COVID-19 and face-to-face services suspended.[12]

In Brazil, COVID-19 has affected an already suboptimal CR system,[11] and programs have developed remote and innovative ways to deliver core components in such a delicate time,[12,13] following local guidelines and recommendations.[14] The rapid speed in which these changes occurred, the economic threats experienced by healthcare providers and their programs, and the inability to navigate the virtual world by many patients have affected CR participants in ways not yet explored. Although there are many publications on the COVID-19 impact on this population,[15,16] to the best of our knowledge there are no studies on how CR participants perceive their health behaviors and what information they need to know in order to continue or adopt behaviors that will make them have a better health. This is particularly important as social distancing, quarantine, and stay-at-home orders impact our lifestyle and, in cardiac patients who are already sedentary and with risk factors due to poor behaviors,[17,18] these measures can increase the risk of acute events. Furthermore, the indirect effects of the COVID-19 pandemic on general mental health are of increasing concern,[19-21] mainly in individuals with cardiovascular conditions, since they are more likely to experience mental health problems (such as depression),[22] which is associated with a two-fold higher risk of cardiovascular mortality.[23]

Therefore, there is an urgent need to monitor cardiac patients virtually and personalize prevention care, helping these individuals in their recovery and in preventing recurrent events.[24-26] In order to design an optimum CR program during the COVID-19 pandemic and beyond, it is important to understand patients' perceptions and needs. Thus, the objective of this study was to examine the perceptions of CR participants regarding their health behaviors and information needs during the COVID-19 pandemic in Brazil.

Methods

Design

This was a cross-sectional study in design. Ethics approval was obtained from the Human Research Ethics Committee of the State University of Santa Catarina (UDESC; Florianopolis, Brazil: 4.341.132). Data was collected between December/2020 and April/2021.

Setting and Participants

A convenience sample of CR participants were recruited from two public programs in the Greater Florianopolis Area (Cardiology Institute of Santa Catarina and Cardio-Oncology and Exercise Medicine Program). Before the pandemic, patients used to go to these centers 3 times a week for 1-hour exercise sessions supervised by a multidisciplinary team. Some of these participants were also attending educational sessions as part of a research project. Due to COVID-19, both programs have been closed since March 2020, and activities were not resumed during this research. The exclusion criteria were the following: being illiterate, and any visual or cognitive condition that would preclude the participant from completing the survey.

Procedures

There were 623 CR participants when both programs were closed due to COVID-19. All of them were contacted by phone and invited to participate in this research. Those interested were scheduled a second call to provide informed consent via video, which was recorded as indicated by the Research Ethics Board. Participants completed the survey online using *Google Docs* during a video chat with a research team member.

Measures

A 27-item questionnaire was developed by the investigators to examine the objectives of this study (Appendix 1). The questionnaire was divided into 5 sections as follows: (1) sociodemographic characteristics, (2) health literacy and technology use, (3) perceptions about the COVID-19 pandemic, (4) perceptions about health behaviors and feelings before and during the COVID-19 pandemic, and (5) information needs during the COVID-19 pandemic.

The items had single-, multiple-choice, and open-ended response options. Perceptions about the pandemic were reported using a Likert-type scale ranging from 1=totally disagree to 5=totally agree. Perceptions about health behaviors and feelings before and during the COVID-19 pandemic were reported using a Likert-type scale ranging from 1=poor to 5=excellent. Information needs specific to educational topics that can help patients adhere to healthy behaviors were reported using a Likert-type scale ranging from 1=really not important to 5=very important; a mean score was computed and analyzed by literacy levels, with higher scores indicating higher information needs. Input from CR experts was solicited before conducting the survey.

Clinical data (CR referral indication and cardiac risk factors) was extracted from medical records and sociodemographic characteristics (level of education, family income, change in family income due to COVID-19, marital status, and number of people living in the same household) were self-reported by participants. Health literacy was assessed using the Brief Health Literacy Screening Tool,[27] which was translated to Portuguese by the research team. Each one of the 4 items was worth 1 to 5 points, depending on participants' responses, which could range from 4 to 20. Total scores from 4 to 12 were classified as limited health literacy, 13 to 16 as marginal health literacy, and 17 to 20 as adequate health literacy.

Data analysis

Statistical analysis was performed using SPSS Version 27.0 (IBM Inc 2020, NYC). Descriptive statistics were used to describe participants' socioeconomic and clinical characteristics. Continuous variables were presented as mean and standard deviation and categorical variables by absolute numbers and percentages. Chi-square analysis for categorical variables and t-tests for continuous variables were used to compare proportions of respondents across different characteristics. All open-ended responses were coded. Pearson correlation coefficients were used to determine the association between health literacy and educational level, the use of technology and socioeconomic characteristics, and health literacy and perceptions about the COVID-19 pandemic.

The normality of data distribution was tested using the *Kolmogorov Smirnov* test. Paired t-tests were used to investigate changes between participants' perceptions of health behaviors and feelings before and during the COVID-19 pandemic. ANOVA One-Way was used to test for significant differences between information needs and health literacy levels. $P < 0.05$ was considered statistically significant for all tests.

Results

Participants' characteristics

Overall, 159 (25.5%) patients signed the consent form and completed the online survey. Reasons for non-participation included the following: 288 (46.2%) patients did not answer the first phone call, 82 (13.2%) patients were not reached due to a change in phone number, 64 (10.3%) patients did not want to participate, 19 (3.0%) patients were not eligible, and 7 (1.8%) patients died. Table 1 presents the socioeconomic and clinical characteristics of participants.

As shown, our sample was consisted mainly of male individuals, married, with a monthly family income of 4-times the Brazilian minimum wage or lower per month (with no reported changes of income due to COVID-19), with a diagnosis of coronary artery disease and hypertension. All participants were taking prescribed medications related to their cardiac condition. Most participants (75.0%) attended CR for more than one year before programs were closed due to the pandemic. As regards health literacy (Table 1), participants presented a mean score of 13.2±2.5, with the majority of the sample (89.9%) classified as having limited or marginal health literacy. Results also showed a significant positive correlation between educational level and health literacy ($r=0.45$; $P=<0.001$).

Regarding technology use, 153 (96.2%) participants reported that they have internet access at home. For those who do not have internet access at home, their reasons for not having are low technological literacy, price, and not perceiving the need to have it (n=2; 1.3% each). Most technology users (n=138; 86.8%) reported using mobile technology, with mobile phones being the most common single technology used at home (n=137; 86.2%). Finally, 99 (62.3%) participants indicated they use the internet to search for information regarding their health condition. No significant correlations between having internet access at home and socioeconomic characteristics were found.

Figure 1 illustrates how participants perceive their overall health. As shown, most participants (n=100; 62.9%) felt their health was good.

Perceptions about the covid-19 pandemic

When asked where they search for information about COVID-19, 135 (84.9%) participants identified the television as the main source for knowledge regarding the pandemic. Other sources include the following: family and friends (n=87; 54.7%), newspaper (n=59; 37.1%), social media (n=59; 37.1%), and their doctors (n=35; 22.0%). Furthermore, safety measures adopted by participants against COVID-19 included the use of facial masks (n=155; 97.5%), social distancing (n=150; 94.3%), frequent hand washing (n=144; 90.6%), and the use of hand sanitizer (n=60; 37.7%).

When asked about their perception regarding the impact of COVID-19 on their cardiac condition, 42 (26.4%) participants reported they felt the pandemic has aggravated their symptoms. Described symptoms were the following: chest pain (n=13; 8.2%), shortness of breath (n=13; 8.2%), tiredness (n=11; 6.9%), heart palpitations (n=5; 3.1%), and body pain (n=5; 3.1%). Anxiety and depression were reported by 6 (3.8%) participants.

Figure 2 illustrates how CR participants perceived the impact of COVID-19 on their lives using a Likert-type scale ranging from 1=totally disagree to 5=totally agree. Results revealed that participants were worried about their family's health (n=119; 74.8%), think that the coronavirus is dangerous to their health (n=110; 69.2%) and changed their lifestyle (n=107; 67.7%), and are worried about catching the coronavirus (n=101; 63.5%). In addition, 94 (59.1%) participants reported they have all the information they need regarding the coronavirus. Furthermore, 75 (48.1%) participants identified that it is likely they (or someone they know) will catch the coronavirus this year, 68 (43.9%) believed that if they get the disease they will die, and 61 (38.4%) participants are ready for an outbreak. Results also showed a significant positive correlation between health literacy and perceptions related to dying from this disease ($r=0.29$; $p=0.01$) and having all the information they need regarding the coronavirus ($r=0.27$; $p=0.01$), with participants with adequate health literacy perceiving the severity of the disease and having access to information.

Perceptions about health behaviors and feelings before and during the covid-19 pandemic

Table 2 presents a comparison of participants' perceptions about health behaviors and feelings before and during the COVID-19 pandemic. Overall, participants perceived that the quality of health behaviors significantly decreased during the pandemic, including being active ($p<0.001$), eating a healthy diet ($p=0.04$), sleeping well ($p=0.04$), and controlling anxiety levels ($p=0.01$). In addition, the quality of the energy level and enthusiasm to make healthy lifestyle changes was perceived to decrease significantly before and during the COVID-19 pandemic ($p<0.001$), as was their perception about overall health ($p=0.02$).

Specifically about physical activity, participants reported the following difficulties related to being active during the pandemic: lack of exercise equipment and a physical location to exercise (n=72; 45.3%), difficulty to breath while using the facial mask during training (n=63; 39.6), lack of motivation to exercise during a pandemic (n=60; 37.7%), not having the adequate physical space to exercise at home (n=43; 27.0%), use of facial mask which makes it difficult to exercise (n=63; 39.6), and lack of professional guidance to exercise safely (n=23; 14.5%).

Information needs during the Covid-19 pandemic

Figure 3 illustrates the main information needs perceived by participants. The most frequent needs during the pandemic

Table 1 – Socioeconomic status, clinical characteristics, and health literacy of participants (n=159)

Characteristic		Overall (n=159)	p*
Sociodemographic			
Age, mean±SD	-	62.7±10.1	-
Age, n (%)	Less than 65 years old	91 (57.2)	0.07
	65 years old or older	68 (42.8)	
Sex, n (%)	Male	96 (60.4)	<0.001
	Female	62 (39.0)	
	Missing	1 (0.6)	
Marital status†, n (%)	Married	106 (66.7)	<0.001
	Widower/widow	21 (13.20	
	Divorced	18 (11.3)	
	Single	13 (8.2)	
	Missing	1 (0.6)	
Number of people living in the same household, mean±SD	-	2.5±1.2	-
People living alone, n (%)	-	26 (16.4)	-
Level of education, n (%)	Elementary school or less	57 (35.8)	0.07
	High school	65 (40.9)	
	University degree	37 (23.3)	
Family income†, n (%)	Under or equal to 4 minimum wages per month	106 (66.7)	<0.001
	Between 5 and 10 minimum wages per month	31 (19.5)	
	Above 10 minimum wages per month	22 (13.8)	
Change in family income due to the COVID-19 pandemic	No change	87 (54.7)	<0.001
	Lower income	62 (39.0)	
	Higher income	6 (3.8)	
	Missing	4 (2.5)	
Clinical			
CR referral indication, n (% yes)	Coronary Artery Disease	100 (62.9)	0.04
	Heart Failure	90 (56.6)	0.10
	Myocardial Infarction	87 (54.7)	0.23
	Percutaneous Coronary Intervention	84 (52.8)	0.47
	Percutaneous Transluminal Coronary Angioplasty	68 (42.8)	0.07
	Coronary Artery Bypass Grafting	46 (28.9)	<0.001
	Peripheral Arterial Disease	11 (6.9)	<0.001
Risk factors and comorbidities, n (% yes)	Hypertension	107 (67.3)	<0.001
	Former smoker	85 (53.5)	0.05
	Dyslipidemia	70 (44.0)	0.13
	Diabetes Type II	37 (23.3)	<0.001
	Obesity	31 (19.5)	<0.001
	Stroke	15 (9.4)	<0.001
	Diabetes Type I	9 (5.7)	<0.001

	Cancer	6 (3.8)	<0.001
	Pacemaker	5 (3.1)	<0.001
Taking prescribed medications, n (% yes)	-	159 (100.0)	-
Duration of participation in CR before the program was closed due to COVID-19, n (% yes)	Less than 1 year	35 (22.0)	<0.001
	More than 1 year	121 (75.1)	
	Missing	3 (1.9)	
Literacy levels			
Health literacy, mean±SD		13.2±2.5	-
Health literacy classification‡, n (% yes)	Limited health literacy	87 (54.7)	<0.001
	Marginal health literacy	56 (35.2)	
	Adequate health literacy	15 (9.4)	
	Missing	1 (0.6)	

*CR: cardiac rehabilitation; SD: standard deviation. *Chi-square analyses for categorical variables. †Family income in Brazil is characterized by minimum wages per month. One minimum wage is 1,100.00 BRL or 193.60 USD (April/2021). ‡ Health literacy classification: total scores from 4 to 12 indicate limited health literacy, 13 to 16 marginal health literacy, and 17 to 20 adequate health literacy.*

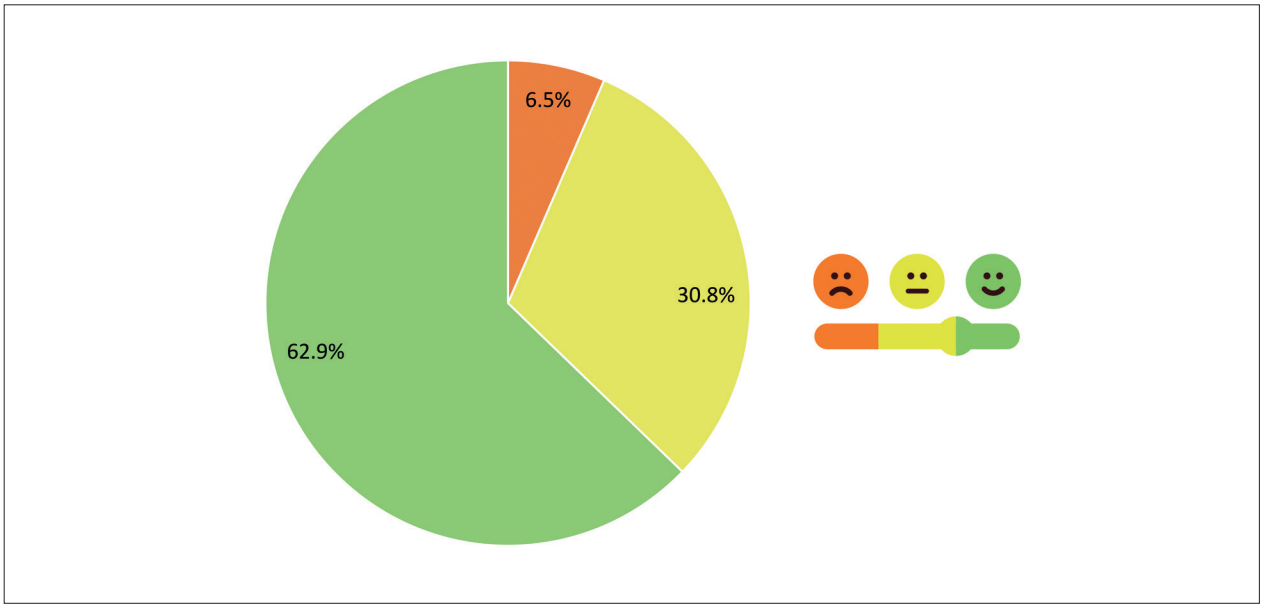

Figure 1 – *How participants perceive their overall health.*

were related to overall health, energy level, and enthusiasm to make healthy lifestyle choices, as well as being active. When asked how they would prefer this information to be delivered to them, 77 (48.4%) responded by WhatsApp, 26 (16.4%) by email, and 7 (4.4%) in person; 49 (30.8%) participants did not answer this question.

When asked to identify their information needs specific to educational topics that can help them adhere to healthy behaviors, the mean score was 4.53±0.36, with participants rating scores higher than 4 (i.e. important) in all 12 educational topics. The topic with the highest need was "Take medicines" and the lowest was "Start a resistance training program" (Table 3). In addition, information needs of participants were significantly different between health literacy levels overall (p=0.01) and in regards to the following educational topics: "Start a resistance training program" (p=0.03); "Develop a healthy relationship with food" (p=0.007); and "Manage depression, stress, and burnout" (p=0.03).

Discussion

The COVID-19 pandemic has substantially changed behaviors around the globe. To the best of our knowledge, this is the first study examining perceptions of CR participants regarding their health behaviors and information needs during the COVID-19 pandemic, which was conducted in one of the countries most affected by this infectious disease in the world.

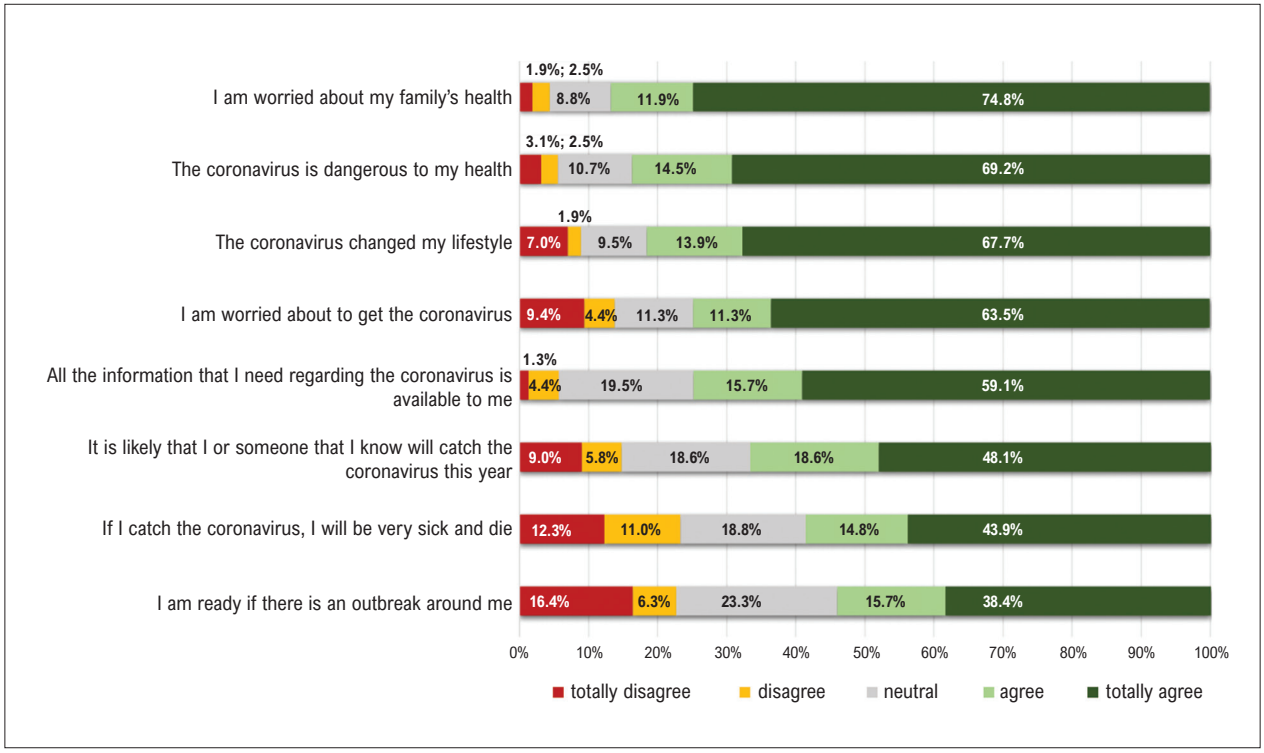

Figure 2 – *How CR participants perceived the impact of COVID-19 on their lives.*

Results confirm that the impact of COVID-19 goes well beyond those suffering from it, affecting not only the delivery of chronic disease care, but also patients' behaviors and mental health. Patients are mainly concerned about their family's health and their own, as well as how the coronavirus is dangerous to their health and how it has changed their lifestyle. Overall, participants perceived that the quality of their health behaviors significantly decreased during the pandemic. The pandemic also changed information needs of CR participants; although they continue to be interested to learn about being active, sleeping well, and eating a healthy diet, new information needs emerged when compared to previous studies with this population.[28,29] This study identified that CR participants are now also in need of learning about controlling their anxiety levels, what they can do to motivated themselves to live healthily during a pandemic, and how COVID-19 can impact their health condition.

Health literacy – the skills and competences of people and organizations to meet the complex demands of health in modern society[30] – plays a key role in this scenario. Limited health literacy has been independently associated with lesser use of preventive services, a greater use of emergency care, more hospital readmissions, a low quality of life, higher anxiety, lower social support, poorer overall health status, and higher mortality rates.[31-33] This study has identified that the majority of participants had limited or marginal health literacy, which has influenced their ability to deal with COVID-19 restrictions. Participants with adequate health literacy perceived the severity of the disease and having access to information significantly more than those with limited health literacy. In addition, those with lower levels of health literacy had higher information needs than participants with adequate levels, which should be used to inform clinical practice. There are multiple interventions to mitigate the impact of inadequate health literacy;[34,35] however, patients' abilities are often overestimated,[36] and problems, which are rarely identified, could be increased in the virtual setting.[37] Effective ways to incorporate health technology in interventions for CR participants with limited health literacy are needed.

Participants of this study have reported that their control over anxiety levels has significantly decreased during the pandemic; in addition, they perceived that the pandemic has aggravated their symptoms of anxiety and depression. The adverse effects of COVID-19 restrictions on mental well-being in patients were noted by other studies.[38-40] Because anxiety and depression are well-known factors associated with poorer outcomes of CVD,[41,42] it is essential that CR participants receive support related to psychological health during this unprecedented time. One of the channels for communication can be education, which can address not only the impact of psychosocial factors on health, but the mental health implications of this pandemic into the post-COVID era.

The media plays a critical role in providing rapid and effective dissemination routes for key information during the pandemic.[43-45] This information has also been confirmed in our study, as most CR participants identified television, newspaper, and social media as the main source for knowledge regarding COVID-19. Although media platforms can disseminate information and educate people to take public

Table 2 – Participants' perceptions of health behaviors and feelings before and during the COVID-19 pandemic (n=159)

Health behaviors and feelings	How would you classify this behavior or feeling…	…before COVID-19?	…during COVID-19?	p*
Being active, mean±SD		4.20±0.77	2.84±1.20	<0.001
	Poor, n (%)	2 (1.3)	25 (15.7)	
	Fair, n (%)	3 (1.9)	43 (27.0)	
	Neutral, n (%)	13 (8.2)	35 (22.0)	
	Good, n (%)	85 (53.5)	45 (28.3)	
	Excellent, n (%)	56 (35.2)	11 (6.9)	
Eating a healthy diet, mean±SD		4.17±0.61	4.01±0.94	0.04
	Poor, n (%)	0 (0.0)	4 (2.5)	
	Fair, n (%)	3 (1.9)	12 (7.5)	
	Neutral, n (%)	9 (5.7)	9 (5.7)	
	Good, n (%)	105 (66.0)	87 (54.7)	
	Excellent, n (%)	42 (26.4)	47 (29.6)	
Sleeping well, mean±SD		3.66±0.95	3.35±1.19	0.04
	Poor, n (%)	4 (2.5)	16 (10.1)	
	Fair, n (%)	21 (13.2)	26 (16.4)	
	Neutral, n (%)	21 (13.2)	22 (13.8)	
	Good, n (%)	91 (57.2)	76 (47.8)	
	Excellent, n (%)	22 (13.8)	19 (11.9)	
Controlling anxiety levels, mean±SD		3.76±0.98	3.00±1.19	0.01
	Poor, n (%)	2 (1.3)	18 (11.3)	
	Fair, n (%)	22 (13.8)	40 (25.2)	
	Neutral, n (%)	22 (13.8)	42 (26.4)	
	Good, n (%)	79 (49.7)	42 (26.4)	
	Excellent, n (%)	34 (21.4)	17 (10.7)	
Energy level and enthusiasm to make healthy lifestyle changes, mean±SD		4.21±0.71	3.26±1.08	<0.001
	Poor, n (%)	1 (0.6)	9 (5.7)	
	Fair, n (%)	2 (1.3)	30 (18.9)	
	Neutral, n (%)	15 (9.4)	51 (32.1)	
	Good, n (%)	85 (53.5)	49 (30.8)	
	Excellent, n (%)	56 (35.2)	20 (12.6)	
Perception about overall health, mean±SD		3.94±0.71	3.45±1.08	0.02
	Poor, n (%)	0 (0.0)	8 (5.0)	
	Fair, n (%)	6 (3.8)	25 (15.7)	
	Neutral, n (%)	27 (17.0)	33 (20.8)	
	Good, n (%)	96 (60.4)	68 (42.8)	
	Excellent, n (%)	29 (18.2)	21 (13.2)	

*SD: standard deviation. *Paired t-tests used as data is normally distributed (p<0.05). Likert-type scores ranged from 1=poor to 5=excellent.*

Figure 3 – *Main information needs perceived by participants during COVID-19.*

health measures, it can also lead to misinformation, a lack of guidance, and information leakage.[44,46] The need for skills to correctly judge the accuracy of health information posted on media channels makes it individuals with limited health literacy at risk of misinformation.[46] Although few participants of this study have reported they seek their doctors for information related to COVID-19, healthcare teams should include these topics to their sessions and, if possible, create social media channels to connect with their patients and share recommendations in times of COVID-19.

Technology is considered a safe way to ensure cardiac patients receive the care they need during the pandemic.[13,15,26] Patients perceptions and higher information needs reported by this study confirm the urge to care for these patients. Studies have identified that most CR components could be safely delivered through remote means, including patient education.[13,24-26,47-50] Thus, a comprehensive, evidence-based virtual patient education is available in 8 languages (including Brazilian-Portuguese) for programs to use freely. The assessment of new formats of CR on implementation and outcomes is needed.

This study has articulated how the COVID pandemic has impacted CR participants' perceptions regarding their health behaviors and information needs, and the influence of health literacy levels in this scenario. Individuals with limited health literacy face challenges in accessing and navigating health care, and such obstacles may be exacerbated by pandemic restrictions. However, results go beyond the individual level and are also targeted to healthcare providers and CR programs. Healthcare providers should start adopting strategies that can potentially mitigate the impact of health literacy in the care of their patients. CR programs should work towards becoming health-literate institutions and develop a best practices approach to health literacy.

Caution is warranted when interpreting these results. First, this was a convenience sample; thus, results may be biased. This was a small sample size, which limits generalizability. Results may not be applicable to other groups of cardiac patients. Second, the reliability and validity of the questionnaire is unknown. Third, this was a cross-sectional study, so data was captured at a single

Table 3 – Information needs specific to educational topics that can help patients adhere to healthy behaviors (n=159)

Educational topic	Mean score overall (mean±SD)	Mean score by health literacy level (mean±SD)			p*
		Limited (n=87)	Marginal (n=56)	Adequate (n=15)	
Create a plan for change Description: learn how to motivated oneself to live a healthy life and how to create a plan for change that will help you to reach this goal.	4.49±0.56	4.48±0.53	4.59±0.53	4.25±0.45	0.10
Start an aerobic exercise program Description: learn what aerobic exercise is, how to plan for exercise, the benefits of aerobic exercise and how to exercise safely.	4.64±0.50	4.60±0.49	4.71±0.50	4.64±0.50	0.43
Start a resistance training program Description: learn what resistance training is and its benefits and how to do resistance training safely.	4.12±0.88	4.12±0.91	4.27±0.80	3.57±0.94	0.03
Sit less and move more Description: learn how sitting too much affects your health and what are the ways to sit less during the day.	4.44±0.61	4.39±0.65	4.50±0.57	4.43±0.51	0.59
Choose healthy foods Description: learn what types of foods can improve your heart health and how to use a nutrition facts table to choose healthy foods.	4.65±0.55	4.61±0.54	4.76±0.54	4.60±0.51	0.22
Develop a healthy relationship with food Description: learn the importance of paying attention to flavor, texture, and your surroundings when you eat and what are the ways to eat with more pleasure and know when you are full.	4.57±0.55	4.57±0.50	4.69±0.47	4.20±0.51	0.007
Eat the Mediterranean diet Description: Learn what foods to include in a heart healthy eating pattern and how to include more whole foods in your eating.	4.56±0.59	4.54±0.57	4.60±0.63	4.64±0.50	0.73
Take medicines Description: learn what are the common classes of heart medicines, how they help you and who can help you manage side effects and answer your questions.	4.77±0.44	4.74±0.47	4.85±0.36	4.67±0.49	0.18
Manage depression, stress, and burnout Description: learn what depression, stress, and burnout are, and what techniques you can try to help you feel in charge of your health.	4.52±0.59	4.54±0.59	4.57±0.54	4.13±0.74	0.03
Sleep well Description: learn what might be stopping you from sleeping well and what are the signs of sleep apnea.	4.57±0.67	4.53±0.78	4.65±0.52	4.40±0.51	0.35
Strengthen social relationships Description: learn how social relationships can improve your health, how heart disease can affect sex and intimacy, and what techniques are available to create healthy relationships.	4.30±0.76	4.31±0.74	4.36±0.78	4.14±0.77	0.62
Choose health everyday Description: learn how to maintain your healthy habits and what to do if you stop your healthy habit.	4.62±0.53	4.61±0.54	4.70±0.46	4.47±0.52	0.25
Total	4.53±0.36	4.51±0.37	4.63±0.31	4.29±0.36	0.01

*SD: standard deviation. *ANOVA One-Way (p<0.05). Likert-type scores ranged from 1=poor to 5=excellent.*

moment in time on specific topics. Since the surge of COVID-19 has changed constantly with different waves and restrictions, it is expected that self-reported perceptions and behaviors could change. Third, the study design may limit the description of perceptions. Subsequent qualitative studies will increase our understanding of this topic. It is also suggested that future studies should test the validity of this study in other groups of patients and describe the methodology applied in detail.

