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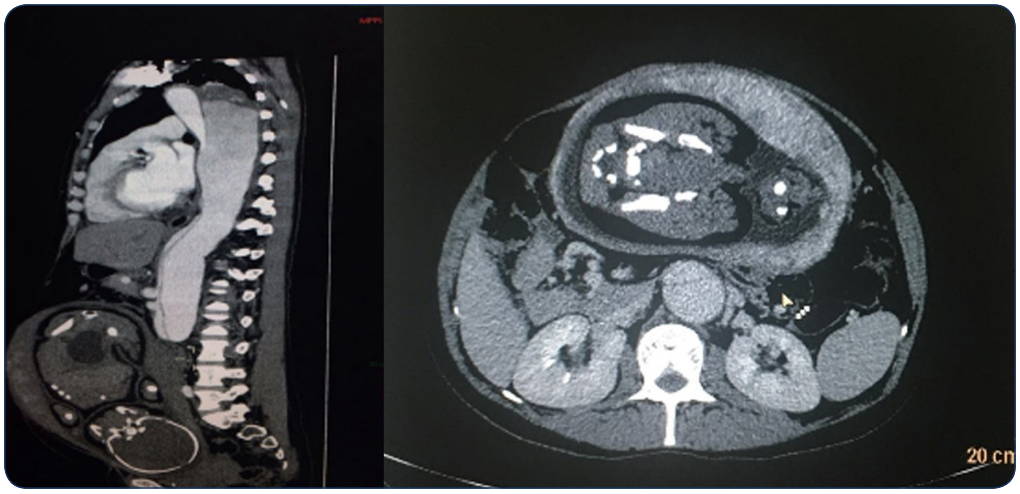

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JOURNAL OF BRAZILIAN SOCIETY OF CARDIOLOGY - Published since 1943

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SUPPORT

Programmed Ventricular Stimulation in the Management of Brugada Syndrome Patients

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Since 1980, the American College of Cardiology (ACC) and the American Heart Association (AHA), by means of a systematic methodology, have incorporated and adapted scientific evidence into practical recommendations aiming to improve preventive and therapeutic measures for cardiovascular diseases. These guidelines have become the current reference for cardiology practices and been adopted by many societies, which adapt them according to local realities.[1]

In 2006, the AHA/ACC, together with the Heart Rhythm Society (HRS), published the first guidelines for the management of patients with ventricular arrhythmias and prevention of sudden death (SD). In 2017, this first document was updated by the same societies and published in October 2018.[2,3]

Despite considerable advances in knowledge of risk stratification, prevention and treatment of SD, many gaps in its understanding still exist. Among many issues raised by the authors of the last review, two were addressed by an independent commission and recently published in an additional document.[4]

One of the issues is the subject of the present editorial and refers to the role of the electrophysiological study in risk stratification of asymptomatic patients with Brugada syndrome (BrS).

BrS was described in 1992 in individuals with structurally normal hearts who had recovered from a cardiac arrest from ventricular fibrillation showing a unique electrocardiographic pattern, characterized by a right bundle-branch block with ST-segment elevation in the right precordial leads V1 -V3.[5]

In the last 25 years, several clinical studies have shown that the BrS is a genetically determined disease, affecting one in 2,000 – 10,000 individuals with apparently normal hearts. The risk of SD is knowingly high in patients who had already had arrhythmic syncope or had recovered from cardiac arrest. There is a consensus that implantation of an automated implantable cardioverter defibrillator (ICD) is the most effective method to prevent SD in these patients.[6]

On the other hand, the risk of SD is apparently low in asymptomatic BrS patients, which makes the decision-making about the use of ICD in these patients difficult. Besides, most of these patients are young and at risk of receiving inappropriate shocks, and experience technical problems with generators and electrodes over the years.[7]

Several clinical, familial, electrophysiological and genetic aspects have been investigated in attempt to determine the risk of SD in asymptomatic individuals with BrS, who may benefit from an early ICD implantation. However, the discriminating ability of these methods is still a matter of controversy.[6,8]

Sustained ventricular tachycardia (SVT) induced by programmed ventricular stimulation (PVS) has been used for many years to identify patients at risk of spontaneous occurrence of SVT/ventricular fibrillation (VF) in patients with structural heart diseases, who may benefit from a prophylactic use of ICD.[2,3] This approach was based on the efficacy of the method in reproducing SVT in a laboratory setting.[9]

Clinical observations have revealed that the capacity of the planned ventricular stimulation in reproducing ventricular arrhythmias, particularly SVT, is very high in the chronic phase of myocardial infarction, lower in non-ischemic heart diseases, and almost absent in cardiac channelopathies.[2,3,9] This distinctive behavior is explained by characteristics of the arrhythmogenic substrate in sustained ventricular arrhythmias. In structural heart diseases, it depends on reentries into stable anatomic substrates, mostly represented by scars caused by diseases. Conditions that cause dense myocardial scars with preserved myocardial tissue channels favor the occurrence of reproducible SVTs. In contrast, EP has low reproducibility in conditions where these characteristics are not present.[9]

Therefore, the initial suggestion of using PVS for risk stratification of SD in patients with BrS caused surprise among traditional electrophysiologists,[10] since BrS was until then considered a channelopathy without anatomic substrate based on gadolinium-enhanced magnetic resonance. Subsequent studies revealed that BrS patients have an arrhythmogenic substrate characterized, by invasive electrophysiological mapping, by late electrical potential, identified predominantly in subepicardial fibers in the right ventricular outflow tract.[11]

Although in some cases, these electrical features have been associated with persistent anatomical changes,[12] in most of the cases, electrophysiologic changes are transient, modulated or induced by hormonal, autonomic, metabolic and drug-related conditions.[6]

This could explain why patients with persistent, spontaneous type 1 Brugada electrocardiographic pattern have higher risk of events compared with patients in whom the BrS pattern occurs occasionally.[5] The possible explanation for that is the fact that, in the former patients, the arrhythmogenic substrate is more extensive and stable, detectable in the ECG, and thereby more suitable to SVT and VF in external modulation,

Keywords

Brugada Syndrome; Tachycardia, Ventricular; Ventricular Fibrillation; Death, Sudden, Cardiac/prevention & control; Risk Factors; Defibrilators, Implantable/utilization.

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whereas in the second condition, a milder substrate would be found, and hence the possibility of malignant arrhythmias would be lower, detected only in very special conditions. In this case, the substrate would be only identified by analysis of electrograms obtained from the epicardial surface or by infusion of potent sodium-channel blockers.

In line with this hypothesis, recent studies on radiofrequency catheter ablation of the subepicardial substrate in BrS have shown that the induction of SVT or VF is common in patients with spontaneous type 1 pattern; these arrhythmias became noninducible after ablation of the arrhythmogenic substrate with normalization of the typical pattern.[11,13] The extension of the BrS substrate at the moment of the ES could then explain the differences in the results reported in several clinical studies and current controversies.[14]

Therefore, patients with BrS recovered from cardiac arrest or patients with persistent type 1 electrocardiographic pattern would have a higher rate of induction of ventricular arrhythmias as compared with those without electrocardiographic manifestations. However, so far, there is not enough information regarding the EKG presentation at the time of the electrophysiological study.[15]

The first study to use programmed ventricular stimulation for screening of asymptomatic BrS patients for ICD implantation involved 252 patients; 116 of them had a history of syncope or had recovered from cardiac arrest, and 136 were asymptomatic at diagnosis. Polymorphic ventricular tachycardia or VF were induced in 130 (51%) patients. induction of ventricular arrhythmias was more frequent (73%) in sympomtatic than asymptomatic (33%) patients (p = 0.0001). Spontaneous arrhythmic event occurred in 52 individuals (21%) in a mean follow-up of 34 ± months, 45 (39%) of 116 symptomatic patients and 7 (5%) of 136 asymptomatic patients. On the other hand, only 1 patient in 91 (1.1%) of the asymptomatic group presented spontaneous arrhythmic event when the ventricular pacing was negative.[15]

These data were corroborated by a second study by the same group, in which patients were followed for up to 20 years. Induction of SVT/VF in the ES had a sensitivity of 75% and specificity of 91.3% for spontaneous occurrence of malignant arrhythmias in asymptomatic patients. Despite the low positive predictive value (18.2%), the procedure had a negative predictive value of 98.3%.[16]

Clinical studies by other authors did not reproduce these findings, generating a debate that persists up to the present days. The PRELUDE was a multicenter prospective study including 273 asymptomatic patients. During the clinical follow-up, with a median of 34 months, there was no significant difference in the rates of events between patients with and without induced ventricular arrhythmias in the ES.[17] In the FINGER BrS registry involving 654 asymptomatic patients, followed by 31.9 (14 to 54.4) months, there was a low rate of events (0.5%). Although this rate was higher in patients with induced ventricular arrhythmias in the ES, there was no statistical significance in the multivariate analysis.[18]

In the meta-analysis by Kusumoto et al.,[2] organized by the AHA/ACC/HRS, six studies on BrS patients were selected of a total of 236 titles retrieved from traditional databases. To minimize possible patient overlap, the primary analysis included five of six studies selected, with exclusion of one study conducted in the same institution. Of 1,138 patients included, SVT or sustained VF was induced in 390 (34.3%) with occurrence of major arrhythmic events (SVT, VF, cardiac MS or appropriate ICD therapy) in 13 (3.3%) patients, compared with 12 events (1.6%) in 748 patients without induced arrhythmia, resulting in an odds ratio (OR) of 2.3 (95%IC: 0.63-8.66; p = 0.2).

A second analysis included all six studies, with potential data duplication. Of 1,401 patients, 481 (34.2%) had SVT or VF induced in the ES. In patients with induced SVT/VF, there were 23 arrhythmic events (5.0%), whereas among those without SVT/VF induction, 14 events occurred (1.5%), resulting in an OR of 3.3 (95%CI: 1.03–10.4; p = 0.04).

Based on these data, the 2017 AHA/ACC/HRS guidelines issued a 2B recommendation with level of evidence B for indication of ES to asymptomatic BrS patients, using less aggressive ventricular stimulation protocols when performed (up to two extrastimulation).[2]

In summary, these data do not establish the real role of SVT/VF induction in asymptomatic patients with BrS, probably due to the lack of homogeneity of samples and methods used in the studies. These data also indicate the need for prospective, multicenter studies involving a larger number of patients.

References

1. Halperin JL, Levine GN, Al-Khatib SM, Birtcher KK, Bozkurt B, Brindis RG, et al. Further evolution of the ACC/AHA clinical practice guideline recommendation classification system: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2016;67(13):1572-4.

2. European Heart Rhythm Association; Heart Rhythm Society, Zipes DP, Camm AJ, Borggrefe M, Buxton AE, et al. ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Develop Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death). J Am Coll Cardiol. 2006;48(5):e247-346.

3. Al-Khatib SM, Stevenson WG, Ackerman MJ, Bryant WJ, Callans DJ, Curtis AB, et al. 2017 AHA/ACC/HRS Guideline for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society.. J Am Coll Cardiol. 2018;72(14):e91-220.

4. Kusumoto FM, Bailey KR, Chaouki AS, Deshmukh AJ, Gautam S, Kim RJ, et al.. Systematic Review for the 2017 AHA/ACC/HRS Guideline for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol. 2018;72(14):1653-76.

5. Brugada P, Brugada J. Right bundle branch block, persistent ST segment elevation and sudden cardiac death: a distinct clinical and electrocardiographic syndrome. A multicenter report. J Am Coll Cardiol. 1992;20(6):1391-6.

6. Priori SG, Wilde AA, Horie M, Cho Y, Behr ER, Berul C, et al. HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes: document endorsed by HRS, EHRA, and APHRS in May 2013 and by ACCF, AHA, PACES, and AEPC in June 2013. Heart Rhythm. 2013;10(12):1932-63.

7. van Rees JB, de Bie MK, Thijssen J, Borleffs CJ, Schalij MJ, van Erven L. Implantation-related complications of implantable cardioverter-defibrillators and cardiac resynchronization therapy devices: a systematic review of randomized clinical trials. J Am Coll Cardiol. 2011;58(10):995-1000.

8. Takagi M, Yokoyama Y, Aonuma K, Aihara N, Hiraoka M, Japan Idiopathic Ventricular Fibrillation Study (J-IVFS) Investigators. Clinical characteristics and risk stratification in symptomatic and asymptomatic patients with Brugada syndrome: multicenter study in Japan. J Cardiovasc Electrophysiol. 2007;18(12):1244-51.

9. Buxton AE, Lee KL, DiCarlo L, Gold MR, Greer GS, Prystowsky EN, et al. Electrophysiologic testing to identify patients with coronary artery disease who are at risk for sudden death. Multicenter Unsustained Tachycardia Trial Investigators. N Engl J Med. 2000;342(26):1937–45.

10. Brugada P, Brugada R, Mont L, Rivero M, Geelen P, Brugada J. Natural history of Brugada syndrome: the prognostic value of programmed electrical stimulation of the heart. J Cardiovasc Electrophysiol. 2003;14(5):455-7.

11. Nademanee K, Veerakul G, Chandanamattha P, Chaothawee L, Ariyachaipanich A, Jirasirirojanakorn K, et al. Prevention of ventricular fibrillation episodes in Brugada syndrome by catheter ablation over the anterior right ventricular outflow tract epicardium. Circulation. 2011;123(12):1270-9.

12. Nademanee K, Raju H, de Noronha SV, Papadakis M, Robinson L, Rothery S, et al. Fibrosis, connexin-43, and conduction abnormalities in the Brugada Syndrome. J Am Coll Cardiol. 2015;66(18):1976-86.

13. Pappone C, Brugada J, Vicedomini G, Ciconte G, Manguso F, Saviano M, et al. Electrical substrate elimination in 135 consecutive patients with Brugada Syndrome. Circ Arrhythm Electrophysiol. 2017;10(5):e005053.

14. Brugada J, Pappone C, Berruezo A, Vicedomini G, Manguso F, Ciconte G, et al. Brugada Syndrome phenotype elimination by epicardial substrate ablation. Circ Arrhythm Electrophysiol. 2015;8(6):1373-81.

15. Brugada P, Geelen P, Brugada R, Mont L, Brugada J. Prognostic value of electrophysiologic investigations in Brugada Syndrome. J Cardiovasc Electrophysiol. 2001;12(9):1004-7.

16. Sieira J, Conte G, Ciconte G, de Asmundis C, Chierchia GB, Baltogiannis G, et al. Prognostic value of programmed electrical stimulation in Brugada syndrome: 20 years experience. Circ Arrhythm Electrophysiol. 2015;8(4):777-84.

17. Priori SG, Gasparini M, Napolitano C, Della Bella P, Ottonelli AG, Sassone B, et al. Risk stratification in Brugada syndrome: results of the PRELUDE (PRogrammed ELectrical stimUlation preDictive valuE) registry. J Am Coll Cardiol. 2012;59(1):37-45.

18. Probst V, Veltmann C, Eckardt L, Meregalli PG, Gaita F, Tan HL, et al. Long-term prognosis of patients diagnosed with Brugada syndrome: results from the FINGER Brugada Syndrome Registry. Circulation. 2010;121(5):635-43.

Indicators of Abdominal Adiposity and Carotid Intima-Media Thickness: Results from the Longitudinal Study of Adult Health (ELSA-Brazil)

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Abstract

Background: **Abdominal adiposity is a risk factor for cardiovascular disease.**

Objective: **To determine the magnitude of the association between abdominal adiposity, according to five different indicators, and the carotid intima-media thickness (CIMT).**

Methods: **Data from 8,449 participants aged 35 to 74 years from the ELSA-Brazil study were used. The effect of waist circumference (WC), waist-to-hip ratio (WHR), conicity index (C index), lipid accumulation product (LAP) and visceral adiposity index (VAI) on CIMT were evaluated. Data were stratified by gender and analyzed using multivariate linear and logistic regressions. A significance level of 5% was considered.**

Results: **Participants with CIMT > P75 showed a higher frequency of abdominal adiposity (men >72% and women >66%) compared to those with CIMT < P75. Abdominal adiposity was associated with the mean CIMT, mainly through WC in men (0.04; 95%CI: 0.033; 0.058). The abdominal adiposity identified by the WC, WHR, LAP, and VAI indicators in women showed an effect of 0.02 mm on the CIMT (WC: 0.025, 95%CI: 0.016, 0.035; WHR: 0.026, 95%CI: 0.016, 0.035; LAP: 0.024, 95%CI: 0.014; 0.034; VAI: 0.020, 95%CI: 0.010, 0.031). In the multiple logistic regression, the abdominal adiposity diagnosed by WC showed an important effect on the CIMT in both genders (men: OR = 1.47, 95%CI: 1.22-1.77, women: OR = 1.38; 95%CI: 1.17-1.64).**

Conclusion: **Abdominal adiposity, identified through WC, WHR, LAP, and VAI, was associated with CIMT in both genders, mainly for the traditional anthropometric indicator, WC. (Arq Bras Cardiol. 2019; 112(3):220-227)**

Keywords: **Cardiovascular Diseases; Risk Factors; Metabolism; Metabolic Syndrome; Abdominal Obesity; Atherosclerosis; Carotid Intima-Media Thickness.**

Introduction

Abdominal obesity is a traditional risk factor for cardiovascular diseases.[1] In Brazil, the prevalence of abdominal obesity, estimated by the National Health Survey *(Pesquisa Nacional de Saúde),* according to the cut-off points for waist circumference (WC) of the World Health Organization,[2] was 52.1% for women and 21.8% for men in 2013.[3]

Several mechanisms have attempted to explain how abdominal adiposity becomes a risk factor for cardiovascular disease. It is a consensus that abdominal adipose tissue has complex metabolic functions and produces numerous mediators that trigger specific, dynamic and inflammatory reactions.[4]

Atherosclerotic lesions increase the risk for cardiovascular diseases. The carotid intima-media thickness (CIMT) is a marker of subclinical atherosclerosis and a predictor of myocardial infarction and cerebrovascular accident.[5] The association between abdominal adiposity and subclinical atherosclerosis has been documented in different populations.[6,7] However, even though the CIMT is associated with abdominal adiposity, it is yet to be fully established how much this adiposity, measured by different clinical and other unusual indicators, is associated with subclinical atherosclerosis.

Studies have suggested that WC, waist-to-hip ratio (WHR) and visceral adiposity index (VAI) may predict subclinical atherosclerosis.[6,8,9] Most studies on this subject were performed in Europe, Asia and the United States, and use the WC and WHR to define abdominal adiposity and its association with cardiovascular diseases. Indicators that provide indirect information on lipid overaccumulation and visceral fat function associated with cardiovascular events, such

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as VAI[10] and the lipid accumulation product (LAP)[11], need to be further explored. The conicity index (C index) stands out as a discriminator of high coronary risk in Brazilian studies, especially when a black population is being investigated.[12] On the other hand, there are no studies that investigated the effect of adiposity diagnosed by this index on CIMT.

The aim of this study was to determine the magnitude of the association between abdominal adiposity, according to different diagnostic indicators (WC, WHR, C Index), and between indexes that reflect visceral adipose tissue dysfunction (LAP and VAI) and CIMT among the participants of ELSA-Brazil.

Methods

Study design and population

The ELSA-Brasil study included in its baseline 15,105 civil servants, aged 35-74 years, connected to six teaching and research institutions in three Brazilian regions (South, Southeast and Northeast). More details on the study methodology can be found in an earlier publication.[13]

Interviews and collection of anthropometric and biochemical measurements were carried out by a trained and certified team. A more detailed publication is available on the standardization and quality assurance procedures and the quality of uniformization regarding the conducts adopted in the ELSA-Brazil.[14]

Exclusion Criteria

In order to keep a healthy sample and to avoid biases related to CIMT, of the 10,943 participants with a valid image for both common carotid arteries, we excluded 569 patients who declared having cardiovascular disease, 36 with serum triglycerides > 800 mg/dL, 1,974 patients using lipid-lowering medication, 144 with BMI > 40 kg/m^2 and 120 who underwent bariatric surgery. To avoid biases related to abdominal fat measurement, 32 participants with body dystrophies and abdominal hernias were excluded. We also excluded the participants who self-declared as having Asian and Native Brazilian ethnicity/skin color due to the small number (297 and 136, respectively), 150 participants who did not declare ethnicity/ skin color and 15 without information on indicators of abdominal adiposity. The final sample consisted of 8,449 participants (Figure 1). Some participants had more than one condition for exclusion.

Carotid intima-media thickness (CIMT)

All the research centers collected the CIMT measurement using a standardized method, utilizing an Aplio XG™, Toshiba equipment, with a 7.5 MHz linear transducer. The technique used in the study has been published elsewhere.[15,16] For this article, CIMT was defined as the mean of the mean values of the right and left carotid arteries. The 75th percentile was used to dichotomize this variable according to gender (male: 0.69 mm, female: 0.64 mm). The 75th percentile was based on technical consensuses and previous studies.[17]

Indicators of abdominal adiposity

Anthropometric measurements were obtained using standardized equipment and techniques. The WC was measured at midpoint between the inferior border of the costal arch and the iliac crest, at the median axillary line and at the hip circumference at the maximal protrusion of the gluteal muscles, over the trousers of the study clothing. These circumferences were used to calculate the WHR. The C index was calculated using the formula: WC(m)/0.109 x √Weight(kg)/Height(m).[18]

The LAP[19] was calculated using gender-specific equations: Men: WC(cm) - 65 x triglycerides(mmol/L); Women: WC(cm) - 58 x triglycerides(mmol/L), as well as the VAI:[19] Men: (WC(cm)/39.68 + (1.88 x body mass index(kg/m^2))) x (triglycerides(mmol/L)/0.81) x (1.31/HDL cholesterol(mmol/L)); Women (WC(cm)/36.58 + 1.89 x body mass index(kg/m^2)) x (triglycerides(mmol/L)/0.81) x (1.52/HDL cholesterol(mmol/L)).

The indicators were categorized in the presence and absence of abdominal adiposity, according to the cut-off points defined by Eickemberg et al.,[20] Respectively, the following values were used for white, brown and black individuals: WC: men 89.9 cm; 90.2 cm and 91.7 cm; women 80.4 cm; 82.7 cm and 85.4 cm; WHR: men 0.92; 0.92 and 0.90; women 0.82; 0.83 and 0.84; C index: men 1.24; 1.24 and 1.24; women 1,20; 1.22 and 1.19; LAP: men 29.81; 32.39 and 33.08; women 22,64; 30.27 and 27.12; VAI: men 1.74; 2.08 and 1.68; women 1.44; 2.16 and 1.65. We chose to use the term "adiposity" instead of obesity for the five indicators, considering that LAP and VAI reflect the function of visceral fat, and not only the accumulation of abdominal fat, such as WC, WHR and C index.[10,11]

Covariates

Ethnicity/skin color was self-attributed and categorized as white, brown and black. The level of schooling was categorized as complete college/university education, complete high school and incomplete and complete elementary school. Smoking was stratified as nonsmokers, ex-smokers, and current smokers.

Weight and height were measured with participants wearing the study clothing, without shoes and accessories. A Toledo scale and a Seca stadiometer were used for the measurements of weight and height, respectively. These variables were used to calculate adiposity indexes.

Blood samples were collected by venipuncture after 12 hours of fasting. Triglyceride and HDL-cholesterol tests were performed by colorimetric enzymatic and homogeneous enzymatic colorimetric methods without precipitation, respectively. LDL-cholesterol levels were obtained using Friedewald's formula. Triglycerides and HDL-cholesterol were used to calculate the LAP and VAI.