Conclusion

In conclusion, our results highlighted the impact of the pandemic on CR participants' perceptions regarding their health behaviors and information needs, which can be influenced by health literacy levels. Findings from this study should be used to inform CR programs and encourage healthcare providers to personalize prevention care, which can ultimately help patients to navigate through such a difficult period, helping them to stay healthy and prevent recurrent events.

Author Contributions

Conception and design of the research: Ghisi GLM, Santos RZ, Oh P, Benetti M; Acquisition of data: Santos RZ, Korbes AS, Souza CA; Analysis and interpretation of the data: Ghisi GLM, Santos RZ, Karsten M; Statistical analysis: Ghisi GLM; Critical revision of the manuscript for intellectual content: Santos RZ, Korbes AS, Souza CA, Karsten M, Oh P, Benetti M.

Potential Conflict of Interest

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Study Association

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References

1. Fauci AS, Lane HC, Redfield RR. Covid-19 - Navigating the Uncharted. N Engl J Med. 2020;382(13):1268-9. doi: 10.1056/NEJMe2002387.
2. Johns Hopkins. COVID-19 Map – Coronavirus Resource Center Johns Hopkins. Baltimore: Johns Hopkins University & Medicine; 2021 [cited 2021 Apr 26]. Available from: https://coronavirus.jhu.edu/map.html.
3. Chu DK, Akl EA, Duda S, Solo K, Yaacoub S, Schünemann HJ. Physical Distancing, Face Masks, and Eye Protection to Prevent Person-to-person Transmission of SARS-CoV-2 and COVID-19: A Systematic Review and Meta-analysis. Lancet. 2020;395(10242):1973-87. doi: 10.1016/S0140-6736(20)31142-9.
4. Kulkarni P, Mahadevappa M, Alluri S. COVID-19 Pandemic and the Impact on the Cardiovascular Disease Patient Care. Curr Cardiol Rev. 2020;16(3):173-7. doi: 10.2174/1573403X16666200621154842.
5. Benziger CP, Roth GA, Moran AE. The Global Burden of Disease Study and the Preventable Burden of NCD. Glob Heart. 2016;11(4):393-7. doi: 10.1016/j.gheart.2016.10.024.
6. Tabnet. Datasus. Sistema de Informações de Mortalidade SIM e IBGE, 2014. Brasília: Ministério da Saúde; c2018 [cited 2018 Oct 06]. Available from: http://tabnet.datasus.gov.br/CGI/idb2006/matriz.html.
7. Oldridge N, Taylor RS. Cost-effectiveness of Exercise Therapy in Patients with Coronary Heart Disease, Chronic Heart Failure and Associated Risk Factors: A Systematic Review of Economic Evaluations of Randomized Clinical Trials. Eur J Prev Cardiol. 2020;27(10):1045-55. doi: 10.1177/2047487319881839.
8. Simon M, Korn K, Cho L, Blackburn GG, Raymond C. Cardiac Rehabilitation: A Class 1 Recommendation. Cleve Clin J Med. 2018;85(7):551-8. doi: 10.3949/ccjm.85a.17037.
9. Kabboul NN, Tomlinson G, Francis TA, Grace SL, Chaves G, Rac V, et al. Comparative Effectiveness of the Core Components of Cardiac Rehabilitation on Mortality and Morbidity: A Systematic Review and Network Meta-Analysis. J Clin Med. 2018;7(12):514. doi: 10.3390/jcm7120514.
10. Supervia M, Turk-Adawi K, Lopez-Jimenez F, Pesah E, Ding R, Britto RR, et al. Nature of Cardiac Rehabilitation Around the Globe. EClinicalMedicine. 2019;13:46-56. doi: 10.1016/j.eclinm.2019.06.006.
11. Britto RR, Supervia M, Turk-Adawi K, Chaves GSDS, Pesah E, Lopez-Jimenez F, et al. Cardiac Rehabilitation Availability and Delivery in Brazil: A Comparison to Other Upper Middle-income Countries. Braz J Phys Ther. 2020;24(2):167-76. doi: 10.1016/j.bjpt.2019.02.011.
12. Ghisi GLM, Xu Z, Liu X, Mola A, Gallagher R, Babu AS, et al. Impacts of the COVID-19 Pandemic on Cardiac Rehabilitation Delivery around the World. Glob Heart. 2021;16(1):43. doi: 10.5334/gh.939.
13. Castro RRT. Coronavirus Disease (COVID-19) Pandemic: An Opportunity Window to Implement Home-Based Cardiac Rehabilitation. Int J Cardiovasc Sci. 2020; 33(3):282-3. doi: https://doi.org/10.36660/ijcs.20200062
14. Grossman GB, Sellera CAC, Hossri CAC, Carreira LTF, Avanza AC Jr, Albuquerque PF, et al. Position Statement of the Brazilian Society of Cardiology Department of Exercise Testing, Sports Exercise, Nuclear Cardiology, and Cardiovascular Rehabilitation (DERC/SBC) on Activities Within its Scope of Practice During the COVID-19 Pandemic. Arq Bras Cardiol. 2020;115(2):284-91. doi: 10.36660/abc.20200797.
15. Neubeck L, Hansen T, Jaarsma T, Klompstra L, Gallagher R. Delivering Healthcare Remotely to Cardiovascular Patients during COVID-19 : A Rapid Review of the Evidence. Eur J Cardiovasc Nurs. 2020;19(6):486-94. doi: 10.1177/1474515120924530.
16. Duffy EY, Cainzos-Achirica M, Michos ED. Primary and Secondary Prevention of Cardiovascular Disease in the Era of the Coronavirus Pandemic. Circulation. 2020;141(24):1943-5. doi: 10.1161/CIRCULATIONAHA.120.047194.
17. Doukky R, Mangla A, Ibrahim Z, Poulin MF, Avery E, Collado FM, et al. Impact of Physical Inactivity on Mortality in Patients with Heart Failure. Am J Cardiol. 2016;117(7):1135-43. doi: 10.1016/j.amjcard.2015.12.060.
18. Warren TY, Barry V, Hooker SP, Sui X, Church TS, Blair SN. Sedentary Behaviors Increase Risk of Cardiovascular Disease Mortality in Men. Med Sci Sports Exerc. 2010;42(5):879-85. doi: 10.1249/MSS.0b013e3181c3aa7e.
19. Pfefferbaum B, North CS. Mental Health and the Covid-19 Pandemic. N Engl J Med. 2020;383(6):510-2. doi: 10.1056/NEJMp2008017.
20. Vindegaard N, Benros ME. COVID-19 Pandemic and Mental Health Consequences: Systematic Review of the Current Evidence. Brain Behav Immun. 2020;89:531-42. doi: 10.1016/j.bbi.2020.05.048.

21. Cullen W, Gulati G, Kelly BD. Mental Health in the COVID-19 Pandemic. QJM. 2020;113(5):311-2. doi: 10.1093/qjmed/hcaa110.

22. De Hert M, Detraux J, Vancampfort D. The Intriguing Relationship Between Coronary Heart Disease and Mental Disorders. Dialogues Clin Neurosci. 2018;20(1):31-40. doi: 10.31887/DCNS.2018.20.1/mdehert.

23. Huffman JC, Celano CM, Beach SR, Motiwala SR, Januzzi JL. Depression and Cardiac Disease: Epidemiology, Mechanisms, and Diagnosis. Cardiovasc Psychiatry Neurol. 2013;2013:695925. doi: 10.1155/2013/695925.

24. Besnier F, Gayda M, Nigam A, Juneau M, Bherer L. Cardiac Rehabilitation During Quarantine in COVID-19 Pandemic: Challenges for Center-Based Programs. Arch Phys Med Rehabil. 2020;101(10):1835-8. doi: 10.1016/j.apmr.2020.06.004.

25. Scherrenberg M, Wilhelm M, Hansen D, Völler H, Cornelissen V, Frederix I, et al. The Future is Now: A Call for Action for Cardiac Telerehabilitation in the COVID-19 Pandemic from the Secondary Prevention and Rehabilitation Section of the European Association of Preventive Cardiology. Eur J Prev Cardiol. 2020:2047487320939671. doi: 10.1177/2047487320939671.

26. Babu AS, Arena R, Ozemek C, Lavie CJ. COVID-19: A Time for Alternate Models in Cardiac Rehabilitation to Take Centre Stage. Can J Cardiol. 2020;36(6):792-4. doi: 10.1016/j.cjca.2020.04.023.

27. Haun J, Luther S, Dodd V, Donaldson P. Measurement Variation Across Health Literacy Assessments: Implications for Assessment Selection in Research and Practice. J Health Commun. 2012;17(Suppl 3):141-59. doi: 10.1080/10810730.2012.712615.

28. Ghisi GL, Santos RZ, Bonin CB, Roussenq S, Grace SL, Oh P, et al. Validation of a Portuguese Version of the Information Needs in Cardiac Rehabilitation (INCR) Scale in Brazil. Heart Lung. 2014;43(3):192-7. doi: 10.1016/j.hrtlng.2014.01.009.

29. Ghisi GLM, Grace SL, Thomas S, Evans MF, Sawula H, Oh P. Healthcare Providers' Awareness of the Information Needs of Their Cardiac Rehabilitation Patients Throughout the Program Continuum. Patient Educ Couns. 2014;95(1):143-50. doi: 10.1016/j.pec.2013.12.020.

30. Sørensen K, Van den Broucke S, Fullam J, Doyle G, Pelikan J, Slonska Z, et al. Health Literacy and Public Health: A Systematic Review and Integration of Definitions and Models. BMC Public Health. 2012;12:80. doi: 10.1186/1471-2458-12-80.

31. Ghisi GLM, Chaves GSDS, Britto RR, Oh P. Health Literacy and Coronary Artery Disease: A Systematic Review. Patient Educ Couns. 2018;101(2):177-84. doi: 10.1016/j.pec.2017.09.002.

32. Walters R, Leslie SJ, Sixsmith J, Gorely T. Health Literacy for Cardiac Rehabilitation: An Examination of Associated Illness Perceptions, Self-Efficacy, Motivation and Physical Activity. Int J Environ Res Public Health. 2020;17(22):8641. doi: 10.3390/ijerph17228641.

33. Dunn P, Conard S. Improving Health Literacy in Patients with Chronic Conditions: A Call to Action. Int J Cardiol. 2018;273:249-51. doi: 10.1016/j.ijcard.2018.08.090.

34. Sheridan SL, Halpern DJ, Viera AJ, Berkman ND, Donahue KE, Crotty K. Interventions for Individuals with Low Health Literacy: A Systematic Review. J Health Commun. 2011;16(Suppl 3):30-54. doi: 10.1080/10810730.2011.604391.

35. Schaffler J, Leung K, Tremblay S, Merdsoy L, Belzile E, Lambrou A, et al. The Effectiveness of Self-Management Interventions for Individuals with Low Health Literacy and/or Low Income: A Descriptive Systematic Review. J Gen Intern Med. 2018;33(4):510-23. doi: 10.1007/s11606-017-4265-x.

36. Kelly PA, Haidet P. Physician Overestimation of Patient Literacy: A Potential Source of Health Care Disparities. Patient Educ Couns. 2007;66(1):119-22. doi: 10.1016/j.pec.2006.10.007.

37. Conard S. Best Practices in Digital Health Literacy. Int J Cardiol. 2019;292:277-9. doi: 10.1016/j.ijcard.2019.05.070.

38. Brooks SK, Webster RK, Smith LE, Woodland L, Wessely S, Greenberg N, et al. The Psychological Impact of Quarantine and How to Reduce it: Rapid Review of the Evidence. Lancet. 2020;395(10227):912-20. doi: 10.1016/S0140-6736(20)30460-8.

39. O'Neil A, Nicholls SJ, Redfern J, Brown A, Hare DL. Mental Health and Psychosocial Challenges in the COVID-19 Pandemic: Food for Thought for Cardiovascular Health Care Professionals. Heart Lung Circ. 2020;29(7):960-3. doi: 10.1016/j.hlc.2020.05.002.

40. Bérard E, Huo Kai SY, Coley N, Bongard V, Ferrières J. Lockdown-related Factors Associated with the Worsening of Cardiovascular Risk and Anxiety or Depression during the COVID-19 Pandemic. Prev Med Rep. 2020;21:101300. doi: 10.1016/j.pmedr.2020.101300.

41. Dhar AK, Barton DA. Depression and the Link with Cardiovascular Disease. Front Psychiatry. 2016;7:33. doi: 10.3389/fpsyt.2016.00033.

42. Celano CM, Daunis DJ, Lokko HN, Campbell KA, Huffman JC. Anxiety Disorders and Cardiovascular Disease. Curr Psychiatry Rep. 2016;18(11):101. doi: 10.1007/s11920-016-0739-5.

43. Chan AKM, Nickson CP, Rudolph JW, Lee A, Joynt GM. Social Media for Rapid Knowledge Dissemination: Early Experience from the COVID-19 Pandemic. Anaesthesia. 2020;75(12):1579-82. doi: 10.1111/anae.15057.

44. Limaye RJ, Sauer M, Ali J, Bernstein J, Wahl B, Barnhill A, et al. Building Trust While Influencing Online COVID-19 Content in the Social Media World. Lancet Digit Health. 2020;2(6):277-8. doi: 10.1016/S2589-7500(20)30084-4.

45. Cuello-Garcia C, Pérez-Gaxiola G, van Amelsvoort L. Social Media can Have an Impact on How we Manage and Investigate the COVID-19 Pandemic. J Clin Epidemiol. 2020;127:198-201. doi: 10.1016/j.jclinepi.2020.06.028.

46. Pennycook G, McPhetres J, Zhang Y, Lu JG, Rand DG. Fighting COVID-19 Misinformation on Social Media: Experimental Evidence for a Scalable Accuracy-Nudge Intervention. Psychol Sci. 2020;31(7):770-80. doi: 10.1177/0956797620939054.

47. Schmidt C, Magalhães S, Barreira A, Ribeiro F, Fernandes P, Santos M. Cardiac Rehabilitation Programs for Heart Failure Patients in the Time of COVID-19. Rev Port Cardiol (Engl Ed). 2020;39(7):365-6. doi: 10.1016/j.repc.2020.06.012.

48. Nakayama A, Takayama N, Kobayashi M, Hyodo K, Maeshima N, Takayuki F, et al. Remote Cardiac Rehabilitation is a Good Alternative of Outpatient Cardiac Rehabilitation in the COVID-19 Era. Environ Health Prev Med. 2020;25(1):48. doi: 10.1186/s12199-020-00885-2.

49. Roifman I, Arora RC, Bewick D, Chow CM, Clarke B, Cowan S, et al. Cardiovascular Care Delivery During the Second Wave of COVID-19 in Canada. Can J Cardiol. 2021 May;37(5):790-3. doi: 10.1016/j.cjca.2020.11.016.

50. Nabutovsky I, Breitner D, Heller A, Klempfner Y, Klempfner R. Adherence to Remote Cardiac Rehabilitation During the Coronavirus Pandemic: A Retrospective Cohort Analysis. J Cardiopulm Rehabil Prev. 2021;41(2):127-9. doi: 10.1097/HCR.0000000000000593.

*Supplemental Materials

For additional information, please click here.

Prognostic Value of Aortic Stiffness using Cardiovascular Magnetic Resonance in The Elderly with Known or Suspected Coronary Artery Disease

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Abstract

Background: **Aortic stiffness is established as a marker of cardiovascular disease. Cardiovascular magnetic resonance (CMR) provides a comprehensive assessment of aortic stiffness and myocardial ischemia in a single examination. However, prognostic data concerning aortic stiffness in elderly patients remain limited.**

Objective: **To determine the prognostic value of aortic stiffness using CMR-based pulse wave velocity (PWV) in elderly patients with known or suspected coronary artery disease (CAD).**

Methods: **This study enrolled consecutive patients aged >70 referred for adenosine stress perfusion CMR including PWV between 2010 and 2014. Patients were followed up for occurrence of major adverse cardiovascular events (MACE), including cardiac mortality, nonfatal myocardial infarction, hospitalization for heart failure, late revascularization (>180 days after CMR), and ischemic stroke. Univariable and multivariable analyses were performed to determine the predictors of MACE. A p-value of <0.05 is considered statistically significant.**

Results: **Mean PWV was 13.98±9.00 m/s. After a median follow-up period of 59.6 months in 263 patients (55% female, 77±5 years), 61 MACE occurred. Patients with elevated PWV (>13.98 m/s) had significantly higher rates of MACE (HR 1.75; 95% CI 1.05-2.94; p=0.03) than those with non-elevated PWV (<13.98 m/s). Multivariate analysis demonstrated diastolic blood pressure, left ventricular ejection fraction (LVEF), myocardial ischemia, and elevated PWV as independent predictors for MACE (p<0.05 for all). PWV provided an incremental prognostic value over clinical data, LVEF, and ischemia (increased global chi-square=7.25, p=0.01).**

Conclusion: **Aortic stiffness using CMR is a strong and independent predictor of cardiovascular events in elderly patients with known or suspected CAD.**

Keywords: **Aortic Stiffness; Cardiovascular Magnetic Resonance; Coronary Artery Disease; Elderly; Prognosis.**

Introduction

Arterial stiffness increases with aging as an independent predictor of cardiovascular events, including mortality.[1-4] There are several ways to measure arterial stiffness, including ultrasonography, carotid-femoral tonometer, and cardiovascular magnetic resonance (CMR). Measurement of aortic pulse wave velocity (PWV) by a tonometer has been extensively used. However, CMR is often the preferred method. CMR-based PWV measurements have been well validated (compared with invasive pressure recordings) with high reproducibility.[5] Benefits of CMR include the provision of cross-sectional images covering the desired aortic length, high spatial resolution, and direct measurement of aortic length without geometric assumptions of the distance (in contrast to a tonometer), with no ionizing radiation.

Increased age is one of the most influential risk markers for cardiovascular disease (CVD), including coronary artery disease (CAD). CVD is responsible for over 80% of all deaths of individuals aged 65 or older in developed countries.[6] Therefore, diagnosis and risk stratification of CAD in elderly patients is crucial. CMR provides a comprehensive assessment of CAD with very high accuracy.[7] Moreover, adenosine stress CMR offers strong evidence for the prognosis of future cardiovascular events in patients with known or suspected CAD.[8] Previous data indicated that stress CMR performed in ambulatory elderly is safe and well tolerated.[9,10] CMR can assess PWV and perform a stress test in a single examination. We recently demonstrated the association of aortic stiffness and myocardial ischemia, as well as the prognostic value of aortic stiffness using CMR.[11,12] Nevertheless, limited data exist concerning the prognosis of PWV by CMR in elderly patients.

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This study objective aimed to determine the prognostic value of PWV in terms of major adverse cardiovascular events (MACE) in elderly patients with known or suspected CAD.

Methods

Study population

This study enrolled consecutive patients older than 70 years with known or suspected CAD who were referred for adenosine stress CMR from October 2010 to February 2014 to our outpatient center. In our institution, aortic stiffness using PWV has been routinely incorporated in comprehensive CMR protocol for CAD evaluation. Detailed medical history was collected on the day of the CMR study.

Exclusion criteria included (1) incomplete CMR examination, (2) contraindications to CMR (e.g., pacemaker) or adenosine (e.g., high-grade atrioventricular block), (3) unstable clinical condition, (4) patients with aortic diseases involving PWV measurement (e.g., an aortic aneurysm[13]), (5) poor CMR image quality, and (6) patients lacking follow-up data. Patients with a glomerular filtration rate of <30 ml/min/1.73 m^2 within 30 days before CMR were also excluded.

The institutional ethics committee approved this retrospective study and waived the need for additional written informed consent.

CMR protocol (Supplemental Materials)

Cine, perfusion, and LGE image analyses (Supplemental Materials)

PWV analysis[11]

Dedicated cardiovascular imaging software was applied for PWV analysis and performed independently from the perfusion study and LGE. Contours of mid-ascending and mid-descending thoracic aorta were drawn manually to achieve the flow (m/s) at both locations throughout all phases of the cardiac cycle. The corresponding flow-time curve was generated. Pulse wave arrival time was measured as the interception point of the linear extrapolation of the baseline and the steep early systolic stage, while aortic path length was determined by a multiplanar reconstruction of the axial half-Fourier acquisition from the steady-stage image. The reconstructed sagittal view of the path length was depicted as the centerline from the levels of the mid-ascending to the mid-descending thoracic aorta, corresponding to the same level obtained in VE-CMR.[11]

The PWV between the mid-ascending and mid-descending thoracic aorta was calculated as:

$PWV = \Delta x / \Delta T$ (m/s)

Where Δx reflects the length of the aortic path between the mid-ascending and mid-descending thoracic aorta and ΔT represents the time delay between the arrival of the foot of the pulse wave at these two corresponding levels (Supplemental Figure 1).

Intraobserver and interobserver variability of PWV measurement

Approximately 10% of the study cohort were randomly selected, using a Random Number Generator in Microsoft Excel, ver. 2016, to measure variability of the first observer 4 weeks after the initial analysis, and variability of the second independent observer, who was blinded to the initial results.

Clinical follow-up

Follow-up data were collected from clinical visits and medical records. Event adjudication was blinded to clinical and CMR data. Patients were followed up for MACE defined as composite outcomes for cardiac mortality, non-fatal myocardial infarction (MI), hospitalization for heart failure, late coronary revascularization (>180 days after CMR), and ischemic stroke. Need for revascularization therapy within 180 days after the CMR was considered to be triggered by the CMR results and therefore censored from analysis.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 20.0 (IBM Corp., Armonk, NY, USA). Continuous variables with normal distribution were presented as mean ± standard deviation (SD), and continuous variables with non-normal distribution were presented as median and interquartile range. Normality distribution of the variables was examined by the Kolmogorov-Smirnov test. Categorical variables were presented as absolute numbers and percentages. Patients were divided into two groups based on their PWV values. Elevated PWV and non-elevated PWV groups used the mean PWV value of all patients as the cut-off level. Intraobserver and interobserver variability for PWV measurements were expressed as intraclass correlation coefficient (ICC), 95% confidence interval (CI) and bias ±2 SDs (for limits of agreement) using the Bland-Altman analysis.

Differences between patients with elevated and non-elevated PWV, as well as with and without MACE, were compared using the student's unpaired t-test or Mann-Whitney U test for continuous variables, and the chi-square test or Fisher's exact test for categorical variables, as appropriate.

Composite outcomes between both groups were estimated using the Kaplan-Meier method and compared with the log-rank test. To analyze the predictors of MACE, a Cox-regression analysis was performed to assess univariable predictors. Variables (baseline characteristics, medications at the time of CMR, and CMR parameters) with a p-value <0.05 in the univariable analysis were included for multivariable analysis using the ENTER method. A receiver operating characteristic (ROC) analysis was used to determine the best value of PWV predicting MACE.

To assess the incremental prognostic value of significant predictors, global chi-square values were calculated after

adding predictors in the following order: clinical, LVEF, myocardial ischemia, and PWV.

All statistical tests were two-tailed, while all p-values of less than 0.05 were considered to indicate statistical significance.

Results

Patient characteristics

A total of 269 patients were enrolled, with two excluded due to having an aortic aneurysm and four excluded due to a loss of follow-up data. No patients were excluded because of poor image quality, and 263 were included in the final analysis. Mean age was 77.3±5.2 years. Table 1 summarizes patient clinical data. Two hundred and eight patients were referred for the first diagnosis of CAD. Fifty-five had been previously diagnosed with CAD, including 4 with previously documented MI. Overall, the study cohort had a mean LVEF of 68.1±15.1%. Myocardial ischemia was detected in 95 (36.1%) patients. Thirty-nine (14.8%) had LGE, and all showed a CAD pattern (subendocardial or transmural LGE). No patient presented an irregular heart rate (such as atrial fibrillation) during the PWV acquisition. Mean PWV was 13.98±9.00 m/s. History of hypertension, diabetes mellitus, and systolic blood pressure were independent predictors of elevated PWV (>13.98 m/s) (Table 2).

Intraobserver and interobserver variability for PWV measurement

There was less intraobserver and interobserver variability for PWV measurements by VE-CMR (Figure 1). For the 30

Table 1 – Clinical Characteristics of Patients with and without Elevated PWV

	Total (n=263)	Elevated PWV (n=83)	Non-elevated PWV (n=180)	p-Value
Age (years)	77.3±5.2	77.9±5.1	77.1±5.2	0.19
Female	144 (54.8)	50 (60.2)	94 (52.2)	0.23
Body mass index (kg/m^2)	26.3±4.1	26±4.1	26.4±4.2	0.49
Systolic BP (mmHg)	139.3±19.7	144.7±18.1	136.9±19.9	**0.003**
Diastolic BP (mmHg)	70.5±11.1	71.4±11.3	70.2±10.9	0.42
Heart rate (beats/minute)	76.6±13.9	76.6±15.5	76.6±13.2	0.99
Clinical history				
Hypertension	235 (89.4)	81 (97.6)	154 (85.6)	**0.01**
Diabetes mellitus	145 (55.1)	58 (69.9)	87 (48.3)	**0.001**
Hyperlipidemia	197 (74.9)	60 (72.3)	137 (76.1)	0.51
Coronary artery disease	55 (20.9)	20 (24.1)	35 (19.4)	0.39
Prior revascularization	12 (4.6)	4 (4.8)	8 (4.4)	0.89
Ischemic stroke	13 (4.9)	3 (3.6)	10 (5.6)	0.50
Cigarette smoker	28 (10.6)	7 (8.4)	21 (11.7)	0.43
Medications				
ACEI or ARB	130 (49.4)	43 (51.8)	87 (48.3)	0.60
Aspirin	134 (50.9)	45 (54.2)	89 (49.4)	0.47
Beta blocker	124 (47.2)	38 (45.8)	86 (47.8)	0.76
Calcium channel blocker	96 (36.5)	27 (32.5)	69 (38.3)	0.36
Statin	147 (55.9)	50 (60.2)	97 (53.9)	0.34
CMR				
LV mass (g)	84.3±24.5	83.6±25.5	84.7±24.0	0.74
LV ejection fraction (%)	68.1±15.1	69.8±14.1	67.3±15.5	0.21
Myocardial ischemia	95 (36.1)	28 (33.7)	67 (37.2)	0.58
Late gadolinium enhancement	39 (14.8)	15 (18.1)	24 (13.3)	0.32
PWV (m/s)	13.98±9.00	22.09±12.28	10.24±2.22	**<0.001**

*Values are number (percentages) or mean±SD. **Bold** values are <0.05. ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blocker; BP: blood pressure; CMR: cardiovascular magnetic resonance; LV: left ventricular; PWV: pulse wave velocity; SD: standard deviation.*

Table 2 – Predictors of Elevated PWV (>13.98 m/s)

	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	p-Value	HR (95% CI)	p-Value
Age (years)	1.03 (0.98. 1.09)	0.19		
Female	1.39 (0.82. 2.35)	0.23		
Body mass index (kg/m^2)	0.98 (0.92. 1.04)	0.49		
Systolic BP (per 10 mmHg)	1.23 (1.07. 1.41)	**0.003**	1.23 (1.07. 1.42)	**0.01**
Diastolic BP (per 10 mmHg)	1.10 (0.87. 1.40)	0.42		
Hypertension	6.84 (1.58. 29.54)	**0.01**	6.06 (1.36. 26.97)	**0.02**
Diabetes mellitus	2.48 (1.43. 4.31)	**0.001**	2.09 (1.18. 3.70)	**0.01**
Hyperlipidemia	0.82 (0.45. 1.48)	0.51		
Coronary artery disease	1.32 (0.71. 2.54)	0.39		
Prior revascularization	1.09 (0.32. 3.72)	0.89		
Ischemic stroke	0.64 (0.17. 2.38)	0.50		
Cigarette smoker	0.70 (0.28. 1.71)	0.43		
ACEI or ARB	1.15 (0.68. 1.93)	0.60		
Aspirin	1.21 (0.72. 2.04)	0.47		
Beta blocker	0.92 (0.55. 1.56)	0.76		
Calcium channel blocker	0.78 (0.45. 1.34)	0.36		
Statin	1.30 (0.76. 2.20)	0.34		
LV mass (g)	0.99 (0.98. 1.01)	0.74		
LV ejection fraction (per 10%)	1.13 (0.94. 1.35)	0.21		
Myocardial ischemia	0.86 (0.50. 1.48)	0.58		
Late gadolinium enhancement	1.43 (0.71. 2.90)	0.32		

Bold *values are <0.05. ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blocker; BP: blood pressure; CMR: cardiovascular magnetic resonance; LV: left ventricular; PWV: pulse wave velocity; CI: confidence interval; HR: hazard ratio.*

randomly selected patients, mean PWV±SD values were 9.88±2.73 m/s and 9.87±2.59 m/s for the first observer in the initial analysis and 4 weeks later, respectively, and 9.94±2.67 m/s for the second observer in the initial analysis. There was no significant bias (mean difference for intraobserver=0.01±0.49 m/s, p=0.98 and for interobserver=-0.03±0.35 m/s, p=0.93) (Figure 1B and 1D, respectively).

Primary outcome: MACE

During the median follow-up period of 59.6 months (interquartile range: 36.6, 68.2 months), 61 MACE occurred. Clinical characteristics including CMR variables of patients with and without MACE are shown in Supplemental Table 1. Patients with MACE had significantly lower diastolic blood pressure, higher LV mass, lower LVEF, and a higher prevalence of ischemia and LGE.