Arterial hypertension was defined with a mean systolic blood pressure ≥ 140 mmHg and a mean diastolic ≥ 90 mmHg; or if the individual was undergoing antihypertensive treatment. Blood pressure was measured three times, considering the mean of the last two measurements for calcualtion.[15]

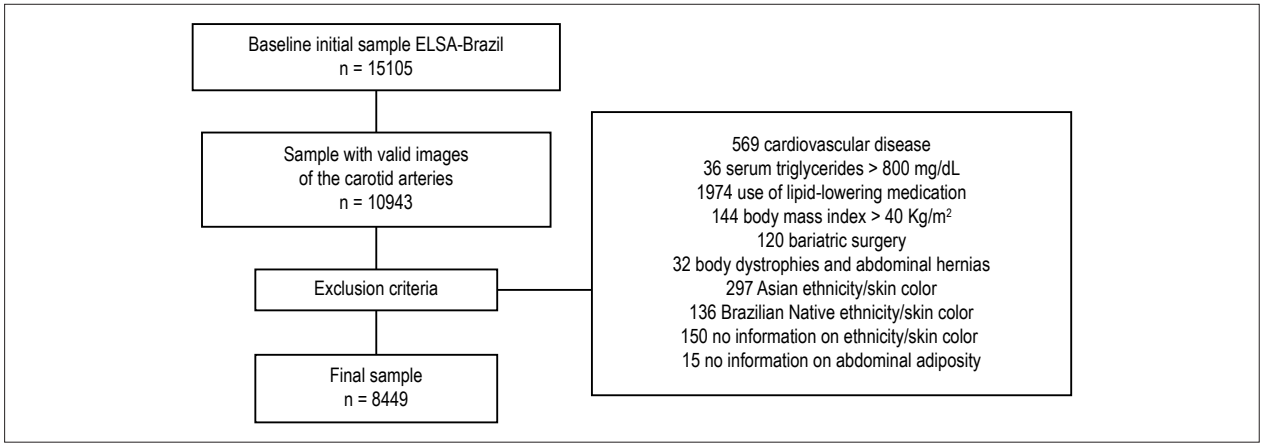

Figure 1 – *Study sample selection flowchart. Note: Percentage of exclusion (sample with valid images and final sample): 23%.*

Statistical analysis

A data descriptive analysis was carried out to evaluate the distribution of participants according to the characteristics of interest. Due to the asymmetric distribution of some variables it was decided to show the continuous variables as median and interquartile range. Categorical variables were expressed as absolute and relative frequencies.

The frequency of high CIMT (≥75th percentile) and abdominal adiposity through WC, WHR, C index, LAP and VAI indicators were estimated. Regression coefficients and odds ratios (OR), with their respective 95% confidence intervals, were calculated using linear regression and multivariate logistic analyses, respectively. Regression analyses were used to identify the magnitude of the effect of the abdominal adiposity presence, measured by the indicators in a categorical scale, on the mean of the CIMT in the linear model and on the diagnosis of high CIMT in the logistic analysis.

Due to the asymmetric distribution, CIMT values were transformed into natural logarithm for linear regression. For the logistic regression, the dichotomized CIMT was used in the 75th percentile of the distribution. The main independent variables (abdominal adiposity indicators) were introduced separately in five models for each regression analysis (linear and logistic) by gender. All models were adjusted for age, ethnicity/skin color, level of schooling, smoking status, HDL-cholesterol, LDL-cholesterol, and arterial hypertension, chosen for their proximity to the atherosclerosis condition.[21]

An effect modification analysis was performed to test the variables gender and ethnicity/skin color in all proposed models using the maximum likelihood ratio test. No effect modification was detected; however, we maintained the analyses stratified by gender based on theoretical references.[5,22] A diagnostic evaluation of the multiple linear regression models was carried out through graphic analysis of residues, evaluation of influential points and multicollinearity. The Hosmer-Lemeshow test, goodness-of-fit test using the Pearson's residuals and Deviance residues, McFadden's Adjusted R^2 and ROC curve, were used to diagnose logistic model adjustment. A significance level of 5% was established and the Stata 12 software (Stata Corporation, College Station, Texas, USA) was used for the analyses.

Results

The sample characteristics are shown in Table 1. Men and women with high CIMT had an older median age (47 and 48 years *versus* 57 years) and a higher frequency of abdominal adiposity (men 71.9% to 78.4%; and women 66% to 73.1%).

The values of abdominal adiposity indicators were higher in men and in men and women with CIMT > 75th percentile. The men had a median CIMT of 0.59 mm (0.52-0.69), and women of 0.56 mm (0.50-0.64) (data not shown).

In both genders, the adiposity measured by the five indicators was associated with the mean log of CIMT. The C index showed the smallest effect (Table 2).

According to the multivariate logistic regression analysis (Table 3), there was an association between the diagnosis of adiposity by WC, WHR, LAP and VAI with CIMT in both genders. The adiposity diagnosed by WC showed a greater effect on CIMT in both genders. According to the diagnostic analyses of the models, there were no assumption violations, indicating the models' adequacy.

Discussion

Using data from the ELSA-Brasil study, associations were observed between abdominal adiposity measurements and CIMT, a noninvasive marker of subclinical atherosclerosis capable of predicting cardiovascular disease.[23] It has been documented, in a study carried out in Southeast Brazil, the definition of CIMT as the thickening of the intima-media complex starting from 1.0mm.[24] Considering this value, in our study, the presence of abdominal adiposity diagnosed by WC, WHR, LAP and VAI showed an important effect, with a variation of 0.02 mm to 0.04 mm in the log of CIMT in both genders. Polack et al.,[23] using data from the Framingham offspring cohort study, found that an annual change in CIMT > 0.02 mm was associated with a more than two-fold risk of cerebrovascular accident.[23]

Table 1 – Baseline characteristics, according to the carotid intima-media thickness and gender. ELSA-Brazil, 2008-2010

	Male		Female	
	CIMT < P75	CIMT ≥ P75	CIMT < P75	CIMT ≥ P75
	n = 2,779	n = 958	n = 3,503	n = 1,209
Age, median (IQR)	48 (43-54)	57 (51-63)	47 (43-53)	57 (51-62)
Ethnicity/skin color, n (%)				
White	1,562 (56.2)	545 (56.8)	2,010 (57.3)	705 (58.3)
Brown	836 (30.0)	266 (27.7)	883 (25.2)	306 (25.3)
Black	381 (13.7)	147 (15.3)	610 (17.4)	198 (16.3)
Level of schooling, n (%)				
Complete College/University	1,352 (48.6)	420 (43.8)	1,976 (56.4)	613 (50.7)
Complete High School	1,049 (37.7)	310 (32.3)	1,292 (36.8)	413 (34.1)
Incomplete + complete Elementary School	378 (13.6)	228 (23.8)	235 (6.7)	183 (15.1)
Smoking status, n (%)				
Never smoked	1,588 (57.1)	366 (38.2)	2,284 (65.2)	695 (57.4)
Former smoker	811 (29.1)	404 (42.2)	803 (22.9)	334 (27.6)
Current smoker	380 (13.6)	187 (19.5)	416 (11.8)	180 (14.8)
HDL-cholesterol, median (IQR)	49 (43-57)	49 (43-57)	60 (52-71)	59 (51-70)
LDL-cholesterol, median (IQR)	130 (110-152)	138.5 (117-161)	127 (106-149)	140 (119-164)
Arterial hypertension, n (%)	709 (25.5)	499 (52.1)	644 (18.3)	540 (44.7)
Mean BMI (IQR)	26.0 (23.6-28.5)	27.2 (24.6-29.9)	25.3 (22.7-29.5)	27.3 (24.1-30.4)
Abdominal adiposity, median (IQR)				
Waist circumference	92.3 (85.5-99.4)	96.6 (89.4-104.1)	83.2 (76.5-91.4)	88.9 (81-97.3)
Waist-to-hip ratio	0.93 (0.88-0.97)	0.96 (0.92-1.00)	0.82 (0.78-0.87)	0.86 (0.81-0.91)
Conicity index	1.26 (1.21-1.30)	1.29 (1.24-1.34)	1.19 (1.14-1.25)	1.23 (1.18-1.29)
Lipid accumulation product	38.8 (22.1-65.3)	51.2 (30.4-82.2)	26.48 (15.3-44.4)	39.9 (23.4-63.3)
Visceral adiposity index	2.41 (1.47-3.95)	2.91 (1.74-4.66)	1.62 (1.06-2.61)	2.15 (1.37-3.43)
Abdominal adiposity, n (%)				
Waist circumference	1,599 (57.5)	690 (72.0)	1,939 (55.3)	884 (73.1)
Waist-to-hip ratio	1,628 (58.5)	751 (78.3)	1,744 (49.7)	847 (70.0)
Conicity index	1,740 (62.6)	738 (77.0)	1,657 (47.3)	798 (66.0)
Lipid accumulation product	1,670 (60.0)	715 (74.6)	1,834 (52.3)	865 (71.5)
Visceral adiposity index	1,774 (63.8)	708 (73.9)	1,733 (49.4)	799 (66.0)

The sum of observations may differ in some variables due to data loss; CIMT: carotid intima-media thickness; P75: 75th percentile; IQR: interquartile range; n (%): number of observations (frequency); BMI: body mass index.

Few studies have compared different indicators of adiposity with CIMT, and the present study is the first one that separately investigated the contribution of different indicators of abdominal adiposity. Previous studies also carried out with ELSA-Brazil data also evaluated the association between traditional risk factors and CIMT.[25,26] WC, WHR, waist-to-height ratio (WHtR) and neck circumference (NC) were included in the analysis. The latter indicator had the strongest association with CIMT. The authors suggest that the local effect produced by neck fat acts directly on the carotid arteries.[25,26] Our study did not include neck circumference; however, the measures used in the study are relatively simple and reflect important information about the risk of developing cardiovascular diseases, at individual and population levels.[27]

Most studies that evaluated the association between abdominal adiposity and CIMT used visceral fat measured by imaging tests. In these studies, visceral fat was strongly associated with CIMT,[28,29] but the comparison with these findings is limited by the different methods used to identify abdominal and visceral fat. The association between abdominal adiposity and subclinical atherosclerosis is possibly related to the visceral component of abdominal fat. The indicators evaluated in the present study are

Table 2 – Multivariate linear regression analysis between abdominal adiposity, measured by five indicators alone, and CIMT, according to gender. ELSA-Brazil 2008-2010

	Male		Female	
	n = 3,737		n = 4,712	
	β (SE)	95%CI	β (SE)	95%CI
Waist circumference	0.045 (0.006)	0.033;0.058	0.025 (0.004)	0.016;0.035
Waist-to-hip ratio	0.032 (0.006)	0.019;0.045	0.026 (0.004)	0.016;0.035
Conicity index	0.016 (0.006)	0.003;0.029	0.011 (0.004)	0.002;0.020
Lipid accumulation product	0.030 (0.006)	0.016;0.043	0.024 (0.004)	0.014;0.034
Visceral adiposity index	0.022 (0.007)	0.007;0.037	0.020 (0.005)	0.010;0.031

The models were adjusted for age, ethnicity/skin color, level of schooling, smoking status, HDL-cholesterol, LDL-cholesterol and arterial hypertension.

Table 3 – Odds ratio and respective 95% confidence intervals for the association between abdominal adiposity, diagnosed by five indicators alone, with CIMT, according to gender. ELSA-Brazil 2008-2010

	Male	Female
	n = 3,737	n = 4,712
	OR (95%CI)	OR (95%CI)
Waist circumference	1.47 (1.22;1.77)	1.38 (1.17;1.64)
Waist-to-hip ratio	1.37 (1.12;1.67)	1.33 (1.13;1.57)
Conicity index	1.02 (0.83;1.24)	1.12 (0.95;1.32)
Lipid accumulation product	1.39 (1.13;1.69)	1.28 (1.08;1.53)
Visceral adiposity index	1.42 (1.13;1.77)	1.31 (1.08;1.59)

The models were adjusted for age, ethnicity/skin color, level of schooling, smoking status, HDL-cholesterol, LDL-cholesterol and arterial hypertension.

indirect measures of this component, but they show good correlation with visceral fat and are accessible to the overall population.[27]

The WC was the indicator most strongly associated with CIMT. Similar to our data, other studies have also found an association between WC and CIMT in healthy 45- to 65-year-old Dutch adults, hospitalized Irish adults, and hospitalized subjects aged 21-83 years in China.[7,30,31] WC is described as an indicator of abdominal adiposity with a greater capacity to predict metabolic alterations and cardiovascular diseases, being one of the measures that most closely approximates to visceral fat measured by imaging tests.[27]

In this study, WHR also showed an important association with CIMT between men and women. Large epidemiological studies have described the strongest associations not only between adiposity diagnosed by WHR and CIMT, but also with the prevalence of myocardial infarction, incidence of coronary artery disease, high coronary risk and coronary events.[6,32,33] However , evidence shows that the gluteofemural region consists mainly of subcutaneous adipose tissue. This tissue does not seem to play an important role in the pathogenesis of cardiovascular disease. By including hip measurement, WHR reflects the effect of total adiposity as a risk factor for atherosclerosis and other cardiovascular outcomes.[32] Thus, WHR can be useful as a simple and consistent indicator by reflecting the combination of total and abdominal adiposity.

The C index was the indicator that showed the lowest effect of abdominal adiposity on the CIMT in this study. No studies were found that investigated this indicator in relation to subclinical atherosclerosis. Previous publications have observed the association of this indicator with high coronary risk in Brazilians from the Northeast region[34] and metabolic alterations in Indian civil servants.[35] Although the C index is not a new indicator, it remains little explored and there is no consensus on ideal cutoff points for the Brazilian population. As it considers weight and height, similar to the WHR, it may be useful to demonstrate the combination of total and abdominal adiposities on cardiovascular outcomes. One hypothesis for the absence of association in this study is the large percentage of participants of white ethnicity/skin color, since the performance of this indicator as a discriminator of coronary risk works better in black populations.[34]

VAI is an indicator originally proposed to identify the distribution and function of adipose tissue, indirectly expressing cardiovascular risk. Due to the inclusion of physical and metabolic parameters (anthropometric measures and biochemical tests), this indicator may reflect the altered production of adipocytokines, increase in lipolysis and free fatty acids in plasma.[10]

Evidence indicates that VAI was independently associated with cardiovascular (OR = 2.45, 95%CI: 1.52, 3.95) and cerebrovascular events (OR = 1.63, 95%CI: 1.06, 2.50) in

healthy and non-obese Italians.[10] The only study found that evaluated the association between VAI and a subclinical measure of atherosclerosis – the CAC – coronary artery calcium score – was carried out with 33,468 Koreans with a mean age of 42 years. Similar to the present findings, but with a lower magnitude of association, the highest chance of having subclinical atherosclerosis (OR = 1.26, 95%CI: 1.14, 1.38) was shown in individuals with the highest tertile of VAI.[9] It was found in the current study that the chance of men and women with abdominal adiposity assessed by VAI of having high CIMT was 42% and 31%, respectively. This difference between the studies was possibly observed due to the characteristics of the investigated populations (healthy participants *versus* patients from a Korean university hospital).[9]

Similar to VAI, the LAP showed an association between the presence of abdominal adiposity and CIMT. No previous evidence was found on the association between LAP and subclinical atherosclerosis. The LAP was developed to reflect combined metabolic and physical alterations, using WC and triglycerides. Therefore, it measures lipid overaccumulation and stands out as a cardiovascular risk factor in adults. This indicator has been investigated in the context of metabolic and cardiovascular diseases and mortality. An American cohort study with approximately 5,000 subjects treated at a cardiologic clinic between 1995-2006 showed an association between LAP and cardiovascular mortality (HR: 1.52 95%CI: 1.27, 1.82), adjusted for age, gender, smoking, diabetes, blood pressure, LDL-cholesterol and HDL-cholesterol.[36]

However, more studies are needed, especially in Brazil, to broaden the knowledge of less popular indicators such as VAI and LAP. Evidence suggests that information not only on the fatty tissue accumulated in the abdominal region is provided through LAP and VAI, but also on fat deposition in areas such as the liver, muscle, heart and arteries. This lipid overaccumulation causes changes in intracellular metabolism and contributes to the occurrence of cardiovascular disease, including atherogenesis and death.[19]

In the present study the associations between adiposity measures and CIMT were more significant for men than for women. Women have more total body fat (and subcutaneous), often in the legs and buttocks and, especially, before menopause. Men tend to accumulate fat in the abdominal region throughout life, so they are at higher risk for developing cardiovascular outcomes,[22] including atherosclerosis.

Evidence shows differences in the progression of CIMT and adiposity due to the ethnicity/ skin color.[37] The cut-off points used in this study incorporated the differences between gender and ethnicity/skin color[20] and, perhaps because of that, no effect modification was detected.

Through the coefficients of determination (R^2), the linear regression model variables, including each indicator alone, explained approximately 30% of the total CIMT variability. In our study, the models were adjusted for age, ethnicity/ skin color, level of schooling, smoking, HDL-cholesterol, LDL-cholesterol and arterial hypertension. The study carried out by Santos et al.,[25] using the ELSA-Brazil sample, found coefficients of determination (R^2) close to 40% when investigating the association of risk factors with CIMT through the variables: blood pressure, glucose metabolism, lipid profile and adiposity (body mass index, WC, hip circumference, WHR, waist-to-height ratio, neck circumference). It is noteworthy that, in addition to adiposity patterns, geographic, genetic, environmental and behavioral characteristics are also associated with the occurrence of atherosclerosis.

The 75th percentile of the distribution was used to categorize CIMT in the logistic regression analysis. Other values for this classification might have yielded more consistent results. However, studies show subjects with CIMT values above the 75th percentile with a higher risk of developing cardiovascular disorders.[17,38] It is known that the atheroma plaques may be more representative of atherosclerosis than CIMT.[39] However, our population is relatively young, and when CIMT was dichotomized at 1.5 mm, a proposed classification for atheroma plaque according to the international consensus,[5] it showed a low frequency of participants with this condition (4% in men and 2% in women) (data not shown).

The use of a stringent protocol for image acquisition and quality control provided reliable and accurate data of CIMT measurements in this study. To reduce the influence of the evaluator, the reading of all images was centralized, and the automated measurements were performed by software. Although we did not adjust the models by body mass index, we excluded subjects with class III obesity and those who underwent bariatric surgery from the analysis, aiming to filter the effect of abdominal adiposity without influence of excessive total body fat.

This study has limitations. Data on menopause were not considered. When women reach menopause they lose the protection provided by the hormone estrogen and, as they get older, there is a greater accumulation of abdominal fat, as well as an increase in the occurrence of cardiovascular problems.[22] The literature is clear about the effect of age on atherosclerosis.[5] Although the analyzes were adjusted for age in this article, it did not allow the observation of the effect of adiposity on CIMT at different age groups. It is not possible to affirm causality due to the cross-sectional design of this study; however, it seems unlikely that arterial thickening occurs before the high accumulation of abdominal fat. ELSA-Brazil is an occupational cohort and generalizations for the Brazilian population are limited, despite similarities in the prevalence indicators observed in ELSA-Brasil and VIGITEL studies.[40]

Conclusion

The observed results reinforce the importance of abdominal adiposity for the condition of subclinical atherosclerosis. Abdominal adiposity, identified through WC, WHR, LAP and VAI, was associated with CIMT in both genders, with the traditional WC anthropometric indicator standing out. WC, when compared to the other indicators, and men, when compared to women, showed the most significant effects.

Author contributions

Conception and design of the research, analysis and interpretation of the data, statistical analysis and writing of the

manuscript: Eickemberg M, Amorim LDAF, Matos SMA; critical revision of the manuscript for intellectual content: Amorim LDAF, Almeida MCC, Aquino EML, Fonseca MJM, Santos IS, Diniz MFS, Barreto SM, Matos SMA

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 ISC/UFBA, da FIOCRUZ, do Hospital Universitário-USP, da UFMG, do Centro de Ciências de Saúde da UFES, do Hospital de Clinicas de Porto Alegre under the protocol number 027/06, 343/06, 669/06, 186/06, 041/06, 194/06 respectively. 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. Gast KB, den Heijer M, Smit JWA, Widya RL, Lamb HJ, de Roos A, et al. Individual contributions of visceral fat and total body fat to subclinical atherosclerosis: The NEO study. Atherosclerosis. 2015;241(2):547–54.
2. World Health Organization.(WHO). Waist circumference and waist-hip ratio. Report of a WHO expert consultation. Geneva;2008. P.8-11.
3. Instituto Brasileiro de Geografia e Estatística (IBGE). Pesquisa nacional de saúde 2013: Ciclos de vida - Brasil e grandes regiões. 2015.
4. Almeida-Pititto B, Ribeiro-Filho FF, Santos IS, Lotufo PA, Bensenor IM, Ferreira SR. Association between carotid intima-media thickness and adiponectin in participants without diabetes or cardiovascular disease of the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil). Eur J Prev Cardiol. 2017;24(2):116–22.
5. Nezu T, Hosomi N, Aoki S, Matsumoto M. Carotid intima-media thickness for atherosclerosis. J Atheroscler Thromb. 2016;23(1):18–31.
6. Yan RT, Yan AT, Anderson TJ, Buithieu J, Charbonneau F, Title L, et al. The differential association between various anthropometric indices of obesity and subclinical atherosclerosis. Atherosclerosis. 2009;207(1):232–8.
7. Zhang L, Shen Y, Zhou J, Pan JM, Yu HY, Chen HB, et al. Relationship between waist circumference and elevation of carotid intima-media thickness in newly-diagnosed diabetic patients. Biomed Environ Sci. 2014;27(5):335–42.
8. Zhang F, Feng L, Chen Y, Geng Z, Xu X. Relationship between carotid artery intima-media thickness and cardiovascular risk factors in Chinese Uygur population. Int J Clin Exp Med. 2014;7(12):5412–20.
9. Park HJ, Kim J, Park SE, Park CY, Lee WY, Oh KW, et al. Increased risk of subclinical atherosclerosis associated with high visceral adiposity index in apparently healthy Korean adults: the Kangbuk Samsung Health Study. Ann Med. 2016;48(6):410-6.
10. Amato MC, Giordano C, Galia M, Criscimanna A, Vitabile S, Midiri M, et al. VAI: A reliable indicator of visceral fat function associated with cardiometabolic risk. Diabetes Care. 2010;33(4):920–2.
11. Kahn HS. The Lipid Accumulation Product Is Better Than BMI for Identifying Diabetes. Diabetes Care. 2006;29(1):151–3.
12. Roriz AK, Passos LC, de Oliveira CC, Eickemberg M, Moreira PD, Sampaio LR. Evaluation of the accuracy of anthropometric clinical indicators of visceral fat in adults and elderly. PLoS One. 2014;9(7): e103499.
13. 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):315–24.
14. Schmidt MI, Griep RH, Passos VM, Luft VC, Goulart AC, Menezes GM de S, et al. Estrategias e desenvolvimento de garantia e controle de qualidade no ELSA-Brasil. Rev Saude Publica. 2013;47(Supl 2):105–12.
15. Mill JG, Pinto K, Griep RH, Goulart A, Foppa M, Lotufo P, et al. Medical assessments and measurements in ELSA-Brasil. Rev Saude Publica. 2013;47(2):54–62.
16. Santos IS, Bittencourt MS, Oliveira IRS, Souza AG, Meireles DP, Rundek T, et al. Carotid intima-media thickness value distributions in the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil). Atherosclerosis. 2014;237(1):227–35.
17. Rosvall M, Persson M, Östling G, Nilsson PM, Melander O, Hedblad B, et al. Risk factors for the progression of carotid intima-media thickness over a 16-year follow-up period: The Malmö Diet and Cancer Study. Atherosclerosis. 2015;239(2):615–21.
18. Valdez R, Seidell JC, Ahn YI, Weiss KM. A new index of abdominal adiposity as an indicator of risk for cardiovascular disease. A cross-population study. Int J Obes. 1993;17(77):77–82.
19. Kahn HS. The "lipid accumulation product" performs better than the body mass index for recognizing cardiovascular risk: a population-based comparison. BMC Cardiovasc Disord. 2005;5:26.
20. Eickemberg M, Amorim LDAF, Pitanga FJG, Aquino EML de, Fonseca M de JM da, Maria da Conceição Chagas de Almeida, et al. Obesidade abdominal no Estudo Longitudinal de Saúde do Adulto (ELSA-Brasil): avaliação da acurácia de indicadores diagnósticos na ausência de padrão ouro.
21. Qu B, Qu T. Causes of changes in carotid intima-media thickness: a literature review. Cardiovasc Ultrasound. 2015;13:46.
22. Palmer BF, Clegg DJ. The sexual dimorphism of obesity. Mol Cell Endocrinol. 2015 Feb 15;402:113–9.
23. Polak JF, Pencina MJ, Pencina KM, O'Donnell CJ, Wolf PA, D'Agostino RB. Carotid-Wall Intima–Media Thickness and Cardiovascular Events. N Engl J Med. 2011;365(3):213–21.
24. Casella IB, Sotelo FJB, Yamazaki Y, Presti C, Vassoler A, Melo HAH. Comparison of common carotid artery intima-media thickness between Brazilian Euro-descendants and Afro-descendants with atherosclerosis risk factors. Clinics. 2009;64(7):657–64.
25. Santos IS, Alencar AP, Rundek T, Goulart AC, Barreto SM, Pereira AC, et al. Low impact of traditional risk factors on carotid intima-media thickness: The ELSA-brasil cohort. Arterioscler Thromb Vasc Biol. 2015;35(9):2054–9.