Table 3 demonstrates cardiovascular events in the study cohort. Figure 2A shows the Kaplan-Meier curves of patients with and without elevated PWV. Patients with elevated PWV had significantly higher rates of MACE than those with non-elevated PWV. Figure 2B demonstrates the Kaplan-Meier curves stratified by the presence of ischemia with and without elevated PWV. Patients with non-elevated PWV and negative ischemia had the best outcome, while the patients with elevated PWV and positive ischemia had the worst outcome. Note that the patients with non-elevated PWV and positive ischemia had no difference in the rate of MACE compared to the patients with elevated PWV and negative ischemia (HR 2.03, 95% CI 0.89-4.63, p=0.09).

A ROC curve (Figure 3) demonstrated the best value of PWV of 11.16 m/s to predict MACE with a sensitivity of 71% and specificity of 50%.

Univariate and multivariate analyses for prediction of MACE are shown in Table 4. Univariate analysis demonstrated diastolic blood pressure, history of CAD, LV mass, LVEF, ischemia, LGE, and elevated PWV as predictors. Multivariate analysis revealed diastolic blood pressure, LVEF, ischemia, and elevated PWV as independent predictors for MACE.

Incremental prognostic value of PWV

Table 5 shows an incremental prognostic value of clinical and CMR data for the prediction of MACE. When the

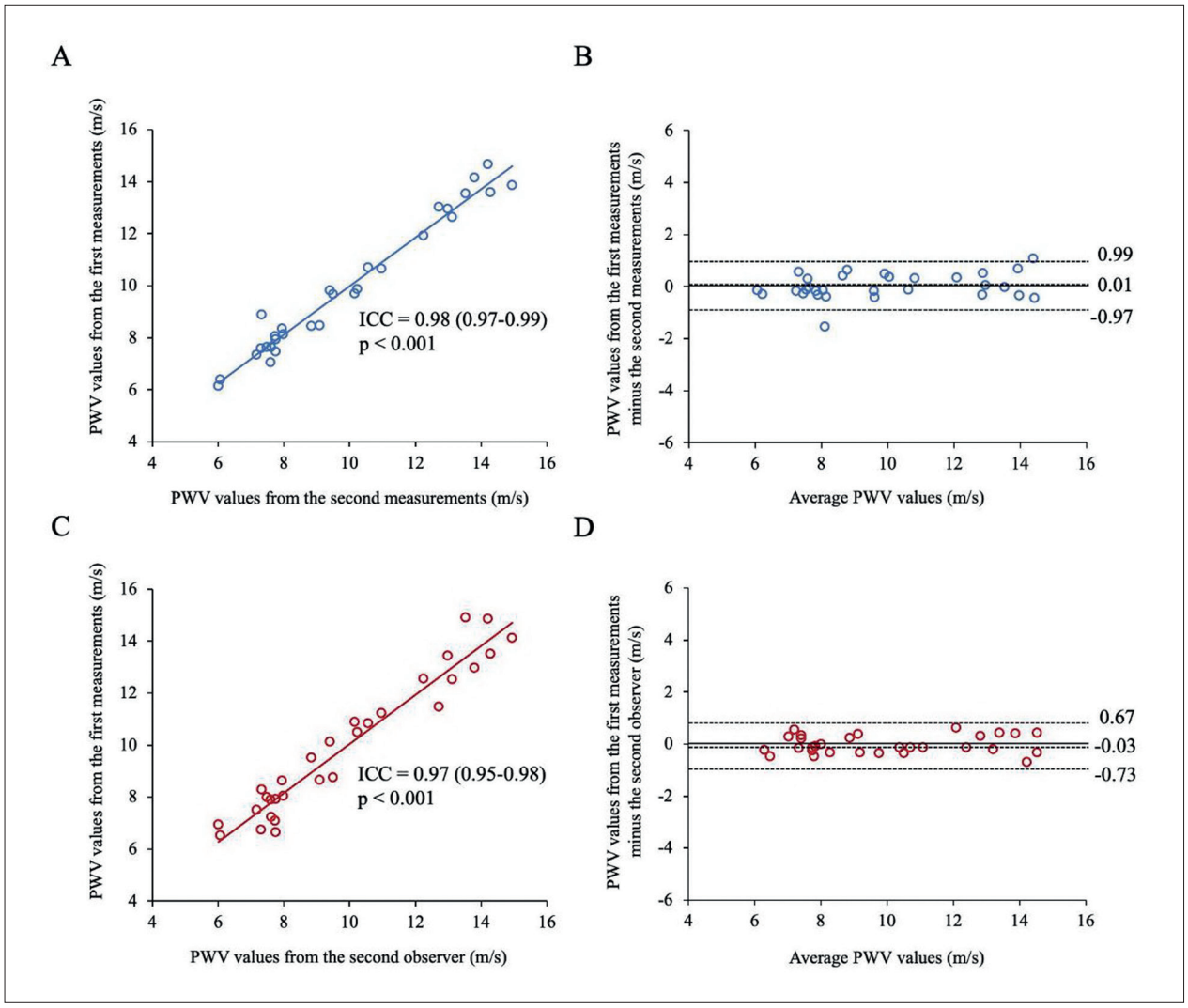

Figure 1 – *Intraobserver and interobserver variability of PWV measurements. Intraclass correlation (A for intraobserver and C for interobserver) and Bland-Altman plot (B for intraobserver and D for interobserver). ICC: intraclass correlation coefficient; PWV: pulse wave velocity.*

Table 3 – Cardiovascular Events

	Total (n=263)	Elevated PWV (n=83)	Non-elevated PWV (n=180)	HR (95% CI)	p-Value
MACE[a]	61 (23.2)	24 (28.9)	37 (20.6)	1.75 (1.05. 2.94)	**0.03**
Cardiac mortality	5 (1.9)	2 (2.4)	3 (1.7)	1.68 (0.28. 10.07)	0.57
Nonfatal myocardial infarction	24 (9.1)	9 (10.8)	15 (8.3)	1.60 (0.70. 3.67)	0.27
Hospitalization for heart failure	36 (13.7)	15 (18.1)	21 (11.7)	1.94 (0.99. 3.81)	0.05
Late coronary revascularization	16 (6.1)	5 (6.0)	11 (6.1)	1.17 (0.41. 3.39)	0.77
Ischemic stroke	11 (4.2)	7 (8.4)	4 (2.2)	5.04 (1.47. 17.32)	**0.01**

MACE = composite outcomes of cardiac mortality, nonfatal myocardial infarction, hospitalized for heart failure, late coronary revascularization, and ischemic stroke. [a] Nineteen patients had more than one event. Values are numbers (percentages). ***Bold*** *values are <0.05. CI: confidence interval; HR: hazard ratio; MACE: major adverse cardiovascular events; PWV: pulse wave velocity.*

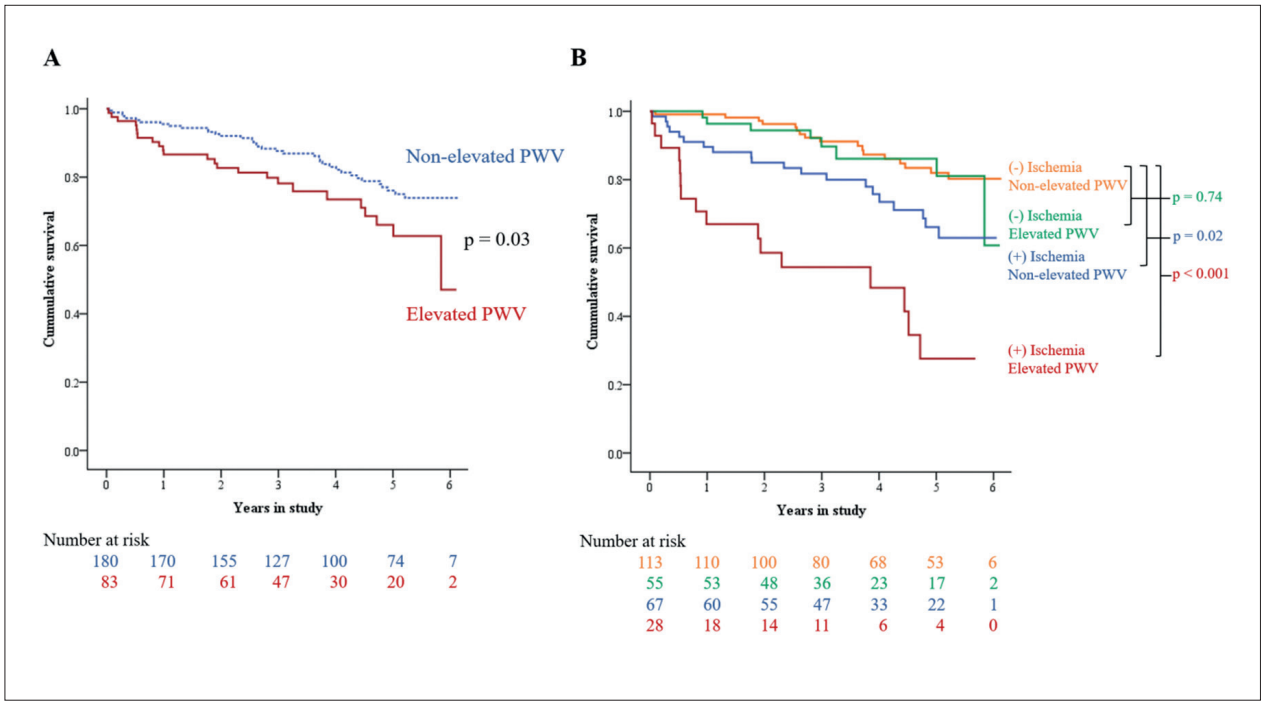

Figure 2 – *Kaplan-Meier curves for MACE. For the whole cohort, patients with elevated PWV had significantly higher rates of MACE than those with non-elevated PWV (Figure 2A). Figure 2B demonstrates the Kaplan-Meier curves stratified by the presence of ischemia with and without elevated PWV. MACE: major cardiovascular events; PWV: pulse wave velocity.*

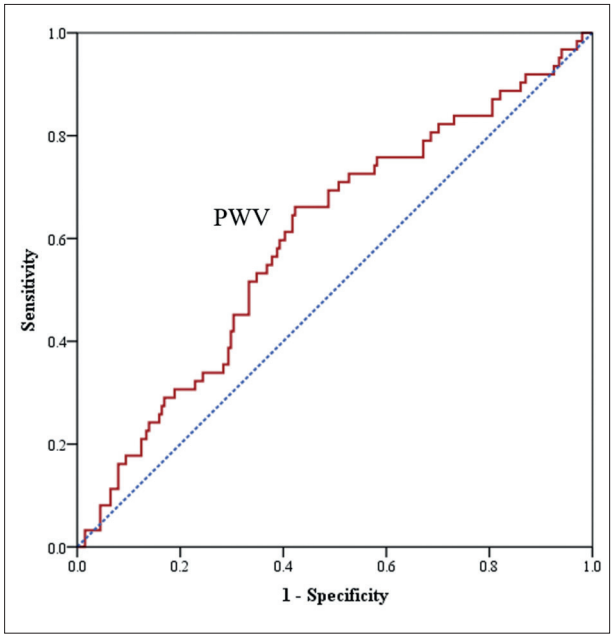

Figure 3 – *A ROC curve demonstrates the best value of PWV to predict MACE. MACE: major cardiovascular events; PWV: pulse wave velocity; ROC: receiver operating characteristic.*

prognosis was assessed in a hierarchical manner (clinical only, clinical+LVEF, clinical+LVEF+myocardial ischemia, and clinical+LVEF+myocardial ischemia+PWV), LVEF and ischemia provided an incremental prognostic value over clinical data. PWV added a further incremental prognostic value over LVEF, and ischemia.

Discussion

Results demonstrated aortic stiffness, assessed by VE-CMR, as a strong predictor of MACE, regardless of traditional risk factors, cardiac function, myocardial ischemia, and LGE in elderly patients with known or suspected CAD. PWV also provided an incremental prognostic value over clinical data, LVEF, and myocardial ischemia.

Aging and vascular change

Vascular aging is associated with changes in the mechanical and structural properties of the vascular wall, leading to a loss of arterial elasticity and reduced arterial compliance. Arterial compliance can be measured by different parameters, such as pulse wave velocity, augmentation index, and systemic arterial compliance.

Many studies have investigated the effects of age on arterial stiffness,[1,2] with most suggesting a linear, age-related increase in PWV and augmentation index. Kim et al. demonstrated the relationship between age and regional aortic stiffness using CMR. They found that the regional PWV was highest in the descending thoracic aorta and increased with age.[14] Several other factors and diseases also influence arterial stiffness,

Table 4 – Predictors of MACE

	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	p-Value	HR (95% CI)	p-Value
Age (years)	1.03 (0.98. 1.08)	0.29	1.02 (0.97. 1.08)	0.43
Female	1.01 (0.61. 1.67)	0.98		
Body mass index (kg/m^2)	0.95 (0.89. 1.01)	0.08		
Systolic BP (per 10 mmHg)	0.89 (0.78. 1.02)	0.10		
Diastolic BP (per 10 mmHg)	0.75 (0.59. 0.96)	**0.01**	0.76 (0.59. 0.97)	**0.03**
Hypertension	1.49 (0.60. 3.71)	0.40		
Diabetes mellitus	1.17 (0.70. 1.94)	0.55		
Hyperlipidemia	1.37 (0.73. 2.58)	0.33		
Coronary artery disease	1.80 (1.02. 3.17)	**0.04**	1.25 (0.69. 2.26)	0.47
Prior revascularization	1.56 (0.62. 3.89)	0.35		
Ischemic stroke	0.63 (0.15. 2.58)	0.52		
Cigarette smoker	1.37 (0.65. 2.88)	0.41		
ACEI or ARB	1.39 (0.84. 2.31)	0.20		
Aspirin	1.35 (0.81. 2.25)	0.25		
Beta blocker	1.15 (0.69. 1.89)	0.60		
Calcium channel blocker	0.88 (0.52. 1.49)	0.62		
Statin	0.99 (0.60. 1.64)	0.97		
LV mass (g)	1.02 (1.01. 1.03)	**0.001**	1.01 (0.99. 1.02)	0.41
LV ejection fraction (per 10%)	0.75 (0.65. 0.86)	**<0.001**	0.84 (0.70. 0.99)	**0.04**
Myocardial ischemia	3.10 (1.86. 5.18)	**<0.001**	2.26 (1.23. 4.14)	**0.01**
Late gadolinium enhancement	2.30 (1.27. 4.19)	**0.01**	1.08 (0.55. 2.12)	0.8
Elevated PWV (>13.98 m/s)	1.75 (1.05. 2.94)	**0.03**	1.99 (1.17. 3.40)	**0.01**

Bold *values are <0.05. ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blocker; BP: blood pressure; CMR: cardiovascular magnetic resonance; LV: left ventricular; PWV: pulse wave velocity; CI: confidence interval; HR: hazard ratio; MACE: major adverse cardiovascular events; PWV: pulse wave velocity.*

Table 5 – Incremental Prognostic Value of PWV for MACE

	Global χ^2	Increase in χ^2	p-value
Clinical	10.19	–	–
Clinical + LVEF	27.11	14.17	**<0.001**
Clinical + LVEF + Myocardial ischemia	38.55	10.02	**0.01**
Clinical + LVEF + Myocardial ischemia + PWV	45.21	7.25	**0.01**

Bold *values are <0.05. Clinical=age, female gender, diastolic blood pressure, and history of coronary artery disease.* χ^2 *= chi-square. LVEF: left ventricular ejection fraction; PWV: pulse wave velocity.*

including hypertension, diabetes mellitus, hyperlipidemia, and smoking.[15-18] In our study, patients with elevated PWV also showed an increased prevalence of hypertension, diabetes mellitus, and higher systolic blood pressure when compared to those with non-elevated PWV, which is consistent with previous reports.[15,16]

Measurement of aortic stiffness

Carotid-femoral PWV using a tonometer is the generally accepted measurement method for aortic stiffness. This technique is used in most clinical studies as a strong predictor of cardiovascular events.[3,4] However, this method requires the assumed measurement of the aortic distance from the carotid to femoral arteries. Most studies measured this distance with tape over the surface of the body, leading to an overestimation of the real distance traveled by the pulse wave.[3,4]

PWV measurement using CMR is one of the preferred methods to evaluate aortic stiffness, providing high resolution without ionizing radiation. Moreover, CMR can measure aortic distance without geometrical assumptions, unlike carotid-femoral PWV using tonometry. PWV values measured by CMR in our study demonstrated high-quality images with excellent reproducibility, which is consistent with a previous study.[5]

Aging and coronary artery disease

Age is a strong and independent risk factor for the development of coronary atherosclerosis. A significant proportion of elderly patients presented atypical symptoms, such as fatigue, dyspnea, and epigastric discomfort. Exercise testing is also less feasible in elderly patients due to the lower exercise capacity associated with advanced age and co-morbidities, as well as baseline ECG abnormalities that limit ischemic assessments. Vasodilatory stress CMR is a preferred non-invasive modality used to detect myocardial ischemia with viability in this population.

Myocardial ischemia was detected in 36.1% of the patients as the strongest predictor of MACE from a multivariate analysis. Findings concurred with previous reports.[9,19] Recent evidence suggests that LGE is a powerful predictor of future cardiovascular events in wide-ranging patient populations, including older adults.[20] LGE was detected in 14.8% of the patients. Given the very small proportion of patients with a history of MI (<2%), our results demonstrated 'unrecognized MI' in elderly patients, which is compatible with previous data.[21,22]

PWV as a strong and independent prognosticator in the elderly

Arterial stiffness is a well-known predictor of cardiovascular events. Several studies investigated the prognostic value of arterial stiffness in apparently healthy older adults,[3,4,23] with certain inconsistencies. Two studies found an association between arterial stiffness and cardiovascular events, but this association appeared to be limited in another study.[3,4,23] All studies measured arterial distance to calculate PWV by the tape method.[3,4,23] Given previous inconsistent results and limitations of PWV measurement, our study sought to prove the hypothesis and assess PWV by VE-CMR, which has advantages over tonometry, as previously mentioned.

Lui et al. reported a strong association between aortic stiffness and biomarkers of both myocardial stress (natriuretic peptide) and damage (high-sensitivity cardiac troponin-T) among older adults without cardiac disease.[24] Our research team also recently reported the association of aortic stiffness and myocardial ischemia as well as the prognostic value of aortic stiffness using CMR.[11,12] Our results showed an almost 2-fold increase in MACE among the elderly with elevated PWV, which also provided an incremental prognostic value over clinical data and CMR variables, including LVEF and myocardial ischemia. The main driver of higher MACE in our patients with elevated PWV was a higher rate of ischemic stroke. This was consistent with previous studies that aortic stiffness increased the risk of ischemic stroke (HR ranged from [2-4], depending on the cutoff of PWV), while PWV remained significantly predictive of stroke after adjustment for classical cardiovascular risk factors.[3,4] Additionally, these studies included older adults and the elderly, similar to our study.[3,4]

Usefulness of CMR for a comprehensive assessment of CAD and aortic stiffness

The use of CMR to evaluate CAD is being increasingly recognized, particularly as vasodilator stress perfusion CMR and viability assessments by LGE technique. In our study, PWV and stress tests were incorporated into a comprehensive protocol as the unique advantage of CMR. PWV was measured during the waiting period between the stress and viability studies, and the non-breath-hold technique proved convenient for patients. PWV images were acquired approximately 10 minutes after adenosine injection. Adenosine may affect arterial compliance, but this did not alter PWV measurements in this study, given its very rapid half-life (<10 seconds).

Therapy of aortic stiffness

To better prevent the occurrence of cardiovascular events, lifestyle modification, as well as antihypertensive treatment that reduce aortic stiffness should be considered, i.e., drugs that have demonstrated their efficacy in reducing PWV regardless of the reduction in blood pressure, including the renin-angiotensin-aldosterone-system antagonists and smooth muscle cell relaxation by nitric oxide donors or related molecules.[25,26] However, large clinical trials have yet to be performed to demonstrate that the prevention of cardiovascular events by these agents is associated with the reduction in aortic stiffness, regardless of blood pressure reduction.[25,26]

Study limitations

First, our study had a limited population, and some degree of overfitting may have occurred during the multivariate analyses; however, the prognostic significance of PWV was demonstrated. Second, the study was conducted on elderly Asian subjects, and data generalizability to younger individuals or other ethnicities remains uncertain. Third,

there were some PWV cutoff values in older adults/elderly without cardiovascular disease from prior studies (ranged 9.5-13.2 m/s).[4,24] However, no standard cutoff level was determined for PWV using CMR for this population. Finally, variations in heart rates could have resulted in slightly different velocity waveforms between cardiac cycles, resulting in PWV measurement errors. However, a previous validation study of PWV measured by CMR determined agreement between invasive intra-aortic pressure measurements.[5]

Conclusions

Aortic stiffness assessed by CMR-based PWV was determined as a strong and independent risk marker in elderly patients with known or suspected CAD. Given the predictive power of PWV, identifying strategies that can prevent or reduce stiffening may be important in the prevention of cardiovascular events. This aspect requires further investigation.

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Author Contributions

Conception and design of the research, Analysis and interpretation of the data, Writing of the manuscript and Critical revision of the manuscript for intellectual content: Kaolawanich Y, Boonyasirinant T; Acquisition of data and Statistical analysis: Kaolawanich Y.

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

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Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Siriraj Institutional Review Board under the protocol number 782/2016. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013.

References

1. Mitchell GF, Parise H, Benjamin EJ, Larson MG, Keyes MJ, Vita JA, et al. Changes in Arterial Stiffness and Wave Reflection with Advancing Age in Healthy Men and Women: The Framingham Heart Study. Hypertension. 2004;43(6):1239-45. doi: 10.1161/01.HYP.0000128420.01881.aa.
2. Wu S, Jin C, Li S, Zheng X, Zhang X, Cui L, et al. Aging, Arterial Stiffness, and Blood Pressure Association in Chinese Adults. Hypertension. 2019;73(4):893-9. doi: 10.1161/HYPERTENSIONAHA.118.12396.
3. Mattace-Raso FU, van der Cammen TJ, Hofman A, van Popele NM, Bos ML, Schalekamp MA, et al. Arterial Stiffness and Risk of Coronary Heart Disease and Stroke: The Rotterdam Study. Circulation. 2006;113(5):657-63. doi: 10.1161/CIRCULATIONAHA.105.555235.
4. Sutton-Tyrrell K, Najjar SS, Boudreau RM, Venkitachalam L, Kupelian V, Simonsick EM, et al. Elevated Aortic Pulse Wave Velocity, a Marker of Arterial Stiffness, Predicts Cardiovascular Events in Well-functioning Older Adults. Circulation. 2005;111(25):3384-90. doi: 10.1161/CIRCULATIONAHA.104.483628.
5. Grotenhuis HB, Westenberg JJ, Steendijk P, van der Geest RJ, Ottenkamp J, Bax JJ, et al. Validation and Reproducibility of Aortic Pulse Wave Velocity as Assessed with Velocity-encoded MRI. J Magn Reson Imaging. 2009;30(3):521-6. doi: 10.1002/jmri.21886.
6. Yazdanyar A, Newman AB. The Burden of Cardiovascular Disease in the Elderly: Morbidity, Mortality, and Costs. Clin Geriatr Med. 2009;25(4):563-77. doi: 10.1016/j.cger.2009.07.007.
7. Li M, Zhou T, Yang LF, Peng ZH, Ding J, Sun G. Diagnostic Accuracy of Myocardial Magnetic Resonance Perfusion to Diagnose Ischemic Stenosis with Fractional Flow Reserve as Reference: Systematic Review and Meta-analysis. JACC Cardiovasc Imaging. 2014;7(11):1098-105. doi: 10.1016/j.jcmg.2014.07.011.
8. Jahnke C, Nagel E, Gebker R, Kokocinski T, Kelle S, Manka R, et al. Prognostic Value of Cardiac Magnetic Resonance Stress Tests: Adenosine Stress Perfusion and Dobutamine Stress Wall Motion Imaging. Circulation. 2007;115(13):1769-76. doi: 10.1161/CIRCULATIONAHA.106.652016.
9. Ashrafpoor G, Prat-Gonzalez S, Fassa AA, Magliano Y, Naïmi A, Sztajzel J. Stress Cardiac Magnetic Resonance Imaging in Elderly Patients. J Cardiovasc Magn Reson. 2011, 13(Suppl 1): 102. doi: 10.1186/1532-429X-13-S1-P102.
10. Pezel T, Sanguineti F, Kinnel M, Hovasse T, Garot P, Unterseeh T, et al. Prognostic Value of Dipyridamole Stress Perfusion Cardiovascular Magnetic Resonance in Elderly Patients >75 Years with Suspected Coronary Artery Disease. Eur Heart J Cardiovasc Imaging. 2021;22(8):904-11. doi: 10.1093/ehjci/jeaa193.
11. Kaolawanich Y, Boonyasirinant T. Aortic Stiffness is Increased in Positive Adenosine Stress Cardiac Magnetic Resonance. J Med Assoc Thai. 2018;101(12):1659-65.
12. Kaolawanich Y, Boonyasirinant T. Incremental Prognostic Value of Aortic Stiffness in Addition to Myocardial Ischemia by Cardiac Magnetic Resonance Imaging. BMC Cardiovasc Disord. 2020;20(1):287. doi: 10.1186/s12872-020-01550-w.
13. Hiratzka LF, Bakris GL, Beckman JA, Bersin RM, Carr VF, Casey DE Jr, et al. 2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM Guidelines for the Diagnosis and Management of Patients with Thoracic Aortic Disease: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, American Association for Thoracic Surgery, American College of Radiology, American Stroke Association, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of Thoracic Surgeons, and Society for Vascular Medicine. Circulation. 2010;121(13):266-369. doi: 10.1161/CIR.0b013e3181d4739e.

14. Kim EK, Chang SA, Jang SY, Kim Y, Kim SM, Oh JK, et al. Assessment of Regional Aortic Stiffness with Cardiac Magnetic Resonance Imaging in a Healthy Asian Population. Int J Cardiovasc Imaging. 2013;29(Suppl 1):57-64. doi: 10.1007/s10554-013-0206-x.

15. Simon AC, Levenson J, Bouthier J, Safar ME, Avolio AP. Evidence of Early Degenerative Changes in Large Arteries in Human Essential Hypertension. Hypertension. 1985;7(5):675-80. doi: 10.1161/01.hyp.7.5.675.

16. Schram MT, Henry RM, van Dijk RA, Kostense PJ, Dekker JM, Nijpels G, et al. Increased Central Artery Stiffness in Impaired Glucose Metabolism and Type 2 Diabetes: The Hoorn Study. Hypertension. 2004;43(2):176-81. doi: 10.1161/01.HYP.0000111829.46090.92.

17. Wilkinson IB, Prasad K, Hall IR, Thomas A, MacCallum H, Webb DJ, et al. Increased Central Pulse Pressure And Augmentation Index in Subjects with Hypercholesterolemia. J Am Coll Cardiol. 2002;39(6):1005-11. doi: 10.1016/s0735-1097(02)01723-0.

18. Kool MJ, Hoeks AP, Boudier HAS, Reneman RS, Van Bortel LM. Short- and Long-term Effects of Smoking on Arterial Wall Properties in Habitual Smokers. J Am Coll Cardiol. 1993;22(7):1881-6. doi: 10.1016/0735-1097(93)90773-t.

19. Hachamovitch R, Berman DS, Shaw LJ, Kiat H, Cohen I, Cabico JA, et al. Incremental Prognostic Value of Myocardial Perfusion Single Photon Emission Computed Tomography for the Prediction of Cardiac Death: Differential Stratification for Risk of Cardiac Death and Myocardial Infarction. Circulation. 1998;97(6):535-43. doi: 10.1161/01.cir.97.6.535.

20. Shanbhag SM, Greve AM, Aspelund T, Schelbert EB, Cao JJ, Danielsen R, et al. Prevalence and Prognosis of Ischaemic and Non-ischaemic Myocardial Fibrosis in Older Adults. Eur Heart J. 2019;40(6):529-38. doi: 10.1093/eurheartj/ehy713.

21. Sheifer SE, Gersh BJ, Yanez ND 3rd, Ades PA, Burke GL, Manolio TA. Prevalence, Predisposing Factors, and Prognosis of Clinically Unrecognized Myocardial Infarction in the Elderly. J Am Coll Cardiol. 2000;35(1):119-26. doi: 10.1016/s0735-1097(99)00524-0.

22. Kim HW, Klem I, Shah DJ, Wu E, Meyers SN, Parker MA, Crowley AL, Bonow RO, Judd RM, Kim RJ. Unrecognized non-Q-wave myocardial infarction: prevalence and prognostic significance in patients with suspected coronary disease. PLoS Med. 2009 Apr 21;6(4):e1000057. doi: 10.1371/journal.pmed.1000057.

23. Störk S, van den Beld AW, von Schacky C, Angermann CE, Lamberts SW, Grobbee DE, et al. Carotid Artery Plaque Burden, Stiffness, and Mortality Risk in Elderly Men: A Prospective, Population-based Cohort Study. Circulation. 2004;110(3):344-8. doi: 10.1161/01.CIR.0000134966.10793.C9.

24. Liu S, Kim ED, Wu A, Meyer ML, Cheng S, Hoogeveen RC, et al. Central and Peripheral Pulse Wave Velocity and Subclinical Myocardial Stress and Damage in Older Adults. PLoS One. 2019;14(2):e0212892. doi: 10.1371/journal.pone.0212892.