26. Baena CP, Lotufo PA, Santos IS, Goulart AC, Bittencourt MS, Duncan BB, et al. Neck circumference is associated with carotid intimal-media thickness but not with coronary artery calcium: Results from The ELSA-Brasil. Nutr Metab Cardiovasc Dis. 2016;26(3):216–22.

27. Carneiro Roriz AK, Santana Passos LC, Cunha de Oliveira C, Eickemberg M, de Almeida Moreira P, Barbosa Ramos L. Anthropometric clinical indicators in the assessment of visceral obesity : an update. Nutr Clín Diet Hosp. 2016;36(2):168–79.

28. Rallidis LS, Baroutsi K, Zolindaki M, Karagianni M, Varounis C, Dagres N, et al. Visceral adipose tissue is a better predictor of subclinical carotid atherosclerosis compared with waist circumference. Ultrasound Med Biol. 2014;40(6):1083–8.

29. Oike M, Yokokawa H, Fukuda H, Haniu T, Oka F, Hisaoka T, et al. Association between abdominal fat distribution and atherosclerotic changes in the carotid artery. Obes Res Clin Pract. 2014;8(5):e448–58.

30. Maher V, O'Dowd M, Carey M, Markham C, Byrne A, Hand E, et al. Association of central obesity with early Carotid intima-media thickening is independent of that from other risk factors. Int J Obes. 2009;33(1):136–43.

31. Gast KB, Smit JWA, Heijer M den, Middeldorp S, Rippe RCA, le Cessie S, et al. Abdominal adiposity largely explains associations between insulin resistance, hyperglycemia and subclinical atherosclerosis: The NEO study. Atherosclerosis. 2013;229(2):423–9.

32. Canoy D. Distribution of body fat and risk of coronary heart disease in men and women. Ischemic Heart Dis. 2008;23(6):591–600.

33. Pitanga FJG, Lessa I. Associação entre indicadores antropométricos de obesidade e risco coronariano em adultos na cidade de Salvador, Bahia, Brasil. Rev Bras Epidemiol. 2007;10(2):239–48.

34. Pitanga JFG, Lessa I. Indicadores antropométricos de obesidade como instrumento de triagem para risco coronariano elevado em adultos na cidade de Salvador – Bahia. Arq Bras Cardiol. 2005;85(1):26–31.

35. Ghosh A, Bose K, Das Chaudhuri AB. Association of food patterns, central obesity measures and metabolic risk factors for coronary heart disease (CHD) in middle aged Bengalee Hindu men, Calcutta, India. Asia Pac J Clin Nutr. 2003;12(2):166–71.

36. Ioachimescu AG, Brennan DM, Hoar BM, Hoogwerf BJ. The lipid accumulation product and all-cause mortality in patients at high cardiovascular risk: a PreCIS database study. Obesity (Silver Spring). 2010;18(9):1836–44.

37. Goh LGH, Dhaliwal SS, Welborn TA, Lee AH, Della PR. Ethnicity and the association between anthropometric indices of obesity and cardiovascular risk in women : a cross-sectional study. BMJ Open. 2014;4(5):e004702.

38. Goulart AC, Santos IS, Bittencourt MS, Lotufo PA, Benseñor IM. Migraine and subclinical atherosclerosis in the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil). Cephalalgia. 2016;36(9):840–8.

39. Spence JD. Carotid plaque measurement is superior to IMT. Atherosclerosis. 2012;220(1):34–5.

40. 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.

Abdominal Adiposity and Intima-Media Carotid Thickness: An Association

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Short Editorial relate to the article: Indicators of Abdominal Adiposity and Carotid Intima-Media Thickness: Results from the Longitudinal Study of Adult Health (ELSA-Brazil)

Atherosclerosis is the main cause of morbidity and mortality in adults in Brazil and worldwide. Classical risk factors have shown its causal association from randomized experimental studies, such with cholesterol and hypertension. Other risk factors, including abdominal adiposity, show positive associations with atherosclerosis-related outcomes.

The ELSA-Brazil observational study[1] began collecting data in 2008 with clinical, epidemiological and laboratorial variables of 15,105 public servants aged 35 to 74 years. Several articles on these data have already been published and have brought relevant information about the association between risk factors and varied outcomes. In the present issue, Michaela Eickemberg et al.[2] present data from a cross-sectional study that explores different measures of abdominal adiposity and its association with carotid intima-media thickness (C-IMT) measurement.

Epidemiological studies seek to find plausible associations between risk factors and clinical outcomes or "surrogates" (here represented by C-IMT). Associations may or may not be causal. For an association between variables to indicate possible causality, it is necessary that some criteria, proposed by British statistician Austin Bradford Hill,[3] be considered. They are:

a) strength of association (magnitude of effect);
b) consistency (or reproducibility);
c) specificity (one disease, one variable);
d) temporality (cause before effect);
e) biological gradient (greater exposure, more disease);
f) plausibility (known mechanism);
g) coherence (between laboratory and clinical data);
h) experiment (not always possible);
i) analogy (comparison with similar situations).

Keywords

Cholesterol; Hypertension; Risk Factors; Obesity, Abdominal; Carotid Artery Diseases/mortality; Media-Carotidea.

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When applying these criteria to the study in question we have: a) the magnitude of effect of abdominal adiposity on C-IMT is a modest one (odds ratio around 1.4); b) there are other studies that prove this association; c) abdominal adiposity is not the only cause of atherosclerosis; d) it is probable that the adiposity precedes the intima-media thickening; e) we do not have definitive evidence of a biological gradient; f) there is biological plausibility for the assessed association; g) coherence between laboratory and clinical data is present; h) animal experiments have shown that a hyperlipidemic diet directly affects the arteries; i) in analogy with other risk factors, abdominal adiposity may indicate more arterial adiposity.

Of all these criteria, only one is a prerequisite for causality: temporality, that is, the cause before the effect. As the present study has a cross-sectional design, temporality is, by definition, excluded. Therefore, we are discussing a non-causal association. The main conclusion of the study is that there is a statistically significant association between the different rates of abdominal adiposity and C-IMT, and the simplest of these (the abdominal circumference) showed the greatest association strength in the logistic model, adjusted for selected confounding variables.

With these comments, we want to put into perspective the importance of the critical analysis of observational studies. This criticism is necessary, but we have to emphasize that without observational studies, medical science would not have developed so far. The knowledge of the diseases that affect the human being was based on data from careful observations analyzed in order to reduce the effect of statistical and systematic biases.

The ELSA-Brazil study and its sub-studies, such as that of Eickemberg et al.,[1] fit this quality profile, which are so necessary to science. With careful data collection and a group of researchers committed to an excellent quality standard, ELSA-Brazil has brought valuable information about risk factors in a specific group of Brazilians, data that can guide future health policies.

The causality of abdominal adiposity over atherosclerosis-related clinical events has been recently confirmed by mendelian randomization, an observational method of estimating causal effects using genetic variants, such as instrumental variables.[4,5]

References

1. Aquino EML, Barreto SM, Bensenor IM, Carvalho MS, Chor D, Duncan BB, Lotufo PA, Mill JG, Molina MDC, Mota ELA, Passos VMA, Schmidt MI e Skklo M. Brazilian Longitudinal Study of Adult Health (ELSA-Brasil): Objectives and Design. Am J Epidemiol. 2012; 175 (4): 315-324.
2. Eickemberg M, Amorim LDAF, Almeida MCC, Aquino EML, Fonseca MJM, Santos IS, Chor D, Diniz MFS, Barreto SM e Matos SMA. Indicadores de Adiposidade Abdominal e Espessura Médio-Intimal de Carótidas: Resultados do Estudo Longitudinal de Saúde do Adulto – ELSA-Brasil. Arq Bras Cardiol. 2019; 112(3):220-227.
3. Hill AB. The Enviroment and Disease: Association or Causation ? Proc Roy Soc Med. 1965;58(5):295-300
4. Hägg S,Fall T, Pioner A, Magi R, Fischer K, Daisma HH, et al. Adiposity as a cause of cardiovascular disease: a Mendelian randomization study. Int J Epidemiol. 2015; 44 (2):578-86.
5. Dale CE, Fatemifar G, Palmer TM, White J, Pieto-Merno D, Zabaneh D, et al. Causal associations of adiposity and body fat distribution with coronary heart disease, stroke subtypes and type 2 diabetes: A Mendelian randomization analysis. Circulation. 2017;135(24):2373-88.

Elevated High-Sensitivity Troponin I in the Stabilized Phase after an Acute Coronary Syndrome Predicts All-Cause and Cardiovascular Mortality in a Highly Admixed Population: A 7-Year Cohort

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Abstract

Background: High-sensitivity cardiac troponin I (hs-cTnI) has played an important role in the risk stratification of patients during the in-hospital phase of acute coronary syndrome (ACS), but few studies have determined its role as a long-term prognostic marker in the outpatient setting.

Objective: To investigate the association between levels of hs-cTnI measured in the subacute phase after an ACS event and long-term prognosis in a highly admixed population.

Methods: We measured levels of hs-cTnI in 525 patients 25 to 90 days after admission for an ACS event; these patients were then divided into tertiles according to hs-cTnI levels and followed for up to 7 years. We compared all-cause and cardiovascular mortality using Cox proportional hazards models and adopting a significance level of 5%.

Results: After a median follow-up of 51 months, patients in the highest tertile had a greater hazard ratio (HR) for all-cause mortality after adjustment for age, sex, known cardiovascular risk factors, medication use, and demographic factors (HR: 3.84, 95% CI: 1.92-8.12). These findings persisted after further adjustment for estimated glomerular filtration rate < 60 ml/min/1.73 m² and left ventricular ejection fraction < 0.40 (HR: 6.53, 95% CI: 2.12-20.14). Cardiovascular mortality was significantly higher in the highest tertile after adjustment for age and sex (HR: 5.65, 95% CI: 1.94-16.47) and both in the first (HR: 4.90, 95% CI: 1.35-17.82) and second models of multivariate adjustment (HR: 5.89, 95% CI: 1.08-32.27).

Conclusions: Elevated hs-cTnI levels measured in the stabilized phase after an ACS event are independent predictors of all-cause and cardiovascular mortality in a highly admixed population. (Arq Bras Cardiol. 2019; 112(3):230-237)

Keywords: Coronary Artery Disease / mortality; Troponin I; Prognosis; Metabolic Syndrome; Biological Variation, Population; Risk Factors.

Introduction

Acute coronary syndrome (ACS) is a major driver of mortality and the leading cause of years of life lost worldwide.[1] In recent decades, several therapeutic interventions have been proven beneficial in the treatment of ACS, and structured strategies for early diagnosis and appropriate treatment have been recommended by several cardiology societies.[2-5] Because of the progress made in therapeutics for ACS, a heterogeneous group of survivors from this condition has received long-term follow-up from medical services. The prognosis of patients in the stabilized phase after ACS varies widely;[6] validation of easily obtainable, low-cost prognostic markers may enhance long-term risk stratification in this population.

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Several studies showed cardiac troponins (cTns) to be more sensitive and specific for diagnosing myocardial infarction, and to have greater correlation with higher mortality than the previous reference standard, creatine kinase isoenzyme MB (CK-MB).[7-11] Over the past two decades, new assays have been developed which conferred greater sensitivity to the diagnosis of myocardial infarction; these high-sensitivity cardiac troponins (hs-cTns) showed greater accuracy in discriminating patients at higher risk for death, even in those who had undetectable first-generation cTn levels.[12] More recently, the use of hs-cTnT as a prognostic marker in the subacute phase after an ACS episode has been studied in an European cohort of white patients.[13] These findings have not been replicated in more heterogeneous populations in the developing world. In this single-center observational cohort, we aimed to study the association of elevated levels of hs-cTnI with long-term all-cause and cardiovascular mortality in a highly admixed population in Brazil.

Methods

The Strategy of Registry of Acute Coronary Syndrome (ERICO) study design has been described in detail elsewhere.[14,15] In brief, ERICO is a prospective cohort

study of ACS patients enrolled between February 2009 and December 2013 at a community hospital in Sao Paulo, Brazil. All patients with suspected acute coronary syndrome in the emergency department were screened for participation in the study. ERICO participants must fulfill diagnostic criteria for ST elevation myocardial infarction (STEMI), non-ST elevation myocardial infarction (NSTEMI), or unstable angina (UA); the criteria used to define acute coronary syndromes were:[14]

1) Myocardial infarction (MI): presence of symptoms consistent with cardiac ischemia within 24 hours of hospital presentation, and troponin I levels above the 99th percentile with a test-specific coefficient of variation < 10%.

1a) STEMI: presence of criteria for MI plus one of the following: persistent ST segment elevation ≥ 1 mm in two contiguous electrocardiographic leads, or the presence of a new or presumably new left bundle branch block.

1b) NSTEMI: presence of criteria for MI, but not STEMI.

2) UA: symptoms consistent with cardiac ischemia 24 hours prior to hospital admission, absence of MI criteria, and at least one of the following: history of coronary heart disease; positive coronary disease stratification test (invasive or noninvasive); transient ST segment changes ≥ 0.5 mm in two contiguous leads, new T-wave inversion ≥ 1 mm, and/or pseudonormalization of previously inverted T-waves; troponin I ≥ 0.4 ng/ml; or diagnostic concordance of two independent physicians.

During the in-hospital phase, all subjects were treated at the discretion of the hospital staff with standard procedures, without influence from the study. The study protocol was approved by the Institutional Review Board addressing research in human participants. All participants provided written informed consent for the study.

Participants were interviewed during admission to the hospital and provided data regarding sociodemographic factors, medical history, and main cardiovascular risk factors (hypertension, diabetes, obesity, dyslipidemia, smoking, physical inactivity, cocaine use, menopause, and familial and personal history of coronary heart disease). Three physicians were responsible for reviewing patient information and for validating ACS cases. According to the study protocol, a blood sample was drawn for laboratory tests (troponin I, MB-creatine kinase, serum glucose, total cholesterol, HDL and LDL-cholesterol, triglycerides and total blood cell count).

At approximately 30 days after the event, participants were invited to undergo a new on-site evaluation by a physician to update data on cardiovascular risk stratification, current medication use, and additional clinical data. New blood samples were also collected. At six months after the index event and annually thereafter, all participants were contacted by phone to update information about their vital status, cardiovascular history, medications and symptoms.

All participants enrolled in the ERICO study who had blood samples collected 25 to 90 days after an ACS episode were included in this analysis. The lower limit of this interval was chosen to avoid confounding by the expected elevated circulating cTn levels in the first few days after an ACS episode; the upper limit of 90 days allows comparison with previous studies,[13,16] although there is currently no widely accepted definition of subacute phase after ACS in the literature. High-sensitivity cardiac troponin I was measured in all patients at presentation and in the subacute phase after the event. The assay used to measure hs-cTnI was the Advia Centaur TnI-Ultra Assay (Siemens Medical Solutions Diagnostics, Tarrytown, NY, USA), with the 99th percentile reference value of 0.04 mcg/L in healthy subjects and coefficient of variance lower than 10% at this range. Subjects were classified into three subgroups according to hs-cTnI tertiles in the subacute phase after the index ACS event.

In this study, our endpoints were all-cause mortality and cardiovascular mortality. We searched official death records on a regular basis for information about all participants if (1) we received information that they had died or (2) we could not contact them at the time. Municipal and state health offices searched their files to obtain death certificates and returned the results of this search to the ERICO research team. Two medical doctors reviewed these data and classified the cause of death for deceased participants according to the information from the death certificates. Participants were defined to have died from a cardiovascular cause (cardiovascular mortality) if we identified a cause of death classified in Chapter IX of the 10th version of the International Classification of Diseases (ICD-10), entitled "Diseases of the circulatory system", or if we identified a cause of death classified with the ICD-10 code R57.0 "Cardiogenic shock".

Statistical analysis

The statistical analyses were performed with R for Mac version 3.5.0. Categorical variables are presented as proportions and compared using the chi-square test. To test the assumption of normality in the distribution of continuous variables, we used the Shapiro-Wilk test. Continuous variables with normal distribution are presented as means (standard deviations) and compared using one-way ANOVA. Continuous variables with non-normal distribution are presented as medians (interquartile intervals) and compared using the Kruskal-Wallis test. Cumulative survival probabilities across the tertiles are presented as Kaplan-Meier curves and compared using the log-rank test.

We built Cox proportional hazard models for all-cause mortality and cardiovascular mortality, and presented them as crude, age-sex adjusted, and two multivariate models. Model 1 was adjusted for age, sex, ACS subtype, traditional cardiovascular risk factors (hypertension, diabetes, dyslipidemia, smoking history, and body mass index), and medication use at the first follow-up visit (aspirin, clopidogrel, beta blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers and statins). Model 2 was additionally adjusted for estimated glomerular filtration rate (GFR) < 60 ml/min/1.73 m^2 and left ventricular ejection fraction < 0.40, two variables associated with worse prognosis in previous studies.[13,17] All tests were two-sided, and p value < 0.05 was considered significant.

Results

From February 2009 to December 2013, 1085 patients were enrolled in the ERICO study. Blood samples were collected at the emergency room and between 25 and 90 days after the initial event from 525 of these participants, who were included

in the present study (median second collection interval: 39 days after the index event; interquartile range: 33-50 days). The initial diagnosis was STEMI in 144 (27.4%) patients, NSTEMI in 230 (43.8%), and UA in 151 (28.8%). The mean age was 61.6 years and 60.2% were men. The main cardiovascular risk factors found in this population were hypertension (75.5%), current or previous smoking (66.9%), and sedentary lifestyle (69.9%). Cutoff values for hs-cTnI among the tertiles were: < 0.012, 0.013-0.023 and > 0.023 mcg/L. Most hs-cTnI samples collected from patients in the subacute phase after ACS were below the 99th percentile of the method (83.8%). Patients were followed for a median of 51 months; baseline characteristics of the study according to hs-cTnI tertiles are shown in Table 1. Individuals in the highest tertile were more likely to be male, have STEMI or NSTEMI diagnoses at the index event, and chronic kidney disease and sedentary lifestyle at baseline.

From the data collected after patient admission, lower glomerular filtration rate (calculated according to CKD-Epi) and lower ejection fraction estimated in echocardiography were strongly correlated with persistently elevated levels of hs-cTnI ($p < 0.001$).

Figure 1 shows the Kaplan-Meier curves for cumulative survival according to each hs-cTnI tertile during follow-up. We found significantly lower survival rates in individuals in the highest tertile ($p < 0.001$). Analyses evaluating cardiovascular mortality as the main outcome showed similar findings (Figure 2).

Table 2 shows the results of the Cox regression analyses. Participants in the third tertile of troponin, using the first tertile as the reference, presented a hazard ratio (HR) of 4.14 (95% Confidence Interval [95% CI]: 2.19-7.86) for all-cause mortality after adjustment for age and sex; this effect persisted in multivariate adjustment models 1 (HR: 3.84, 95% CI: 1.92- 8.12) and 2 (HR: 6.53, 95% CI: 2.12-20.14). For cardiovascular mortality, there were significant differences between the first and the third tertiles after adjustment for age and sex (HR: 5.65, 95% CI: 1.94-16.47), and both multivariate adjustment models 1 (HR: 4.90, 95% CI: 1.35-17.82) and 2 (HR: 5.89, 95% CI: 1.08-32.27).

Discussion

In this cohort of patients with hs-cTnI levels measured 25 to 90 days after an ACS event, participants had sociodemographic characteristics and cardiovascular comorbidities similar to that of large international registries, like the Global Registry of Acute Coronary Events (GRACE).[18] As in this registry, our cohort had a predominantly male population with a high prevalence of hypertension; other cardiovascular risk factors, such as heart failure and smoking history, were more prevalent in our study. The most frequent ACS type in our study was NSTEMI (41.5% of participants), which is also consistent with the current trend in the incidence of MI,[19] although contrasting with the smaller frequency of NSTEMI in the GRACE cohort (26% of participants).[18]

Medication use on the first follow-up visit was similar to the treatment received on discharge by participants in the Brazilian Registry on Acute Coronary Syndromes (BRACE) study, which included hospitals of all regions of Brazil.[20] When we evaluated the percentage of patients receiving each therapeutic group, we found clear similarities between our study and BRACE for the use of aspirin (83.6% vs 86.0%, respectively), clopidogrel (53.0% vs 50.1%), betablockers (64.2% vs 69.8%), ACE inhibitors/angiotensin receptor blockers (68.3% vs 70.6%) and statins (76.4% vs 82.7%). These data also show that adherence to guideline-recommended therapies was still not optimal by the time of enrollment of these participants.

Most patients in our study (83.8%) had hs-cTnI levels below the 99th percentile during the subacute phase after an ACS event; nevertheless, even at this range, those in the highest tertile had a greater hazard ratio for all-cause and cardiovascular mortality compared to the first tertile. Elevated levels of hs-cTnI at 25 to 90 days post-ACS remained an independent risk factor for all-cause and cardiovascular mortality after adjustment for multiple confounders.