25. Laurent S, Kingwell B, Bank A, Weber M, Struijker-Boudier H. Clinical Applications of Arterial Stiffness: Therapeutics and Pharmacology. Am J Hypertens. 2002;15(5):453-8. doi: 10.1016/s0895-7061(01)02329-9.

26. PROGRESS Collaborative Group. Randomised Trial of a Perindopril-based Blood-pressure-lowering Regimen Among 6,105 Individuals with Previous Stroke or Transient Ischaemic Attack. Lancet. 2001;358(9287):1033-41. doi: 10.1016/S0140-6736(01)06178-5.

*Supplemental Materials

For additional information, please click here.

Aortic Stiffness by Cardiac Magnetic Resonance: Prognostic tool or Bystander?

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Short Editorial related to the article: Prognostic Value of Aortic Stiffness using Cardiovascular Magnetic Resonance in The Elderly with Known or Suspected Coronary Artery Disease

Arterial stiffness increases with age and may relate to higher rates of cardiovascular events, including mortality.[1-4] This predictive capacity has been demonstrated in various longitudinal cohorts, including 'healthy' community population studies and those with diabetes, hypertension, chronic kidney disease, and established coronary artery disease.[5,6] There are several ways to measure arterial stiffness, such as doppler-ultrasound, carotid-femoral tonometer, and cardiac magnetic resonance (CMR). CMR provides information regarding cardiac function, perfusion, and myocardial scarring in a single exam and may also be the preferred method for assessing arterial stiffness using aortic pulse wave velocity (PWV).[7-9] While the association between aortic stiffness and myocardial ischemia has been demonstrated, as well as the prognostic value of aortic stiffness using CMR,[7] there is limited data regarding the prognostic value of PWV by CMR in elderly patients in whom cardiovascular diseases (CVD) account for the vast majority of mortality causes.

In this issue of the journal, Kaolawanich and Boonyasirinant[10] evaluated the occurrence of major adverse cardiac and cerebrovascular events (MACCE), including cardiac mortality, nonfatal myocardial infarction, hospitalization for heart failure, late revascularization (>180 days after CMR) and ischemic stroke in elderly patients (> 70 years) with suspected or confirmed CAD undergoing adenosine stress CMR including PWV. The main objective was to determine the prognostic value of aortic stiffness using CMR-based PWV in elderly patients with CAD. Two hundred sixty-three consecutive patients (55% female; 77±5 years) between 2010 and 2014 were included with a median follow-up of 59.6 months and a mean PWV of 13.98 ± 9.00 m/s. A higher PWV (>13.98 m/s) was associated with greater MACCE rates (HR 1.75; 95% CI 1.05 - 2.94; p=0.03), as compared to non-elevated PWV (<13.98 m/s). By multivariable analysis, diastolic blood pressure, left ventricular ejection fraction (LVEF), myocardial ischemia and elevated PWV were independent predictors of MACCE at long-term follow-up (p<0.05 for all). PWV had an incremental prognostic value concerning clinical history, LVEF and ischemia (increased global chi-square = 7.25; p=0.01). In this evaluation, elderly patients with elevated PWV also had a higher prevalence of hypertension, diabetes mellitus and higher systolic blood pressure than those with non-elevated PWV, consistent with prior studies in younger populations.[11]

Some aspects of Kaolawanich and Boonyasirinant's work and CMR evaluation of PWV merit further discussion. First, measurement of PWV using CMR might be one of the preferred methods for assessing aortic stiffness as it offers high resolution, without ionizing radiation,[10] and unlike carotid-femoral PWV using tonometry, CMR can measure aortic distance without geometric assumptions.[11] Likewise, consistent with previous studies, PWV measured by CMR had excellent reproducibility.[3,11,12] PWV was measured during the period of viability and stress studies, and the non-breath holding technique proved to be convenient for such patients. Notably, PWV images were acquired approximately 10 minutes after adenosine injection. In the present study, the mean value of 13.98 m/s was used as the cut-off to determine patients with higher arterial stiffness. Prior studies have used various cut-off values for PWV in older/elderly adults without cardiovascular disease, ranging from 9.5-13.2 m/sec. Nevertheless, no standard cut-off level has been well determined for PWV using CMR for the different populations. Furthermore, as this study has been conducted among elderly Asian patients, the possibility of generalizing the data to younger patients and those from another ethnicity is also uncertain.

Another important aspect of the present study is that higher PWV resulted in ~2-fold higher rates of MACCE, with an incremental prognostic value over clinical and CMR variables, including LVEF and myocardial ischemia. The main factors increasing MACCE rates were ischemic stroke (8.4% vs. 2.2%; p=0.01), consistent with previous data.[2,13,14] It should also be underlined the similar mortality rates according to the different PWV rates. Several studies have investigated the prognostic value of arterial stiffness in different populations with certain inconsistencies. While prior studies found an association between arterial stiffness and cardiovascular events,[2,14,15] this association appeared limited in another study, especially for the older population.[11] Therefore, the real impact of arterial stiffness on MACCE rates in older populations, especially regarding mortality (global and cardiovascular), will merit further confirmation from larger studies.

Keywords

Pulse Wave Analysis/methods; Aortic Stiffness; Diagnostic Imaging; Magnetic Resonance Imaging/methods; Prognosis; Vascular Stiffness

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In conclusion, aortic stiffness using CMR could be an additional prognostic marker of cardiovascular events in elderly patients with suspected or confirmed CAD. However, larger studies with a more heterogeneous population with various ethnicities should confirm such finding and further determine the more appropriate cut-off point of PWV related to a worse prognosis. The work by Kaolawanich and Boonyasirinant has certainly shed some light on the importance of aortic stiffness in the armamentarium of the already vast diagnostic and prognostic possibilities of CMR among patients with suspected CAD. Whether aortic stiffness will be an additional prognostic tool or a mere bystander in clinical practice remains to be determined, as well as by what matters the clinical management of such patients with a higher aortic stiffness should be further modified.

References

1. Razik NA, Kishk YT, Essa M, Ghany MA. Aortic Distensibility Can Predict Events in Patients With Premature Coronary Artery Disease: A Cardiac Magnetic Resonance Study. Angiology 2021;72(4):332-8. 391. doi: 10.1177/0003319720968
2. Mattace-Raso FU, van der Cammen TJ, Hofman A, van Popele NM, Bos ML, Schalekamp MA, et al.Arterial stiffness and risk of coronary heart disease and stroke: the Rotterdam Study. Circulation 2006;113(5):657-63. doi: 10.1161/CIRCULATIONdoAHA.105.555235.
3. Mikael LR, Paiva AMG, Gomes MM, Sousa AL, Jardim PCB, Vitorino PV, et al. Vascular Aging and Arterial Stiffness. Arq Bras Cardiol 2017;109(3):253-8. doi: 10.5935/abc.20170091
4. Wu S, Jin C, Li S, Zheng X, Zhang X, Cui L, et al. Aging, Arterial Stiffness, and Blood Pressure Association in Chinese Adults. Hypertension 2019;73(4):893-9. doi: 10.1161/HYPERTENSIONAHA.118.12396.
5. Nelson AJ, Puri R, Nicholls SJ,Dundon B, Richardson JD, Sidharta S, et al. Aortic distensibility is associated with both resting and hyperemic coronary blood flow. Am J Physiol Heart Circ Physiol 2019;317(4):H811-H9. doi: 10.1152/ajpheart.00067.2019.
6. Yazdanyar A, Newman AB. The burden of cardiovascular disease in the elderly: morbidity, mortality, and costs. Clin Geriatr Med 2009;25(4):563-77, vii. doi: 10.1016/j.cger.2009.07.007.
7. Kaolawanich Y, Boonyasirinant T. Incremental prognostic value of aortic stiffness in addition to myocardial ischemia by cardiac magnetic resonance imaging. BMC Cardiovasc Disord 2020;20(1):287. doi: 10.1186/s12872-020-01550-w.
8. Li M, Zhou T, Yang LF, Peng ZH, Ding J, Sun G. Diagnostic accuracy of myocardial magnetic resonance perfusion to diagnose ischemic stenosis with fractional flow reserve as reference: systematic review and meta-analysis. JACC Cardiovasc Imaging 2014;79(11):1098-105. doi: 10.1016/j.jcmg.2014.07.011.
9. Ribeiro SM, Azevedo Filho CF, Sampaio R, et al. Longitudinal Shortening of the Left Ventricle by Cine-CMR for Assessment of Diastolic Function in Patients with Aortic Valve Disease. Arq Bras Cardiol 2020;114(2):284-92. doi: 10.5935/abc.20190193. .
10. Kaolawanich Y, Boonyasirinant T. Prognostic Value of Aortic Stiffness using Cardiovascular Magnetic Resonance in The Elderly with Known or Suspected Coronary Artery Disease. Arq Bras Cardiol 2022;in press - ABC-2021-0452.
11. Ohyama Y, Ambale-Venkatesh B, Noda C, Kim JY, Tanami Y, Teixido-Tura G, et al. Aortic arch pulse wave velocity assessed by magnetic resonance Imaging as a predictor of incident cardiovascular e(vents: The MESA (Multi-Ethnic Study of Atherosclerosis). Hypertension 2017;70(3):524-30. DOI: 10.1161/HYPERTENSIONAHA.116.08749
12. Grotenhuis HB, Westenberg JJ, Steendijk P, van der Geest RJ, Tanami Y, Teixido-Tura G, et al. Validation and reproducibility of aortic pulse wave velocity as assessed with velocity-encoded MRI. J Magn Reson Imaging 2009;30(3):521-6. doi: 10.1002/jmri.21886.
13. Pereira T, Maldonado J, Pereira L, Conde J. Aortic stiffness is an independent predictor of stroke in hypertensive patients. Arq Bras Cardiol 2013;100(5):437-43. doi: 10.5935/abc.20130079
14. Sutton-Tyrrell K, Najjar SS, Boudreau RM, et al. Elevated aortic pulse wave velocity, a marker of arterial stiffness, predicts cardiovascular events in well-functioning older adults. Circulation 2005;111(25):3384-90. doi: 10.1161/CIRCULATIONAHA.104.483628.
15. Stork S, van den Beld AW, von Schacky C, et al. Carotid artery plaque burden, stiffness, and mortality risk in elderly men: a prospective, population-based cohort study. Circulation 2004;110(3):344-8. doi: 10.1161/01.CIR.0000134966.10793.C9

Ventriculography: When to Choose to Perform It?

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Short Editorial related to the article: Factors That Impact the Decision to Perform Left Ventriculography in Coronary Artery Disease

The current guidelines address the indications for left heart catheterization associated with coronary angiography, but most of these instructions do not mention ventriculography, as this test is often at the operator's discretion. For many years, ventriculography was used as the gold standard method for ventricular function. This mini editorial presents some insights to fill this gap.[1]

Some complications may occur concerning ventriculography, such as contrast-induced nephropathy (CIN) in approximately 1% of patients without predisposing factors and in 10% to 30% of those with risk factors, embolization, arrhythmia, cardiac tamponade, and increased radiation exposure.[2]

Ventriculography must be performed with good quality, and, for that, some points of attention need to be considered, such as manual injections, the amount of pressure or even manual injections that can be dangerous if performed using a catheter with a single end hole. Furthermore, contrast volumes must be sufficient to opacify the ventricle and properly position, allowing accurate automated quantification of left ventricular volumes and aortic dimensions.[3]

The ejection fraction visually determined by left ventriculography is variably correlated with the ejection fraction of the echocardiography. Regarding biplane left ventriculography, it correlates better than monoplane left ventriculography compared to cardiac magnetic resonance (CMR) imaging for ejection fraction, ventricular volumes, and wall motion.[4]

The decision to perform ventriculography when there are other diagnostic methods has been individualized, also varying between geographic regions and hospitals.[5]

In the study carried out by Lima Santos et al., medical records of 600 patients who underwent coronary angiography were analyzed, of which 324 underwent ventriculography.[6] Besides, patients aged 18 years or older, treated urgently or with suspected CAD, who underwent angioplasty, were selected.

In the study, regarding the variables, 89.8% of the patients underwent the examination during the day, 33.75% had known ventricular function, and 283 (47.2%) had a chronic coronary syndrome. Furthermore, regarding the use of contrast, it was found that only 3 ml more were used, compared to patients who did not use ventriculography, which drew attention since 30 ml more is usually used to perform the test.

Patients diagnosed with chronic coronary syndrome are independently more likely to undergo ventriculography. On the other hand, having known left ventricular function, being hypertensive, having undergone coronary artery bypass grafting, and having increased creatinine levels were associated with greater chances of not having the technique performed.

Such data, until then, were consistent with those found in the literature; however, an unexpected finding emerged: ventriculography was mostly used in patients with chronic coronary syndromes than in those with acute coronary syndromes, which, in theory, could require a more immediate assessment.

Non-invasive methods, such as the new technologies developed in echocardiography devices, have been possible through global longitudinal strain (GLS) of the LV walls to diagnose early ischemic abnormalities in patients with abnormal troponin levels, however, without abnormal ECG or resting echocardiogram findings.[7]

In patients with cardiogenic shock, assessment of ventricular function may be impaired, as the myocardium is stunned.[8] It is important to emphasize that, in these acute cases, the presence of an apical filling defect suggestive of thrombus should not be neglected, as it may be viewed on ventriculography but not on non-contrast transthoracic echo.[9]

Another requirement in ST-segment elevation infarction would be to assess complications such as acute free wall rupture, ventricular septal defect, mitral regurgitation and Takotsubo syndrome.[10]

In the sample, there were no patients with mechanical complications; therefore, this situation was not evaluated in the study.

In the case of non-ST-segment elevation coronary syndrome, with uninterpretable electrocardiogram and disease in more than one vessel, ventriculography can help identify the culprit artery.[11]

It is worth noting that there is no discrimination between ST-segment elevation infarction and non-ST-segment elevation infarction in this study.

Finally, it is apparent that the role of left ventriculography has evolved dramatically over the past half-century, but it has received little attention in the academic literature. It is important not to forget that the technique and frequency of use of left ventriculography vary between regions, institutions and according to the operator's decision.

We, therefore, suggest that criteria for using the method be included in the guidelines.

Keywords

Atherosclerosis; Contrast echocardiography; Angioplasty.

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References

1. Gigliotti OS, Babb JD, Dieter RS, Feldman DN, Islam AM. Optimal use of left ventriculography at the time of cardiac cathetrization: a consensus statement from the Society for cardiovascular Angiography and interventions. Catheter Cardiovasc Interv. 2015;85(2):181-91. doi: 10.1002/ccd.25642

2. Guimarães JI, Sociedade Brasileira de cardiologia. Guideline for conducting diagnostic and therapeutic examinations in hemodynamics. Arq Bras Cardiol. 2004;82(Suppl 1):2-6. PMID: 15129651

3. Croft CH, Lipacomb K, Mathis K, Firth BG, Nicod P, Tilton G, et al. Limitations of qualitative angiographic grading in aórtica or mitral regurgitation. Am J Cardiol. 1984;53(11):1593-8. doi: 10.1016/0002-9149(84)90585-x.

4. Grebe O, Kestler HA, Merkle N, Worhrle J, Kochs M, Hohler M, et al. Assessment of left ventricular function with steady-state-free precession magnetic resonance imaging. Reference values and a comparison to left ventriculography. Z Kardiol. 2004;93(9):686-95.

5. ACCF/SCAI/ AATS/AHA/ASNC/HFSA/HRS/SCCM/SCCT/SCMR/STS. 2012 appropriate use criteria for diagnostic catheterization: a report. J Am Coll Cardiol. 2012;59(22):1995-2027. doi: 10.1016/j.jacc.2012.03.003

6. Santos CCL, Oliveira RP, Sena J, Oliveira AD, Ferreira MG, Santos Filho R, et al. Fatores que impactam a decisão de realizar ventriculografia esquerda em doença arterial coronária. Arq Bras Cardiol.2022;118(3):607-13. DOI: https://doi.org/10.36660/abc.20200217

7. Nicolau Jc. Feitosa Filho G, Petriz JL, Furtado RHM, Précoma DB, Santos Filho RD, et al.; Brazilian Society of Cardiology. Guidelines on unstable angina and acute myocardial infarction without ST-segment elevation, Arq Bras Cardiol. 2021;117(1):181-24. doi: 10.36660/abc.20210180

8. Rodrigues JÁ, Melleu K, Schmidt MM, Gottschall CAM, Moraes MAP, Quadros AS. Preditores de apresentação tardia em pacientes com infarto agudo do miocárdio com supradesnivelamento do segmento ST. Arq Bras Cardiol. 2018;111(4):587-93. doi: 10.5935/abc.20180178

9. Starling MR, walsh RA. Accuracy of biplane axial oblique and oblique cineangiographic left ventricular cast volume determinations using a modification of Simpson's rule algorithm. Am Heart J.1985;110(6):1219-25. doi: 10.1016/0002-8703(85)90016-x.

10. Piegas L, Timerman A, Nicolau JC, Mattos LA, Rossi Neto JM, Feitosa G, et al. IV Diretriz sobre tratamento do infarto agudo do miocárdio. Arq Bras Cardiol. 2009;83(supl 4):1-86. | ID: lil-389546

11. Fihn SD, Gardin JM, Abrams J, Berra K, Blankenship JC, Dallas AP, et al. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS. Guideline for the diagnosis and management of patients with stable ischemic heart disease: a report. J Am Coll cardiol.2012;60(24):e44-e164. doi: 10.1016/j.jacc.2012.07.013.

Infective Endocarditis: Still More Challenges Than Convictions

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Abstract

After fourteen decades of medical and technological evolution, infective endocarditis continues to challenge physicians in its daily diagnosis and management. Its increasing incidence, demographic shifts (affecting older patients), microbiology with higher rates of *Staphylococcus* infection, still frequent serious complications and substantial mortality make endocarditis a very complex disease. Despite this, innovations in the diagnosis, involving microbiology and imaging, and improvements in intensive care and cardiac surgical techniques, materials and timing can impact the prognosis of this disease. Ongoing challenges persist, including rethinking prophylaxis, improving the diagnosis criteria comprising blood culture-negative endocarditis and prosthetic valve endocarditis, timing of surgical intervention, and whether to perform surgery in the presence of ischemic stroke or in intravenous drug users. A combined strategy on infective endocarditis is crucial, involving advanced clinical decisions and protocols, a multidisciplinary approach, national healthcare organization and health policies to achieve better results for our patients.

"It is of use from time to time to take stock, so to speak, of our knowledge of a particular disease, to see exactly where we stand in regard to it, to inquire to what conclusions the accumulated facts seem to point, and to ascertain in what direction we may look for fruitful investigations in the future."

William Osler (1885)

Epidemiology

Incidence and demographics

The incidence of infective endocarditis (IE) varies between 3 and 15 cases per 100,000 in population-based studies[1–3] (Table 1). This variation is probably related to several factors: case definition criteria (definitive case, possible case, inclusion of blood culture-negative IE), different sources of cases or the time period analyzed with reference to the publication of the guidelines. In this analysis, we did not include single-center or multicentric observational studies with a high risk of selection bias that could therefore underestimate the real incidence of this disease.

A male predominance can be noted with a male: female ratio varying between 0.96 and 2.8. This is also observed in large international registries such as the ICE study,[4] the GAMES registry in Spain[5] or the recently published EURO-ENDO.[6]

In most populational series and international registries, older patients are normally more affected, the median age from late 50s to 60s (Table 1). Also, the incidence increases with aging.[7-11]

Finally, a meta-analysis published in 2013[12] that included 160 studies worldwide concluded that male gender predominance and age increased over time.

Risk factors

Three main underlying conditions usually predispose patients to acquire IE:

1) Heart valve disease and cardiac valve prothesis, grafts or devices

2) Congenital heart disease (CHD)

3) Previous history of IE

Heart valve disease is a major contributor to the pool of cardiac patients in daily clinical setting, with a significant prevalence in the community,[13] as a result of higher life expectancy, aging of the populations[14] and improved medical and surgical care of valvular patients. A decline in rheumatic valve disease was noted in the last decades,[14-17] with degenerative etiology being the most prevalent in developed countries. Nevertheless, the burden of rheumatic valve disease persists in low-to-middle income countries with significant prevalence (in Brazil, it affects up to 7/1000 school children versus 0.1-0.4/1000 in the USA)[18] and mortality (275,000 deaths each year worldwide).[17] A recent study by Glaser et al.[19] indicated that bioprostheses have a higher risk of infection compared to mechanical valves, but more studies are still needed.

Also, the implantation of cardiac prothesis, grafts or devices is continually increasing, with a growing impact on the number of infections in these implants. It has been estimated that 25-30% of all cases of IE occur in prosthetic valves, according to the registries of the Euro-Heart Survey in 2005,[20] ICE in 2009,[4] GAMES in 2015[5] and EURO-ENDO in 2019.[6] Transcatheter aortic valve implantation (TAVI) has been increasingly used in

Keywords

Infective Endocarditis; Epidemiology; Diagnosis; Prophylaxis.

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Table 1 – Population studies on infective endocarditis incidence, demographic and outcome features

Authors/study	Country	Population Size (Source)	Time period	Source list of cases	Number of cases	Crude incidence/100,000	Age range	Male/Female ratio	Negative Blood culture (%)	Outcomes: Valve surgery and mortality
Fonager et al.[1]	Denmark	5.2 million	1980-1997	Danish National Registry	3,351	Gender analysis: Men 4 - 6 Women 3 - 4	60.4	1.32	NA	30-d case fatality rate 23%
Tleyjeh et al.[2]	USA (Olmsted County)	1970 - 51 000 2000 - 90 000	1970-2000	Rochester Epidemiology Project	107	5.0-7.0	61.5 (18.8-90.6)	2.7	1	Valve surgery 15% 6 mo mortality 14-33%
Sy et al.[7]	Australia (New South Wales)	6.6 million	2000-2006	Statewide database	1,536	4.7	62 (42-75)	1.8	15	Valve surgery 20% In Hospital mortality 14% 6 mo. mortality 18%
Fedeli et al. [8]	Italy (Veneto region)	4.8 million	2000-2008	Electronic archives of hospital discharge records	1,863	4.4	68	1.4 - 2	NA	Valve surgery 23% In Hospital mortality 14.3%
Selton-Suty et al.[108]	France (greater Paris, Lorraine, Rhone-Alpes, Franche-Comte´, Marne, Ille-et-Vilaine, and Languedoc-Roussillon)	15.3 million	2008	Case report forms sent to physicians likely to be in charge of IE cases	497	3.2	62.3	2.8	5	Valve surgery 44.9% In-hospital mortality 22.7%
Bikdeli et al.[109]	USA	NA (inpatients >65 yrs. old)	1999-2010	Medicare & Medicaid Services, Medicare inpatient Standard Analytic Files	262,658	7.2	79	0.7-0.8	NA	In hospital mortality 9-11% 30 d mortality – 14-16.5% 1 yr. mortality – 32.6-36.2%
Duval et al.[9]	France (Greater Paris, Lorraine, and Rhône-Alpes)	11 million	1 yr. survey 1991, 1999 and 2008	Case report forms sent to physicians likely to be in charge of IE cases	1991 - 323 1999 – 331 2008 - 339	1991 – 3.5 1999 – 3.3 2008 – 3.2	1991 – 57.9 1999 – 59.8 2008 – 61.6	1991 – 1.9 1999 – 2.3 2008 – 2.9	NA	Valve surgery (1991 – 31.3%; 1999 – 50.2%; 2008 – 49.6%) In Hospital mortality (1991 – 20.7%; 1999 – 15.4%; 2008 – 21.2%)
Ternhag et al.[110]	Sweden		1997-2007	Swedish Hospital Discharge Register	7,603	7.7	65.7	1.45	NA	30-day mortality rate – 10.4% 1-5 yr. mortality rate – 14.7%

Dayer et al.[111]	England	NA	2000-2013	Secondary Uses Service	19,804	2.7	NA	NA	NA	NA
Pant et al.[112]	USA	NA	2000-2011	Nationwide Inpatient Sample database	457,052	11-15	NA	NA	NA	NA
Erichsen et al.[10]	Denmark	NA	1994–2011	Danish nationwide registry	5,486	7.55 (2009–2011)	63	1.8	NA	NA
Keller et al.[62]	Germany	80 million	2005-2014	Nationwide database of the Federal Statistical Office of Germany	94,364	11.6	NA	NA	NA	In hospital mortality 17%
Toyoda et al.[11]	USA (California and New York State)	NA	1998-2013	Statewide Planning and Research Cooperative System database (New York); Office of Statewide Health Planning and Development database (California)	75,829	7.6 to 9.3	62.3	1.2	25	Valve surgery - 11-13% 90-day mortality – 24%
Van der Brink et al.[113]	Netherlands	NA	2005-2011	Dutch Healthcare Authority	5213	2005-3.0 2011- 6.3	66.4	2.3	9.3	All-cause mortality 36.1%
Cresti et al.[3]	Italy (Grosseto)	217778	1998-2014	Healthcare system database	170	4.6	69.5	1.54	19	Valve surgery – 46% In hospital mortality 25% 1 yr. mortality 32%
Ahtela et al.[114]	Finland	NA	2005-2014	Care Register for Health Care (CRHC) data- base	2611	6.3	60.0	2.1	NA	30 d mortality – 11%
Olmos et al. [97]	Spain	NA	2003-2014	Spanish National Health System	16867	2.7 in 2003 3.5 in 2014 per 100,000 person/year	NA	2	NA	In hospital mortality rate 20%
Shah et al.[65]	Scotland	NA	1990-2014	National hospitalization registry National microbiology register	7638	5.3 in 1990	65	0.96	58	30-day outcome: All cause death – 9.6-17.3% Valve surgery – 3.8-6.3% 1-year outcome: All cause death – 27-33.3% Valve surgery – 9.2-15.5%

NA: non-available; IE: infective endocarditis.

severe symptomatic aortic stenosis.[21] A metanalysis[22] of four studies, with 3,761 patients, published in 2019, concluded that the risk of IE with TAVI was not different as compared with conventional surgical aortic valve replacement.

Infections related to permanent pacemakers and implantable cardioverter-defibrillators have also been increasing over time[23] and account for about 10% of IE episodes.[4,5,24]

Regarding CHD, the 25-year cumulative incidence[25] of IE after surgery varied between 1.3 and 13.3%, being highest in the aortic valve stenosis group. In fact, complex CHD, ventricular septal defect, bicuspid aortic valve, tetralogy of Fallot and aortic valve replacement, constitute important predisposing factors for IE[26-28] and with a high mortality risk, estimated between 6 and 14%.[26-29]

Long-term follow-up series of IE patients reveal that a significant proportion of patients that survive their first episode of IE carry a higher risk of relapse (new IE episode caused by the same microorganism within the first six months after the initial episode[30]) or re-infection[31-33] (infection by a different microorganism), estimated in 2.6-8.8%,[31,33-35] with a high rate of complications and mortality.[34,36]

Other important conditions increase the risk of IE and need to be considered clinically.

Although the use of injection drugs, mainly opioids, may be decreasing in the European Union, the risk of blood infections remain high, with an increase in methicillin-sensitive and methicillin-resistant *Staphylococcus aureus* infection registered in the last six years.[37]

The growing evidence on vascular manipulation- and catheter-induced bacteremia[38,39] can explain the increased risk of IE in the health care setting[40,41] ranging up to 35% of total cohorts, in tattooing and body piercing[42] and in patients with chronic renal disease on hemodialysis,[43,44] which has strongly influenced the most contemporary pattern of predominant microorganisms in this disease.

Besides chronic renal failure, other comorbidities increase the risk of IE such as diabetes mellitus,[45] chronic lung disease,[46] chronic liver disease,[46] cancer,[47,48] in particular colorectal and urogenital cancer, and periodontal disease.[49]

Diagnosis

The role of imaging

Clinical history and examination are pivotal in the diagnosis of IE. Even so, imaging contributes exponentially for its confirmation.

Echocardiography, keystone in every day clinical practice, has developed considerably, from 2D, transesophageal echo (TEE),[50] harmonic imaging,[51,52] to the increment value of 3D TEE in prosthetic valve imaging,[53] improving echocardiographic sensitivity to detect endocarditis and its local cardiac complications.

Nevertheless, the modified Duke criteria continue to have a limited role in confirming the diagnosis in more complex cases such as in prosthetic valves, cardiac device and Negative Blood Culture (NBC) cases.[54]

New imaging modalities, such as cardiac computed tomography (CT) and metabolic imaging by 18-fluorodeoxyglucose positron emission tomography (^{18}FDG-PET) or leukocyte scintigraphy (radiolabeled leukocyte single-photon emission CT [SPECT])[55] have been shown to complement the use of echocardiography specially in prosthetic valves[56] with improvement in sensitivity when aggregated to the modified Duke criteria. This fact led the European Society of Cardiology[57] to issue, in 2015, a new set of criteria based on the modified Duke criteria with added value (major criteria) of these new imaging techniques.

Also, the active search of embolic events or infectious aneurisms by cerebral magnetic resonance imaging (MRI), whole-body CT and/or PET/CT was added as a minor criterion.

Microbiology

Almost any agent can cause IE, although the most frequent are gram positive bacteria, namely *Staphylococcus* and *Streptococcus* and more recently *Enterococcus*.