The mechanisms by which some patients present persistent elevations in cardiac troponin levels are not well established. Previous experimental studies demonstrated the incidence of chronic myocardial injury after induced mechanical coronary obstruction in rats;[21] accelerated apoptosis due to chronic myocardial dysfunction has also been shown in patients with heart failure.[22] Other speculated mechanisms include normal myocyte turnover, cellular release of proteolytic degradation products, higher myocyte cell wall permeability, and the formation of blebs in the cellular walls with the presence of these proteins.[23]

The association between higher levels of cardiac troponins and worse outcomes in out- of-hospital settings has been reported by previous studies. In 2007, Eggers et al.[16] analyzed a cohort of patients with earlier-generation cardiac troponin I (cTnI) measured at 6 weeks, 3 and 6 months after an ACS event. Throughout this study, the subgroup of patients with permanently elevated levels of cTnI (≥ 0.01) had a greater probability of death during follow-up than patients with transiently elevated or negative cTnI.[16]

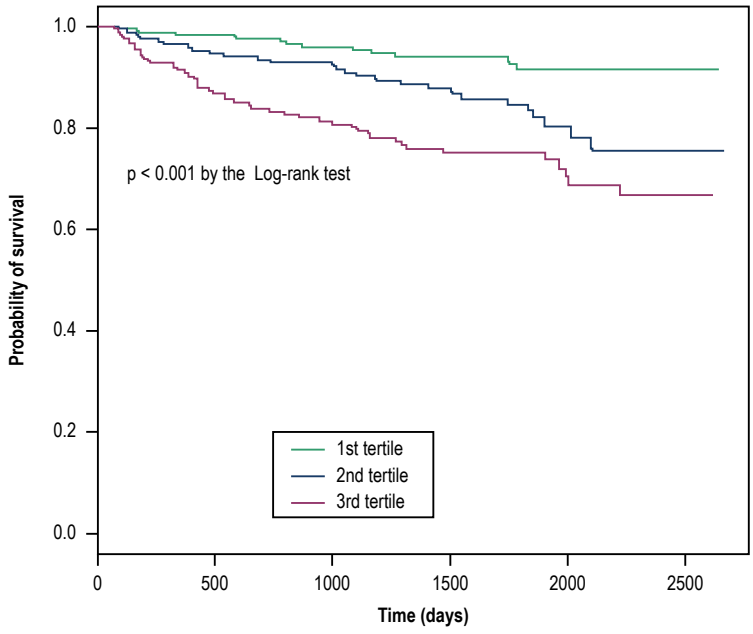
In 2012, two studies addressed the prognostic role of high-sensitivity cardiac troponin T (hs-cTnT) in the stabilized phase after a cardiac event. Ang et al.[13] followed 326 patients for a median of 30 months, after measurement of hs-cTnT 7 weeks post-ACS; after adjustment for age, ACS subtype, hypertension, type 2 diabetes, smoking, anemia, BNP, estimated GFR, and echocardiographic findings, hs-cTnT remained a strong predictor of death and AMI during follow-up.[1] Koenig et al.[24] studied 1050 patients for a median of 8.1 years after an ACS event or CABG, with hs-cTnT levels measured approximately 43 days after the event; patients in the highest quartile were at increased risk for new cardiac events throughout the observation period. One study published in 2014 also addressed the prognostic role of hs-cTnI after an ACS episode. White et al.[25] followed 7,836 patients who had suffered an ACS event; after a median of 6 years follow-up, patients in the highest tertile were at increased risk for CAD death and MI. Compared to our study population, these studies followed patients with similar ages and estimated GFR, but with lower baseline frequency of hypertension, diabetes, and dyslipidemia.

Table 1 – Baseline characteristics of the study population according to 25–90 day troponin tertile

Characteristic	1st tertile	2nd tertile	3rd tertile	p-value
Number of participants	179	171	175	
25–90 day troponin range	< 0.012	0.012–0.023	> 0.023	
ACS subtype (%)				
UA	80 (44.9)	47 (27.5)	24 (13.7)	
NSTEMI	67 (37.4)	77 (45.0)	86 (49.1)	< 0.001
STEMI	32 (17.9)	47 (27.5)	65 (37.1)	
Age* (years)	60 (51-68)	63 (55-70)	61 (53-73)	0.05
Male gender (%)	95 (53.1)	102 (59.6)	119 (68.0)	0.02
Previous history of CHD (%)	49 (29.2)	39 (23.8)	40 (25.2)	0.51
Family history of CHD (%)	52 (36.4)	43 (31.4)	50 (38.46)	0.46
Hypertension (%)	136 (78.2)	127 (75.1)	126 (73.3)	0.56
Diabetes (%)	61 (35.7)	61 (37.2)	67 (39.6)	0.75
Dyslipidemia (%)	87 (54.4)	85 (55.6)	75 (48.4)	0.40
Heart failure (%)	27 (16.2)	36 (22.4)	39 (23.8)	0.19
Chronic kidney disease (%)	5 (3.1)	6 (4.1)	15 (10.3)	0.02
Previous stroke (%)	17 (9.9)	15 (9.1)	21 (12.1)	0.91
Sedentary lifestyle (%)	117 (68.8)	106 (63.5)	127 (77.4)	0.02
Smoking status (%)				
Current	44 (25.6)	48 (28.7)	58 (33.9)	
Past	68 (39.5)	64 (38.3)	69 (40.4)	0.31
Never	60 (34.9)	55 (32.9)	44 (25.7)	
Body mass index*	27.1 (24.5-30.4)	26.6 (24.2-29.4)	26.0 (23.5-29.4)	0.05
Total cholesterol* (mg/dL)	174 (145-205)	169 (139-207)	174 (141-205)	
LDL cholesterol* (mg/dL)	101 (79-133)	103 (79-136)	109 (80-135)	0.65
HDL cholesterol* (mg/dL)	37 (31-44)	36 (31-44)	36 (30-44)	
Triglycerides* (mg/dL)	131 (100–190)	141 (97–192)	130 (97–181)	
Hemoglobin* (g/dL)	14.3 (13.4-15.2)	14.1 (13.1-15.2)	14.2 (12.9-15.4)	0.84
Troponin levels on admission† (mcg/L)	1.88 (0.09–9.20)	7.03 (1.16–41.97)	16.82 (3.05–44.16)	0.32
Estimated GFR-CKD-Epi* (ml/min/1.73 m^2)	83 (67-95)	79 (62-92)	71 (48-94)	<0.001
LVEF < 0.40 (%)	4 (3.5)	8 (6.6)	28 (21.9)	<0.001
Medication at 1st follow-up (%)				
Aspirin	155 (87.6)	143 (83.6)	134 (79.3)	0.12
Clopidogrel	92 (52.0)	100 (58.5)	82 (48.5)	0.17
Beta blocker	117 (66.1)	119 (69.6)	96 (56.8)	0.04
Statin	137 (77.4)	135 (78.9)	123 (72.8)	0.38
ACE inhibitor	120 (67.8)	108 (63.2)	94 (55.6)	0.06
Angiotensin receptor blocker	10 (5.6)	15 (8.8)	6 (3.6)	0.12

ACS: acute coronary syndrome; UA: unstable angina; NSTEMI: non-ST-elevation myocardial infarction; STEMI: ST-elevation myocardial infarction; CHD: coronary heart disease; LDL: low-density lipoprotein; HDL: high-density lipoproteina; GFR: glomerular filtration rate; LVEF: left ventricular ejection fraction; ACE: angiotensin-converting enzyme.

Outside the scope of ACS, several studies have also found an association between elevated cTn levels and risk of death. In patients with stable coronary heart disease, a greater risk for cardiovascular mortality and incidence of heart failure has been found in those with higher levels of hs-cTnT[26-28] and hs-cTnI.[29] Elevated circulating hs-cTnT was also shown to be independently associated with higher mortality in outpatients with stable heart failure,[30,31] and in patients with aortic stenosis.[32] Even in the general population, de Lemos et al.[33] found an association between high levels of hs-cTnT and poorer survival in a population-based cohort of 3546 individuals. These results suggest that persistently



Numbers at risk						
1st tertile	179	173	162	109	33	3
2nd tertile	171	157	147	98	39	5
3rd tertile	175	149	131	90	43	5

Figure 1 – *Kaplan-Meier curve for all-cause mortality according to hs-cTnI tertile measured 25 to 90 days after acute coronary syndrome.*

elevated levels of circulating cardiac troponins are general markers of higher risk for death in different populations, independently of age and comorbidities.

Some aspects of our study should be highlighted. First, it was conducted at a community-based hospital with no in-house cardiology staff; this type of medical care is received by many ACS patients in Brazil, but few prognostic studies have been published in this setting. Second, our sample size and long-term follow-up make this one of the largest studies with prognostic biomarkers in ACS patients in Brazil. In addition, because we searched for the death records of all patients who could not be contacted during follow-up, our analysis of all-cause mortality was not significantly affected by selection bias.

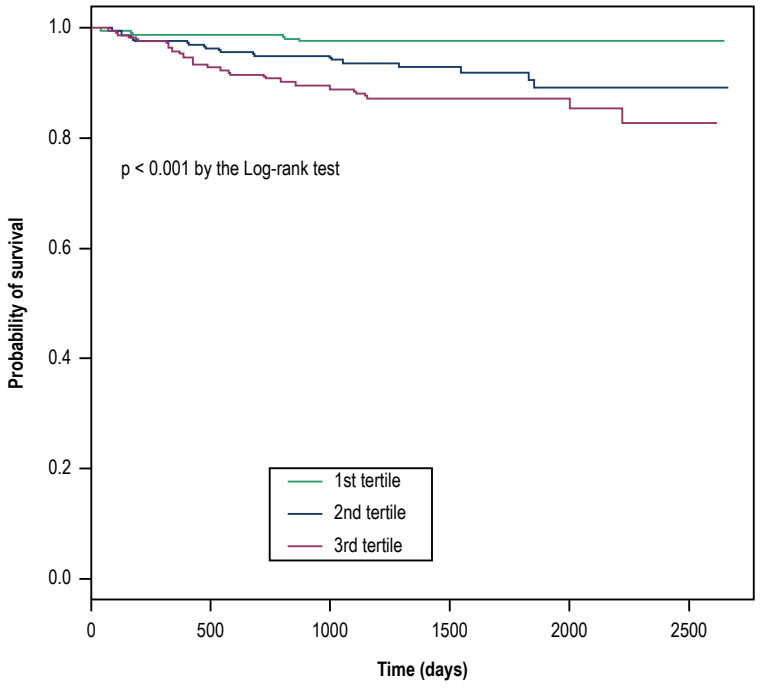
This study has some limitations. As in all single-center studies, outcomes in both groups could have been influenced by local practices. Since coronary interventions were not performed on-site, data regarding type of revascularization (if any) were not accessible for most patients and could not be accounted for in our Cox model. We also did not have data about the proportion of patients presenting with STEMI who received reperfusion therapy. Additionally, adherence to guideline recommended therapies for ACS was suboptimal in our cohort. Lastly, even though we used standardized assays to measure all troponin levels in the subacute phase of ACS, these were not the same assays used on admission of these patients to the hospital; this precluded further analyses of evolutive trends in hs-cTnI levels through time. Despite these limitations, our findings could demonstrate an association between elevated levels of hs-cTnI and worse outcomes in this highly admixed population.

Conclusions

Elevated levels of hs-cTnI in the stabilized phase after an ACS event are associated with higher all-cause and cardiovascular mortality that is independent from comorbidities, renal function and left ventricular ejection fraction. These findings may potentially enhance risk stratification of post-ACS patients in the ambulatory setting.

Author contributions

Conception and design of the research: Castro LT, Bittencourt MS, Lotufo PA, Bensenor IM; acquisition of data: Castro LT, Santos IS, Goulart AC, Lotufo PA, Bensenor IM; analysis and interpretation of the data: Castro LT, Santos IS, Goulart AC, Pereira AC, Staniak HL, Bittencourt MS, Bensenor IM; statistical analysis: Castro LT, Santos IS, Goulart AC, Bittencourt MS, Bensenor IM; writing of the manuscript: Castro LT, critical



1st tertile	179	173	162	109	33	3
2nd tertile	171	157	147	98	39	5
3rd tertile	175	149	131	90	43	5

Numbers at risk

Figure 2 – *Kaplan-Meier curve for cardiovascular mortality according to hs-cTnI tertile measured 25 to 90 days after acute coronary syndrome.*

Table 2 – Hazard ratios and respective 95% confidence intervals on crude and age-sex adjusted models, and two multivariate adjusted models of Cox regression analysis

	Crude	Age-sex adjusted	Multivariate adjusted (Model 1)	Multivariate adjusted (Model 2)
All-cause mortality				
1st tertile	(reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)
2nd tertile	2.44 (1.23-4.81)	2.02 (1.02-4.01)	1.86 (0.86-4.05)	2.33 (0.74-7.33)
3rd tertile	4.20 (2.22-7.94)	4.14 (2.19-7.86)	3.84 (1.92-8.12)	6.53 (2.12-20.14)
Cardiovascular mortality				
1st tertile	(reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)
2nd tertile	3.77 (1.24-11.47)	2.90 (0.95-8.90)	2.66 (0.72-9.84)	1.30 (0.21-8.00)
3rd tertile	6.05 (2.08-17.57)	5.65 (1.94-16.47)	4.90 (1.35-17.82)	5.89 (1.08-32.27)

Model 1: Adjusted for age, sex, ACS subtype, hypertension, diabetes, dyslipidemia, smoking history, body mass index, and medication use at first follow-up (25–90 days after ACS). Model 2: Model 1 with addition of estimated GFR < 60 ml/min/1.73 m² and LVEF < 0.40.

revision of the manuscript for intellectual content: Castro LT, Santos IS, Goulart AC, Pereira AC, Staniak HL, Bittencourt MS, Lotufo PA, Bensenor IM.

Potential Conflict of Interest

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

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Study Association

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Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Hospital Universitário da USP under the protocol number 866/08. 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. GBD 2013 Mortality and Causes of Death Collaborators. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2015;385(9963):117-71.
2. Amsterdam EA, Wenger NK, Brindis RG, Casey DE, Ganiats TG, Holmes DR, et al; ACC/AHA Task Force Members. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;130(25):e344-426. Erratum in: Circulation. 2014 Dec;130(25):e433-4.
3. O'Gara PT, Kushner FG, Ascheim DD, Casey DE, Chung MK, de Lemos JA, et al; American College of Emergency Physicians; Society for Cardiovascular Angiography and Interventions. 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2013;61(4):e78-140.
4. Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F, et al; ESC Scientific Document Group. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). Eur Heart J. 2016;37(3):267-315.
5. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, et al; ESC Scientific Document Group. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J. 2018;39(2):119-77.
6. Théroux P, Fuster V. Acute coronary syndromes: unstable angina and non-Q-wave myocardial infarction. Circulation. 1998;97(12):1195-206.
7. Hamm CW, Ravkilde J, Gerhardt W, Jorgensen P, Peheim E, Ljungdahl L, et al. The prognostic value of serum troponin T in unstable angina. N Engl J Med. 1992;327(3):146-50.
8. Antman EM, Tanasijevic MJ, Thompson B, Schactman M, McCabe CH, Cannon CP, et al. Cardiac-specific troponin I levels to predict the risk of mortality in patients with acute coronary syndromes. N Engl J Med. 1996;335(18):1342-9.
9. James SK, Armstrong P, Barnathan E, Califf R, Lindahl B, Siegbahn A, et al; GUSTO-IV-ACS Investigators. Troponin and C-reactive protein have different relations to subsequent mortality and myocardial infarction after acute coronary syndrome: a GUSTO-IV substudy. J Am Coll Cardiol. 2003;41(6):916-24.
10. Lindahl B, Toss H, Siegbahn A, Venge P, Wallentin L. Markers of myocardial damage and inflammation in relation to long-term mortality in unstable coronary artery disease. FRISC Study Group. Fragmin during Instability in Coronary Artery Disease. N Engl J Med. 2000;343(16):1139-47.
11. Lindahl B, Diderholm E, Lagerqvist B, Venge P, Wallentin L, FRISC II (Fast Revascularization during InStability in CAD) Investigators. Mechanisms behind the prognostic value of troponin T in unstable coronary artery disease: a FRISC II substudy. J Am Coll Cardiol. 2001;38(4):979-86.
12. Ndrepepa G, Braun S, Mehilli J, Birkmeier KA, Byrne RA, Ott I, et al. Prognostic value of sensitive troponin T in patients with stable and unstable angina and undetectable conventional troponin. Am Heart J. 2011;161(1):68-75. Erratum in: Am Heart J. 2013;165(6):1032.
13. Ang DS, Kao MP, Dow E, Lang C, Struthers A. The prognostic value of high sensitivity troponin T 7 weeks after an acute coronary syndrome. Heart. 2012;98(15):1160-5.
14. Goulart A, Santos IS, Sitnik D, Staniak HL, Fedeli LM, Pastore CA, et al. Design and baseline characteristics of a coronary heart disease prospective cohort: two-year experience from the strategy of registry of acute coronary syndrome study (ERICO study). Clinics (Sao Paulo). 2013;68(3):431-4.
15. Santos IS, Goulart AC, Brandão RM, Santos RC, Bittencourt MS, Sitnik D, et al. One-year mortality after an acute coronary event and its clinical predictors: the ERICO study. Arq Bras Cardiol. 2015;105(1):53-64.
16. Eggers KM, Lagerqvist B, Venge P, Wallentin L, Lindahl B. Persistent cardiac troponin I elevation in stabilized patients after an episode of acute coronary syndrome predicts long-term mortality. Circulation. 2007;116(17):1907-14.
17. Vashistha V, Lee M, Wu YL, Kaur S, Ovbiagele B. Low glomerular filtration rate and risk of myocardial infarction: a systematic review and meta-analysis. Int J Cardiol. 2016 Nov 15;223:401-9.
18. Goodman SG, Huang W, Yan AT, Budaj A, Kennelly BM, Gore JM, et al; Expanded Global Registry of Acute Coronary Events (GRACE2) Investigators. The expanded Global Registry of Acute Coronary Events: baseline characteristics, management practices, and hospital outcomes of patients with acute coronary syndromes. Am Heart J. 2009;158(2):193-201.
19. Roger VL, Weston SA, Gerber Y, Killian JM, Dunlay SM, Jaffe AS, et al. Trends in incidence, severity, and outcome of hospitalized myocardial infarction. Circulation. 2010;121(7):863-9.
20. Nicolau JC, Franken M, Lotufo PA, Carvalho AC, Neto JA, Lima FG, et al. Use of demonstrably effective therapies in the treatment of acute coronary syndromes: comparison between different Brazilian regions. Analysis of the Brazilian Registry on Acute Coronary Syndromes (BRACE). Arq Bras Cardiol. 2012;98(4):282-9.
21. Capasso JM, Malhotra A, Li P, Zhang X, Scheuer J, Anversa P. Chronic nonocclusive coronary artery constriction impairs ventricular function, myocardial structure, and cardiac contractile protein enzyme activity in rats. Circ Res. 1992;70(1):148-62.
22. Olivetti G, Abbi R, Quaini F, Kajstura J, Cheng W, Nitahara JA, et al. Apoptosis in the failing human heart. N Engl J Med. 1997;336(16):1131-41.
23. White HD. Pathobiology of troponin elevations: do elevations occur with myocardial ischemia as well as necrosis? J Am Coll Cardiol. 2011;57(24):2406-8. Erratum in: J Am Coll Cardiol. 2011;58(22):2356.
24. Koenig W, Breitling LP, Hahmann H, Wüsten B, Brenner H, Rothenbacher D. Cardiac troponin T measured by a high-sensitivity assay predicts recurrent cardiovascular events in stable coronary heart disease patients with 8-year follow-up. Clin Chem. 2012;58(8):1215-24.
25. White HD, Tonkin A, Simes J, Stewart R, Mann K, Thompson P, et al; LIPID Study Investigators. Association of contemporary sensitive troponin I levels at baseline and change at 1 year with long-term coronary events following myocardial infarction or unstable angina: results from the LIPID Study (Long-Term Intervention With Pravastatin in Ischaemic Disease). J Am Coll Cardiol. 2014;63(4):345-54.
26. Biener M, Giannitsis E, Kuhner M, Zelniker T, Mueller-Hennessen M, Vafaie M, et al. Risk prediction in stable cardiovascular disease using a high-sensitivity cardiac troponin T single biomarker strategy compared to the ESC-SCORE. Open Heart. 2018;5(1):e000710.

27. McQueen MJ, Kavsak PA, Xu L, Shestakovska O, Yusuf S. Predicting myocardial infarction and other serious cardiac outcomes using high-sensitivity cardiac troponin T in a high-risk stable population. Clin Biochem. 2013;46(1-2):5-9.

28. Omland T, de Lemos JA, Sabatine MS, Christophi CA, Rice MM, Jablonski KA, et al; Prevention of Events with Angiotensin Converting Enzyme Inhibition (PEACE) Trial Investigators. A sensitive cardiac troponin T assay in stable coronary artery disease. N Engl J Med. 2009;361(26):2538-47.

29. Omland T, Pfeffer MA, Solomon SD, de Lemos JA, Rosjo H, Šaltytė Benth J, et al; PEACE Investigators. Prognostic value of cardiac troponin I measured with a highly sensitive assay in patients with stable coronary artery disease. J Am Coll Cardiol. 2013;61(12):1240-9. Erratum in: J Am Coll Cardiol. 2014;63(2):195-200.

30. Latini R, Masson S, Anand IS, Carlson M, Vago T, Angelici L, et al; Val-HeFT Investigators. Prognostic value of very low plasma concentrations of troponin T in patients with stable chronic heart failure. Circulation. 2007;116(11):1242-9.

31. Grodin JL, Neale S, Wu Y, Hazen SL, Tang WH. Prognostic comparison of different sensitivity cardiac troponin assays in stable heart failure. Am J Med. 2015;128(3):276-82.

32. Røsjø H, Andreassen J, Edvardsen T, Omland T. Prognostic usefulness of circulating high-sensitivity troponin T in aortic stenosis and relation to echocardiographic indexes of cardiac function and anatomy. Am J Cardiol. 2011;108(1):88-91.

33. de Lemos JA, Drazner MH, Omland T, Ayers CR, Khera A, Rohatgi A, et al. Association of troponin T detected with a highly sensitive assay and cardiac structure and mortality risk in the general population. JAMA. 2010;304(22):2503-12. Erratum in: JAMA. 2011;305(12):1200.

Cohort Studies with Mortality Data from the Brazilian Population: a Rising National Requirement

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Short Editorial related to the article: Elevated High-Sensitivity Troponin I in the Stabilized Phase after an Acute Coronary Syndrome Predicts All-Cause and Cardiovascular Mortality in a Highly Admixed Population: A 7-Year Cohort

Cohort studies assessing mortality predictors are extremely important to determine public health priorities and are a central issue in clinical decision making. These studies are particularly relevant in low-to-middle income countries whereas resources addressed to health care are limited and can be better managed. Nevertheless, traditionally epidemiological studies assessing the impact of different risk factors on mortality have historically been conducted in high-income countries.[1]

Results from cohort studies conducted in the developed world have been extrapolated and widely used in developing countries. This can be an issue given population and disease management differences, reinforcing the need to increase publications of long-term follow-up cohort studies with mortality data from low-to-middle income countries.

Efforts have been made along the years by a number of research groups in Brazil and around the world to progressively generate mortality data from low-to-middle income countries that are accurate, reliable and derived from well-designed cohort studies. In this number of ABC Cardiol, Castro et al.[2] published one of the many examples of these efforts.

Aiming to assess the hypothesis that elevated levels of High-Sensitivity Troponin I (hs-cTnI) measured 25 to 90 days after an acute coronary syndrome (ACS) are associated with higher all-cause and cardiovascular mortality the authors used data from the ERICO study (Strategy of Registry of Acute Coronary Syndrome).[3,4] This prospective cohort was designed to investigate the ACS epidemiology in Brazil and conducted at a secondary general hospital in São Paulo. Patients who were 35 years old or older with the acute coronary syndrome were enrolled consecutively. Sociodemographic, medical, and treatment data were obtained at admission, along with the blood sample collection. After 30 days, medical history was updated, blood and urinary samples were recollected, and additionally, a retinography, carotid intima-media thickness, heart rate variability and pulse-wave velocity were performed. Food frequency, physical activity, sleep apnea and depression were evaluated using specific questionnaires. Six months and annually after the acute event, telephone information was collected.[3,4]

Keywords

Cohort Studies; Mortality; Public Health; Clinical Decision Making; Risk factors; Acute Coronary Syndrome.

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Levels of hs-cTnI in 525 patients 25 to 90 days after admission for an ACS event were measured and mortality data were obtained in a seven years follow-up period. Patients in the highest tertile of hs-cTnI had a greater hazard ratio (HR) for all-cause mortality compared to the lowest tertile, after adjustment for age, sex, known cardiovascular risk factors, medication use, and demographic factors (HR: 3.84, 95% CI: 1.92-8.12). These findings persisted after further adjustment for estimated glomerular filtration rate < 60 ml/min/1.73m^2 and left ventricular ejection fraction < 0.40 (HR: 6.53, 95% CI: 2.12-20.14). Cardiovascular mortality was significantly higher in the highest tertile after adjustment for age and sex (HR: 5.65, 95% CI: 1.94-16.47) and both in the first (HR: 4.90, 95% CI: 1.35-17.82) and second models of multivariate adjustment (HR: 5.89, 95% CI: 1.08-32.27). The authors conclude that elevated levels of hs-cTnI in the stabilized phase after an ACS event carry long-term prognostic information that is independent of comorbidities, renal function and left ventricular ejection fraction.

Although the findings are not completely unique as the authors mention in the manuscript, they are unique for the Brazilian population (a highly admixed population). Additionally, some aspects of Castro`s study improve its strengths. It was performed at a community hospital, without a specific cardiologic team which is the reality of most hospitals in Brazil. Large sample size and long-term follow-up, probably representing one of the most important studies with prognostic data using biomarkers in patients with ACS in our country. Death records of all patients (either contacted or not during follow-up) were obtained, suggesting no bias in the mortality from all causes assessment.

The main limitation of Castro's et al.[2] study is the single centre aspect. It was discussed in the manuscript, but some aspects of the results should be highlighted since they minimize this limitation. Most participants were males and had a high prevalence of hypertension. Those sociodemographic characteristics and cardiovascular comorbidities are similar to those of large international records, such as the registry Global Acute coronary events (GRACE).[5] Another similarity with international trends[6] is in the frequency of ST-segment elevation myocardial infarction (41.5% of the participants), which represented the most frequent type of SCA in Castro`s study. Similarities were also found with the Brazilian Registry of acute coronary syndromes (BRACE), which included hospitals from all regions of Brazil. Medications used in the first follow-up visit were similar in comparison with the treatment received at the discharge of the participants in the BRACE registry:[7] use of aspirin (83.6% vs. 86.0%, respectively), clopidogrel (53.0% vs. 50.1%), beta-blockers (64.2% vs. 69.8%), ACE inhibitors/angiotensin receptor blockers (68.3% vs. 70.6 %) and statins (76.4% vs. 82.7%).

Short Editorial

ABC Cardiol is the most important journal dedicated to publishing cardiovascular research generated in Brazil. Publish national cohort studies with mortality data, particularly cardiovascular mortality data should be a priority. In this number, this priority was fulfilled with a great manuscript.

References

1. Inuzuka S, Jardim PCV, Abrahams-Gessel S, Souza LG, Rezende AC, Perillo NB, et al. Self-rated health status and illiteracy as death predictors in a Brazilian cohort. PLoS One. 2018;13(7):e020050
2. Castro LT, Santos IS, Goulart AC, Pereira AC, Staniak HL, Bittencourt MS, et al. Elevated High-Sensitivity Troponin I in the Stabilized Phase after an Acute Coronary Syndrome Predicts All-Cause and Cardiovascular Mortality in a Highly Admixed Population: A 7-Year Cohort. Arq Bras Cardiol. 2019; 112(3):230-237.
3. Goulart A, Santos IS, Sitnik D, Staniak HL, Fedeli LM, Pastore CA, et al. Design and baseline characteristics of a coronary heart disease prospective cohort: two-year experience from the strategy of registry of acute coronary syndrome study (ERICO study). Clinics (Sao Paulo). 2013;68(3):431-4.
4. Santos IS, Goulart AC, Brandão RM, Santos RC, Bittencourt MS, Sitnik D, et al. One-year mortality after an acute coronary event and its clinical predictors: the ERICO study. Arq Bras Cardiol. 2015;105(1):53-64.
5. Goodman SG, Huang W, Yan AT, Budaj A, Kennelly BM, Gore JM, et al; Expanded Global Registry of Acute Coronary Events (GRACE2) Investigators. The expanded Global Registry of Acute Coronary Events: baseline characteristics, management practices, and hospital outcomes of patients with acute coronary syndromes. Am Heart J. 2009;158(2):193-201.
6. Roger VL, Weston SA, Gerber Y, Killian JM, Dunlay SM, Jaffe AS, et al. Trends in incidence, severity, and outcome of hospitalized myocardial infarction. Circulation. 2010;121(7):863-9.
7. Nicolau JC, Franken M, Lotufo PA, Carvalho AC, Neto JA, Lima FG, et al. Use of demonstrably effective therapies in the treatment of acute coronary syndromes: comparison between different Brazilian regions. Analysis of the Brazilian Registry on Acute Coronary Syndromes (BRACE). Arq Bras Cardiol. 2012;98(4):282-9.

Cardiac Evaluation in the Acute Phase of Chagas' Disease with Post-Treatment Evolution in Patients Attended in the State of Amazonas, Brazil

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Abstract

Background: In the past two decades, a new epidemiological profile of Chagas' disease (CD) has been registered in the Brazilian Amazon where oral transmission has been indicated as responsible for the increase of acute cases. In the Amazonas state, five outbreaks of acute CD have been registered since 2004. The cardiac manifestations in these cases may be characterized by diffuse myocarditis, with alteration in the electrocardiogram (ECG) and transthoracic echocardiogram (TTE).

Objective: To perform a cardiac evaluation in autochthonous patients in the acute phase and at least one year after submitted to treatment for acute CD and evaluate the demographic variables associated with the presence of cardiac alterations.

Methods: We evaluated patients diagnosed with acute CD through direct parasitological or serological (IgM) methods from 2007 to 2015. These patients were treated with benznidazole and underwent ECG and TTE before and after treatment. We assumed a confidence interval of 95% (CI 95%, $p < 0.05$) for all variables analyzed.

Results: We observed 63 cases of an acute CD in which oral transmission corresponded to 75%. Cardiac alterations were found in 33% of the cases, with a greater frequency of ventricular repolarization alteration (13%), followed by pericardial effusion (10%) and right bundle branch block and left anterior fascicular block (2%). The follow-up occurred in 48 patients with ECG and 25 with TTE for a mean period of 15.5 ± 4.1 months after treatment. Of these, 8% presented normalization of the cardiac alterations in ECG, 62.5% remained with the normal exams. All of the patients presented normal results in TTE in the post-treatment period. As for the demographic variables, isolated cases presented more cardiac alterations than outbreaks ($p = 0.044$) as well as cases from Central Amazonas mesoregion ($p = 0.020$).

Conclusions: Although cardiac alterations have not been frequent in most of the studied population, a continuous evaluation of the clinical-epidemiological dynamics of the disease in the region is necessary in order to establish preventive measures. (Arq Bras Cardiol. 2019; 112(3):240-246)

Keywords: Chagas Disease/epidemiology; Amazoniany Ecosystem; Trypanosoma cruzi; Chagas Cardiomiopathy/physiopathology.

Introduction

Chagas disease (CD) is an emerging infection caused by *Trypanosoma cruzi,* discovered by the physician Carlos Chagas, in 1909. He described the clinical manifestations, as well as the morphological features of the parasite.[1] It is estimated that approximately 75 million people are at risk of acquiring the disease and 8 million are indeed infected by the parasite worldwide.[2]

CD presents two clinical phases: an acute and a chronic phase. In acute CD, nonspecific clinical symptoms may delay early diagnosis and treatment representing a public health concern. In some cases, the absence of symptoms may lead to a chronic indeterminate form or later evolving to a digestive, cardiac or mixed form.[3,4] Oral infection is more likely to cause a symptomatic response and increase the susceptibility to higher mortality rate and may result in unique cardiac characteristics with the most concerning symptom of this phase being diffuse myocarditis with alterations in the ECG and TTE results.[5,6]

Due to the parasite's genetic characteristics that are thought to be associated with the clinical manifestations of CD, in 1998 Tibayrenc[7] proposed a new classification for the parasites' genetic diversity. In a review in 2009, a consensus established the division into six genotypes, named "Discrete Typing Units" (DTUs): TcI-TVI.[8]

Multiple acute cases have been reported in the Brazilian Amazon with most cases concentrated in Pará and Amazonas,[9-14] being the first cases registered in 1968 and 1980, respectively.[15,16] Afterwards, micro-epidemics of acute cases have been reported and mostly associated with the ingestion of contaminated food, such as açaí fruits, bacaba

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fruits and meat of wild mammals.[3,17,18] In the last two decades, many new oral transmissions related acute cases have been registered with six outbreaks in the state of Amazonas[5,19-21] and *T. cruzi* DTU described to be related to these cases are TcIV and Z3 (TcIII/TcIV).[21,22]

Although in the Brazilian Amazon region CD has been widely studied, in the state of Amazonas there still are few data regarding the epidemiological profile of acute CD and more importantly, works related to the cardiac manifestations and post-treatment follow-up are scarce in this group of patients. For that matter, this work aimed to describe cardiac alterations in autochthones patients who had acute CD at least one year after submitted to treatment with benznidazole.

Methods

This was a longitudinal study of patients attended at the Francisca Mendes University Hospital for cardiac follow-up. All of these patients have a confirmed diagnosis of acute CD at the Tropical Medicine Foundation Dr Heitor Vieira Dourado, from January of 2007 to July of 2015.

Study population

Patients were included considering the following criteria: a positive laboratory exam, direct parasitological test (thick blood smear or natural xenodiagnosis) or a reactive immunological essay (IgM anti-*T. cruzi*) (Enzyme-linked immunoassay – ELISA and/or indirect immunofluorescence assay– IFA) with an epidemiological history such as being originally from the Brazilian Amazon region. All patients were excluded if they referred any previous travel to another Brazilian region or foreign country, did not adhere to or had an incomplete treatment.

Procedures for data collection and treatment

Cardiological exams, standard 12-lead electrocardiogram (ECG) and transthoracic echocardiogram (TTE), was analyzed before treatment and at least one year after the end of treatment. In order to obtain data of patients in pre-treatment stage, a retrospective analysis was made of cases registered in the electronic medical record iDoctor® from 2007 to 2015 in order to access the results of the ECG and TTE as well as demographical, epidemiological and clinical data. During the stage of post-treatment, a prospective evaluation was made which included a clinical examination and performing ECG and TTE in all patients.

The standard 12-lead ECG tracing was done using the software Wincardio (Micromed) and the TTE was performed following the recommendations of the American Society of Echocardiography, using the GE, Vivid 3 equipment.

All patients underwent treatment with benznidazole (Rochagan®) 5-7 mg/kg, for 60 days according to the II Brazilian Guidelines in Chagas Disease of 2015.[23] And any cardiac alteration in the ECG or TTE was considered for the description as cardiac alterations in the acute phase of CD.

Statistical analysis

Clinical and epidemiological data were organized using *Excel 2016* and the analysis was done using *Stata/MP 13.0*. For categorical variables, Fisher's exact test was used and the results are presented in tables of absolute and relative frequencies followed by the corresponding p-value. For continuous variables, normal distribution was tested using Shapiro-Wilk normality test, if the normal distribution was observed, an unpaired t-test (Student t-test) was executed and results presented by mean ± SD, otherwise, the Wilcoxon rank-sum (Mann-Whitney) test was used and the results are presented by median and interquartile intervals. We assumed a confidence interval of 95% (CI 95%, $p < 0.05$) for all statistical tests.

Ethical consideration

This study was approved by the Research Ethics Committee of the Universidade do Estado do Amazonas and is in agreement with the Resolution 466/12 of the Brazilian National Health Council (approval number 923.701/2014).

Results

Case distribution, route of transmission and T. cruzi strain

During the study period, 63 patients with confirmed acute CD were evaluated, all originally from the state of Amazonas. The diagnosis was 98% by a direct parasitological method, thick blood smear. The median age was 29 [16-44] years old, predominantly male (60%). Of these, 44 (70%) were part of an outbreak that was registered from 2007 to 2015, the other 19 (30%) cases are distributed between isolated acute cases associated with oral transmission or classical vector transmission. There were more registered cases of cardiac alterations in the isolated cases reported then in the outbreaks (48% vs. 21%, $p = 0.044$).

A wide distribution of acute cases is best shown in Figure 1, there can be noticed that most municipalities of the Central Amazonas mesoregion are affected. On the other hand, the Southwest mesoregion concentrated the higher frequency of acute cases corresponding to 33 (53%) cases, and 31 of them being from the outbreaks that happened in Carauari in 2011 and 2015. Cardiac alterations were present in 69% in the Central Amazonas mesoregion which represented a statistical significance ($p = 0.020$).

With regards to the strains of *T. cruzi,* it was possible to isolate in 35 cases (56%) of which 22 (63%) were Z3 (TcIII/TcIV) and 11 (31%) were TcIV and 2 (6%) TcI, both Z3 (TcIII/TcIV) and TcIV associated with acute oral transmission from outbreaks (Table 1).

Cardiac evaluation in Group 1 (pre-treatment)

We observed 33% of any cardiac alterations in our study population. All 63 patients had an ECG prior to initiate the standard treatment with benznidazole. Of these, 44 (70%) presented normal results. Yet, abnormalities such as ventricular repolarization alterations were common. Regarding the TTE results, 87% presented normal parameters. (Table 2). Although the majority of our population presented normal exams, it is noteworthy the death of a three-month-old infant due to severe cardiac condition.

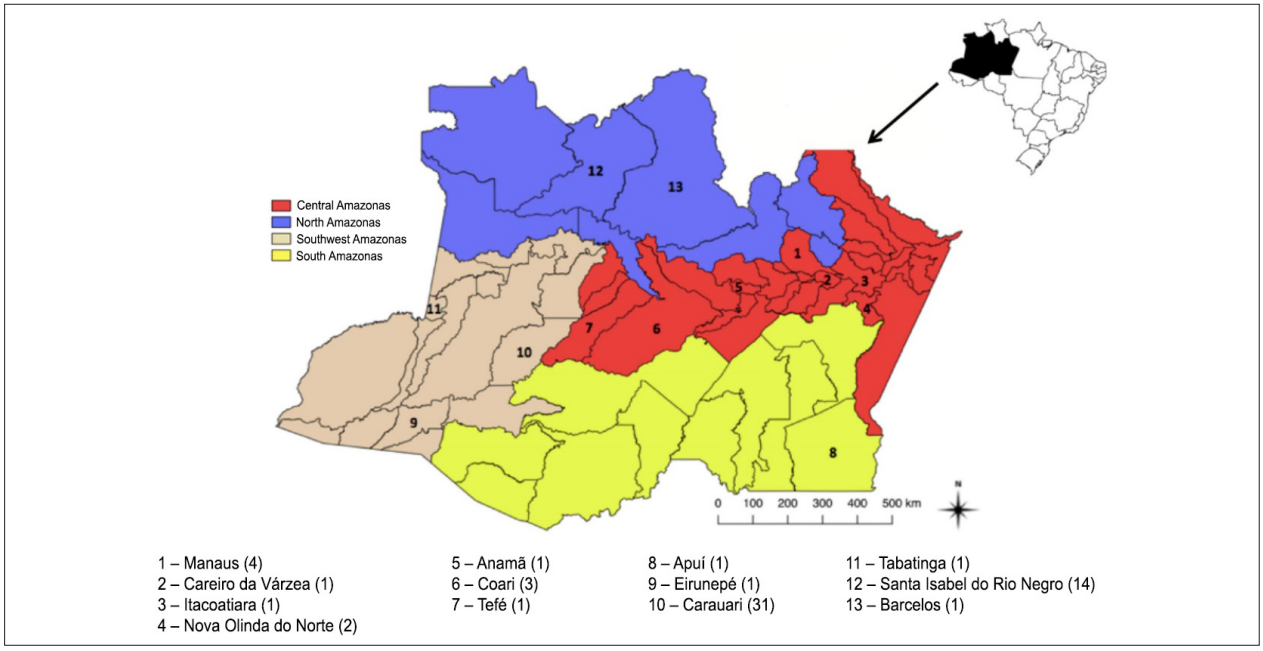

Figure 1 – *Geographical distribution of the acute cases evaluated in the state of Amazonas. In parenthesis, the number of patients for each municipality.*

Cardiac evaluation in Group 2 (post-treatment)

The follow up cardiac evaluation was done at least one year after the end of the treatment regimen established. It occurred in a mean period of 15.5 months. It was possible to reevaluate 48 patients with ECG and 25 with TTE. Among the 48 patients that were evaluated with an ECG, 35 were normal in the pre-treatment period, of the 30 (86%) continued with normal results and 5 (14%) presented alterations in the post-treatment period. Thirteen patients had alterations in ECG before treatment, 9 (69%) of them remained altered and 4 (31%) evolved to a normal ECG. Also, during the pre-treatment period, 4 (16%) out of the 25 patients reevaluated had abnormalities examined in TTE and all of them evolved completely after treatment (Table 3 and 4).

Discussion

Case distribution, route of transmission and T. cruzi strain

CD in the Brazilian Amazon Region has changed its epidemiological profile in the past several years and most of the cases as being acute and due to oral transmission. A peculiarity of our region is the distance between the municipality of the outbreaks occurrence and the state's capital, Manaus. Therefore, most patients are unable to travel and get the complete cardiac follow-up.

During the period that comprised the study, 2007 to 2015, four outbreaks of six already registered in the Amazonas state with a total of 85 cases reported. All of them somehow associated with oral transmission due to açaí consumption. Most times, individuals don't present cardiac alterations during the acute phase, thus, it's thought that our region presents milder symptoms that might be associated with the *T. cruzi* DTU present in the Brazilian Amazon.

We observed that only one patient was diagnosed by an immunological assay (IgM anti-*T. cruzi*) while all the others had their diagnosis confirmed by thick blood smear. This can be related to the intense qualification of microscopists and all health professionals working in the Malaria Laboratory at the Tropical Medicine Foundation. Considering that most patients arrive with febrile syndrome mostly suspected to malaria infection, they are constantly being trained for the identification of the protozoan *Trypanosoma cruzi* which allows improving the surveillance of acute cases of CD in the state.[24]

In our study population, we were able to find that among acute cases that had *Trypanosoma cruzi* strain identified, TcIV was present in patients from outbreaks. This is best described by Monteiro et al.[21] Although TcI and Z3 (TcIII/TcIV) have also been identified in humans,[22] the pathogenicity of these strains is still not well known, but it's believed to be the cause of low morbidity when compared to endemic areas that present other strain of *T. cruzi,* TcII.[25]

Evaluation of cardiac alterations during the pre-treatment and post-treatment stages

Cardiac alterations during acute phase though in small proportion (33%) has highlighted the importance of continuous investigation for chronic chagasic cardiopathy, as it is not certain that treatment with benznidazole can indeed eliminate the chance of the patient not evolving to a chronic condition of the disease.[6,26]

Analyzing the demographical variables with the presence of any cardiac alterations due to acute infection by *T. cruzi,* it is possible to observe a significant statistical result for the Central Amazonas mesoregion ($p = 0.020$) and the isolated cases ($p = 0.044$). Although it's possible to think that the higher frequency of cardiopathy in the Central mesoregion might be

Table 1 – Baseline characteristics of acute Chagas' disease patients treated with benznidazol

		Group		
Variable	**Total (n = 63)**	**Cardiac alterations (n = 21)**	**No Cardiac alterations (n = 42)**	**p-value**
Age (y)	29 [16-44]	38 [15-44]	26.5 [17-44]	0.694*
Gender				**0.588†**
Male	38 (60%)	14 (67%)	24 (57%)	
Female	25 (40%)	7 (33%)	18 (43%)	
Transmission				**0.364†**
Oral	47 (75%)	14 (67%)	33 (79%)	
Vector	16 (25%)	7 (33%)	9 (21%)	
Case				**0.044†**
Outbreak	44 (70%)	11 (52%)	33 (79%)	
Isolated	19 (30%)	10 (48%)	9 (21%)	
Origin (Mesoregion)				**0.020†**
Central Amazonas	13 (21%)	9 (43%)	4 (10%)	
North Amazonas	15 (24%)	3 (14%)	12 (29%)	
Southwest Amazonas	33 (53%)	9 (43%)	24 (59%)	
South Amazonas	1 (2%)	-	1 (2%)	
T. cruzi DTU				**0.355†**
TcI	2 (3%)	2 (9%)	-	
TcIV	11 (17%)	2 (9%)	9 (21%)	
Z3 (TcIII/TcIV)	22 (35%)	9 (43%)	13 (31%)	
ND	28 (44%)	8 (38%)	20 (48%)	
Follow-up period (y)	15.5 ± 4.1	14 ± 4	16.4 ± 4.1	0.050**

*Data are expressed as median [IQ25%-IQ75%] and mean ± SD; In parenthesis are the percentage of the total group; ND: not described; Obs.: It was not possible to obtain the provenance of one case. *Wilcoxon rank-sum (Mann-Whitney) test. **Unpaired t-test (Student t test). † Fisher's exact test.*

due to the location of state's capital, Manaus, the number of cardiopathy cases in Manaus was very low (n = 4).

Also, higher frequency of cardiopathy reported in isolated acute cases (48%) might suggest a possible association either by oral or classical vector transmission with the strain of the protozoan, for which TcI was already found in all isolated cases of CD, associated to chronic CD and Chagas cardiomyopathy.[27,28] And the strain TcIV has been reported in outbreaks.[21] But this association is not possible to affirm considering the low number of patients with identified strain of the parasite.

During cardiac evaluation of the acute phase, most of the patients presented normality in both ECG or TTE examination. In the post-treatment period, we observed that most of the patients evolved to a normal result in the cardiological examinations. Pericardial effusion resolved very well, but ventricular repolarization alteration remained in four patients even after treatment. A factor that has been reported in other follow-up examination of acute cases to be undefined due to an unfamiliarity of a predictor parameter of cure.[6,13,14]

Cardiac alterations in the state of Amazonas are not frequent, but the knowledge is still scarce regarding the whole transmission dynamic and possible influences in a long-term period. Acute cases reported in the neighboring state of Pará presented serious cardiac involvement, with three died due to severe myocarditis, renal failure and cardiac tamponade.[19] In a study carried out by Ferreira et al.[29] in the Amazon region, five cases were reported of which two were from Pará and three from Amazonas, all of them presented reversed cardiac alterations and no deaths. In this study, one death was registered in a three-month-old infant, who presented a cardiogenic shock and meningoencephalitis due vector transmission with the presence of chagoma, a localized swelling at the site of inoculation. This remarkable difference suggests that the clinical manifestations and mortality is lower in the state of Amazonas, though is unknown the reason.