In the 1970's, hospital series reported *Streptococcus viridans* as the most frequent causal agent of IE,[58-60] but simultaneously acknowledged that *Staphylococcus* frequency among IE patients was increasing. Among *Streptococcus spp*, the most frequent is *Streptococcus viridans* (a common pathogen in the oral mucosa) followed by *Streptococcus bovis* (associated with colonic neoplasms). In 2007, a metanalysis[61] concluded on an increase incidence of *Staphylococci* and *Enterococci* with a significant decrease in IE caused by *Streptococci* and NBC IE. This trend is worrying as these agents are associated with a high mortality rate,[26,40,62] being locally destructive with a high capacity to embolize (septic metastasis).[63]

In fact, a recently published systematic review[64] concerning the causative agent of IE in 105 studies concluded that *Staphylococcus aureus* was the most common agent; *S. viridans* was also among the most common agents in the subgroups of pediatric and CHD patients, and intravenous drug users. A selection bias cannot be excluded, though, as most included studies were from Europe and North America, with less representation from Asia, South America and Africa, where *S. viridans* is still a very relevant and common pathogen, despite fewer studies focused on it.

The HACEK (H*aemophilus* species, *Aggregatibacter* species, *Cardiobacterium hominis, Eikenella corrodens*, and *Kingella kingae*) microorganisms, normally present in the oropharynx, are described as fastidious bacteria with a low growth rate in cultures, and responsible for less than 5% of IE.

Regarding NBC IE, it occurs in about 10-20% of cases, according to most populational studies (Table 1), excluding the Scotland study by Shah et al.[65] that reported an unusually high rate of 58% in their cohort. Previous/concomitant antibiotic use is a common etiology.[66] Sampling and testing differences,[67] as well as infection due to fastidious, intracellular or challenging to culture organisms also contributes to blood culture-negative IE. A delay in the clinical diagnosis and choice of antibiotic regimen associated with hemodynamic deterioration has been observed,[66,68] although conflicting evidence exists regarding its impact on mortality.[69] Still, fungi

and fastidious bacteria should be suspected and cultures in specialized media should be performed, considering that a slow growth rate is expected. Serological testing for Coxiella burnetii, Bartonella spp, Aspergillus spp., Mycoplasma pneumonia, Brucella spp. and Legionella pneumophila should be performed. Blood polymerase chain reaction (PCR) assays for Tropheryma whipplei, Bartonella spp and fungi (Candida spp, Aspergillus spp)[57] can be performed although low sensitivity is acknowledged.[70] In the surgical field, Brandão et al.[71] reported that the inclusion of histopathologic and PCR analysis in surgically explanted cardiac valves proved more useful in diagnosing the IE etiology than valve culture by itself.

Therefore, a systematic approach with a complete patient's history (including geography, recent travel, contact with animals), histopathology, culture-based, molecular and serological investigations are essential in every-day pratice[64] to increase the likelihood of identifying the causal agent.

Management and outcomes

Antibiotics

The selection of antimicrobials, either while waiting for the cultures, or when the responsible microorganism is known, and in NBC IE, is well defined and can be found in the European Society of Cardiogy[65] and American Heart Association[72] guidelines. Therapy is usually prolonged and parenteral.

The length of antibiotic therapy should be calculated from the first day the effective treatment was established. Only in case of a positive surgical valve culture should the time of antibiotic therapy be restarted, counting from the surgical date; otherwise it may be safe to administer antibiotic therapy for another two weeks.[46,73] Long-term antibiotic administration is the rule, from two to four weeks in oral *Streptococcus* native-valve IE to six weeks in *Enterococcus* infection; prosthetic valve IE requires a six-week duration course. This usually means a prolonged hospital stay to complete the full cycle of antibiotic.

The Outpatient Parenteral Antimicrobial Therapy (OPAT) is generally used for delivery of parenteral antimicrobial therapy in at least two doses on different days without intervening hospitalization,[74] and it has been used in different infectious settings such as pneumonia, pyelonephritis, osteomyelitis, skin infection, decreasing hospital length of stay. Regarding IE, current European guidelines support the use of OPAT in endocarditis patients after the first two weeks of hospitalization and in cooperative and medically stable patients (the OPAT can actually be started earlier in native valve oral *Streptococci* or *Streptococcus bovis*) as long as an outpatient program is set with daily evaluation by a nurse and weekly by an experienced physician.

Nevertheless, parenteral outpatient therapy has also limitations: prolonged parenteral therapy can be logistically challenging and difficult in intravenous drug users or cancer patients with poor venous access. Few studies on the use of oral antibiotic to complete the full cycle of antibiotic therapy in IE have been performed.[75] After a short course of triple intravenous antibiotic, oral ciprofloxacin and rifampicin has been shown to be effective in a small trial of uncomplicated right-side *Staphylococcus* IE in intravenous drug users where parenteral therapy was not feasible.[76] A recent trial, POET,[77] also tested the efficacy and safety of switching from intravenous to oral antibiotics in 400 stable patients who had left-sided IE. It concluded that changing to oral regimen was not inferior to continuous conventional parenteral regimen in these patients.

Surgery

Surgery plays a crucial role in IE.[78] Europe presents higher rates of surgical intervention in IE than the rest of the world. Populational series present rates between 15% and 50% (Table 1). At the EURO-ENDO[6] or ICE[4] registries, almost half the patients were operated.

Several observational studies have concluded on the protective effect of surgery during the active phase of IE.[80-83] Nevertheless, not all patients with a clinical indication for surgery are in fact operated. The ICE-Plus registry[84] and the GAMES study[5] estimated that approximately a quarter of patients with surgical indication did not undergo surgery. Reasons for this included poor prognosis, hemodynamic instability, stroke, sepsis, and death before surgery. Also, only a moderate agreement was found between clinical practice and recommended guidelines regarding surgical indication in EI.[85]

The best timing for surgery continues to be controversial; "early" *versus* "late" may have different translations. While European guidelines[57] emphasize that surgery should be performed on an emergent (within 24 h) or urgent (within a few days) basis, American guidelines[42] refer to "early" surgery as during initial hospitalization and before completion of a full course of antibiotics. Observational studies have shown a reduction of in-hospital mortality with early surgery,[83,86,87] and a metanalysis conducted in 2016 also concluded on the protective role of early surgery on prognosis.

Regarding the type of valve procedure, a choice between repair and replacement must be made. International guidelines[88] emphasize that valve repair should be the option in native valves with limited involvement of leaflets or cusps. In a population-based study[89] concerning the New York State and California, USA, 19% of patients with native mitral valve IE underwent repair, which was associated with better survival and lower risk of recurrence. This may however not represent the real-world practice. On the other hand, if the native valve is largely disrupted, the choice on the type of prosthesis should consider patient-related factors such as age, compliance to anticoagulants, and life expectancy. In fact, there is currently no evidence of superiority of bioprosthesis or mechanical valves[90] as they present similar survival and recurrence rates of endocarditis.[91]

Also, the continuing search for the ideal prognostic score for risk stratification in cardiac surgery in IE has been

undertaken by several groups,[92-95] although currently no risk score has proven to be superior in IE setting.[96] Risk stratification before surgery is however crucial and should take into account patient's clinical status, comorbidities and operative risk.[57] A decisive role of the multidisciplinary "Endocarditis Team" in timely referral for cardiac surgery and clinical evaluation, especially in left-sided IE cases, has been recognized.[57,69]

Post-operative surgical mortality ranges from 6 to 29% in observational series (Table 2). A meta-analysis published by Varela-Barca[79] in 2019 identified the following factors linked to increased mortality after surgery: age, female, urgent or emergency surgery, previous cardiac surgery, NYHA class ≥ III, cardiogenic shock, prosthetic valve, multivalvular affection, renal failure, perivalvular abscess and *Staphylococcus aureus* infection.

Although surgical rates tended towards an increase by 7% per decade from 1969 to 2000,[61] since the beginning of this century, the general trend is towards stability,[4,8,9,61] even though populational studies conducted in Spain[97] and the USA[98] have continuously presented increasing rates. This probably results from recent scientific guidelines, continuous advances in intensive care and surgical management of these patients.

Mortality

In-hospital mortality rate varies between countries, from 8 to 40%.[12] Regarding short-term mortality (up to 30-day follow-up) in populational studies in the last two decades, the rates have ranged between 11-25%, whereas a one-year follow-up revealed a 32% mortality rate (Table 1). A meta-analysis published in 2017[99] including 25 observational studies, estimated a short- (six months) and long-term follow-up (up to 10 years) mortality rate of 20% and 37% respectively. Fernandez et al.,[33] Toyoda et al.[11] and Ilhão Moreira et al.[80] reported a five-year mortality rate of 52%, 53% and 43%, and Netzer et al.[100] reported a seven-year mortality rate of 56%.[100] Although data on long-term follow-up are scarce, current evidence discloses a trend toward a poor prognosis of these patients even if they survive hospitalization for active IE.

Several factors have been linked to increased IE-related mortality. In 2019, a metanalysis[79] of 16 studies, including 7,484 patients identified female, urgent or emergency surgery, previous cardiac surgery, NYHA class ≥ III, cardiogenic shock, prosthetic valve, multivalvular affection, renal failure, perivalvular abscess and *Staphylococcus aureus* infection as important markers of in-hospital mortality.

Causes of death have been poorly addressed in most series. Fernandez-Hidalgo et al.[33] described in their prospective observational cohort study of 438 IE patients, an in-hospital mortality rate of 29%, 80% of deaths directly related to IE, whereas the remaining were mostly due to nosocomial infection or major bleeding. Prospective registries[6,20] identified cardiovascular causes, mainly heart failure, and sepsis as main causes of in-hospital mortality in these patients. Long term mortality causes have not been explored.

IE prophylaxis

In 2007 in the USA[101] and 2009 in Europe[57] indications for antibiotic prophylaxis have been downgraded, with important limitations on the use of antibiotics during dental procedures and withdrawal of antibiotic administration during genitourinary and gastrointestinal procedures. In 2008, the National Institute for Health and Care Excellence (NICE) of the United Kingdom issued guidelines[102] completely removing all indications on the use of antibiotic prophylaxis for dental and non-dental procedures.

According to European guidelines,[57] IE antibiotic prophylaxis should be administered to high-risk patients:

(1) Patients with a prosthetic valve or with prosthetic material used for cardiac valve repair;

(2) Patients with previous IE;

(3) Patients with untreated cyanotic CHD and CHD patients with postoperative palliative shunts and conduits, or other prostheses.

In this subpopulation of patients, antibiotic prophylaxis should be used for dental procedures requiring manipulation of the gingival or periapical region of the teeth or perforation of the oral mucosa.

These decisions are not consensual among countries, though. Latin American countries including Brazil remain conservative. IE antibiotic prophylaxis still includes patients with significant valve disease such as degenerative or bicuspid aortic valve, mitral valve prolapse with regurgitation, or rheumatic valve disease. It is also used before genitourinary or gastrointestinal procedures involving mucosa in high-risk patients.[103]

Incidence and mortality trends

In developed countries such as Denmark, Italy, England, Spain, Germany, Finland, and Netherlands, there has been an increasing trend in the incidence of IE in the last two decades (Table 3). This may be explained by demographic reasons (e.g., aging population), changes in the etiology of valve disease, an increasing number of patients with implanted cardiac devices or prosthesis, an increasing survival of patients with structural and CHD, need for long-term vascular access for different conditions, and advances in prophylaxis measures.

On the other hand, this trend has not been seen in other countries including France, Australia, Scotland or the United States of America (USA).[2,9] These disparities are probably related to the different sources and definition of cases, and impact timing of improvements in diagnostic methods (imaging, microbiology).

The greater impact of IE prophylaxis on IE incidence in high-risk patients (2007's American Heart Association[101] and 2009's European Society Cardiology[104]) has been evaluated in different studies, but uncertainty persists, as Khant et al.[105] concluded in a metanalysis in 2016. In fact, several authors showed a more pronounced increase in the IE incidence in countries such as United Kingdom, Germany and Netherland (Table 3), whereas DeSimone et al.[106] and Duval et al.,[9] from the USA and France respectively, have not detected this trend. Efforts should be made to assess, worldwide, the

Table 2 – Characteristics of observational surgical series on infective endocarditis patients

Study	Country	Study design	Temporal period	N	Native valve (%)/ Prosthetic valve (%)	Mortality rate (%)
Jassal et al.[115]	USA	Retrospective	1995-2004	91	85.7/14.3	15.4
Bannay et al.[116]	France	Prospective	1998-2000	240	67.5/32.5	19.4
Lalani et al.[83]	Multicentric	Prospective	2000-2005	720	100/0	12.1
Gaca et al.[95]	USA	Retrospective	2002-2008	19543	NA	8.2
Lalani et al.[86]	Multicentric	Prospective	2000-2005	490	0/100	22
Pang et al.[117]	Singapore	Retrospective	2000-2012	191	92.7/7.3	6.3
Machado et al.[118]	Brazil	Prospective	2003-2010	64	NA	17
Madeira et al.[94]	Portugal	Retrospective	2007-2014	128	75.7/15	16
Olmos et al.[97]	Spain	Prospective	1996-2014	671	60/40	28.6
Pivatto et al.[93]	Brazil	Retrospective	2007-2016	107	-/31	29
Varela el al.[119]	Spain	Retrospective	2002-2016	180	62.6/37.5	26.8
Guiomar et al.[120]	Portugal	Retrospective	2006-2017	145	68/32	13.1

NA: non-available.

Table 3 – Evolution of incidence and/or mortality rates in populational studies on infective endocarditis

Authors/Study	Country	Time period	Increasing incidence trends	Surgical rate trends	Mortality trends
Fonager et al.[1]	Denmark	1980-1997	Yes	NA	Decreasing
Tleyjeh et al.[2]	USA (Olmsted County)	1970-2000	No	Stable	Stable
Sy et al.[7]	Australia (New South Wales)	2000-2006	No	NA	Stable
Fedeli et al.[8]	Italy (Veneto region)	2000-2008	Yes	Stable	Increasing
Bikdeli et al.[109]	USA	1999-2010	No	NA	Stable
Duval et al.[9]	France (Greater Paris, Lorraine, and Rhône-Alpes)	1 yr. survey 1991, 1999 and 2008	No	Increase from 1991-1999. Then stable.	NA
Dayer et al.[111]	England	2000-2013	Yes (more pronounced after 2008)	NA	NA
Pant et al.[112]	USA	2000-2011	Yes (to *Streptococcus* IE after 2007)	Increase 2000-2007/stable 2007-2011	NA
Erichsen et al.[10]	Denmark	1994–2011	Yes (in men and older age)	NA	NA
Keller et al.[62]	Germany	2005-2014	Yes (more pronounced after 2009)	NA	Stable
Toyoda et al.[11]	USA (California and New York State)	1998-2013	No	NA	Stable
Van der Brink et al.[113]	Netherlands	2005-2011	Yes	NA	NA
Cresti et al.[3]	Italy (Grosseto)	1998-2014	Yes	NA	Mild increase (p=0.055)
Olmos et al.[97]	Spain	2003-2014	Yes	Increase	Decrease (0.2%/year)
Ahtela et al.[114]	Finland	2005-2014	Yes	NA	Stable
Shah et al.[65]	Scotland	1990-2014	No (increase in patients >80 years old)	NA	NA
Khan et al.[98]	USA	2002-2016	NA	Increase	A decrease (from 16.7% to 9.7%)

NA: non-available.

impact of local guidelines and physician's compliance on the incidence of IE.

Despite significant advances in the field of diagnosis and management (medical and surgical) of IE, stability is noted regarding in hospital mortality in most populational series. Exceptions were Italy, where an increase was noted,[3,8] and in Denmark,[1] Spain[97] and the USA[98] where a decrease was registered. The ICE[4] and EURO-ENDO[6] registries displayed a mildly increased mortality rate of 18% and 17% respectively, compared to the Euro Heart Survey[20] (13%). Finally, in 2013 a metanalysis[12] concluded on a decrease in in-hospital mortality from 1960 to 1980 with stability afterwards.

Challenges and future directions

In the last century, medical and surgical advances allowed for a remarkable improvement in the management and prognosis of IE. Still, physicians face daily challenges when dealing with such patients (Table 4).

Prevention should be a priority in national health policies. Patient and physician education campaigns are of crucial importance, and IE prophylaxis, analyzing which patients benefit the most, should be optimized.

Centers of expertise gathering experts in imaging, infectious disease, and cardiology should be established, aiming at better clinical and surgical outcomes. Straightforward communication with non-referral centers should be highly supported. Multimodality imaging protocols should be established, and technological improvements researched. The need to reduce hospital length of stay with the establishment of well-trained, outpatient teams and educated patients that would allow for OPAT, whenever feasible, must also be endorsed by institutions.

Evidence-based investigation is still quite exceptional and globally heterogeneous. In fact, most of our data were obtained from registries, populational studies and single/multicenter experiences in middle-to-high income countries, allowing for a non-neglectable selection bias when considering the worldwide condition. Randomized controlled trials should be performed to provide further evidence specifically regarding timing of surgery, antibiotic schemes, the effect of adjunctive medical therapy during the active treatment of IE or use of prosthetic material less predisposed to bacteria adhesion.

As a final comment, the use of artificial intelligence networks that are currently being built in high-volume centers[107] will allow an accurate estimation of the risk of complications and the ideal surgical timing, ultimately improving patient's prognosis.

Author Contributions

Conception and design of the research: Sousa C, Pinto F; Acquisition of data, Analysis and interpretation of the data and Writing of the manuscript: Sousa C; Critical revision of the manuscript for intellectual content: Pinto F.

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

Table 4 – Current major challenges of infective endocarditis

Main area	Challenges
Prevention	- IE prophylaxis (the use of stricter or broader indications) - clinicians/patients' awareness
Diagnosis	- criteria - negative blood cultures - prosthesis and cardiac devices – the value of imaging
Medical therapy	- robust evidence (randomized controlled clinical trials) - use of OPAT
Surgery	- robust evidence (randomized controlled clinical trials) - timing - valve repair versus replacement (technical expertise) - in patients with ischemic stroke - in intravenous drug users - in prosthetic endocarditis (always versus occasionally)
Overall management	- heart team versus multidisciplinary IE team - referral centres

OPAT: Outpatient Parenteral Antimicrobial Therapy. IE: infective endocarditis.

References

1. Fonager K, Lindberg J, Thulstrup AM, Pedersen L, Schønheyder HC, Sørensen HT. Incidence and Short-Term Prognosis of Infective Endocarditis in Denmark, 1980-1997. Scand J Infect Dis. 2003;35(1):27-30. doi: 10.1080/0036554021000026993.

2. Tleyjeh IM, Steckelberg JM, Murad HS, Anavekar NS, Ghomrawi HM, Mirzoyev Z, et al. Temporal Trends in Infective Endocarditis: A Population-Based Study in Olmsted County, Minnesota. JAMA. 2005;293(24):3022-8. doi: 10.1001/jama.293.24.3022.

3. Cresti A, Chiavarelli M, Scalese M, Nencioni C, Valentini S, Guerrini F, et al. Epidemiological and Mortality Trends in Infective Endocarditis, a 17-Year Population-Based Prospective Study. Cardiovasc Diagn Ther. 2017;7(1):27-35. doi: 10.21037/cdt.2016.08.09.

4. Murdoch DR, Corey GR, Hoen B, Miró JM, Fowler VG Jr, Bayer AS, et al. Clinical Presentation, Etiology, and Outcome of Infective Endocarditis in the 21st Century: The International Collaboration on Endocarditis-Prospective Cohort Study. Arch Intern Med. 2009;169(5):463-73. doi: 10.1001/archinternmed.2008.603.

5. Muñoz P, Kestler M, Alarcon A, Miro JM, Bermejo J, Rodríguez-Abella H, et al. Current Epidemiology and Outcome of Infective Endocarditis: A Multicenter, Prospective, Cohort Study. Medicine (Baltimore). 2015;94(43):e1816. doi: 10.1097/MD.0000000000001816.

6. Habib G, Erba PA, Iung B, Donal E, Cosyns B, Laroche C, et al. Clinical Presentation, Aetiology and Outcome of Infective Endocarditis. Results of the ESC-EORP EURO-ENDO (European Infective Endocarditis) Registry: A Prospective Cohort Study. Eur Heart J. 2019;40(39):3222-32. doi: 10.1093/eurheartj/ehz620.

7. Sy RW, Kritharides L. Health Care Exposure and Age in Infective Endocarditis: Results of a Contemporary Population-Based Profile of 1536 Patients in Australia. Eur Heart J. 2010;31(15):1890-7. doi: 10.1093/eurheartj/ehq110.

8. Fedeli U, Schievano E, Buonfrate D, Pellizzer G, Spolaore P. Increasing Incidence and Mortality of Infective Endocarditis: A Population-Based Study Through a Record-Linkage System. BMC Infect Dis. 2011;11:48. doi: 10.1186/1471-2334-11-48.

9. Duval X, Delahaye F, Alla F, Tattevin P, Obadia JF, Moing V, et al. Temporal Trends in Infective Endocarditis in the Context of Prophylaxis Guideline Modifications: Three Successive Population-Based Surveys. J Am Coll Cardiol. 2012;59(22):1968-76. doi: 10.1016/j.jacc.2012.02.029.

10. Erichsen P, Gislason GH, Bruun NE. The Increasing Incidence of Infective Endocarditis in Denmark, 1994-2011. Eur J Intern Med. 2016;35:95-9. doi: 10.1016/j.ejim.2016.05.021.

11. Toyoda N, Chikwe J, Itagaki S, Gelijns AC, Adams DH, Egorova NN. Trends in Infective Endocarditis in California and New York State, 1998-2013. JAMA. 2017;317(16):1652-60. doi: 10.1001/jama.2017.4287.

12. Slipczuk L, Codolosa JN, Davila CD, Romero-Corral A, Yun J, Pressman GS, et al. Infective Endocarditis Epidemiology Over Five Decades: A Systematic Review. PLoS One. 2013;8(12):e82665. doi: 10.1371/journal.pone.0082665.

13. Nkomo VT, Gardin JM, Skelton TN, Gottdiener JS, Scott CG, Enriquez-Sarano M. Burden of Valvular Heart Diseases: A Population-Based Study. Lancet. 2006;368(9540):1005-11. doi: 10.1016/S0140-6736(06)69208-8.

14. Iung B, Baron G, Butchart EG, Delahaye F, Gohlke-Bärwolf C, Levang OW, et al. A Prospective Survey of Patients with Valvular Heart Disease in Europe: The Euro Heart Survey on Valvular Heart Disease. Eur Heart J. 2003;24(13):1231-43. doi: 10.1016/s0195-668x(03)00201-x.

15. Iung B, Vahanian A. Epidemiology of Acquired Valvular Heart Disease. Can J Cardiol. 2014;30(9):962-70. doi: 10.1016/j.cjca.2014.03.022.

16. Rheumatic fever and rheumatic heart disease. World Health Organ Tech Rep Ser. 2004;923:1-122.

17. Watkins DA, Johnson CO, Colquhoun SM, Karthikeyan G, Beaton A, Bukhman G, et al. Global, Regional, and National Burden of Rheumatic Heart Disease, 1990-2015. N Engl J Med. 2017;377(8):713-22. doi: 10.1056/NEJMoa1603693.

18. Figueiredo ET, Azevedo L, Rezende ML, Alves CG. Rheumatic Fever: A Disease Without Color. Arq Bras Cardiol. 2019;113(3):345-54. doi: 10.5935/abc.20190141.

19. Glaser N, Jackson V, Holzmann MJ, Franco-Cereceda A, Sartipy U. Prosthetic Valve Endocarditis After Surgical Aortic Valve Replacement. Circulation. 2017;136(3):329-31. doi: 10.1161/CIRCULATIONAHA.117.028783.

20. Tornos P, Iung B, Permanyer-Miralda G, Baron G, Delahaye F, Gohlke-Bärwolf CH, et al. Infective Endocarditis in Europe: Lessons from the Euro Heart Survey. Heart. 2005;91(5):571-5. doi: 10.1136/hrt.2003.032128.

21. Baumgartner H, Falk V, Bax JJ, Bonis M, Hamm C, Holm PJ, et al. 2017 ESC/EACTS Guidelines for the Management of Valvular Heart Disease. Eur Heart J. 2017;38(36):2739-91. doi: 10.1093/eurheartj/ehx391.

22. Ando T, Ashraf S, Villablanca PA, Telila TA, Takagi H, Grines CL, et al. Meta-Analysis Comparing the Incidence of Infective Endocarditis Following Transcatheter Aortic Valve Implantation Versus Surgical Aortic Valve Replacement. Am J Cardiol. 2019;123(5):827-32. doi: 10.1016/j.amjcard.2018.11.031.

23. Athan E, Chu VH, Tattevin P, Selton-Suty C, Jones P, Naber C, et al. Clinical Characteristics and Outcome of Infective Endocarditis Involving Implantable Cardiac Devices. JAMA. 2012;307(16):1727-35. doi: 10.1001/jama.2012.497.

24. Fernandes A, Cassandra M, Trigo J, Nascimento J, Cachulo MC, Providência R, et al. Cardiac Device Infection: Review Based in the Experience of a Single Center. Rev Port Cardiol. 2016;35(6):351-8. doi: 10.1016/j.repc.2015.12.005.

25. Morris CD, Reller MD, Menashe VD. Thirty-Year Incidence of Infective Endocarditis After Surgery for Congenital Heart Defect. JAMA. 1998;279(8):599-603. doi: 10.1001/jama.279.8.599.

26. Moore B, Cao J, Kotchetkova I, Celermajer DS. Incidence, Predictors and Outcomes of Infective Endocarditis in a Contemporary Adult Congenital Heart Disease Population. Int J Cardiol. 2017;249:161-5. doi: 10.1016/j.ijcard.2017.08.035.

27. Cahill TJ, Jewell PD, Denne L, Franklin RC, Frigiola A, Orchard E, et al. Contemporary Epidemiology of Infective Endocarditis in Patients with Congenital Heart Disease: A UK Prospective Study. Am Heart J. 2019;215:70-7. doi: 10.1016/j.ahj.2019.05.014.

28. Feliciano JG, Agapito A, Branco LM, Sousa L, Pelicano N, Fiarresga AF, et al. Infective Endocarditis in Adolescents and Adults with Congenital Heart Disease: Clinical and Echocardiographic Data. Eur J Echocardiogr. 2005;6(Suppl 1):56. doi: 10.1016/S1525-2167(05)80206-9.

29. Shih CJ, Chu H, Chao PW, Lee YJ, Kuo SC, Li SY, et al. Long-Term Clinical Outcome of Major Adverse Cardiac Events in Survivors of Infective Endocarditis: A Nationwide Population-Based Study. Circulation. 2014;130(19):1684-91. doi: 10.1161/CIRCULATIONAHA.114.012717.

30. Chu VH, Sexton DJ, Cabell CH, Reller LB, Pappas PA, Singh RK, et al. Repeat Infective Endocarditis: Differentiating Relapse from Reinfection. Clin Infect Dis. 2005;41(3):406-9. doi: 10.1086/431590.

31. Mansur AJ, Bó CMD, Fukushima JT, Issa VS, Grinberg M, Pomerantzeff PM. Relapses, Recurrences, Valve Replacements, and Mortality During the Long-Term Follow-up After Infective Endocarditis. Am Heart J. 2001;141(1):78-86. doi: 10.1067/mhj.2001.111952.

32. Castillo JC, Anguita MP, Ramírez A, Siles JR, Torres F, Mesa D, et al. Long Term Outcome of Infective Endocarditis in Patients Who Were Not Drug Addicts: A 10 Year Study. Heart. 2000;83(5):525-30. doi: 10.1136/heart.83.5.525.

33. Fernández-Hidalgo N, Almirante B, Tornos P, González-Alujas MT, Planes AM, Galiñanes M, et al. Immediate and Long-Term Outcome of Left-Sided Infective Endocarditis. A 12-Year Prospective Study from a Contemporary Cohort in a Referral Hospital. Clin Microbiol Infect. 2012;18(12):522-30. doi: 10.1111/1469-0691.12033.

34. Thuny F, Giorgi R, Habachi R, Ansaldi S, Dolley Y, Casalta JP, et al. Excess Mortality and Morbidity in Patients Surviving Infective Endocarditis. Am Heart J. 2012;164(1):94-101. doi: 10.1016/j.ahj.2012.04.003.

35. Heiro M, Helenius H, Hurme S, Savunen T, Metsärinne K, Engblom E, et al. Long-Term Outcome of Infective Endocarditis: A Study on Patients Surviving Over One Year After the Initial Episode Treated in a Finnish Teaching Hospital During 25 Years. BMC Infect Dis. 2008;8:49. doi: 10.1186/1471-2334-8-49.

36. Thornhill MH, Jones S, Prendergast B, Baddour LM, Chambers JB, Lockhart PB, et al. Quantifying Infective Endocarditis Risk in Patients with Predisposing Cardiac Conditions. Eur Heart J. 2018;39(7):586-95. doi: 10.1093/eurheartj/ehx655.

37. European Monitoring Centre for Drugs and Drug Addiction. Drug-Related Infectious Diseases in Europe. Lisboa: EMCDDA; 2019.

38. Safdar N, Maki DG. Risk of Catheter-Related Bloodstream Infection with Peripherally Inserted Central Venous Catheters Used in Hospitalized Patients. Chest. 2005;128(2):489-95. doi: 10.1378/chest.128.2.489.

39. Lomas JM, Martínez-Marcos FJ, Plata A, Ivanova R, Gálvez J, Ruiz J, et al. Healthcare-Associated Infective Endocarditis: An Undesirable Effect of Healthcare Universalization. Clin Microbiol Infect. 2010;16(11):1683-90. doi: 10.1111/j.1469-0691.2009.03043.x.

40. Francischetto O, Silva LA, Senna KM, Vasques MR, Barbosa GF, Weksler C, et al. Healthcare-Associated Infective Endocarditis: A Case Series in a Referral Hospital from 2006 to 2011. Arq Bras Cardiol. 2014;103(4):292-8. doi: 10.5935/abc.20140126.

41. Martín-Dávila P, Fortún J, Navas E, Cobo J, Jiménez-Mena M, Moya JL, et al Nosocomial Endocarditis in a Tertiary Hospital: An Increasing Trend in Native Valve Cases. Chest. 2005;128(2):772-9. doi: 10.1378/chest.128.2.772.

42. Habib G, Gouriet F, Casalta JP. Infective Endocarditis in Injection Drug Users: A Recurrent Disease. J Am Coll Cardiol. 2019;73(5):571-2. doi: 10.1016/j.jacc.2018.10.081.

43. Chaudry MS, Carlson N, Gislason GH, Kamper AL, Rix M, Fowler VG Jr, et al. Risk of Infective Endocarditis in Patients with End Stage Renal Disease. Clin J Am Soc Nephrol. 2017;12(11):1814-22. doi: 10.2215/CJN.02320317.

44. McCarthy JT, Steckelberg JM. Infective Endocarditis in Patients Receiving Long-Term Hemodialysis. Mayo Clin Proc. 2000;75(10):1008-14. doi: 10.4065/75.10.1008.

45. Strom BL, Abrutyn E, Berlin JA, Kinman JL, Feldman RS, Stolley PD, et al. Risk Factors for Infective Endocarditis: Oral Hygiene and Nondental Exposures. Circulation. 2000;102(23):2842-8. doi: 10.1161/01.cir.102.23.2842.

46. Cahill TJ, Baddour LM, Habib G, Hoen B, Salaun E, Pettersson GB, et al. Challenges in Infective Endocarditis. J Am Coll Cardiol. 2017;69(3):325-44. doi: 10.1016/j.jacc.2016.10.066.

47. Fernández-Cruz A, Muñoz P, Sandoval C, Fariñas C, Gutiérrez-Cuadra M, Pulido JMP, et al. Infective Endocarditis in Patients with Cancer: A Consequence of Invasive Procedures or a Harbinger of Neoplasm?: A Prospective, Multicenter Cohort. Medicine (Baltimore). 2017;96(38):e7913. doi: 10.1097/MD.0000000000007913.

48. Sun LM, Wu JN, Lin CL, Day JD, Liang JA, Liou LR, et al. Infective Endocarditis and Cancer Risk: A Population-Based Cohort Study. Medicine (Baltimore). 2016;95(12):e3198. doi: 10.1097/MD.0000000000003198.

49. Lockhart PB, Brennan MT, Thornhill M, Michalowicz BS, Noll J, Bahrani-Mougeot FK, et al. Poor Oral Hygiene as a Risk Factor for Infective Endocarditis-Related Bacteremia. J Am Dent Assoc. 2009;140(10):1238-44. doi: 10.14219/jada.archive.2009.0046.

50. Shapiro SM, Young E, Guzman S, Ward J, Chiu CY, Ginzton LE, et al. Transesophageal Echocardiography in Diagnosis of Infective Endocarditis. Chest. 1994;105(2):377-82. doi: 10.1378/chest.105.2.377.

51. Chirillo F, Pedrocco A, Leo A, Bruni A, Totis O, Meneghetti P, et al. Impact of harmonic Imaging on Transthoracic Echocardiographic Identification of Infective Endocarditis and its Complications. Heart. 2005;91(3):329-33. doi: 10.1136/hrt.2003.031583.

52. Jassal DS, Aminbakhsh A, Fang T, Shaikh N, Embil JM, Mackenzie GS, et al. Diagnostic Value of Harmonic Transthoracic Echocardiography in Native Valve Infective Endocarditis: Comparison with Transesophageal Echocardiography. Cardiovasc Ultrasound. 2007;5:20. doi: 10.1186/1476-7120-5-20.

53. Pfister R, Betton Y, Freyhaus HT, Jung N, Baldus S, Michels G. Three-Dimensional Compared to Two-Dimensional Transesophageal Echocardiography for Diagnosis of Infective Endocarditis. Infection. 2016;44(6):725-31. doi: 10.1007/s15010-016-0908-9.

54. Vieira ML, Grinberg M, Pomerantzeff PM, Andrade JL, Mansur AJ. Repeated Echocardiographic Examinations of Patients with Suspected Infective Endocarditis. Heart. 2004;90(9):1020-4. doi: 10.1136/hrt.2003.025585.

55. Sarrazin JF, Philippon F, Trottier M, Tessier M. Role of Radionuclide Imaging for Diagnosis of Device and Prosthetic Valve Infections. World J Cardiol. 2016;8(9):534-46. doi: 10.4330/wjc.v8.i9.534.

56. Saby L, Laas O, Habib G, Cammilleri S, Mancini J, Tessonnier L, et al. Positron Emission Tomography/Computed Tomography for Diagnosis of Prosthetic Valve Endocarditis: Increased Valvular 18F-Fluorodeoxyglucose Uptake as a Novel Major Criterion. J Am Coll Cardiol. 2013;61(23):2374-82. doi: 10.1016/j.jacc.2013.01.092.

57. Habib G, Lancellotti P, Antunes MJ, Bongiorni MG, Casalta JP, Del Zotti F, et al. 2015 ESC Guidelines for the Management of Infective Endocarditis: The Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC). Eur Heart J. 2015;36(44):3075-128. doi: 10.1093/eurheartj/ehv319.

58. Gonçalves J. Endocardite Infecciosa. Sete décadas de Evolução. Acta Med Port. 1979;1(2):267-77.

59. McCartney AC. Changing Trends in Infective Endocarditis. J Clin Pathol. 1992;45(11):945-8. doi: 10.1136/jcp.45.11.945.

60. Pelletier LL Jr, Petersdorf RG. Infective Endocarditis: A Review of 125 Cases from the University of Washington Hospitals, 1963-72. Medicine (Baltimore). 1977;56(4):287-313.

61. Tleyjeh IM, Abdel-Latif A, Rahbi H, Scott CG, Bailey KR, Steckelberg JM, et al. A Systematic Review of Population-Based Studies of Infective Endocarditis. Chest. 2007;132(3):1025-35. doi: 10.1378/chest.06-2048.

62. Keller K, von Bardeleben RS, Ostad MA, Hobohm L, Munzel T, Konstantinides S, et al. Temporal Trends in the Prevalence of Infective Endocarditis in Germany Between 2005 and 2014. Am J Cardiol. 2017;119(2):317-22. doi: 10.1016/j.amjcard.2016.09.035.

63. Thuny F, Di Salvo G, Belliard O, Avierinos JF, Pergola V, Rosenberg V, et al. Risk of Embolism and Death in Infective Endocarditis: Prognostic Value of Echocardiography: A Prospective Multicenter Study. Circulation. 2005;112(1):69-75. doi: 10.1161/CIRCULATIONAHA.104.493155.

64. Vogkou CT, Vlachogiannis NI, Palaiodimos L, Kousoulis AA. The Causative Agents in Infective Endocarditis: A Systematic Review Comprising 33,214 Cases. Eur J Clin Microbiol Infect Dis. 2016;35(8):1227-45. doi: 10.1007/s10096-016-2660-6.

65. Shah ASV, McAllister DA, Gallacher P, Astengo F, Pérez JAR, Hall J, et al. Incidence, Microbiology, and Outcomes in Patients Hospitalized with Infective Endocarditis. Circulation. 2020;141(25):2067-77. doi: 10.1161/CIRCULATIONAHA.119.044913.

66. Lamas CC, Fournier PE, Zappa M, Brandão TJ, Januário-da-Silva CA, Correia MG, et al. Diagnosis of Blood Culture-Negative Endocarditis and Clinical Comparison Between Blood Culture-Negative and Blood Culture-Positive Cases. Infection. 2016;44(4):459-66. doi: 10.1007/s15010-015-0863-x.

67. Fournier PE, Gouriet F, Casalta JP, Lepidi H, Chaudet H, Thuny F, et al. Blood Culture-Negative Endocarditis: Improving the Diagnostic Yield Using New Diagnostic Tools. Medicine (Baltimore). 2017;96(47):e8392. doi: 10.1097/MD.0000000000008392.

68. Olmos C, Vilacosta I, Fernández-Pérez C, Bernal JL, Ferrera C, García-Arribas D, et al. The Evolving Nature of Infective Endocarditis in Spain: A Population-Based Study (2003 to 2014). J Am Coll Cardiol. 2017;70(22):2795-804. doi: 10.1016/j.jacc.2017.10.005.

69. Lamas CC. Endocardite Infecciosa: Ainda uma Doença Mortal. Arq Bras Cardiol. 2019;114(1):9–11. doi: 10.36660/abc.20190809.

70. Fournier PE, Thuny F, Richet H, Lepidi H, Casalta JP, Arzouni JP, et al. Comprehensive Diagnostic Strategy for Blood Culture-Negative Endocarditis: A Prospective Study of 819 New Cases. Clin Infect Dis. 2010;51(2):131-40. doi: 10.1086/653675.

71. Brandão TJ, Januario-da-Silva CA, Correia MG, Zappa M, Abrantes JA, Dantas AM, et al. Histopathology of Valves in Infective Endocarditis, Diagnostic Criteria and Treatment Considerations. Infection. 2017;45(2):199-207. doi: 10.1007/s15010-016-0953-4.

72. Baddour LM, Wilson WR, Bayer AS, Fowler VG Jr, Tleyjeh IM, Rybak MJ, et al. Infective Endocarditis in Adults: Diagnosis, Antimicrobial Therapy, and Management of Complications: A Scientific Statement for Healthcare Professionals from the American Heart Association. Circulation. 2015;132(15):1435-86. doi: 10.1161/CIR.0000000000000296.

73. Morris AJ, Drinković D, Pottumarthy S, MacCulloch D, Kerr AR, West T. Bacteriological Outcome After Valve Surgery for Active Infective Endocarditis: Implications for Duration of Treatment After Surgery. Clin Infect Dis. 2005;41(2):187-94. doi: 10.1086/430908.

74. Tice AD, Rehm SJ, Dalovisio JR, Bradley JS, Martinelli LP, Graham DR, et al. Practice Guidelines for Outpatient Parenteral Antimicrobial Therapy. IDSA Guidelines. Clin Infect Dis. 2004;38(12):1651-72. doi: 10.1086/420939.

75. Al-Omari A, Cameron DW, Lee C, Corrales-Medina VF. Oral antibiotic therapy for the treatment of infective endocarditis: a systematic review. BMC Infect Dis. 2014;14:140. doi: 10.1186/1471-2334-14-140.

76. Heldman AW, Hartert TV, Ray SC, Daoud EG, Kowalski TE, Pompili VJ, et al. Oral Antibiotic Treatment of Right-Sided Staphylococcal Endocarditis in Injection Drug Users: Prospective Randomized Comparison with Parenteral Therapy. Am J Med. 1996;101(1):68-76. doi: 10.1016/s0002-9343(96)00070-8.

77. Iversen K, Ihlemann N, Gill SU, Madsen T, Elming H, Jensen KT, et al. Partial Oral Versus Intravenous Antibiotic Treatment of Endocarditis. N Engl J Med. 2019;380(5):415-24. doi: 10.1056/NEJMoa1808312.

78. Antunes MJ, Saraiva JC. Is the Role of Surgery in Infective Endocarditis Changing? Rev Port Cardiol (Engl Ed). 2018;37(5):395-7. doi: 10.1016/j.repc.2017.09.021.

79. Varela Barca L, Elorza EN, Fernández-Hidalgo N, Mur JLM, García AM, Fernández-Felix BM, et al. Prognostic Factors of Mortality After Surgery in Infective Endocarditis: Systematic Review and Meta-Analysis. Infection. 2019;47(6):879-95. doi: 10.1007/s15010-019-01338-x.

80. Ilhão Moreira R, Cruz MC, Branco LM, Galrinho A, Coutinho Miranda L, Fragata J, et al. Infective Endocarditis: Surgical Management and Prognostic Predictors. Rev Port Cardiol (Engl Ed). 2018;37(5):387-94. doi: 10.1016/j.repc.2017.08.007.

81. Ferreira JP, Gomes F, Rodrigues P, Abreu MA, Maia JM, Bettencourt P, et al. Left-Sided Infective Endocar|ditis: Analysis of in-Hospital and Medium-Term Outcome and Predictors of Mortality. Rev Port Cardiol. 2013;32(10):777-84. doi: 10.1016/j.repc.2012.11.015.

82. Yun SC, Kim YJ, Kim SH, Sun BJ, Kim DH, Song JM, et al. Early Surgery Versus Conventional Treatment for Infective Endocarditis. N Engl J Med. 2012;366(26):2466-73. doi: 10.1056/NEJMoa1112843.

83. Lalani T, Cabell CH, Benjamin DK, Lasca O, Naber C, Fowler VG Jr, et al. Analysis of the Impact of Early Surgery on in-Hospital Mortality of Native Valve Endocarditis: Use of Propensity Score and Instrumental Variable Methods to Adjust for Treatment-Selection Bias. Circulation. 2010;121(8):1005-13. doi: 10.1161/CIRCULATIONAHA.109.864488.

84. Chu VH, Park LP, Athan E, Delahaye F, Freiberger T, Lamas C, et al. Association Between Surgical Indications, Operative Risk, and Clinical Outcome in Infective Endocarditis: A Prospective Study from the International Collaboration on Endocarditis. Circulation. 2015;131(2):131-40. doi: 10.1161/CIRCULATIONAHA.114.012461.

85. Iung B, Doco-Lecompte T, Chocron S, Strady C, Delahaye F, Moing VL, et al. Cardiac Surgery During the Acute Phase of Infective Endocarditis: Discrepancies BETWEEN European Society of Cardiology Guidelines and Practices. Eur Heart J. 2016;37(10):840-8. doi: 10.1093/eurheartj/ehv650.

86. Lalani T, Chu VH, Park LP, Cecchi E, Corey GR, Durante-Mangoni E, et al. In-Hospital and 1-Year Mortality in Patients Undergoing Early Surgery for Prosthetic Valve Endocarditis. JAMA Intern Med. 2013;173(16):1495-504. doi: 10.1001/jamainternmed.2013.8203.

87. Kang DH, Kim YJ, Kim SH, Sun BJ, Kim DH, Yun SC, et al. Early surgery versus conventional treatment for infective endocarditis. N Engl J Med. 2012 Jun 28;366(26):2466-73. doi: 10.1056/NEJMoa1112843.

88. Pettersson GB, Hussain ST. Current AATS Guidelines on Surgical Treatment of Infective Endocarditis. Ann Cardiothorac Surg. 2019;8(6):630-44. doi: 10.21037/acs.2019.10.05.

89. Toyoda N, Itagaki S, Egorova NN, Tannous H, Anyanwu AC, El-Eshmawi A, et al. Real-World Outcomes of Surgery for Native Mitral Valve Endocarditis. J Thorac Cardiovasc Surg. 2017;154(6):1906-12.e9. doi: 10.1016/j.jtcvs.2017.07.077.

90. Antunes MJ. The Role of Surgery in Infective Endocarditis Revisited. Rev Port Cardiol (Engl Ed). 2020;39(3):151-3. doi: 10.1016/j.repc.2020.03.009.

91. Toyoda N, Itagaki S, Tannous H, Egorova NN, Chikwe J. Bioprosthetic Versus Mechanical Valve Replacement for Infective Endocarditis: Focus on Recurrence Rates. Ann Thorac Surg. 2018;106(1):99-106. doi: 10.1016/j.athoracsur.2017.12.046.

92. Martins A. Avaliação de Desempenho de Escores de Prognóstico de Cirurgia Cardíaca em Pacientes Submetidos à Troca Valvar por Endocardite Infecciosa no Instituto Nacional de Cardiologia, anos de 2006 a 2016. 2016 [dissertation]. Rio de Janeiro: Instituto Nacional de Cardiologia; 2016.

93. Pivatto F Jr, Bellagamba CCA, Pianca EG, Fernandes FS, Butzke M, Busato SB, Gus M, et al. Analysis of Risk Scores to Predict Mortality in Patients Undergoing Cardiac Surgery for Endocarditis. Arq Bras Cardiol. 2020;114(3):518-24. doi: 10.36660/abc.20190050.

94. Madeira S, Rodrigues R, Tralhão A, Santos M, Almeida C, Marques M, et al. Assessment of Perioperative Mortality Risk in Patients with Infective Endocarditis Undergoing Cardiac Surgery: Performance of the EuroSCORE I and II Logistic Models. Interact Cardiovasc Thorac Surg. 2016;22(2):141-8. doi: 10.1093/icvts/ivv304.

95. Gaca JG, Sheng S, Daneshmand MA, O'Brien S, Rankin JS, Brennan JM, et al. Outcomes for Endocarditis Surgery in North America: A Simplified Risk Scoring System. J Thorac Cardiovasc Surg. 2011;141(1):98-106.1-2. doi: 10.1016/j.jtcvs.2010.09.016.

96. Martins ABB, Lamas CDC. Prognostic Scores for Mortality in Cardiac Surgery for Infective Endocarditis. Arq Bras Cardiol. 2020;114(3):525-9. doi: 10.36660/abc.20200070.

97. Olmos C, Vilacosta I, Fernández-Pérez C, Bernal JL, Ferrera C, García-Arribas D, Pérez-García CN, San Román JA, Maroto L, Macaya C, Elola FJ. The Evolving Nature of Infective Endocarditis in Spain: A Population-Based Study (2003 to 2014). J Am Coll Cardiol. 2017;70(22):2795-2804. doi: 10.1016/j.jacc.2017.10.005.

98. Khan MZ, Munir MB, Khan MU, Khan SU, Benjamin MM, Balla S. Contemporary Trends in Native Valve Infective Endocarditis in United States (from the National Inpatient Sample Database). Am J Cardiol. 2020;125(11):1678-87. doi: 10.1016/j.amjcard.2020.02.035.

99. Abegaz TM, Bhagavathula AS, Gebreyohannes EA, Mekonnen AB, Abebe TB. Short- and Long-Term Outcomes in Infective Endocarditis Patients: A Systematic Review and Meta-Analysis. BMC Cardiovasc Disord. 2017;17(1):291. doi: 10.1186/s12872-017-0729-5.

100. Netzer RO, Altwegg SC, Zollinger E, Täuber M, Carrel T, Seiler C. Infective Endocarditis: Determinants of Long Term Outcome. Heart. 2002;88(1):61-6. doi: 10.1136/heart.88.1.61.

101. Wilson W, Taubert KA, Gewitz M, Lockhart PB, Baddour LM, Levison M, et al. Prevention of Infective Endocarditis: Guidelines from the American Heart Association: A Guideline from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group. Circulation. 2007;116(15):1736-54. doi: 10.1161/CIRCULATIONAHA.106.183095.

102. National Institute for Health and Care Excellence. Prophylaxis Against Infective Endocarditis. London: NICE; 2017.

103. Tarasoutchi F, Montera MW, Ramos AIO, Sampaio RO, Rosa VEE, Accorsi TAD, et al. Update of the Brazilian Guidelines for Valvular Heart Disease - 2020. Arq Bras Cardiol. 2020;115(4):720-75. doi: 10.36660/abc.20201047.

104. Habib G, Hoen B, Tornos P, Thuny F, Prendergast B, Vilacosta I, et al. Guidelines on the prevention, diagnosis, and treatment of infective endocarditis (new version 2009): the Task Force on the Prevention, Diagnosis, and Treatment of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and the International Society of Chemotherapy (ISC) for Infection and Cancer. Eur Heart J. 2009;30(19):2369-413. doi: 10.1093/eurheartj/ehp285.

105. Khan O, Shafi AM, Timmis A. International Guideline Changes and the Incidence of Infective Endocarditis: A Systematic Review. Open Heart. 2016;3(2):e000498. doi: 10.1136/openhrt-2016-000498.

106. DeSimone DC, Tleyjeh IM, Sa DDC, Anavekar NS, Lahr BD, Sohail MR, et al. Temporal Trends in Infective Endocarditis Epidemiology from 2007 to 2013 in Olmsted County, MN. Am Heart J. 2015;170(4):830-6. doi: 10.1016/j.ahj.2015.07.007.

107. Hubers SA, DeSimone DC, Gersh BJ, Anavekar NS. Infective Endocarditis: A Contemporary Review. Mayo Clin Proc. 2020;95(5):982-97. doi: 10.1016/j.mayocp.2019.12.008.

108. Selton-Suty C, Célard M, Moing VL, Doco-Lecompte T, Chirouze C, Iung B, et al. Preeminence of Staphylococcus Aureus in Infective Endocarditis: A 1-year Population-Based Survey. Clin Infect Dis. 2012;54(9):1230-9. doi: 10.1093/cid/cis199.

109. Bikdeli B, Wang Y, Kim N, Desai MM, Quagliarello V, Krumholz HM. Trends in Hospitalization Rates and Outcomes of Endocarditis Among Medicare Beneficiaries. J Am Coll Cardiol. 2013;62(23):2217-26. doi: 10.1016/j.jacc.2013.07.071.

110. Ternhag A, Cederström A, Törner A, Westling K. A Nationwide Cohort Study of Mortality Risk and Long-Term Prognosis in Infective Endocarditis in Sweden. PLoS One. 2013;8(7):e67519. doi: 10.1371/journal.pone.0067519.

111. Dayer MJ, Jones S, Prendergast B, Baddour LM, Lockhart PB, Thornhill MH. Incidence of Infective Endocarditis in England, 2000-13: A Secular Trend, Interrupted Time-Series Analysis. Lancet. 2015;385(9974):1219-28. doi: 10.1016/S0140-6736(14)62007-9.

112. Pant S, Patel NJ, Deshmukh A, Golwala H, Patel N, Badheka A, et al. Trends in Infective Endocarditis Incidence, Microbiology, and Valve Replacement in the United States from 2000 to 2011. J Am Coll Cardiol. 2015;65(19):2070-6. doi: 10.1016/j.jacc.2015.03.518.

113. van den Brink FS, Swaans MJ, Hoogendijk MG, Alipour A, Kelder JC, Jaarsma W, et al. Increased Incidence of Infective Endocarditis after the 2009 European Society of Cardiology Guideline Update: A Nationwide Study in the Netherlands. Eur Heart J Qual Care Clin Outcomes. 2017;3(2):141-7. doi: 10.1093/ehjqcco/qcw039.

114. Ahtela E, Oksi J, Porela P, Ekström T, Rautava P, Kytö V. Trends in Occurrence and 30-day Mortality of Infective Endocarditis in Adults: Population-Based Registry Study in Finland. BMJ Open. 2019;9(4):e026811. doi: 10.1136/bmjopen-2018-026811.

115. Jassal DS, Neilan TG, Pradhan AD, Lynch KE, Vlahakes G, Agnihotri AK, et al. Surgical Management of Infective Endocarditis: Early Predictors of Short-Term Morbidity and Mortality. Ann Thorac Surg. 2006;82(2):524-9. doi: 10.1016/j.athoracsur.2006.02.023.

116. Bannay A, Hoen B, Duval X, Obadia JF, Selton-Suty C, Moing VL, et al. The Impact of Valve Surgery on Short- and Long-Term Mortality in Left-Sided Infective Endocarditis: Do Differences in Methodological Approaches Explain Previous Conflicting Results? Eur Heart J. 2011;32(16):2003-15. doi: 10.1093/eurheartj/ehp008.

117. Pang PY, Sin YK, Lim CH, Tan TE, Lim SL, Chao VT, et al. Surgical Management of Infective Endocarditis: An Analysis of Early and Late Outcomes. Eur J Cardiothorac Surg. 2015;47(5):826-32. doi: 10.1093/ejcts/ezu281.

118. Machado MN, Nakazone MA, Murad JA Jr, Maia LN. Surgical Treatment for Infective Endocarditis and Hospital Mortality in a Brazilian Single-Center. Braz J Cardiovasc Surg. 2013;28(1):29-35. doi: 10.5935/1678-9741.20130006.

119. Varela L, López-Menéndez J, Redondo A, Fajardo ER, Miguelena J, Centella T, et al. Mortality Risk Prediction in Infective Endocarditis Surgery: Reliability Analysis of Specific Scores. Eur J Cardiothorac Surg. 2018;53(5):1049-54. doi: 10.1093/ejcts/ezx428.

120. Guiomar N, Vaz-da-Silva M, Mbala D, Sousa-Pinto B, Monteiro JP, Ponce P, et al. Cardiac Surgery in Infective Endocarditis and Predictors of in-Hospital Mortality. Rev Port Cardiol (Engl Ed). 2020;39(3):137-149. doi: 10.1016/j.repc.2019.08.009.

Mexiletine in a Newborn with Type 3 Long QT Syndrome: When Access is Difficult

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Introduction

Long QT syndrome type 3 (LQT3) is a highly lethal channelopathy. It is associated with delayed closing of sodium channels, resulting from mutations in the *SCN5A* gene, with an autosomal dominant pattern, responsible for 7-10% of all long QT syndromes (LQTSs).[1] The initial presentation can have a wide spectrum, from asymptomatic to sudden death in the first year of life.[2] The addition of class IB sodium channel blocker (mexiletine) to propranolol or nadolol is considered a gene-guided treatment, as its benefit is proven in LQT3.[3] In some countries, such as Brazil, it is not feasible to treat patients with LQT3, because of the unavailability of mexiletine.

We present here a severe case of a child with LQT3, who underwent multiple implantable cardioverter-defibrillator (ICD) therapies because of difficult access to mexiletine in Brazil.

Case Report

The patient was a girl of healthy parents without consanguinity. She was born by cesarean section because of intrauterine arrhythmia (tachycardia alternating with bradycardia). As a newborn, she had multiple episodes of polymorphic non-sustained ventricular tachycardia (pNSVT). Baseline electrocardiogram (ECG) showed a 2:1 atrioventricular block (AVB) and prolonged QT interval (Figure 1). Treatment with propranolol 1 mg/kg/day was started. and because of worsening of bradycardia, we decided on implantation of a single-chamber intravenous pacemaker (Figure 2).

At three months of age, the patient developed ventricular fibrillation and was promptly resuscitated, with return to spontaneous circulation. Because of suspicion of LQT,[3] even in the absence of genetic testing to guide treatment and the unavailability of mexiletine for therapeutic testing, we chose to increase the dose of propranolol to 4.5 mg/kg and add phenytoin. There was a transient improvement in the recurrence of pNSVT, and we decided to perform cervicothoracic sympathectomy.

At seven months, after new episodes of cyanosis during sleep, the child was taken to the hospital, where she had three episodes of torsades de pointes (TdP), requiring cardiopulmonary resuscitation and defibrillation. During this hospitalization, an ICD was implanted. Genotyping was performed using next-generation sequencing, with a panel of 15 genes associated with long QT syndrome. A missense variant was identified in the *SCN5A* gene, c.5287G>A, which determined the substitution of valine by methionine at position 1763 (p.Val1763Met), located in the S6 transmembrane domain of the sodium channel. This variant is classified as pathogenic according to the American College of Medical Genetics and Genomics (ACMG) criteria. Genetic screening of the parents, using the Sanger technique, did not reveal the index case variant, confirming a *de novo* variant.

At 14 months of age, the patient had multiple ICD shocks, especially during sleep, and mexiletine had not yet been purchased because of the high cost of imported drugs. Treatment with propafenone was not started, because of previous knowledge of patients with the same mutation in whom this drug unmasked the Brugada pattern. The care team imported the drug, and the dose reached 8 mg/kg/day, in combination with propranolol. The child showed substantial clinical improvement, without new arrhythmic events. At 3 years of age, the patient has experienced recurrence of arrhythmia after 1 year of lack of mexiletine and has appropriate neurological development.