Study limitations

This was a unicentric longitudinal study, with a small study population and most of the participants living in the countryside of the state. These factors didn't allow a complete follow-up, contributing to a loss of patients. Also, it was possible to obtain the strains of the parasite only from patients that were recruited more recently, which limited the genetic characterization.

Table 2 – Electrocardiogram, transthoracic echocardiogram alterations of acute Chagas' disease patients before and after treatment

Variable	Group (n = 63)	
	Pre-treatment	Post-treatment
Electrocardiogram	**(n = 63)**	**(n = 48)**
Ventricular reporalization alteration	8 (13%)	4 (8%)
Left anterior fascicular block	1 (2%)	1 (2%)
Right bundle branch block	1 (2%)	1 (2%)
Right bundle branch block + left anterior fascicular block	2 (3%)	2 (4%)
Low QRS voltage	2 (3%)	-
Bradycardia	-	3 (6%)
Incomplete right bundle branch block	1 (2%)	2 (4%)
Ventricular extrasystols	1 (2%)	1 (2%)
Atrial fibrillation	1 (2%)	-
Tachycardia	2 (3%)	-
Normal	44 (70%)	34 (71%)
Echocardiogram	**(n = 31)**	**(n = 25)**
Pericardial effusion	3 (10%)	-
Left ventricular dysfunction	1 (3%)	-
Normal	27 (87%)	25 (100%)

Data are expressed as frequency and in parenthesis are the corresponding percentage for each group.

Table 3 – Frequency of ECG results before and after treatment

Pre-treatment ECG	Post-treatment ECG				
	Normal	%	Altered	%	Total
Normal	30	62.5	5	10.4	35
Altered	4	8.3	9	18.7	13
Total	34	-	14	-	48

ECG: electrocardiogram.

Table 4 – Frequency of TTE results before and after treatment

Pre-treatment TTE	Post-treatment TTE				
	Normal	%	Altered	%	Total
Normal	21	86.9	0	-	21
Altered	4	13.1	0	-	4
Total	25	-	0	-	23

TTE: transthoracic echocardiogram

Conclusion

In our study, we demonstrated the presence of 33% of patient with cardiac alterations in the acute phase of CD. Although most of the cases were located in the Southwest mesoregion, the higher frequency of cardiac alterations belonged to the Central Amazonas mesoregion and isolated acute cases.

Although cardiac alterations were present in low frequency during the pre-treatment phase, this clinical condition suggests that there is a new epidemiological profile in the state of Amazonas which differs with the profile present in neighbouring states. This changing scenario might be associated with the T. cruzi strain, but no more can be specified. Most patients followed up in this study had a successful outcome, however, in some of them, the cardiac alterations persisted or even, developed afterwards.

Therefore, it is evident the need to reinforce surveillance actions for immediate diagnosis and treatment, as well as long-term and continuous cardiac, follow up of patients with acute CD in order establish preventive measures and improve the prognosis of this group of patients in our region.

Author contributions

Conception and design of the research and acquisition of data: Pereira BVM; analysis and interpretation of the data: Ortiz JV, Ferreira JMBB; statistical analysis: Ortiz JV, Lira EF; obtaining funding: Ferreira JMBB; writing of the manuscript: Ortiz JV, Couceiro KN, Doria SS, Silva PRL; critical revision of the manuscript for intellectual content: Ortiz JV, Couceiro KN, Silva e Silva MRH, Doria SS, Silva PRL, Guerra MGVB, Guerra JAO, Ferreira JMBB.

Potential Conflict of Interest

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

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Study Association

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

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Universidade do Amazonas under the protocol number 923.701. 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. Chagas C. Nova tripanozomiaze humana: estudos sobre a morfolojia e o ciclo evolutivo do Schizotrypanum cruzi n. gen., n. sp., ajente etiolojico de nova entidade morbida do homem. Mem Inst Oswaldo Cruz. 1909;1(2):159-218.
2. World Health Organization (WHO). Integrating neglected tropical diseases into global health and development: fourth WHO report on neglected tropical diseases. Geneva: World Health Organization; 2017.
3. Andrade DV, Gollob KJ, Dutra WO. Acute Chagas disease: new global challenges for an old neglected disease. PLoS Negl Trop Dis. 2014;8(7):e3010.
4. Rassi A Jr, Rassi A, Marin-Neto JA. Chagas disease. Lancet. 2010; 375(9723):1388-402.
5. Souza-Lima RC, Barbosa MD, Coura JR, Arcanjo AR, Nascimento AS, Ferreira JM, et al. Outbreak of acute Chagas disease associated with oral transmission in the Rio Negro region, Brazilian Amazon. Rev Soc Bras Med Trop. 2013;46(4):510-4.
6. Pinto AY, Valente VC, Coura JR, Valente SA, Junqueira AC, Santos LC, et al. Clinical follow-up of responses to treatment with benznidazol in Amazon: a cohort study of acute Chagas disease. PLoS One. 2013;8(5):e64450.
7. Tibayrenc M. Genetic epiddemiology of parasitic protozoa and other infectious agents: the need for an integrated approach. Int J Parasitol. 1998;28(1):85-104.
8. Zingales B, Andrade SG, Briones MRS, Campbell DA, Chiari E, Fernandes O, et al. A new consensus for *Trypanosoma cruzi* intraspecific nomenclature: second revision meeting recommends TcI to TcIV. Mem Inst Oswaldo Cruz. 2009;104(7):1051-4.
9. Pinto AY, Valente SA, Valente VC, Ferreira Jr AG, Coura JR. Acute phase of Chagas disease in the Brazilian Amazon region: study of 233 cases from Pará, Amapá and Maranhão observed between 1988 and 2005. Rev Soc Bras Med Trop. 2008;41(6):602-14.
10. Pinto AYN, Farias JR, Marçal AS, Galúcio AL, Costi RR, Valente VC, et al. Serious acute chagas disease authoctonous from Brazilian Amazon. Rev Para Med. 2007;21(2):1-10.
11. Pinto AYN, Harada GS, Valente VC, Abud JEA, Gomes FS, Souza GCR, et al. Cardiac attacks in patients with acute Chagas' disease in microepidemic familiar episode, in Abaetetuba City, Brazilian Amazon. Rev Soc Bras Med Trop. 2001;34(5):413-9.
12. Pinto AY, Valente SA, Valente VC. Emerging acute Chagas disese in Amazonian Brazil: case reports with serious cardiac involvement. Braz J Infect Dis. 2004;8(6):454-60.
13. Pinto AY, Ferreira AG Jr, Valente VC, Harada GS, Valente SAS. Urban outbreak of acute Chagas disease in Amazon region of Brazil : four-year follow-up after treatment with benznidazole. Rev Panam Salud Publica. 2009;25(1):77-83.
14. Pinto AYN, Ferreira SMAG, Valente SAS, Valente VC, Ferreira Jr AG. Electrocardiographic changes during and after benznidazole treatment against acute-stage Chagas disease indigenous to the Brazilian Amazon. Rev Pan-Amaz Saude. 2010;1(2):67-76.
15. Shaw J, Laison R, Fraiha H. Observations on the epidemiology of the first autochthonous cases of Chagas' disease in Belém, State of Pará, Brazil. Rev Saúde Publica. 1969;3(2):153-7.
16. França MS, Frade JM, Konasugawa K, Almeida FB. Doença de Chagas: primeiro caso autóctone na Amazônia Ocidental, Amazonas, Brasil. Acta Amaz. 1980;10(4):759-62.
17. Nobrega AA, Garcia MH, Tatto E, Obara MT, Costa E, Sobel J, et al. Oral transmission of Chagas disease by consumption of açaí palm fruit, Brazil. Emerg Infect Dis. 2009;15(4):653-5.
18. Pereira KS, Schmidt FL, Guaraldo AM, Franco RM, Dias VL, Passos LA. Chagas' disease as a foodborne illness. J Food Prot. 2009;72(2):441-6.
19. Sperandio da Silva GM, Mediano MFF, Hasslocher-Moreno AM, Holanda MT, Silvestre de Sousa A, Sangenis LHC, et al. Benznidazole treatment safety: the Médecins Sans Frontieres experience in a large cohort of Bolivian patients with Chagas' disease. J Antimicrob Chemother. 2017;72(9):2596-2601.
20. Monteiro WM, Barbosa MGV, Toledo MJO, Fé FA, Fé NF. Series of acute Chagas' disease cases attended at a tertiary-level clinic in Manaus, State of Amazonas, from 1980 to 2006. Rev Soc Bras Med Trop. 2010;43(2):207-10.
21. Monteiro WM, Magalhães LK, Sá AR, Gomes ML, Toledo MJ, Borges L, et al. *Trypanosoma cruzi* IV causing outbreaks of acute chagas disease and infections by different haplotypes in the Western Brazilian Amazonia. PLoS One. 2012;7(7):e41284.
22. Monteiro WM, Magalhães LK, Santana Filho FS, Borborema M, Silveira H, Barbosa MD. *Trypanosoma cruzi* TcIII/Z3 genotype as agent of an outbreak of Chagas disease in the Brazilian Western Amazonia. Trop Med Int Health. 2010;15(9):1049-51.
23. Dias JCP, Ramos Jr. AN, Gontijo ED, Luquetti A, Shikanai-Yasuda MA, Coura JR, et at. Brazilian Consensus on Chagas Disease, 2015. Epidemiol Serv Saúde. 2016;25(n. esp.):7-86.
24. Barbosa MGV, Ferreira JMBB, Arcanjo ARL, Santana RAG, Magalhães LKC, Magalhães LKC, et al. Chagas disease in the state of Amazonas: history, epidemiological evolution, risks of endemicity and future perspectives. Rev Soc Bras Med Trop. 2015;48(Suppl. 1):27-33.

25. Aguilar HM, Abad-Franch F, Dias JCP, Junqueira ACV, Coura JR. Chagas disease in the Amazon Region. Mem Inst Oswaldo Cruz. 2007; 102(Suppl. I):47-56.

26. Antunes AF, Maduro SG, Pereira BV, Barbosa MD, Guerra JA, Ferreira JM. Chronic heart disease after treatment of oral acute Chagas disease. Arq Bras Cardiol. 2016;107(2):184-6.

27. Santana RA, Magalhães LK, Magalhães LKC, Prestes SR, Maciel MG, Silva GA, et al. *Trypanosoma cruzi* strain TcI is associated with chronic Chagas disease in the Brazilian Amazon. Parasit Vectors. 2014 Jun 11;7:267.

28. Ramirez JD, Guhl F, Rendón LM, Rosas F, Marin-Neto JA, Morillo CA. Chagas cardiomyopathy manifestations and *Trypanosoma cruzi* genotypes circulating in chronic chagasic patients. PLoS Negl Trop Dis. 2010;4(11):e899.

29. Barbosa-Ferreira JM, Guerra JA, Santana Filho FS, Magalhães BM, Coelho LI, Barbosa MD. Cardiac involvement in acute Chagas' disease cases in the Amazon Region. Arq Bras Cardiol. 2010;94(6):147-9.

An Approach to The Acute Phase of Chagas' Disease: The Continuing Challenge it Presents in the 21st Century

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Short Editorial related to the article: Cardiac Evaluation in the Acute Phase of Chagas' Disease with Post-Treatment Evolution in Patients Attended in the State of Amazonas, Brazil

Chagas disease, in addition to being widespread on the American continent with around six million persons infected, is currently present in various regions of the world as a result of the migration of individuals with the disease.[1,2]

The statistics show that the incidence of acute cases has fallen from 700,000 new cases in 1990 to the current estimate of 29,000 – 30,000 per year by vector-borne transmission, plus 8,000 other cases by other modes such as transfusion and the digestive tract, owing to ingestion of food contaminated by *Trypanosoma cruzi*,[2] as described by Ortiz et al.[3] in their publication in this journal, in which they report 63 cases of cases of the acute form of Chagas disease in the state of Amazonas over a period of eight years, with oral transmission in 75% of the patients.

Despite the significant annual fall in its incidence and prevalence in the Americas, Chagas disease remains a serious public health problem, causing the death of approximately 12,000 persons per year. It also has a high socioeconomic cost, recently estimated at 500 million dollars in Latin America, with an annual loss of 770,00 life-years (adjusted) per premature death or loss of productive years resulting from physical disability.[4]

The slow progression of laboratory methods of diagnosis and of the development of new, more efficacious drugs, better tolerated by the patient, as well as the precarious nature of public health policies aimed at the extinction of the disease cause it to be classified as a "neglected disease".[1,2,5,6] It is estimated that only 1% of the patients infected with T cruzi receive the appropriate diagnosis and treatment every year.[2]

The article by Ortiz et al.[3] draws attention to some important facts: the first of these is the increased incidence of acute cases by oral transmission in the Amazon region, where acute cases in isolation or during an outbreak have been recorded in familial micro-epidemics by oral transmission through food contaminated by triatomine or their stools. Other authors have highlighted the regional nature of the epidemic,[1,7-10] noting that this form of transmission of the disease is much more effective than the vector mode of transmission.

The other aspect emphasized by those authors is the less aggressive effect of the disease on the heart, with a high percentage of the patients in their sample without any signs of myocarditis when assessed by electrocardiography (70% normal) and transthoracic echocardiography (87% normal). Despite the debatable limitations of these two methods for the detection of myocarditis, it is likely that peculiar regional features can account for these findings.

From the genotyping studies of T. cruzi, Ortiz et al.[3] suggest that the lower prevalence of cardiac disorders in their patients may be related to the T. cruzi lineage known as TcIV found in outbreak patients, whose pathogenicity, albeit poorly understood, may have a lower morbidity when compared with the TcII lineage found in other endemic areas.[11]

The application of new knowledge of genetics and longitudinal studies designed to test this hypothesis is likely to produce important information for the management of these patients.

Lastly, the findings of Ortiz et al.[3] on the treatment of the acute phase of the treatment of Chagas disease with Benznidazole deserve to be emphasized. However, information on this subject is scanty, being based on nonrandomized studies with insufficient numbers of patients and observation time. Although the definition of the criteria for a cure remains controversial, there is currently a consensus that treatment with Benznidazole should be carried out in the acute forms of the disease and that the patient is likely to benefit in the long term.[1,2,10,12]

The small size of the sample, the relatively short period of follow-up and the adoption of substitute outcomes in the evaluation of the results are limitations occurring with some frequency in the publications on this subject and these considerations also apply to the study by Ortiz et al.[3] Nonetheless the information presented is significant and may provide new information for improving the diagnosis and treatment of Chagas disease.

Keywords

Chagas Disease/epidemiology; Trypanosoma Cruzi; Chagas cardiomyopathy/epidemiology; Amazonian Ecosystem.

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References

1. Dias JC, Ramos AN Jr, Gontijo ED, Luquetti A, Shikanai-Yasuda MA, Coura JR, et al. 2nd Brazilian Consensus on Chagas Disease, 2015. Rev Soc Bras Med Trop. 2016;49(Suppl 1):3-60.
2. Organización Panamericana de la Salud. Guía para el diagnóstico y el tratamiento de la enfermedad de Chagas. Washington, DC: WHO/PAHO; 2018.
3. Ortiz JV, Pereira BVM, Couceiro KN, Guerra MGV, Guerra JAO, Ferreira JMB. Avaliação cardíaca na fase aguda da Doença de Chagas com evolução pós tratamento em pacientes atendidos no Estado do Amazonas-Brasil. Arq Bras Cardiol. 2019; 112(3):240-246.
4. Lee B, Bacon KM, Bottazzi ME, Hotez PJ. Global economic burden of Chagas disease: a computational simulation model. Lancet Infect Dis. 2013;13(4):342-8.
5. WHO - World Healt Organization. Enfermedades tropicales desatendidas. 66.ª Asamblea Mundial De La Salud. Resolución WHA66.12, 2013.
6. Bartsch SM, Avelis CM, Asti L, Hertenstein DL, Ndeffo-Mbah M, Galvani A, et al. The economic value of identifying and treating Chagas disease patients earlier and the impact on Trypanosoma cruzi transmission. PLoS Negl Trop Dis. 2018;12(11):e0006809.
7. Shikanai-Yasuda MA, Carvalho NB. Oral transmission of Chagas disease. Clin Infect Dis. 2012;54(6):845-52.
8. OPAS - Organização Pan-americana da Saúde. Doença de Chagas: guia para vigilância, prevenção, controle e manejo clínico da doença de Chagas aguda transmitida por alimentos. Rio de Janeiro: OPAS/OMS; 2009. (Série de Manuais Técnicos, 12).
9. Chagas disease in Latin America: an epidemiological update based on 2010 estimates. Wkly Epidemiol Rec. 2015;90(6):33-43.
10. Terhoch CB, Moreira HF, Ayub-Ferreira SM, Conceição-Souza GE, Salemi VMC, Chizzola PR, et al Clinical findings and prognosis of patients hospitalized for acute decompensated heart failure: Analysis of the influence of Chagas etiology and ventricular function. PLoS Negl Trop Dis. 2018;12(2):e0006207.
11. Monteiro WM, Magalhães LK, de Sá AR, Gomes ML, Toledo MJ, Borges L, et al. Trypanosoma cruzi IV causing outbreaks of acute Chagas disease and infections by different haplotypes in the Western Brazilian Amazonia. PLoS One. 2012;7(7):e41284.
12. Pinto AY, Valente VC, Coura JR, Valente SA, Junqueira AC, Santos LC, et al. Clinical follow-up of responses to treatment with benznidazol in Amazon: a cohort study of acute Chagas disease. Plos One. 2013;8(5):e64450.

Echocardiographic Correlation between Right Ventricular Function and Left Atrial Volume

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Abstract

Background: Few reports exist on the relationship of the left ventricular diastolic dysfunction (LVDD) with its most important features including enlargement of the left atrium and left ventricular hypertrophy (LVH), and with the right ventricular (RV) function.

Objective: To determine the correlation between the left atrial size and the RV function and dimensions in patients with and without LVDD and LVH.

Methods: Fifty patients were included, 25 (40% men) of them with LVDD, aged 67.1 ± 10.6 years (study group) and 25 without LVDD (52% men) aged 49.9 ± 16.3 years (control group). Patients underwent transthoracic echocardiography with evaluation of the left atrial size and volume (LAV), LVDD, LVH, and RV function and dimensions. P-values < 0.05 were considered statistically significant.

Results: LAV > 34 mL/m² and left atrial size > 40 mm were associated with lower absolute values of tricuspid annular plane systolic excursion (TAPSE) and RV lateral S' (p ≤ 0.001, Pearson's correlation coefficient -0.4 and -0.38, respectively) in the study group. Patients in the study group showed higher incidence of LVH (p = 0.02) and greater left atrial diameter (p = 0.03) compared with the control group. In addition, greater left atrial diameter (p = 0.02) and LAV (p = 0.01) values were found in patients with LVDD grade II compared with LVDD grade I.

Conclusions: The present study determined, for the first time, the correlation of left atrial enlargement with progressive RV dysfunction in patients with LVDD. (Arq Bras Cardiol. 2019; 112(3):249-257)

Keywords: Ventricular Dysfunction Right; Atrial Function/Physiology; Echocardiography/Methods; Blood Pressure; Heart Failure; Stroke Volume.

Introduction

Morphological and functional interdependence between the two ventricles may be explained by three mechanisms: (1) increase in right ventricular (RV) end-diastolic pressure in response to an increase in the left ventricular (LV) volume; (2) increased LV filling pressure inducing mechanical stress of the muscle fibers common to both ventricles; and (3) humoral factors, including catecholamines, that may regulate ventricular hypertrophy in response to pressure overload of one of the ventricles.[1-4] The function and dimensions of the right ventricle are directly associated with the LV function. Dilatation of the right ventricle and reduction of its contractile strength is usually found in advanced stages of LV dysfunction, reinforcing the close relationship between the two ventricles.[5-7] It is known that in heart failure patients with reduced LV ejection fraction both ventricular dynamic and pressures are altered, affecting the size and function of other cardiac chambers. However, few reports exist about the relationship between heart failure with preserved LV ejection fraction and increased RV dimensions with reduced systolic function fraction.[4] Also, there are few reports on LV diastolic dysfunction and related findings, such as enlargement of the left atrium (LA), LV hypertrophy (LVH), and their influence on systolic function and RV volume. The LA seems to reflect LV diastolic dysfunction (LVDD), since the parietal tension caused by increased filling pressures leads to dilation of the atrial chamber.[4] In addition, there are no studies specifically evaluating the influence of LA size and LA volume on diameter and function of the right ventricle. Therefore, the aim of the present study was to evaluate the correlation of left atrial volume (LAV) and left atrial diameter with the presence of LVH and RV function and diameter in patients with and without LVDD.

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Methods

Patients

This was a cross-sectional cohort study. We studied a convenience sample of 50 consecutive outpatients that underwent transthoracic echocardiogram (TTE) with

quantification of LV diastolic function, left atrial diameter and LAV, and RV systolic function and diameter at public healthcare centers. Patients on both sexes, aged older than 18 years, and of any ethnicity, referred for TTE by assistant physicians for any cause were selected. Exclusion criteria were presence of global (ejection fraction < 52% for men and < 54% for women) or segmental LV systolic dysfunction, infiltrative diseases, pericardial diseases, chronic obstructive pulmonary disease, asthma, moderate-to-severe valve diseases with hemodynamic repercussion, interatrial or interventricular septal defects, conditions that impaired the analysis of LV diastolic function (valve diseases with hemodynamic repercussion, atrial fibrillation at the electrocardiogram, definite pacemaker), presence of complete left or right bundle-branch block at the electrocardiogram and patients with LV diastolic dysfunction grade III. The following clinical data were collected: age, sex, weight, height, body mass index, presence of systemic arterial hypertension (SAH), diabetes mellitus (DM), coronary artery disease (CAD), smoking status (current or former smokers) and dyslipidemia. SAH, DM, dyslipidemia and smoking status were either collected from patients' medical records or self-reported by patients. The diagnosis of SAH was defined by systolic and diastolic blood pressure ≥ 140 mmHg and 90 mmHg, respectively, on two or more occasions, or use of anti-hypertensive drugs;[8] and DM diagnosis was confirmed by: (1) symptoms of polyuria, polydipsia, weight loss and casual (at any time of day, regardless of the time since last meal) glucose > 200 mg/dL; and (4) glycated hemoglobin A1c ≥ 6.5% or use of hypoglycemiant agents or insulin.[9] Dyslipidemia was defined according to the V Brazilian Guidelines on Dyslipidemias and Prevention of Atherosclerosis[10] criteria – total cholesterol > 200 mg/dL, high density lipoprotein cholesterol (HDL) < 40 mg/dL for men and < 50 for women, low density lipoprotein cholesterol (LDL) > 160 mg/dL, triglycerides > 150 mg/dL or use of lipid lowering drugs. The presence of CAD was confirmed by data from the medical records including: non-fatal myocardial infarction and surgical or percutaneous myocardial revascularization.

All patients signed the informed consent form in duplicate and kept one of the copies. The study was approved by the local ethics committee.