Discussion

We present the case of a child with LQT3, with severe and rare arrhythmic manifestations since birth. 2:1 AVB bradycardia and recurrent episodes of neonatal TdP are seen more frequently in patients with LQT3, especially in *de novo* mutations in the *SCN5A* gene.[4]

Fetal bradycardia is a known phenomenon in patients with LQTS. Sinus bradycardia is more commonly observed in patients with LQTS type 1.[5] It is considered that 2:1 AVB with LQTS results from the relationship between the short duration of the sinoatrial cycle and the very long ventricular refractory period of patients with LQTS. The presence of 2:1 AVB is an indicator of a high risk of potentially fatal arrhythmias, as observed in our patient.[6]

Okuwaki et al.[7] described a child with a phenotype very similar to that observed in our care, including a carrier of the same *de novo* Val1763Met variant, who showed control of

Keywords

Infant, Newborn; Long QT syndrome; Tachycardia, Ventricular; Mexiletine/therapeutic; Torsades de Pointes; Cardiopulmonary Resuscitation

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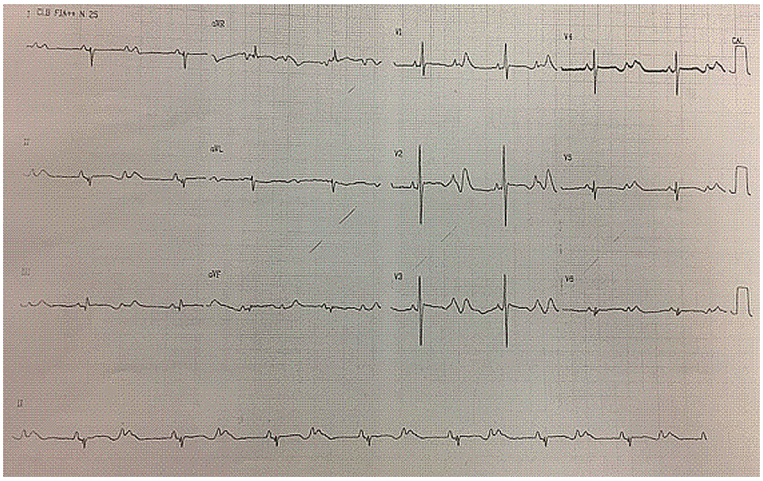

Figure 1 – *First electrocardiogram, performed one day after the patient's birth. Sinus rhythm with 2:1 atrioventricular block and QT prolongation.*

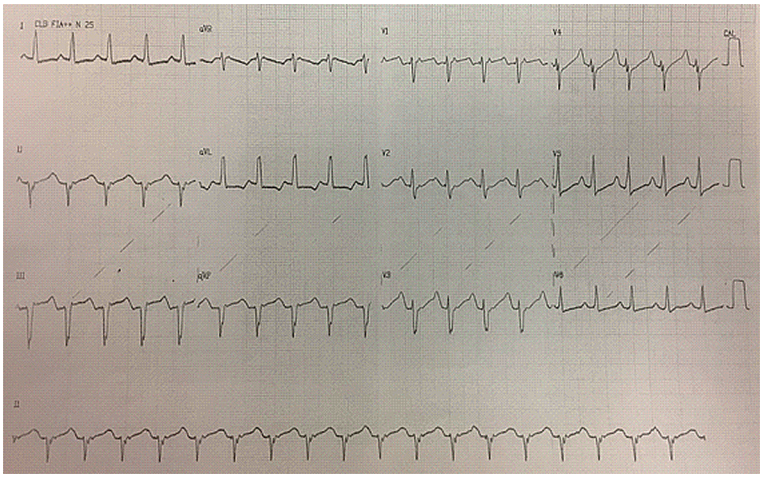

Figure 2 – *Electrocardiogram showing pacemaker-stimulated ventricular rhythm and QT prolongation.*

the QT interval and ventricular arrhythmias with intravenous mexiletine.[7] Yao et al.[8] described a case of LQTS with severe arrhythmogenic phenotype, which showed significant improvement after empirical propranolol and mexiletine, without molecular diagnosis.[8] Schulze-Bahr et al. described a similar case of LQTS with 2:1 AVB and ventricular arrhythmias.[6]

Sodium channel blockers, including flecainide, ranolazine and mexiletine, share binding sites in the inner pore region of the Nav1.5 sodium channel, and have documented efficacy in LQTS carriers.[3] Propafenone, the only sodium channel blocker available in Brazil, was avoided because of the risk of exacerbation of the Brugada pattern and ventricular fibrillation as proarrhythmias. There are several reports in the literature warning about the risk of proarrhythmia in patients with LQTS3 and mutations in the regions close to residue 1763.[9] Ranolazine, although approved for use as an antianginal agent in Brazil, has a complex metabolic profile in children. Tan et al.[10] described a case report in a child, demonstrating a very short half-life and several drug interactions in this age group, which could generate significant proarrhythmic side effects.[10]

Thus, the lack of alternative choices and the unavailability of mexiletine led to an important and potentially fatal delay in the treatment of the case presented. After the introduction of mexiletine, there was a significant reduction in the number of ICD therapies.

Conclusion

This case illustrates the complexity and responsibility assumed by the medical team in the treatment of this child with early manifestation of the disease, in Brazil. Difficult access to mexiletine, which is necessary for gene-guided therapy in high-risk patients with LQT3, has had a critical impact on their quality of life and risk of sudden death.

References

1. Refsgaard L, Holst AG, Sadjadieh G, Haunsø S, Nielsen JB, Olesen MS. High prevalence of genetic variants previously associated with LQT syndrome in new exome data. Eur J Hum Genet.2012;20(8):905-8. doi: 10.1038/ejhg.2012.23
2. Wilde AAM, Moss AJ, Kaufman ES, Shimizu W, Peterson DR, Benhorin J, et al. Clinical Aspects of Type 3 Long-QT Syndrome: An International Multicenter Study. Circulation.2016;134(12):872-82. doi: 10.1161/CIRCULATIONAHA.116.021823.
3. Mazzanti A, Maragna R, Faragli A, Monteforte N, Bloise R, Memmi M, et al. Gene-Specific Therapy With Mexiletine Reduces Arrhythmic Events in Patients With Long QT Syndrome Type 3. J Am Coll Cardiol. 2016;67(9):1053–8. doi: 10.1016/j.jacc.2015.12.033.
4. Chang C-C, Acharfi S, Wu M-H, Chiang F-T, Wang J-K, Sung T-C, et al. A novel SCN5A mutation manifests as a malignant form of long QT syndrome with perinatal onset of tachycardia/bradycardia. Cardiovasc Res. 2004;64(2):268–78. doi: 10.1016/j.cardiores.2004.07.007.
5. Cuneo BF, Etheridge SP, Horigome H, Sallee D, Moon-Grady A, Weng H-Y, et al. Arrhythmia phenotype during fetal life suggests long-QT syndrome genotype: risk stratification of perinatal long-QT syndrome. Circ Arrhythm Electrophysiol. 2013;6(5):946–51. doi: 10.1161/CIRCEP.113.000618.
6. Schulze-Bahr E, Fenge H, Etzrodt D, Haverkamp W, Mönnig G, Wedekind H, et al. Long QT syndrome and life threatening arrhythmia in a newborn: molecular diagnosis and treatment response. Heart. 2004;90(1):13–6. doi: 10.1136/heart.90.1.13.
7. Okuwaki H, Kato Y, Lin L, Nozaki Y, Takahashi□Igari M, Horigome H. Mexiletine infusion challenge test for neonatal long QT syndrome with 2:1 atrioventricular block. J Arrhythmia. 2019;35(4):685–8. doi: 10.1002/joa3.12209.
8. Yao C-T, Wang J-N, Tsai Y-C, Lin C-S, Wu J-M. Congenital long QT syndrome with functionally impaired atrioventricular conduction: successful treatment by mexiletine and propranolol. J Formos Med Assoc Taiwan Yi Zhi. 2002;101(4):291–3. PMID: 12101867
9. Nakaya H. SCN5A mutations associated with overlap phenotype of long QT syndrome type 3 and Brugada syndrome. Circ J Off J Jpn Circ Soc. 2014;78(5):1061–2. doi: 10.1253/circj.cj-14-0319
10. Tan RB, Chakravarti S, Busovsky-McNeal M, Walsh A, Cecchin F. Complexity of ranolazine and phenytoin use in an infant with long QT syndrome type 3. Heart Case Rep. 2017;3(1):104–8. doi: 10.1016/j.hrcr.2016.10.001.

Torrent Guasp's Helicoid Pattern Myocardial Calcification

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Clinical case

72-year-old male patient with a past medical history of arterial hypertension, non-insulin-dependent diabetes, active tobacco consumption and chronic stable angina (coronary angiography showed severe stenosis in small size obtuse marginal branch). He also had a history of alcohol consumption, pancreatic calcification and renal lithiasis, without a history of Cancer, Sepsis or Tuberculosis to justify these diffuse calcifications.

He presented to the outpatient cardiology clinic complaining of angina and dyspnea New York Heart Association (NYHA) class II. His electrocardiogram (ECG) showed sinus rhythm and suggested left ventricular hypertrophy (LVH) without signs of ischemia.

The echocardiogram images were suboptimal due to poor acoustic window but showed mild left ventricular systolic dysfunction with severe diastolic dysfunction (non-reversible restrictive mitral filling was seen), LVH and severe pulmonary hypertension (systolic pulmonary artery pressure 78 mmHg) with normal right ventricle diameters and systolic function. Furthermore, multiple hyperechogenic images with acoustic shadows were seen within the myocardium, predominantly infiltrating the interventricular septum.

He was admitted to the Hospital due to signs of acute heart failure, with orthopnea, bilateral pulmonary rales, and bilateral peripheral edema, without the need for supplementary oxygen. The serum laboratory demonstrated normal creatinine clearance (>60 mg/ml), high N terminal pro-brain natriuretic peptide (NT-pro-BNP) and troponin serum levels (6740 pg/ml and 32 pg/ml, respectively). Serum phospho-calcic parameters were within the normal range. Notably, a multidisciplinary team evaluated the patient, including a nephrologist, endocrinologist, and clinical cardiologists.

Due to the abnormal and suboptimal findings in the echocardiogram, a computed tomography angiography (CTA) was performed, which was positive for extensive intramyocardial calcium deposits (myocardial Agatston Score of 112929) with a helicoid distribution that resembled Torrent Guasp's myocardial fibers pattern (Figure 1). The Coronary Artery Calcium Scoring was not as high as the myocardial Agatston score (Agatston score of 670).

A Cardiac Magnetic Resonance (CMR) with contrast was performed to identify the tissue characteristics further. It showed normal left ventricular systolic function (left ventricular ejection fraction of 54%), with an enlarged myocardial mass and basal and septal hypokinesis (Figure 2). The right ventricle had a normal systolic function. T1 and T2 weighted images showed focal intramyocardial nulling areas suggesting myocardial calcium deposits. Late gadolinium enhancement (LGE) was positive for intramyocardial enhancement in the basal, medial, and antero-apical segments, compatible with non-ischemic fibrosis. The pericardial compromise was absent (Figure 3). In addition, myocardial calcification areas in CTA correlated to LGE around calcium deposits on CMR.

The patient was treated with intravenous loop diuretics and was ultimately discharged with symptom improvement. 99m-technetium pyrophosphate scintigraphy was performed during the follow-up, negative for cardiac amyloidosis. Also, to obtain material for histologic sampling, an endomyocardial biopsy was performed, showing normal histology findings.

Discussion

Myocardial calcifications deposits may be present in multiple pathophysiological scenarios, such as dystrophic calcifications due to underlying cardiac disease and idiopathic or metastatic systemic diseases.[1] Moreover, myocardial calcifications generally represent the sequelae of local tissue damage and cellular necrosis and are associated with an increased risk of cardiovascular events (ventricular arrhythmias and systolic/diastolic dysfunction leading to heart failure).[1,2] The patient presented with a history of hypertension, diabetes, and coronary artery disease. Frequently, hypertension is not enough to fully explain myocardial calcification, and it is commonly associated with chronic kidney disease (CKD), where calcification is associated with a phospho-calcic disorder.[3] Furthermore, diabetes produces a systemic inflammatory disorder which may contribute to an increased coronary calcification.[4] In addition, coronary artery disease is a very common cause of dystrophic myocardial calcification.[1] Hypertensive or infiltrative cardiomyopathy cannot be fully excluded despite the CT and CMR findings.

These calcification patterns may be diagnosed with multiple imaging modalities, being the CTA the gold standard modality for identifying and characterizing myocardial calcifications. Indeed, unlike the well-defined

Keywords

Vascular Calcification. Cardiac Imaging Techniques. Heart Failure.

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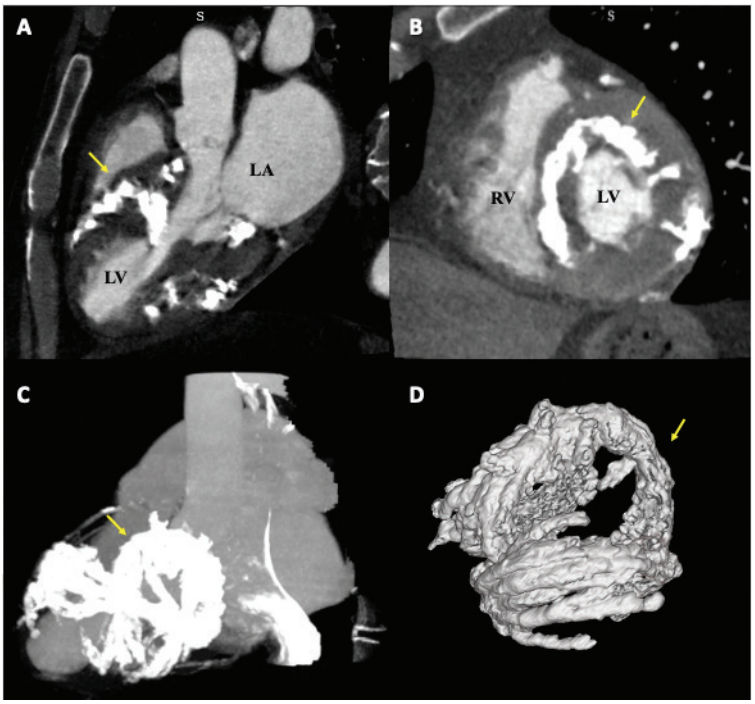

Figure 1 – *Computed tomography angiography (CTA) shows extensive intramyocardial calcification (A and B). CTA volumetric reconstruction shows extensive calcification with Torrent Guasp pattern (C and D). The yellow markers highlight calcium distribution. LA: left atrium; LV: left ventricle; RV: right ventricle.*

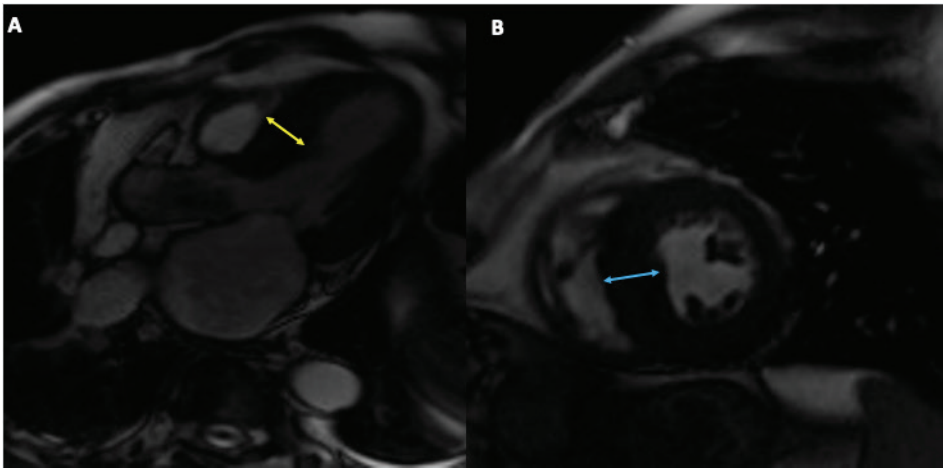

Figure 2 – *Cardiac Magnetic Resonance Imaging (CMR). Cine sequence show enlarged mass. The yellow marker shows the largest width of the LV septal hypertrophy in five chambers (A). The blue marker shows the largest width of LV in the short axis (B). LV: left ventricle.*

calcification pattern in intrinsic myocardial pathologies, calcium infiltration due to systemic diseases generally has a diffuse pattern. Moreover, CMR might provide further tissue characterization by suggesting myocardial calcification in low signal intramyocardial areas and scarred myocardium surrounding calcifications by LGE images.[5,6]

The Torrent Guasp Theory was originally described macroscopically in post mortem patients, in which myocardial fibers were structured as an extended band from the root of the pulmonary artery to the root of the aorta circumscribing the two ventricles in a double helix pattern fiber. This pattern is responsible for the normal and effective function of the heart,

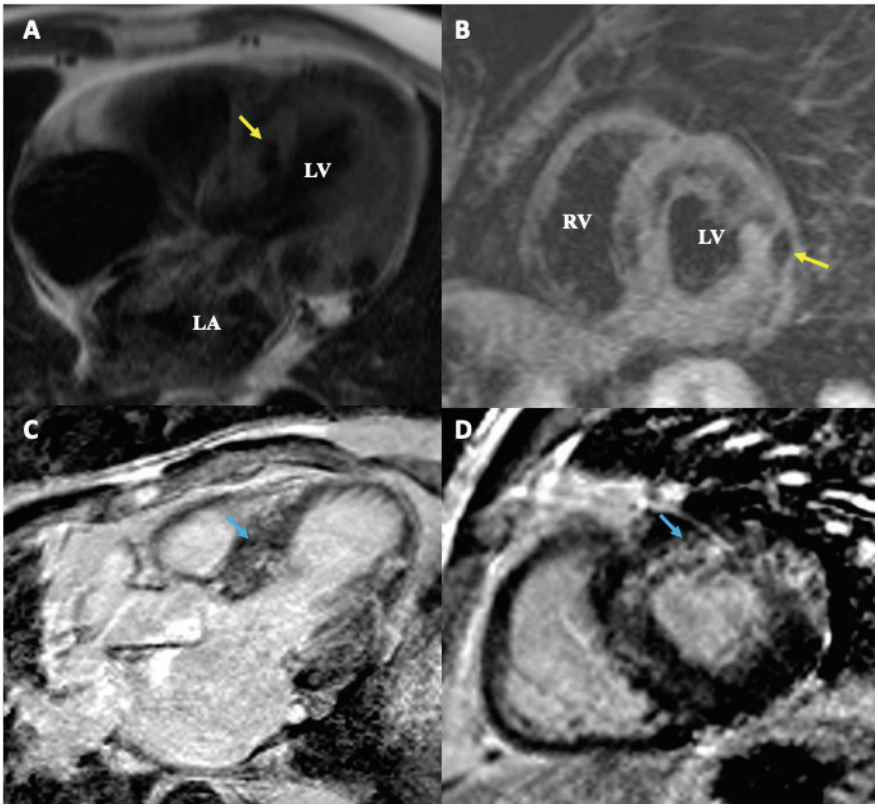

Figure 3 – *Cardiac Magnetic Resonance Imaging (CMR). T1 weighted sequence show signs of left ventricle hypertrophy with intramyocardial low signals compatible with calcium (A), T2 weighted sequence without edema and intramyocardial low signal (B). Diffuse intramyocardial Late gadolinium enhancement (LGE), without a characteristic pattern (C and D). The yellow markers show myocardial calcium distribution. The blue markers show myocardial LGE. LV: left ventricle; RV: right ventricle; LA: left atrium.*

explaining the variation of intraventricular volume within each beat.[7,8] Research has shown that this double helix distribution is rarely found in non-invasive imaging modalities, making this case a living representation of the Torrent Guasp pattern.

Conclusion

A case of heart failure with preserved ejection fraction with a diffuse and atypical myocardial calcification following the Torrent Guasp distribution is presented. Multiple causes (i.e., ischemic, hypertensive, or infiltrative) may contribute to the origin of the calcification, which is ultimately associated with a worse clinical outcome. Diverse imaging modalities are fundamental to achieving a specific diagnosis and eventually a specific treatment.

Author Contributions

Conception and design of the research and Acquisition of data: Abraham-Foscolo MM; Writing of the manuscript and Critical revision of the manuscript for intellectual contente: Abraham-Foscolo MM, Blanco R, Chiabrando JG, Llamedo MC, Arenaza DP, Falconi ML.

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Study Association

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Ethics approval and consent to participate

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

References

1. Salisbury AC, Shapiro BP, Martinez MW. Extensive Myocardial and Mitral Annular Calcification Leading to Mitral Regurgitation and Restrictive Cardiomyopathy: An Unusual Case of Caseous Calcification of the Mitral Annulus. J Cardiovasc Comput Tomogr. 2009;3(5):351-3. doi: 10.1016/j.jcct.2009.05.016.
2. Okada M, Kyakuno M, Imamura J, Nakamura T, Takahara S. An Autopsy Case of Sudden Death in Renal Transplant Recipient. Clin Transplant. 2002;16 Suppl 8:58-61. doi: 10.1034/j.1399-0012.16.s8.3.x.
3. Rahman M, Kim SJ, Kim JS, Kim SZ, Lee YU, Kang HS. Myocardial Calcification and Hypertension Following Chronic Renal Failure and Ameliorative Effects of Furosemide and Captopril. Cardiology. 2010;116(3):194-205. doi: 10.1159/000315146.
4. Yahagi K, Kolodgie FD, Lutter C, Mori H, Romero ME, Finn AV, et al. Pathology of Human Coronary and Carotid Artery Atherosclerosis and Vascular Calcification in Diabetes Mellitus. Arterioscler Thromb Vasc Biol. 2017;37(2):191-204. doi: 10.1161/ATVBAHA.116.306256.
5. Aras D, Topaloglu S, Demirkan B, Deveci B, Ozeke O, Korkmaz S. Porcelain Heart: A Case of Massive Myocardial Calcification. Int J Cardiovasc Imaging. 2006;22(1):123-6. doi: 10.1007/s10554-005-9006-2.
6. Ionescu CN, Marcu CB. Unexpected Massive Myocardial Calcification. Neth Heart J. 2009;17(12):491. doi: 10.1007/BF03086310.
7. Torrent-Guasp F. Structure and function of the heart. Rev Esp Cardiol. 1998;51(2):91-102. doi: 10.1016/s0300-8932(98)74718-9.
8. Boineau JP. Left Ventricular Muscle Band (VMB): Thoughts on its Physiologic and Clinical Implications. Eur J Cardiothorac Surg. 2006;29 Suppl 1:56-60. doi: 10.1016/j.ejcts.2006.02.045.

An Unusual Manifestation of Rejection

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Introduction

Orthotopic heart transplantation is the current treatment of choice for selected patients with end-stage heart failure.[1] With the improvement of surgical techniques and the efficiency of new immunosuppressive treatments, short-term survival has markedly improved throughout the years.[2] However, these patients still suffer from important comorbidities caused by chronic transplant complications such as rejection, coronary allograft vasculopathy (CAV) and malignancy. Rhythm disorders are common in heart transplant patients and in some circumstances, they can be the first clinical manifestation of rejection.[3] Coronary vasospasm has been recently associated with acute rejection and CAV,[4] but the mechanisms underlying this phenomenon are still speculative.

We present a clinical case of acute heart transplant rejection, manifested by coronary vasospasm and advanced rhythm disorder.

Case presentation

A 55-year-old male patient with end-stage ischemic heart failure underwent orthotopic heart transplantation in March 2019. The first-year follow-up endomyocardial biopsy (EMB) showed mild 1R cellular rejection (ISHLT) in 3 samples and moderate rejection (2R) in two samples, treated with increased doses of oral corticosteroids. At his last ambulatory appointment, the patient showed normal left ventricular function, with no humoral or cellular rejection identified in the last EMB (performed 4 months before admission). His blood samples showed infra-therapeutic levels of cyclosporine (94.2 ng/mL), leading to an increase in the ambulatory dose. He was also medicated with mycophenolate mofetil (MMF) (2g/day), prednisolone (5mg), atorvastatin, aspirin, cotrimoxazol and oral anti-diabetic drugs.

One year and five months after the transplantation, he was admitted to our emergency department with sudden altered state of consciousness. He showed a Glasgow Coma Score of 11 and was hemodynamically stable. On physical examination, the EKG, brain computed tomography and TTE were unremarkable. Blood samples revealed mild anemia (10 g/dL) and infra-therapeutic levels of cyclosporine (92 ng/mL), but no elevation of inflammatory markers; the toxicology was negative for alcohol or drugs of abuse. The patient did not collaborate during the electroencephalogram and due to his marked psychomotor agitation and confusion he was sedated and intubated. A lumbar puncture was performed, with no signs of infection in the cerebrospinal fluid. Cyclosporine was replaced by tacrolimus, considering the possibility of posterior reversible encephalopathy syndrome.

The patient was admitted to the intensive care unit, and suffered sudden cardiac arrest on the second day of hospitalization, with return of spontaneous circulation (ROSC) after two advanced life support cycles. The electrocardiogram after the ROSC (Figure 1B) documented ST-segment elevation in V2-V5. A second EKG 10 minutes after the event was normal (Figure 1C). After analysis of telemetry monitoring, complete heart block was identified before cardiac arrest (Figure 1A). On the same day, a second episode of complete heart block was documented with hemodynamic deterioration and a temporary pacemaker was implanted.

Coronary angiography was performed on the following day, showing markedly diffuse vasospasm in the left anterior descending and circumflex arteries, which resolved with intracoronary nitrate administration (Figure 2A and B). Moderate stenosis was identified in the proximal left anterior descending and first diagonal arteries. An endomyocardial biopsy was also performed.

On the subsequent days, a new episode of cardiac arrest was preceded by ventricular tachycardia, again with documentation of transient ST-segment elevation changes after ROSC (Figure 3A). Sporadic temporary pacemaker stimulation was also documented (Figure 3B). Given the suspicion of coronary vasospasm episodes, calcium channel blockers (CCB) and nitrate administration was initiated.

The endomyocardial biopsy results showed moderate 2R cellular rejection (ISHLT) and C4d positive humoral rejection with subsequent identification of donor specific anti-HLA class II antibodies (HLA-DR53). The patient was therefore treated with intravenous methylprednisolone pulses and remained clinically stable. With immunosuppressive treatment intensification, CCB and nitrate administration, the patient was hemodynamically stable with no new rhythm or EKG sudden changes. The diagnosis of acute allograft rejection causing coronary vasospasm and advanced rhythm disorders was presumed.

Keywords

Heart Failure, Heart Transplantation; Research; Graft Rejection; Diagnostic Imaging; Drug Therapy; Heart Block; Arrhythmias Cardiac;Coronary Vasospasm.

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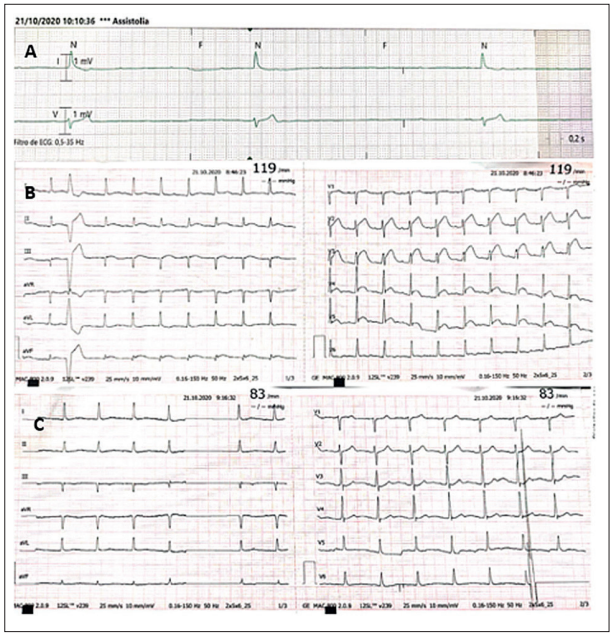

Figure 1 – *A) Third-degree atrioventricular block before cardiac arrest; B) EKG after ROSC showing supra ST-elevation in V2-V5, isolated extra systole; C) Normal EKG 10 minutes after the event.*

Two weeks after treatment, the endomyocardial biopsy was repeated, showing mild 1R cellular rejection (ISHLT) and no signs of humoral rejection. Due to the clinical and histological response, no additional pharmacological treatment was initiated. A cardioverter defibrillator was implanted, without complications.

During hospitalization, the patient suffered multiple nosocomial infections, requiring mechanical ventilation in two different occasions due to severe pneumonia. Because of the severe myopathy caused by prolonged hospitalization, he was discharged to a rehabilitation center and remains stable.

Discussion

Since the first human heart transplantation performed by Dr. Christian Barnard in December 1967,[5] several improvements have been observed throughout the years in relation to procedural and particularly postoperative management. The introduction of immunosuppression therapy in 1980 was a landmark, allowing a significant improvement in early survival rates.[6] However, rejection remains one of the major causes of death after transplantation.[7] Because the symptoms of rejection are often nonspecific, high clinical suspicious is paramount for prompt detection and treatment. In this context, serial EMBs remain the cornerstone for rejection diagnosis.

Rhythm disorders are common in heart transplant patients. However, with the worldwide implementation of the bicaval approach, which preserves the right atrium and the sinus node, the number of postoperative bradyarrhythmia events requiring permanent pacemaker implantation were significantly reduced.[8] Bradycardia presenting late after heart transplantation has been associated with episodes of acute rejection[9] and CAV, with the latter possibly leading to sinus node ischemia.[10] This highlights the importance of recalling that in patients presenting with late-onset bradycardia or heart block after transplantation, the possibility of acute rejection and CAV must be investigated through echocardiography, EMB and coronary angiography.[11] In these circumstances, pacemaker implantation is insufficient for an effective treatment until the underlying bradyarrhythmia cause can be treated.

Coronary artery spasm (CAS) is an underdiagnosed disease, particularly in heart transplant patients. This condition was considered to be rare; however, recent evidence shows a significant prevalence of CAS in routine coronary angiography in these patients.[12] Boffa et al.[13] documented coronary vasospasm in 12 patients (5% of the study population) after heart transplantation over a 5-year follow-up. During the follow-up, 80% of the patients developed organic stenosis and 50% of those with multiple vasospasms died. These data highlights the hypothesis that CAS after heart transplantation could be a marker of poor prognosis and early manifestation of CAV.