Echocardiographic assessment

Echocardiographic assessments with harmonic imaging were performed using the IE33™ (Phillips), Envisor™ (Phillips) and Vivid™ (GE) equipment. The tests were conducted by two echocardiographers experienced in TTE. The following parameters were collected for analysis: LV diastolic function (normal, grade I and grade II), presence of concentric or eccentric LVH, LAV, and RV systolic function measurements. Linear dimensions of the left atrial size were visualized from a parasternal long-axis window with two-dimensional and M-mode views. LAV was estimated using apical four- and two-chamber views, according to current recommendations.[5-8] Only highly related variables were used for the LV diastolic function analysis to avoid false positive results - the peak early filling (E wave) and late diastolic filling (A wave) velocities (the E/A ratio) <0.8; tissue Doppler imaging measured from the septal or lateral annulus (e' velocities) (septal < 7 cm/s and lateral < 10 cm/s); average E/e' ratio > 14; LAV index obtained from four- and two-chamber views > 34 mL/m^2; and peak tricuspid regurgitation velocity > 2.8m/s. Classification of diastolic dysfunction was based on the analysis of the transmitral flow. A diastolic dysfunction grade I was defined as an E/A ratio < 0.8 and an E-wave < 50 cm/s, and dysfunction grade III defined as an E/A ratio >2. In case of an E/A ratio < 0.8 and E-wave velocity > 50 cm/s, or an E/A ratio between 0.8 and 2, other parameters were used for the evaluation: velocity of mitral regurgitation, LAV, and E/e' ratio, according to current guidelines.[11] LVH was categorized into concentric (increased LV mass index and increased relative wall thickness) and eccentric (increased LV mass index and normal relative wall thickness), according to relative wall thickness (normal < 0.42) and indexed LV mass (normal < 95 mg/m^2 for women and < 115 mg/m^2 for men), according to current recommendations.[5] Diameter of the right ventricle was measured in the parasternal long-axis window between the RV anterior wall and the interventricular septum in the ventriculo-aortic junction.[5-7] Two parameters were considered in the systolic function analysis: tricuspid annular plane systolic excursion (TAPSE) with M-mode (normal > 16 mm) and lateral S' wave velocity by tissue Doppler imaging (normal > 9.5 cm).[5-7] Patients were then divided into two groups: individuals with normal LV diastolic function (n = 25) (control group) and individuals with LVDD grade I and II (n = 25) (study group).

Statistical analysis

Quantitative variables were described as mean and standard deviation, median and interquartile ranges. Categorical variables were described as frequency and percentages. The Student's t-test was used for two-group comparisons of quantitative variables, and the Fisher's exact test used for categorical variables. Associations between variables were determined using the Pearson correlation coefficient. Normality of distribution of quantitative variables was tested by the Kolmogorov-Smirnov test. P-values < 0.05 were considered statistically significant. All data were analyzed using the IBM SPSS Statistics software v.20.0 (Armonk, NY).

Results

Mean age of the control group was 49.9 ± 16.3 years and 52% of the individuals were men. Mean age of the study group was 67.1 ± 10.6 years (p < 0.001), 40% were men. A higher prevalence of SAH was seen in the study group than in the control group. Other clinical characteristics of participants are described in Table 1. The following variables showed normal distribution: TAPSE, lateral S' velocity, RV diastolic diameter, left atrial size and LAV. A higher incidence of LVH (concentric and eccentric) and a higher left atrial diameter were observed in the study group compared with the control group; no other differences were found between the groups (Tables 2 and 3). Considering the study group, patients with LVDD grade II showed significantly greater left atrial diameter and LAV compared with those with LVDD grade I, with no significant changes in the other parameters (Table 4). The type of LVH (concentric or eccentric) had no effect on the LA or other echocardiographic parameters (Table 4). There was a significant correlation of TAPSE and

Table 1 – Baseline characteristics of the study population

Variable	Classification	Group		p-value*
		Control (n = 25)	Study (n = 25)	
Age (years)	Mean ± DP	49.9 ± 16.3	67.1 ± 10.6	< 0.001
Sex	Male	13 (52%)	10 (40%)	
	Female	12 (48%)	15 (60%)	0.571
SAH	No	17 (68%)	5 (20%)	
	Yes	8 (32%)	20 (80%)	0.001
DM	No	23 (92%)	18 (72%)	
	Yes	2 (8%)	7 (28%)	0.138
Dyslipidemia	No	21 (84%)	18 (72%)	
	Yes	4 (16%)	7 (28%)	0.496
CAD	No	25 (100%)	23 (92%)	
	Yes	0 (0)	2 (8%)	0.490
Smoking	No	22 (88%)	21 (84%)	
	Yes	3 (12%)	4 (16%)	1

*Results expressed as mean ± standard deviation (SD) or frequency and percentage. * Student's t-test for independent samples (age); Fisher's exact test (categorical variables); p < 0.05. SAH: systemic arterial hypertension; DM: diabetes mellitus; CAD: coronary artery disease*

Table 2 – Baseline echocardiographic parameters in the study group and the control group

Variable	Group	n	Mean ± standard deviation	p-value*
RV TAPSE (mm)	Control	25	22.3 ± 2.0	
	Study	25	21.2 ± 2.6	0.103
RV lateral S' (cm/s)	Control	25	13.7 ± 1.8	
	Study	25	13.2 ± 1.7	0.295
RVDD (mm)	Control	25	20.9 ± 2.7	
	Study	25	22.0 ± 3.2	0.219
Left atrial size (mm)	Control	25	33.5 ± 5.1	
	Study	25	37.3 ± 5.5	0.016
Left atrial volume (ml/m²)	Control	25	29.2 ± 5.5	
	Study	25	30.3 ± 6.7	0.508

** Student's t-test for independent samples, p < 0.05; RV: right ventricular; TAPSE: tricuspid annular plane systolic excursion with M-mode; RVDD: right ventricular diastolic diameter.*

lateral S' of the right ventricle with LAV and size. A LAV > 34 mL/m² and left atrial size > 40 mm were associated with lower absolute values of TAPSE and RV lateral S' ($p \leq 0.001$, r= -0.4 and -0.38, respectively). There was a strong positive correlation of TAPSE with RV lateral S' ($r = 0.70$, $p < 0.001$), and of LAV and left atrial size ($r = 0.89$, $p < 0.01$) (Tables 5 and 6, Figures 1 and 2).

Discussion

The role of the LAV as a sensitive index that reflects the severity of LV diastolic function and that provides prognostic information in many heart diseases has been well documented.[4] However, its possible effect on RV performance still requires research. The present study demonstrated a significative inverse correlation of LAV and left atrial size with absolute values of TAPSE and RV lateral S' in patients with LVDD.

In a similar study by Torii et al.,[12] 239 patients with atrial fibrillation (AF) were compared with 281 individuals with sinus rhythm; AF patients showed lower TAPSE values regardless of age, sex, heart rate, LV ejection fraction and tricuspid regurgitation velocity. No correlations were made with LAV or left atrial size. Since we did not include patients with AF, it is possible to infer that an enlarged LA, per se, affects TAPSE and RV lateral S' only. It is known that left atrial enlargement does not occur uniformly due to physical limitations imposed by the sternum and spine, which can also affect dilatation and motion of the other cardiac chambers.[4] TAPSE reflects not only the shortening of RV free wall, but also the traction

Table 3 – Between-group comparison of baseline echocardiographic parameters in the study group and control group

Variable	Classification	Group		p-value*
		Control (n = 25)	Study (n = 25)	
LVDD	Normal	25 (100%)		
	Grade I		21 (84%)	
	Grade II		4 (16%)	-
LVH	Normal	25 (100%)	19 (76%)	
	Concentric (c)	0 (0)	5 (20%)	
	Eccentric (e)	0 (0)	1 (4%)	-
LVH	Normal	25 (100%)	19 (76%)	
	Hypertrophy (c/e)	0 (0)	6 (34%)	0.022
RV TAPSE (mm)	Normal (> 16)	25 (100%)	25 (100%)	
	Altered (≤ 16)	0 (0)	0 (0)	1
RV lateral S' (cm/s)	Normal (> 9.5)	25 (100%)	25 (100%)	
	Altered (≤ 9.5)	0 (0)	0 (0)	1
RVDD (mm)	Normal (16 a 30)	25 (100%)	25 (100%)	
	Altered (< 16 or > 30)	0 (0)	0 (0)	1
Left atrial size (mm)	Normal (< 40)	23 (92%)	16 (64%)	
	Altered (≥ 40)	2 (8%)	9 (36%)	0.037
LAV (ml/m^2)	Normal (< 34)	20 (80%)	18 (72%)	
	Altered (≥ 34)	5 (20%)	7 (28%)	0.742

Results expressed as frequency and percentage. Fisher's exact test (categorical variables); p < 0.05. LVDD: left ventricular diastolic dysfunction; LVH: left ventricular hypertrophy; RV: right ventricular TAPSE: tricuspid annular plane systolic excursion with M-mode; RVDD: right ventricular diastolic diameter; LAV: left atrial volume

of the right ventricle resulting from LV contraction and effects of heart translation in the chest.[13] Left atrial enlargement due to pressure and volume overload causes structural changes in the other chambers, including concomitant tricuspid annulus dilation, increased mobility of the tricuspid leaflets and tricuspid regurgitation.[14,15] One hypothesis is that tricuspid annular dilatation, as a consequence of enlarged LA, could change TAPSE and lateral S' due to displacement of mitral annulus. This would result in RV remodeling and affect RV longitudinal shortening, as the site used for TAPSE and S' measurements is the lateral insertion site of the tricuspid valve. However, we cannot rule out the possibility that such changes in cardiac chambers induced by the enlargement of the LA could also affect the ultrasonic angle beam, leading to changes in tissue Doppler imaging results. One interesting finding was that although the linear dimension of the LA was greater in the study group than in controls, LAV was practically normal in both groups. It is known that this linear measure of the LA has low accuracy and reproducibility due to technical limitations including the angle of the ultrasound beam, and the left atrial irregular geometry.[4]

It is also worth pointing out that the reference values for LAV are derived from international studies involving individuals with higher height; no study involving LAV measurements in a large Brazilian population has been performed so far.[16] However, even small changes in the LAV caused changes in both TAPSE and RV lateral S' values.

Due to the strict exclusion criteria, no signs of RV dysfunction were expected in either study or control group. This was confirmed by the normal values of TAPSE and lateral S' of the right ventricle in all participants. In the study by Bruhl et al.[17] evaluating 51 healthy individuals, with no past history of cardiac disease, found that TAPSE, mitral annular plane of systolic excursion (MAPSE), and tissue Doppler imaging measurements of the right and left ventricles were stable across age, gender, and body surface area. These findings illustrate the ventricular relationship and systolic interdependence. RV size and function correlate with the symptoms and physical capacity of patients with many clinical conditions. An accurate echocardiographic assessment of the right ventricle allows early detection of cardiac diseases, improves risk stratification and may indicate the right moment to start drug therapy.[18,19] Zakir et al.,[20] addressed, appropriately and in detail, the correlation of LV diastolic function with RV systolic dysfunction, based on the invasive measurement of the pulmonary venous system. LV diastolic dysfunction causes an increase in left atrial filling pressure, which can be transmitted backwards, leading to pulmonary arterial hypertension and RV pressure overload. According to Simon et al.[21] the first stage of RV dysfunction is pulmonary hypertension, which causes RV hypertrophy and ultimately right systolic dysfunction. However, in the present study, even patients with LVDD grade II showed normal TAPSE and RV lateral S'. In addition, difficulties in the analysis of the RV function may also result from RV

Table 4 – Echocardiographic parameters in the study group by left ventricular diastolic dysfunction grade and presence of concentric (c) and eccentric (e) left ventricular hypertrophy

Variable	LVDD	n	Mean ± standard deviation	p-value*
RV TAPSE (mm)	Grade I	21	21.2 ± 2.5	
	Grade II	4	21.5 ± 3.5	0.832
RV S' (cm/s)	Grade I	21	13.2 ± 1.7	
	Grade II	4	12.8 ± 1.7	0.604
RVDD (mm)	Grade I	21	21.5 ± 3.2	
	Grade II	4	24.5 ± 1.9	0.085
Left atrial (mm)	Grade I	21	35.9 ± 4.6	
	Grade II	4	44.5 ± 4.4	0.002
LAV (ml/m²)	Grau I	21	29.0 ± 5.5	
	Grau II	4	37.5 ± 8.9	0.017
Variable	**LVH**	**n**	**Mean ± standard deviation**	**p-value***
RV TAPSE (mm)	Normal	19	20.8 ± 2.5	0.176
	LVH (c/e)	6	22.5 ± 2.8	
RV S' (cm/s)	Normal	19	13.1 ± 1.7	0.580
	LVH (c/e)	6	13.5 ± 1.8	
RVDD (mm)	Normal	19	21.5 ± 3.3	0.185
	LVH (c/e)	6	23.5 ± 2.8	
Left atrial (mm)	Normal	19	36.3 ± 5.2	0.104
	LVH (c/e)	6	40.5 ± 6.0	
LAV (ml/m²)	Normal	19	29.7 ± 6.2	0.413

**Student's t-test for independent variables, p < 0.05. RV: right ventricular; TAPSE: tricuspid annular plane systolic excursion with M-mode; RVDD: right ventricular diastolic diameter; LA: left atrium; LAV: left atrial volume*

geometric and the complex correlation of the right ventricle with the LV septum. This could lead to delayed diagnosis of RV systolic dysfunction, which is generally detected in severe disease states. Therefore, serial analysis of the LAV and of TAPSE and lateral S' of the right ventricle in patients with LVDD or heart failure with preserved ejection fraction may provide initial evidence of deterioration of the RV function.

The other findings of the study were in accordance with literature data. In our study group, LVDD patients were older, showed higher incidence of LVH and greater left atrial size, and higher prevalence of SAH when compared with the control group.[22-24] Patients with altered diastolic function had larger LA, which was positively associated with the degree of diastolic dysfunction. This is in line with the study by El Aouar et al.[16]

Regarding the high prevalence of SAH in the study group, it is well known that SAH can cause not only LVH but also RV hypertrophy[25,26] that, in turn, was not assessed in our study. The fact that we did not find significant differences in echocardiographic measures between the groups can be explain by the strict exclusion criteria; it also reflects the fact that the analysis and referral values of echocardiographic parameters used in the assessment of the RV function is a matter of considerable debate in the literature, with wide variability within and between observers.[6,7] In this sense, there is not a gold standard method, but rather a set of group that should be sequentially interpreted considering the clinical conditions of each patient. Thus, subtle changes in the variables used for RV function analysis in our study, as well as their correlation with left atrial enlargement can serve as a basis for future studies in this field. It is pertinent to consider the use of the speckle tracking technique (strain [ε] and strain rate [SR or s^{-1}]) for assessment of the RV function in future studies. The ε and s^{-1} indexes evaluate regional and global myocardial deformation with advantages over the use of the strain measure obtained from tissue Doppler, especially a lower variability within and between observers. The use of two-dimensional speckle tracking echocardiography allows the analysis of longitudinal, circumferential and radial strain, with not influence of the angle.[27]

Finally, this study has important limitations that should be considered: (1) the small number of the sample; studies involving larger sample sizes would be needed to confirm our findings; (2) the groups were not perfectly matched, especially in terms of age; (3) the lack of adequate or precise information about the time of hypertensive disease and its treatment, as well as on medications used by the patients; and (4) we did not analyze the variables tricuspid annulus diameter and right atrial volume, which could provide more information on the RV remodeling. In addition, patients with LVDD was composed of older individuals compared with the control group. This may have

Table 5 – Echocardiographic parameters in the study group by left atrial size (mm) and left atrial volume (mL/m²)

Variable	Left atrial size	n	Mean ± standard deviation	p-value*
RV TAPSE (mm)	Normal (< 40)	16	21.9 ± 2.4	
	Altered (≥ 40)	9	20.1 ± 2.6	0.103
RV lateral S' (cm/s)	Normal (< 40)	16	13.6 ± 1.8	
	Altered (≥ 40)	9	12.4 ± 1.2	0.111
RVDD (mm)	Normal (< 40)	16	21.7 ± 3.2	
	Altered (≥ 40)	9	22.4 ± 3.3	0.584
LAV (ml/m²)	Normal (< 40)	16	26.8 ± 3.8	
	Altered (≥ 40)	9	36.7 ± 6.2	< 0.001
Variable	**LAV**	**n**	**Mean ± standard deviation**	**p-value***
RV TAPSE (mm)	Normal (< 34)	18	22.2±2.4	
	Altered (≥ 34)	7	18.9 ± 0.9	< 0.001
RV lateral S' (cm/s)	Normal (< 34)	18	13.7 ± 1.7	
	Altered (≥ 34)	7	11.9 ± 0.7	0.001
RVDD (mm)	Normal (< 34)	18	21.7 ± 3.3	
	Altered (≥ 34)	7	22.6 ± 3.2	0.565
Left atrial size (mm)	Normal (< 34)	18	34.7 ± 3.6	
	Altered (≥34)	7	43.9 ± 4.0	< 0.001

**Student's t-test for independent samples, p < 0.05. RV: right ventricular TAPSE: tricuspid annular plane systolic excursion with M-mode; RVDD: right ventricular diastolic diameter; LAV: left atrial volume.*

Table 6 – Correlations between quantitative variables in the study group

Variables	n	Pearson's correlation coefficient	p-value
Age × RV TAPSE	25	–0.22	0.281
Age × RV lateral S'	25	–0.42	0.035
Age × RVDD	25	0.04	0.866
Age × left atrial size	25	0.31	0.134
Age × LAV	25	0.40	0.050
RV TAPSE × RV lateral S'	25	0.70	< 0.001
RV TAPSE × RVDD	25	0.33	0.106
RV TAPSE × left atrial size	25	-0.33	0.107
RV TAPSE × LAV	25	-0.40	0.047
RV lateral S' × RVDD	25	0.40	0.051
S' lateral VD × left atrial size	25	-0.26	0.216
RV lateral S' × LAV	25	–0.38	0.063
RVDD × left atrial size	25	0.30	0.149
RVDD × LAV	25	0.23	0.271
Left atrial size × LAV	25	0.89	< 0.001

TAPSE: tricuspid annular plane systolic excursion with M-mode; RVDD: right ventricular diastolic diameter; LAV: left atrial volume.

influenced the results, particularly the LAV. Also, the prevalence of SAH increases with age and differently in men and women.[28,29] Although the study group and the control group were not perfectly matched, the proportion of men and women was not different between the groups; yet, we did not find any significant difference between men and women in the study variables.

Conclusions

The present study determined, for the first time, a correlation of the increase in LAV with progressive RV functional changes in patients with LVDD. However, further studies are needed to confirm these findings.

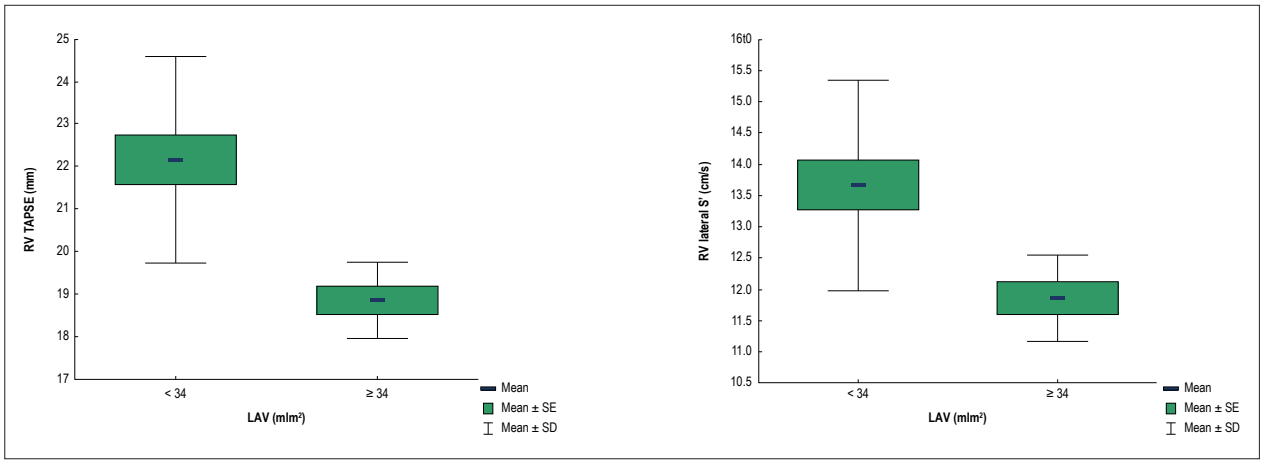

Figure 1 – *Correlation between right ventricular tricuspid annular plane systolic excursion (RV TAPSE) and left atrial volume (LAV) (left panel; p < 0.001), and between lateral S' of the right ventricle and LAV (right panel; p < 0.001). RV: right ventricular; LA: left atrium; SE: standard error; SD: standard deviation; Student's t-test for independent samples; p < 0.05.*

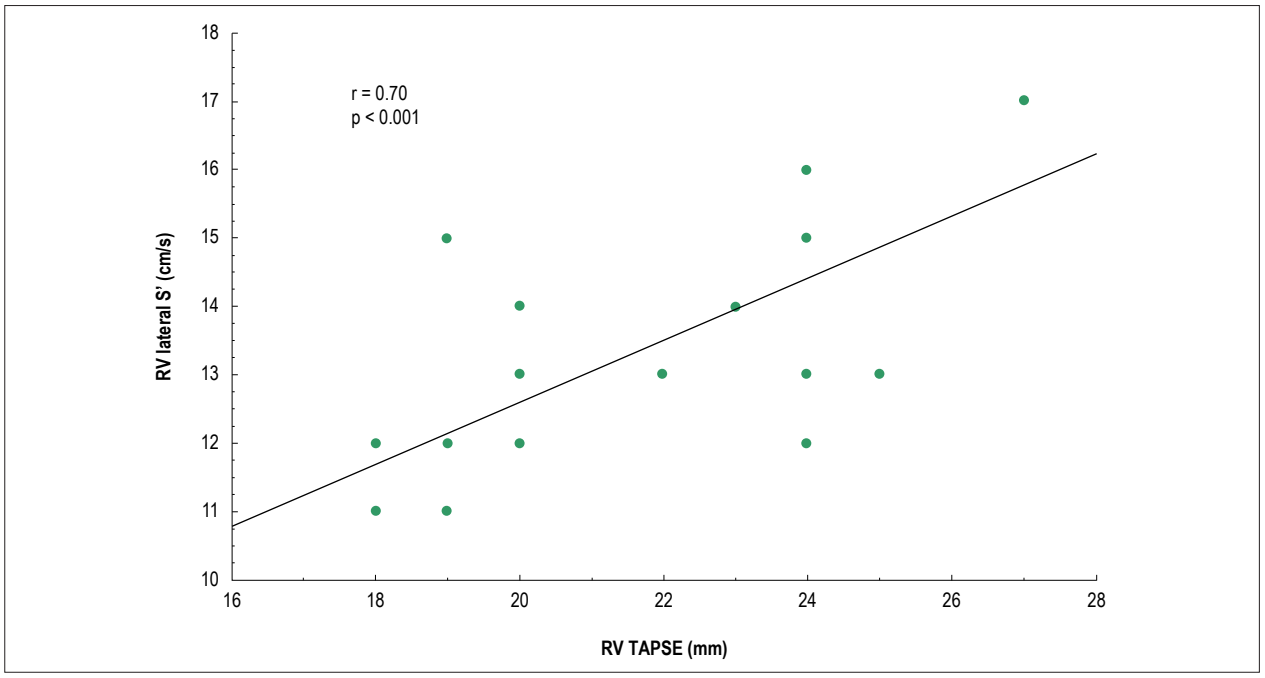

Figure 2 – *Correlation between right ventricular tricuspid annular plane systolic excursion (RV TAPSE) and right ventricular S' lateral.*

Author contributions

Conception and design of the research, acquisition of data and analysis and interpretation of the data: Baroncini LAV, Borges LJL, Camarozano AC, Carmo DC, Darwich RZ, Fortunato Junior JÁ; statistical analysis: Baroncini LAV; writing of the manuscript: Baroncini LAV, Darwich RZ, Fortunato Junior JÁ; critical revision of the manuscript for intellectual content: Baroncini LAV, Borges LJL, Camarozano AC, Carmo DC.