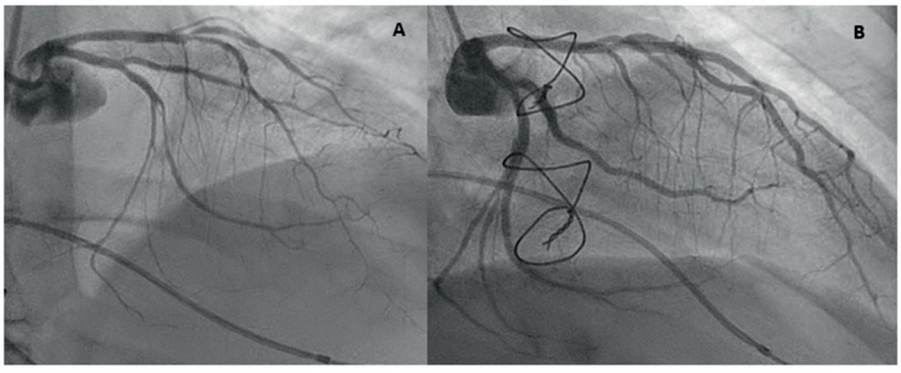

Figure 2 – *A) Coronary angiography showing markedly diffuse vasospasm of left anterior descending and circumflex arteries. B) Complete vasospasm resolution after nitrate intake.*

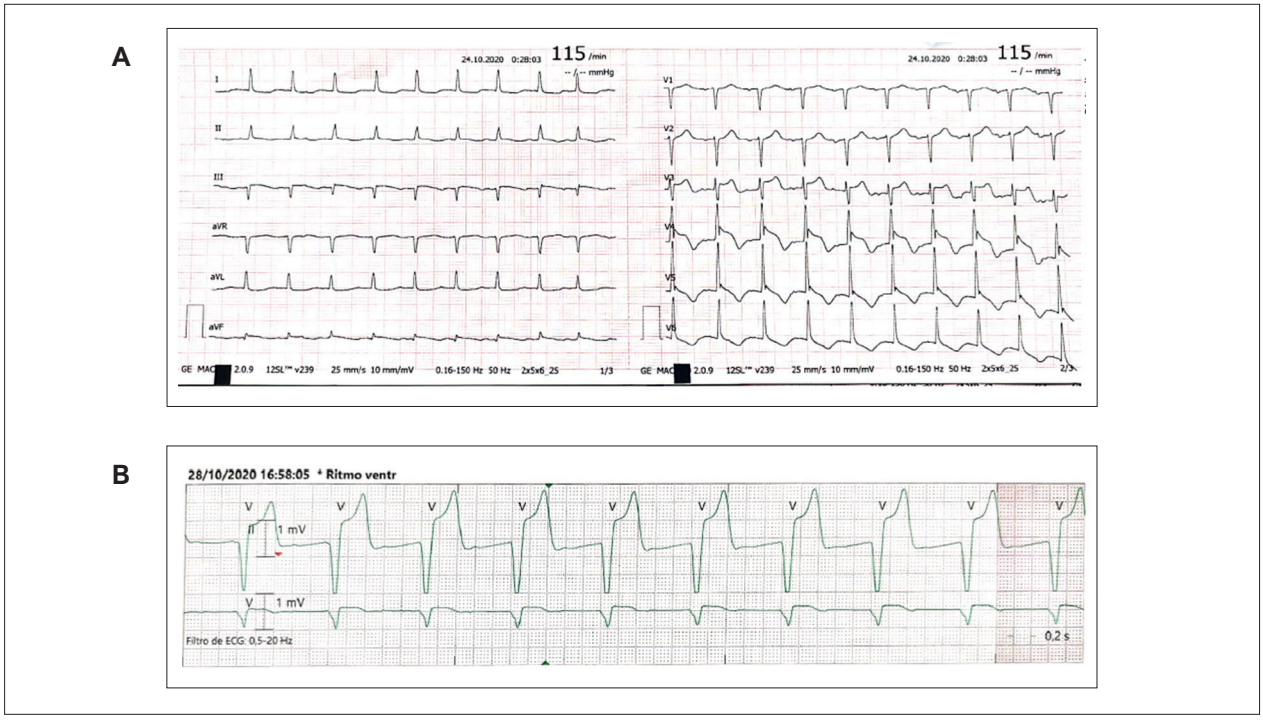

Figure 3 – *A) Transient ST-T changes; B) Sporadic temporary pacemaker stimulation.*

The etiology and pathophysiology of CAS in heart transplant patients remains speculative, but several mechanisms have been reported: abnormal autonomic nervous system, endothelial dysfunction, coronary smooth muscle hyperactivity, and perivascular component inflammation.[14] One of the presumed causes of CAS is cocaine consumption, due to the direct adrenergic stimulation of coronary arteries.[15] Particularly in the context of CAS episodes that present early after transplantation, a thorough medical history of the heart donor and recipient could help to exclude cocaine-induced CAS.

In our clinical case, evidence of CAS was seen in the coronary angiography, transient ST-segment elevation and paroxysmal heart block. We hypothesize that mechanisms underlying antibody-mediated rejection can cause CAS: donor-specific antibodies may initiate the complement cascade in the allograft endothelium and cause tissue injury via inflammatory pathways. Complement fractions are deposited in the allograft microvasculature, resulting in an inflammatory process characterized by endothelial cell activation, macrophage infiltration, cytokine upregulation, increased vascular permeability and microvascular thrombosis.[2] This state of endothelial dysfunction, inflammation and hyperreactivity could precipitate CAS episodes in the context of acute rejection.

Clinical cases of CAS presenting with malignant arrhythmias in heart transplantation patients have been reported by M. Pistono et al.[16] and recently by M. Pagnoni et al.[17]; however, in these two cases no cellular or humoral acute rejection were identified. Nevertheless, the possible association of CAS with acute rejection has been previously considered in other case reports,[4,18] which are consistent with our clinical case.

As previously described, CAS could be an early manifestation of CAV, which was not completely ruled out in our patient, due the low sensitivity of coronary angiography for detecting early-stage CAV. Recent advances in invasive coronary imaging, such as intravascular ultrasound (IVUS) and optical coherence tomography (OCT) have shown promising results in detecting subangiographic CAV.[19] In this context, intracoronary imaging could have a significant role in the diagnosis of CAS in heart patients by excluding early signs of CAV and, consequently, improving risk stratification and patient surveillance.

In our clinical report, cellular and humoral rejection manifested as CAS and malignant arrythmias. These unusual manifestations of acute rejection emphasizes that high clinical suspicion needs to be present for its prompt detection and treatment. Although the etiology of CAS is still speculative and probably multifactorial, our clinical case highlights the hypothesis that endothelium hyperreactivity and inflammation caused by acute rejection precipitated the coronary spasm. Our clinical case also shows that transient ischemia caused by CAS can precipitate deadly rhythm disorders. Further studies are needed to fully understand the mechanisms underlying CAS, their relationship with allograft rejection and prognostic significance.

Author Contributions

Conception and design of the research: Amorim S; Acquisition of data: Resende CXC, Pestana G; Analysis and interpretation of the data: Amorim S, Torres JP; Writing of the manuscript: Resende CXC, Diogo PG; Critical revision of the manuscript for intellectual contente: Resende CXC, Diogo PG, Amorim S, Pestana G, Torres JP, Macedo F.

Potential Conflict of Interest

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References

1. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. ESC Scientific Document Group, 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure, Eur Heart J.2021;42(36):3599-726. doi.org/10.1093/eurheartj/ehab368
2. Kim NC, Youn JC, Kobashigawa JA. The past, present and future of heart transplantation. Korean Circ J.2018;48(7):565-90. https://doi.org/10.4070/kcj.2018.0189
3. Hamon D, Taleski J, Vaseghi M, Shivkumar K, Boyle NG. Arrhythmias in the heart transplant patient. Arrhythm Electrophysiol Rev.2014;3(3):149-55. doi:10.15420/aer.2014.3.3.149.
4. Bisognano JD, Lindenfeld J, Hammond E, Zisman LS. Coronary artery vasospasm causing acute myocardial infarction in a heart transplant recipient. J Heart Lung Transplant. 2005;24(3):355-8. doi:10.1016/j.healun.2003.11.405
5. Barnard CN. The operation. A human cardiac transplant: an interim report of a successful operation performed at Groote Schuur Hospital, Cape Town. S Afr Med J. 1967 Dec 30;41(48):1271-4.
6. Reitz BA, Bieber CP, Raney AA, Pennock JL,Jamieson SW, Oyer PE, et al. Orthotopic heart and combined heart and lung transplantation with cyclosporin-A immune suppression. Transplant Proc. 1981 Mar;13(1 Pt 1):393-6. PMID: 6791329
7. Lund LH, Khush KK, Cherikh WS, Goldfarb S, Kucheryavaya AY, Levvey BJ, et al., et al. The registry of the International Society for Heart and Lung Transplantation: thirty-fourth Adult Heart Transplantation Report - 2017; focus theme: allograft ischemic time. J Heart Lung Transplant.2017;36:1037-46. https://doi.org/10.1016/j.healun.2017.07.016
8. Rivinius R, Helmschrott M, Ruhparwar A, Erbel C , Gleissner CA, Darche FF, et al. The influence of surgical technique on early posttransplant atrial fibrillation - comparison of biatrial, bicaval, and total orthotopic heart transplantation. Ther Clin Risk Manag. 2017;13:287-297. doi:10.2147/TCRM.S126869.
9. Gullestad L, Ross H, Myers J, Hoang k, Hunt S, Stinson EB, et al. Importance of decreased heart rate in predicting transplant coronary artery disease. Clin Transplant. 1997 Dec;11(6):628-32. PMID: 9408698
10. Cooper MM, Smith CR, Rose EA, Schneller SJ, Spotnitz HM. Permanent pacing following cardiac transplantation. J Thorac Cardiovasc Surg. 1992 Sep;104(3):812-6.
11. Mallidi HR, Bates M. Pacemaker use following heart transplantation. Ochsner J. 2017 Spring;17(1):20-4. PMID: 28331443;
12. Akgün NA, Çiftci O, Yılmaz KC,Karaçaglar E, Aydinaep A, Sezgin A, et al. Prevalence and angiographic characteristics of coronary vasospasm detected at surveillance coronary angiograms among patients with heart transplants. Exp Clin Transplant. 2018 Mar;16(Suppl 1):85-8. doi: 10.6002/ect.TOND-TDTD2017.O34.
13. Boffa GM, Livi U, Grassi G, Casarotto D, Isabella G, Cardaioli P, et al. Angiographic presentation of coronary artery spasm in heart transplant recipients. Int J Cardiol.2000;73(1):67-74. doi:10.1016/s0167-5273(99)00225-9.
14. Kobashigawa J. (ed) Clinical guide to heart transplantation. Los Angeles (CA): Springer; 2017. ISBN 978-3319437712
15. Talarico GP, Crosta ML, Giannico MB, Summaria F, Calò L, Patrizi R. Cocaine and coronary artery diseases: a systematic review of the literature. J Cardiovasc Med (Hagerstown). 2017;18(5):291-4. doi:10.2459/JCM.0000000000000511
16. Pistono M, Brentana L, Gnemmi M, Imparato A, Temporelli PL, Zingarelli E, et al. Early right coronary vasospasm presenting with malignant arrhythmias in a heart transplantation recipient without allograft vasculopathy. Int J Cardiol.2009;131(3):e120-e123. https://doi.org/10.1016/j.ijcard.2007.07.078.
17. Pagnoni M, Regamey J, Adjedj J, Rogati G, Muller O, Tozzi P. Case report - coronary vasospasm in transplanted heart: a puzzling phenomenon. BMC Cardiovasc Disord. 2019;19(1):305. doi:10.1186/s12872-019-01280-8
18. Hruban RH, Kasper EK, Gaudin PB, Baughman KL, Baumgarter WA, Reitz BA, et al. Severe lymphocytic endothelialitis associated with coronary artery spasm in a heart transplant recipient. J Heart Lung Transplant. 1992;11(1 Pt 1):42-7. PMID: 1540611
19. Guddeti RR, Matsuo Y, Matsuzawa Y, Aoki T, Lerman LO, Kushwaha SS, et al. Clinical implications of intracoronary imaging in cardiac allograft vasculopathy. Circ Cardiovasc Imaging. 2015;8(1):e002636. doi:10.1161/CIRCIMAGING.114.002636

Intracavitary Right Coronary Artery: An Incidental Finding with Potential Implications for Invasive Cardiac Procedures

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A 66-year-old man with a history of palpitations suggestive of paroxysmal supraventricular tachycardia was referred for CT angiography (CTA) for exertional dyspnea etiology investigation. ECG-gated cardiac CT was performed using the 64-slices dual-source Somatom Go Scanner.

CTA showed the normal origin of the right and left main coronary arteries, and there was no evidence of obstructive coronary artery disease. The proximal right coronary artery (RCA) had a normal epicardial course, but mid-RCA was noted to penetrate the right atrial wall for a 30 mm course within the right atrium, exiting to its usual course in the posterior atrioventricular groove, as demonstrated via the multiplanar reconstruction CT images at maximum intensity projection (Figure 1) as well as 3-dimensional reconstructions (Figure 2).

Coronary artery anomalies (CAAs) are defined as a group of congenital disorders characterized by an abnormal origin or course of one of the main coronary arteries, with an incidence ranging from 1% to 5.6%.[1] Known variants of a coronary artery trajectory can be broadly classified in intramural, intracavitary and aerial courses.

Myocardial bridging is a presence of an intramural course and is most commonly recognized in the middle segment of the left anterior descending (LAD). The most recent studies based on CTA data report a prevalence as high as 30%. On the other hand, the Intracavitary coronary artery is a rare isolated anatomic variation with two described variants – an intracavitary course within the distal left anterior descending artery into the right ventricle and an intracavitary course in mid to distal RCA into the right atrium. The latter is more common, with an estimated prevalence of 0.36%,[2] and is increasingly recognized given the widespread use of advanced cardiac imaging. CTA is well recognized as the gold standard technique for the evaluation of congenital coronary anomalies as it provides the benefits of non-invasive high-quality imaging, low dose radiation exposure and offers a detailed anatomic characterization of origin and course of coronary arteries and its relationship with the surrounding structures.[2]

While usually clinically benign and probably unrelated to our patient's symptoms, this variant may result in a higher risk of RCA inadvertent damage during catheter manipulation in the right atrium.[2-4]

In conclusion, identifying and describing this anomaly provides crucial information to the interventional cardiologist or surgeon and should be promptly highlighted in order to prevent complications.[5]

Author Contributions

Conception and design of the research: Borges SCS, Carvalho CIR, Gonçalves METM, Baptista AIS; Acquisition of data and Analysis and interpretation of the data: Borges SCS, Gonçalves METM, Baptista AIS; Writing of the manuscript: Borges SCS, Carvalho CIR; Critical revision of the manuscript for intellectual contente: Gonçalves METM, Baptista AIS, Moreira JI.

Potential Conflict of Interest

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

Sources of Funding

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Study Association

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

Keywords

Cardiovascular Abnormalities; Coronary Vessel Anomalies; Coronary Angiography/methods; Tomography X-Ray Computed/methods; Anomalous Intracaitary /diagnosis.

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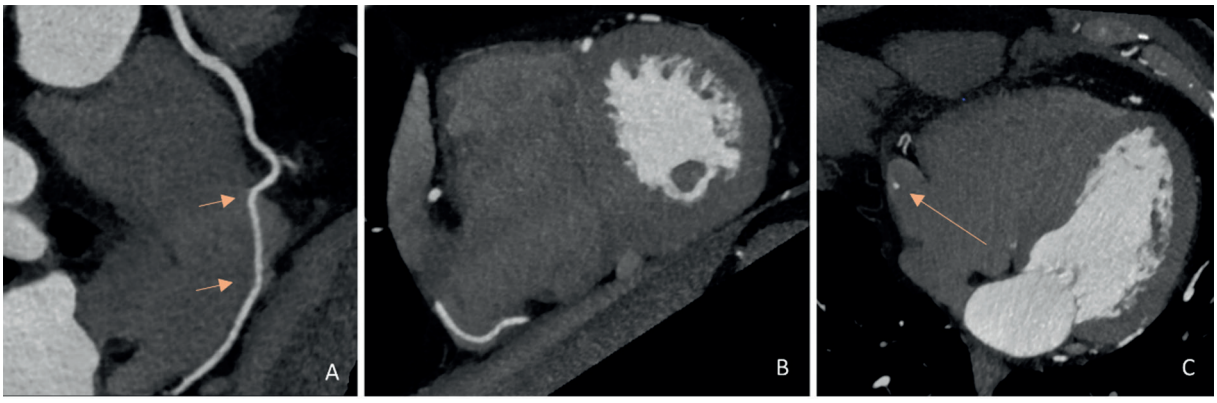

Figure 1 – *Panel A) Curved multiplanar image showing the intra-atrial course of right coronary artery (RCA) (arrow); Panel B) maximum intensity projection image showing the intra-atrial location of the RCA; Panel C) Axial CT image of the intra-atrial course of RCA (arrow).*

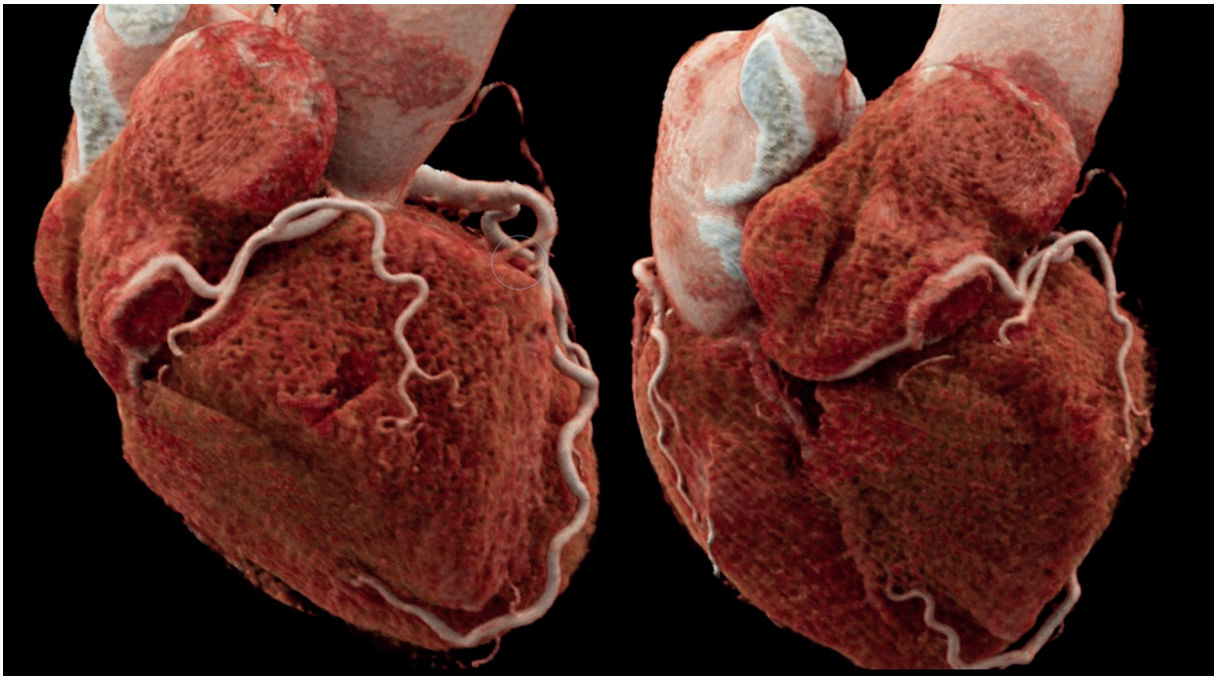

Figure 2 – *CT coronary angiography 3D image shows the proximal RCA's normal epicardial course and its entry through the right atrial wall.*

References

1. Konen E, Goitein O, Sternik L, Eshet Y, Shemesh J, Di Segni E. The prevalence and anatomical patterns of intramuscular coronary arteries. J Am Coll Cardiol 2007;49:587–93. doi: 10.1016/j.jacc.2006.09.039
2. Buckley CM, Rosamond T, Hegde SR, Wetzel L. The intracavitary coronary artery: a rare anomaly with implications for invasive cardiac procedures – demonstration by coronary computed tomography angiography. J Am Coll Cardiol. 2017; 69(Supplement 11):1437.
3. Sherif Gouda, Jane Caldwell, Thanjavur Bragadeesh, Anomalous intra-atrial right coronary artery and atrial flutter ablation, EP Europace, 2021;23(12):2019. Doi: 10.1093/europace/euab151
4. Krishnan B, Cross C, Dykoski R, Benditt DG, Mbai M, McFalls E, et al. Intra-Atrial Right Coronary Artery and its Ablation Implications. JACC Clin Electrophysiol. 2017 Sep;3(9):1037-45. DOI: 10.1016/j.jacep.2017.02.025.
5. Zalamea RM, Entrikin DW, Wannenburg T, Carr JJ. Anomalous intracavitary right coronary artery shown by cardiac CT: a potential hazard to be aware of before various interventions. J Cardiovasc Comput Tomogr. 2009 Jan-Feb;3(1):57-61. doi: 10.1016/j.jcct.2008.11.001

Statin Use Improves Cardiometabolic Protection Promoted By Physical Training in an Aquatic Environment: A Randomized Clinical Trial

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Dear editor,

I read with interest the article published by Costa et al.[1] The use of statins in cardiometabolic protection promoted by physical training of moderate-intensity in an aquatic environment has been little studied, mainly from the clinical point of view. However, as described by Costa et al.,[1] strength training in an aquatic environment combined with statins has been an effective increase in promoting metabolic adaptations and a reduction in lipid levels. The prognostic predictors associated with the risk of death from cardiovascular disease were measured in the three groups: aquatic training (AT), strength training (ST) and control group (CG). However, a healthy control group was not added to the study, and therefore the statistical power of the test could have been greater. According to the analysis of the body mass index (BMI) of the group (CG), the participants were obese, which was not explained in the inclusion criteria. In addition, there was no homogeneity in the number of individuals on medication (MED) and not on medication (NMED). If related to other variables, the aerobic training intensity indicator may add new questions and lines of thought and research. The effect of statins has been investigated on skeletal muscle function, performance and functional capacity of athletes in different sports and intensity modalities.[2,3] A randomized, double-blind study showed the protective effect of a statin in reducing the levels of pro-inflammatory cytokines with an increase in the mean concentrations of creatine phosphokinase (PCK); this enzyme plays an important regulatory role in intracellular metabolism, in contractile tissues, in skeletal striated muscles, heart tissue and brain.[4] Therefore, in the study by Costa et al.,[1] the conclusions respond to the proposed objective, and its theoretical foundations are in line with the question and hypothesis of the study.

Keywords

Statins; Exercise; Physical Activity; Aquatic Environment; Hypertension; Diabetes Mellitus; Metabolica Syndome/complications.

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References

1. Costa RR, Vieira AF, Coconcelli L, Fagundes AO, Buttelli ACK, Pereira LF, Stein R, et al. Uso de Estatinas Melhora a Proteção Cardiometabólica Promovida pelo Treinamento Físico em Ambiente Aquático: Um Ensaio Clínico Randomizado. Arq. Bras. Cardiol. 2021;117(2):270-8. doi: 10.36660/abc.20200197
2. Mougios V. Reference intervals for serum creatine kinase in athletes. Br J Sports Med. 2007;41(10):674-8. doi:10.1136/bjsm.2006.034041
3. Ballard KD, Parker BA, Capizzi JA, Grimaldi A, Clarkson FM, Cole SM, et al. Increases in creatine kinase with atorvastatin treatment are not associated with decreases in muscular performance. Atherosclerosis. 2013;230(1):121-4. doi: 10.1016/j.atherosclerosis.2013.07.001doi :10.1016/j.atherosclerosis.2013.07.001
4. Albert MA, Danielson E, Rifai N, Ridker PM, for the PRINCE Investigators. Effect of Statin Therapy on C-Reactive Protein Levels: The Pravastatin Inflammation/CRP Evaluation (PRINCE): A Randomized Trial and Cohort Study. JAMA. 2001;286(1):64–70. doi:10.1001/jama.286.1.64

Letter to the Editor

Reply

On 09/29/21 we received notification of a Letter to the Editor of the *Arquivos Brasileiros de Cardiologia* journal with some criticisms to our article entitled "Statin Use Improves Cardiometabolic Protection Promoted By Physical Training in an Aquatic Environment: A Randomized Clinical Trial".[1] We would like to thank the editors for the opportunity to respond and would like to clarify some points mentioned in the aforementioned Letter, which, according to our understanding, has serious problems in the interpretation of the scientific methodology processes used in our article.

The authors of the Letter report that a healthy control group was not added to the study. In fact, it was not and we report below the reasons why we made this methodological decision. The objective of the study was to analyze the influence of simvastatin use on the lipid profile adaptations resulting from aerobic and resistance training in aquatic environments in elderly women with dyslipidemia. Considering that the literature is already vast concerning studies of physical training interventions with a healthy population and evaluation of lipid parameters,[2] the focus of our experiment was to study their effects on individuals with dyslipidemia, thus bringing a new result focused on those who need therapeutic interventions the most, aiming at improving the lipid profile. In this context, we did not see the justification for the inclusion of a healthy group. Another reason is the complete lack of intention to compare the effects of using a lipid-lowering medication in healthy individuals *versus* dyslipidemia patients. Therefore, we did not find any justification for the use of this medication in a healthy population.

The Letter also mentioned that the statistical power of the performed test could have been greater. We understand that, although we did not disclose the results of statistical power, it is appropriate, considering that the analyses were performed with a sample size larger than that estimated by the sample size calculation. In addition, all assumptions involving the generalized estimating equations[3] were followed. It should be noted that the sample size calculation was performed as suggested in the rules of scientific methodology *a priori*, that is, in the research project phase, prior to data collection. Therefore, this calculation took into account topics such as predicted statistical analysis, outcome variability and research design.[4-6]

Moreover, the authors of the Letter raise the issue that the body mass index (BMI) of the control group characterizes them as obese and this was not explained in the inclusion criteria. In fact, the BMI of the control group classifies the participants as obese, according to the World Health Organization criteria, but this is just a characteristic of the group, and it was not an inclusion criterion of the study, as shown in the methods section (subsection on participants and eligibility criteria).

The authors of the Letter mention that there was no homogeneity in the number of individuals on medication (MED) and without medication (NMED). However, it is possible to see in Table 1 of our article that there was a balance in the distribution of users and non-users of statins between the three study groups, with 10 users in the aerobic group, 9 in the resistance training group and 9 in the control group, with no statistical difference in the distribution between the groups ($p=0.639$). Likewise, there was no difference in the distribution of users of 20mg of statins between the groups ($p=0.961$) or of 40mg of statins between the groups ($p=0.961$) (Table 1).

Finally, the authors of the Letter report that: "The aerobic training intensity indicator, when related to other variables, may add new questions that indicate lines of thought and research that this study discloses, given that the statin effect has been investigated on the skeletal muscle function, performance and functional capacity of athletes in different sports modalities and intensity". It should be noted that the parameter used to prescribe the aerobic training intensity (heart rate relative to the anaerobic threshold) has been considered, for some decades, the most robust method, as indicated in the literature,[7] which allows estimating the thresholds of aerobic and anaerobic training zones. We understand this as a positive point of the study and that it is not related to the already known effects of statins on musculoskeletal function. In the light of our knowledge, regardless of the parameter used for aerobic training prescription, the effects of statins on musculoskeletal function should be the same.

Finally, we are grateful for the acknowledgement that the conclusions of our study answer the proposed objective and that the theoretical foundations are in line with the study question and hypothesis.

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Leandro Coconcelli
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Adriana Cristine Buttelli
Laura Pereira
Ricardo Stein
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References

1. Costa RR, Vieira AF, Coconcelli L, Fagundes AO, Buttelli CK, Pereira LF. et al. Uso de estatinas melhora a proteção cardiometabólica promovida pelo treinamento físico em ambiente aquático: um ensaio clínico randomizado. Arq Bras Cardiol. 2021;117(2):270-8. doi: 10.36660/abc.20200197.
2. Ferrari F, Santos RD. Atividade física e HDL-C: existem diferenças entre os sexos no efeito dose-resposta. Arq Bras Cardiol. 2021;117(3):501-2. doi: 10.36660/abc.20210551.
3. Ballinger GA. Using generalized estimating equations for longitudinal data analysis. Organizational Research Methods. 2004;7(2):127-50. https://doi.org/10.1177/1094428104263672
4. Hopkins WG, Batterham AM. Estimating sample size for magnitude-based inferences. Med Sci Sports Exerc. 2006;38(5): S528-S9. 6 (sportsci.org/2006/wghss.htm)
5. Gupta KK, Attri JP, Singh A, Kaur H, Kaur G. Basic concepts for sample size calculation: critical step for any clinical trials. Saudi J Anaesth. 2016;10(3):328-31. doi: 10.4103/1658-354X.174918.
6. Gaya A, Garlipp DC, Silva MF, Moreira RB. Ciências do movimento humano: introdução à metodologia da pesquisa. Porto Alegre: Artmed; 2008.
7. Rondon MUPB, Forjaz CLM, Nunes N, Barretto AC, Negrão CE. Comparação entre a prescrição de intensidade de treinamento físico baseada na avaliação ergométrica convencional e na ergoespirométrica. Arq Bras Cardiol. 1998; 70(3):159-66. doi: 10.1590/s0066-782x1998000300004.

Erratum

December 2021 Issue, vol. 117(6), pages 1093-1103

In the Original Article "Antihypertensive Activity of Sauromatum guttatum Mediated by Vasorelaxation and Myocardial Depressant Effects", with DOI: https://doi.org/10.36660/abc.20200055, published in the journal Arquivos Brasileiros de Cardiologia, 117(6):1093-1103, in page 1093, correct the author's name Rabia Bibi to Bibi Rabia.

February 2022 Issue, vol. 118(2), pages 525-529

In the Research Letter "A Rare Presentation of COVID-19 with Pulmonary Embolism", with DOI: https://doi.org/10.36660/abc.20210350, published in the journal Arquivos Brasileiros de Cardiologia, 118(2):525-529, in page 525, correct the author's name Özgenur Günçkan to Özgenur Güçkan.

February 2021 Issue, vol. 118 (2), pages 536-547

In the "Update of the Brazilian Society of Cardiology's Perioperative Cardiovascular Assessment Guideline: Focus on Managing Patients with Percutaneous Coronary Intervention – 2022", with DOI number: https://doi.org/10.36660/abc.20220039, published in the journal Arquivos Brasileiros de Cardiologia, 118(2): 536-547, on page 543 of the Portuguese version, Figure 1, correct the text of the orange square from "30 dias a < 6 meses" to "30 dias a < 3 meses". Figure 1 is correct in the English version.

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