Potential Conflict of Interest

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

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Study Association

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

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Universidade Positivo under the protocol number 2331223. 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. Zile MR, Brutsaer DL. New concepts in diastolic dysfunction and diastolic heart failure: part I: diagnosis, prognosis, and measurement of diastolic function. Circulation. 2002;105(11):1387-93.
2. Hogg K, Swedberg K, McMurray J. Heart failure with preserved left ventricular systolic function; epidemiology, clinical characteristics, and prognosis. J Am Coll Cardiol. 2004;43(3):317-27.
3. Paullus WJ, Tschöpe C, Sanderson JE, Rusconi C, Flachskamp FA, Rademakers FE, et al. How to diagnose diastolic heart failure: a consensus statement on the diagnosis of heart failure with normal left ventricular ejection fraction by the Heart Failure and Echocardiography Associations of the European Society of Cardiology. Eur Heart J. 2007 ;28(20):2539-50.
4. Sousa ACS. Left atrial volume as an index of diastolic function. Arq Bras Cardiol. 2006;86(3):e27-e33.
5. 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.e14.
6. Jurcut R, Giusca S, La Gerche A, Vasile S, Ginghina C, Voigt JU. The echocardiographic assessment of the right ventricle: what to do in 2010? Eur J Echocardiogr. 2010;11(2):81-96.
7. Rudski LG, , Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K, et al. Diretrizes para avaliação ecocardiográfica do coração direito em adultos: um informe da Sociedade Americana de Ecocardiografia. J Am Soc Echocardiogr. 2010;23:685-713.
8. James PA, Oparil S, Carter BL, 2014 Evidence-based guideline for the management of high blood pressure in adults : report from the panel members appointed to the Eight Joint National Committee (JNC 8). JAMA. 2014;311(5):507-20.
9. Standards of medical care in diabetes – 2015: summary of revisons. Diabetes Care. 2015; 38(Supp1):S4.
10. Xavier HT, Izar MC, Faria Neto JR Assad M. H., Rocha V. Z., Sposito A. C., et al. V Diretriz Brasileira de Dislipidemias e Prevenção de Aterosclerose. Arq Bras Cardiol. 2013;101(4 Suppl 1):1-22.
11. Nagueh SF, Smiseth AO, Appleton CP Byrd BF 3rd, 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;17(12):1321-60.
12. Torii Y, Kusunose K, Yamada H, Nishio S, Hirata Y, Amano R, et al. Comparison of tricuspid annular plane systolic excursion in patients with atrial fibrillation versus sinus rhythm. Am J Cardiol. 2016; 117(2):226-32.
13. Lakatos B, Tősér Z, Tokodi M, Doronina A, Kosztin A, Muraru D, et al. Quantification of the relative contribution of the different ventricular wall motion components to right ventricular ejection fraction: the ReVISION method. Cardiovascular Ultrasound. 2017;15(1):8.
14. Katsi V, Raftopoulos L, Aggeli C, Vlasseros I, Felekos I, Tousoulis D, et al. Tricuspid regurgitation after successful mitral valve surgery. Interact Cardiovasc Thorac Surg. 2012;15(1):102-8.
15. Utsunomiya H, Itabashi Y, Mihara H, Berdejo J, Kobayashi S, Siegel RJ, et al. Functional tricuspid regurgitation caused by chronic atrial fibrillation: A real-time 3-dimensional transesophageal echocardiography study. Circ Cardiovasc Imaging. 2017;10(1):pii: e004897.
16. El Aouar LMM, Mayerfreud D, Magalhães P, Rodrigues SL, Baldo MP, Brasil Y, et al. Relationship between left atrial volume and diastolic dysfunction in 500 Brazilian patients. Arq Bras Cardiol. 2013;101(1):52-8.
17. Bruhl SR, Chahal M, Khouri S. A novel approach to standard techniques in the assessment and quantification of the interventricular systolic relationship. Cardiovasc Ultrasound. 2011 Dec 20;9:42.
18. Kossaify A. Echocardiographic assessment of right ventricle, from the conventional approach to speckle tracking and three-dimensional imaging, and insights into the "right-way" to explore the forgotten chamber. Clin Med Insights: Cardiol. 2015 Jul 5;9:65-75.
19. Kjaergaard J, Iversen KK, Akkan D, Møller JE, Køber LV, Torp-Pedersen C, et al. Predictors of right ventricular function as measured by tricuspid anular plane systolic excursion in heart failure. Cardiovasc Ultrasound. 2009 Nov 4; 7:51.
20. Zakir R, Al-Dehneh A, Maher J, Saric M, Berkowitz R. Right ventricular failure in patients with preserved ejection fraction and diastolic dysfunction: an underrecognized clinical entity. Congest Heart Fail. 2007;13(3): 164-9.
21. Simon M, Pinsky MR. Right ventricular dysfunction and failure in chronic pressure overload. Cardiol Res Pract. 2011 Mar 23;2011:568095.
22. Vasan RS, Larson MG, Benjamin EJ, Evans JC, Reiss CK, Levy D. Congestive heart failure in subjects with normal versus reduced left ventricular ejection fraction: prevalence and mortality in a population-based cohort. J Am Coll Cardiol. 1999;33(7):1948-55.
23. Fischer M, Baessler A, Hense HW, Hengstenberg C, Muscholl M, Holmer S,et al.. Prevalence of left ventricular diastolic dysfunction in the community. Results from a Doppler echocardiographic-based survey of a population sample. Eur Heart J. 2003;24(4):320-8.
24. Masoud FA, Havranek EP, Smith G, Fish RH, Steiner JF, Ordin DL, et al.. Gender, age, and heart failure with preserved left ventricular systolic function. J Am Coll Cardiol. 2003;41(2):217-23.
25. Gottdiener JS, Gay JA, Maron BJ, Fletcher RD. Increased right ventricular wall thickness in left ventricular pressure overload: echocardiographic determination of hypertrophic response of the nonstressed ventricle. J Am Coll Cardiol**.** 1985;6(3):550-5.
26. Silva RP, Amodeo C, Ramires JAF. O ventrículo direito e a hipertensão arterial: aspectos ecocardiográficos. Arq Bras Cardiol. 2002;79(3):313-8.
27. Almeida ALC, Gjesdal O, Mewton N, Choi EY, Teixido-Tura G, Yoneyama K,et al.. Speckel-Tracking pela ecocardiografia bidimensional – aplicações clínicas. Rev Bras Ecocardiogr Imagem Cardiovasc. 2013;26(1):38-49.
28. Zabalgoitia M, Rahman SN, Haley WE, Mercado R, Yunis C, Lucas C, et al.. Comparison in systemic hypertension of left ventricular mass and geometry with systolic and diastolic function in patients <65 to > or =65 years of age. Am J Cardiol. 1998;82(5):604-8.
29. Sant'Anna MP, Mello RJ, Montenegro LT, Araújo MM. Left and right ventricular hypertrophy at autopsy of hypertensive individuals. Rev Assoc Med Bras. 201258(1):41-7.

Original Article

Let's Look Right during Diastolic Dysfunction Evaluation?

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Nearly half of heart failure patients have preserved ejection fraction (HFPEF).[1] HFPEF is traditionally attributed to an increased left ventricular end-diastolic filling pressure (Pd2), triggered by structural, metabolic and functional mechanisms. Echocardiography permits to identify HFPEF signs as diastolic dysfunction (DD),[2] enlarged left atrium, and more subtle abnormalities of systolic function detected by global longitudinal strain.[3,4] Right ventricular (RV) abnormalities and pulmonary hypertension are also identified by echocardiography and are frequently seen in HFPEF.[5] However, there are controversies if the abnormalities seen in right cardiac chambers are a consequence of left-sided abnormalities or if they correspond to a direct effect over left and right chambers simultaneously, caused by the same mechanisms, such as diffuse subendocardial fibrosis and subclinical systolic dysfunction.

In this journal, Baroncini et al.[6] sought to bring more evidence to fill this knowledge gap. The authors compared two small samples of individuals with and without DD (25 subjects in each group) and found no significant changes in RV function between the groups measured by tricuspid annular plane excursion (TAPSE) or RV free wall systolic velocity (*s'*). The secondary analysis highlighted by the authors showed that in the subgroup with DD, the 7 individuals with a dilated left atrium presented worse RV function parameters compared to the other patients with DD (n = 18). These results could suggest that RV abnormalities would be present only in those already with a chronic increase in left atrial pressure identified by its dilatation.

Keywords

Heart Failure; Stroke; Ventricular Dysfunction Right; Atrial Function; /physiology; Echocardiography/methods; Hypertension.

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However, this specific finding in one subgroup is very likely to have occurred by chance. In addition to the recognized caveats of *a posteriori* findings, there are other reported findings that weaken the consistency of the biological plausibility of the association described. There was no significant correlation when measurements of the left atrium and right ventricle were analyzed continuously (unlike the article title), neither there was any relevant association identified in the analyzes that included the group of supposedly normal controls. Another important issue is the impossibility of the study, as performed, to adequately adjust for the intricate relationships between confounding variables. This is evident when we analyze the relationships between age, diastolic function, left atrial size and diastolic function in the study.

Alterations in RV function at early stages of DD has already been studied, when the effects of pulmonary circulation on RV have not yet been observed. Brand et al.[7] studying 438 women (BNP = 34.4 ± 31.6 pg/ml, Pulmonary artery systolic pressure = 21.8 ± 6.2 mmHg) showed the group with DD (n = 152) had worse RV systolic function compared to the group without DD (n = 286), either by conventional measures such as TAPSE, S', and fractional area change, or by newer methods such as global and free wall RV strain. It is noteworthy that the group with DD had no echocardiographic signs of increased left ventricular filling pressures, RV dilatation, or pulmonary hypertension, reinforcing the physiopathological concept that the occurrence of RV dysfunction is independent of the pressure overload in this cavity.

The advances in HFPEF knowledge is indisputable, demonstrating the global cardiac, pulmonary, and multisystemic involvement in the syndrome, beyond that of DD. This was largely achieved with the help of noninvasive imaging and is likely to help in the identification of treatment targets and prevention strategies. On the other hand, despite its universal clinical use, the independent diagnostic and prognostic role of any imaging biomarker used individually is still a matter of debate, due to their complex interconnections. Considering this, it is paramount the proper discernment between associations, causality, and clinical utility of any biomarker, particularly in the echocardiographic evaluation of DD.

References

1. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. N Engl J Med. July 2006;355:251-9.
2. Zile MR, Baicu CF, Gaasch WH. Diastolic heart failure-abnormalities in active relaxation and passive stiffness of left ventricle. N Engl J Med. May 6 2004;350:1953-9.
3. Kraigher-Krainer E, Shah AM, Gupta DK, Santos A, Claggett B, Pieske B, et al; PARAMOUNT Investigators. Impaired systolic function by strain imaging in heart failure with preserved ejection fraction. J Am Coll Cardiol. 2014;63(5):447-56.
4. Shah AM , Claggett B, Sweitzer NK, Shah SJ, Anand IS ,Liu L, et al. Prognostic Importance of Impaired Systolic Function in Heart Failure with Preserved Ejection Fraction and the Impact of Spironolactone. Circulation. 2015;132(5):402-14.
5. Gorter TM, van Veldhuisen DJ, Bauersachs J, Borlaug BA, Celutkiene J, Coats AJS, et al. Right heart dysfunction and failure in heart failure with preserved ejection fraction: mechanisms and management. Position statement on behalf of the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail. 2018;20(1):16-37.
6. Baroncini LAV, Borges LJL, Camarozano AC. Carmo Dc, Darwich RZ, Fortunato Jr JA. Correlação ecocardiografica entre função ventricular direita e volume atrial esquerdo. Arq Bras Cardiol. 2019; 112(3):249-257.
7. Brand A, Bathe M, Oertelt-Prigione S, Seeland U, Rücke M, Regitz-Zagrosek V, et al. Right heart function in impaired left ventricular diastolic function: 2D speckle tracking echocardiography-based and Doppler tissue imaging-based analysis of right atrial and ventricular function. Echocardiography. 2018;35(1):47-55.

Ideal Cardiovascular Health and Job Strain: A Cross-Sectional Study from the Amazon Basin

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Abstract

Background: Ideal Cardiovascular (CV) Health is characterized by four ideal lifestyle parameters and absence of cardiovascular risk factors. The prevalence of ideal CV health in the Amazon Basin and the influence of job strain on CV health in this setting are uncertain.

Objective: To evaluate the prevalence of ideal CV health and its relationship with job strain in a secluded area from a developing country.

Methods: Job strain was evaluated in 478 employees from an university in the Amazon Basin by a questionnaire that classified participants as passive, active, low or high strain, according to the demand-control model. CV health was evaluated using the American Heart Association 7 health factors (diet, physical activity, body mass index (BMI), smoking, hypertension, diabetes and hypercholesterolemia). Participants were classified as having ideal, intermediate or poor CV health. The level of significance was set at $p < 0.05$.

Results: The mean age was 44.3 ± 12 years, 65% were men, and 35% were faculty. No participant fulfilled the criteria for ideal CV health. Intermediate CV health was found in 44 (9%) and poor in 434 (91%) individuals. Considering low strain as a reference group, individuals classified as high strain, active and passive had a non-significant ($p > 0.05$) increase in the chances of having poor CV health. When adjusting for possible confounders, high job strain was associated with poor BMI (> 30 kg/m²), (OR 2.11, 95%CI 1.06-4.22; $p = 0.034$) and poor diet (OR 2.31, 95% CI 1.29-4.13; $p = 0.005$).

Conclusion: Job strain was not associated with cardiovascular health, but high job strain was related to obesity and poor diet. Given the high prevalence of poor CV health and lack of participants with ideal CV health, policies focusing on health education and lifestyle interventions are paramount to this population. (Arq Bras Cardiol. 2019; 112(3):260-268)

Keywords: Cardiovascular Diseases/epidemiology; Risk Factors; Prevention and Control; Amazonian Ecosystem; Stress,Psychological; Obesity; Eating Disorders.

Introduction

Cardiovascular diseases (CVD) remain the leading cause of death in both the developed and developing world.[1-3] In order to combat CVD, the American Heart Association (AHA) launched the 2020 impact goal and the Ideal Cardiovascular Health initiative.[4] Ideal Cardiovascular (CV) Health is defined as the presence of both ideal health behaviors (nonsmoking, body mass index (BMI) < 25 kg/m², physical activity at goal levels, and pursuit of a diet consistent with current guideline recommendations) and ideal health factors (untreated total cholesterol < 200 mg/dL, untreated blood pressure < 120/80 mmHg, and fasting blood glucose < 100 mg/dL). Subjects in ideal status have a lower incidence of CVD and an increased life expectancy when compared with those in poor status.[4–6]

CV health seems to be influenced by workplace conditions.[7,8] In a study by Karasek et al.,[8] high job strain was associated with higher chances of having CV disease.[8] The authors proposed that demand and control at the workplace influence health status. Control is defined as how much leeway in decision making the employee has and how much intellectual skills are required when working. Demand is the intellectual pressure that can be either quantitative, for example, time and velocity to work, or qualitative, defined as conflicts between contradictory demands.[7]

Although few studies in this regard have been performed in developed countries, the relationship between job strain and CV health is not completely known in the setting of a developing country. Using the above framework, we hypothesized that ideal CV health has low prevalence in the Amazon Basin. Furthermore, we believe that job strain is associated with a higher prevalence of poor CV health.

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Objective

The aim of this study is to evaluate the prevalence of ideal CV health and its relationship with job strain in a secluded area from a developing country.

Methods

The study was performed between 2012 and 2013 in Rio Branco, Brazil. All 759 employees at the Federal University of Acre were invited to participate. Employees received a call or email to setup an appointment with two trained researchers. A total of 478 employees accepted to participate, including 166(35%) faculty professionals and 312(65%) non-faculty staff. A questionnaire was used to collect information regarding demographics, CV behavior and risk factors. Weight, height, waist circumference and blood pressure were measured twice at different appointments. The average of the two measurements was considered the final value. We excluded those subjects who declined to sign an informed consent. Twenty-seven participants with missing data regarding job strain were not included in the comparisons among CV health factors and job strain. This study was approved by the Institutional Review Board at the Federal University of Acre.

We used the validated Portuguese-language adapted Job Content Questionnaire based in Robert Karesek theoric model to assess job strain.[9] It is composed of 6 questions to evaluate control, 5 questions to assess demand, and 6 questions to assess social support. Each question was composed of 4 possible answers ranging from 1 (strongly disagree) to 4 (strongly agree). We defined as having high demand those participants with scores above the 50th percentile on the Portuguese-language adapted Job Content Questionnaire; low control when below the 50th percentile; High job strain was defined as the combination of high demand and low control; low job strain as low demand and high control; active as high demand and high control; passive as low demand and low control.

This study selected seven health indicators proposed by the AHA as markers of CV health. These seven parameters include four lifestyle variables (smoking, physical activity, diet, and BMI) and three CV risk factors (diabetes, hypercholesterolemia, and high blood pressure). Smoking status was classified as never smoker, former smoker and current smoker. Ideal physical activity was defined by more than 150 minutes/week of moderate intensity exercise, any physical activity lower than 150 minutes/week as intermediate and no physical exercise as poor. BMI was calculated as body weight in kilograms divided by the square of body height in meters (kg/m^2). Values lower than 25 were considered ideal, between 25 and 29.9 intermediate, and greater than 30 were considered poor. Diabetes and hypercholesterolemia were self-reported in a questionnaire as yes or no responses. Blood pressure was obtained by trained researchers. High blood pressure was defined as a measured value greater than 140/90 mmHg or self-reported high blood pressure in use of anti-hypertensive medication or not. Systolic blood pressure between 120 and 139 or diastolic blood pressure between 80 and 89 were classified as intermediate. Blood pressure < 120/80 was considered ideal. According to the AHA, an ideal diet pattern was defined as consumption of 4 portions or more of fruits and/or vegetables per day, less than 1 liter of sugar-sweetened beverages per week and more than two 3.5-oz servings per week of fresh fish. We used a food frequency questionnaire previously validated in a Brazilian cohort.[10] Sodium and fiber-rich whole grains consumption couldn't be accessed by the questionnaire. Individuals were classified as having ideal CV health (ideal lifestyle and absence of CV risk factors), poor (when any of the seven factors was evaluated as poor) or intermediate (participants who did not belong to ideal or poor CV health group).

The covariates used for data analysis were age, gender, income, education level and occupation, which were self-reported in a questionnaire. Income was measured in US dollars and subjects were split in two categories, more or less than $20,000/year. Occupation was classified as teaching and non-teaching staff. We modeled education as a dichotomous variable with subjects classified as college or more or high school or less. Low social support was considered for those participants bellow 50th percentile on the adapted Job Content Questionnaire.

Statistical analysis

The study was designed to detect a difference in the proportion of poor CV health of 15% between high strain (85%) and low strain (70%). Considering a power set at 0.8, an alpha level of 0.05, we estimated a sample size of at least 121 patients per group and a total of 424 participants. We planned including 478 individuals, allowing for non-respondents or incomplete responses up to 12% of participants.

Categorical data was reported as percent frequencies and compared by chi-squared test. Continuous normally distributed variables were displayed as mean and standard deviation, and continuous non-normally distributed variables were displayed as median and 25th and 75th percentiles. Significant pairwise comparisons were adjusted for multiple testing using Bonferroni correction and are shown only for variables in which a significant global difference was detected using one-way ANOVA or Kruskal–Wallis tests. The association between job strain and CV health was assessed using multivariable logistic regression using the low strain group as reference. We also used multivariable logistic regression to assess the association between job strain and CV risk factors. We built two models for analyses; the crude analyses without any covariate and the adjusted analyses, which controlled for age, sex, education, income, and occupation. Exposures included high job strain and also high demand and low control, separately. All statistical analyses were performed with STATA version 13.1 (Stata Corp., College Station, TX, USA). P-values < 0.05 were considered statistically significant.

Results

Participants had a mean age of 44.3 ± 12 years, and 65% were men; In terms of job strain, the most prevalent group was low job strain with 144 (32%) individuals. A total of 86 (19%) participants were found to have high job strain, 93 (21%) were considered active, and 128 (28%) were considered to have passive work. Teaching professionals were less likely to

be among the high strain job group. No significant differences were found between high strain and low strain group in terms of age, sex, and income. Passive participants were more likely to be older and low educated than low strain subjects. Active participants had higher income and were more likely to be professors than low strain participants (Table 1).

Ideal CV health was not found in this sample. Intermediate CV health was found in 44 (9%) and poor in 434 (91%) individuals. Poor physical activity (53%) and poor diet (55%) were the factors with the highest prevalence among the participants. Poor BMI was found in 22% of participants, smoking in 7%, hypertension in 36%, hypercholesterolemia in 26%, and diabetes in 7% (Figure 1). Most participants had one to three CV health factors classified as poor (Table 2).

Considering the outcome CV health and low strain as reference group for comparisons, we found that high strain, active and passive individuals have a non-significant increase in the chances of having poor CV health (Table 3 and Figure 2). Either high demand or low control category when analyzed separately or combined was not associated with poor CV health (Table 3). Individually, the active group had a trend to increase the odds of poor physical activity (OR 1.67, 95% CI 0.96-2.92; p = 0.07). High job strain increased the chance of poor diet by 2.3-fold in comparison with the low strain group (p = 0.005). Similarly, high job strain was associated with poor BMI (> 30 kg/m^2), OR 2.11, 95%CI 1.06-4.22; p = 0.034. We did not find an association between job strain and poor smoking, high blood pressure, hypercholesterolemia, or diabetes (Table 4). When demand and control categories were analyzed separately, low control was associated with poor diet. (Table 5)

Discussion

This study included 451 from an academic center and, to our knowledge, it is the first to describe the prevalence of CV health and explore a possible relationship with job strain in the Amazon Basin. Our main finding was a high prevalence of poor CV health with no individuals in ideal

Table 1 – Characteristics of subjects according to job strain (active, passive, low strain, high strain)

Parameters	Low strain	Active	Passive	High Strain
	n = 144 (32%)	n = 93 (21%)	n = 128 (28%)	n = 86 (19%)
Age (years)	42.9 ± 11.9	43.6 ± 10.7	46.7 ± 13.2†	42.8 ± 13.3
Gender - male n (%)	94 (65)	56 (60)	82 (64)	55 (64)
Income - > $20.000/yr n (%)	57 (42)	62 (67)*	42 (35)	31 (37)
Highly educated n (%)	112 (78)	82 (88)	63 (49) †	64 (76)
Occupation- professor n (%)	63 (44)	65 (70)*	10 (8) †	18 (21) ‡
Low social support N (%)	66 (40)	59 (66)*	39 (31)	56 (66) ‡
Smoking n (%)				
Poor	8 (6)	7 (8)	9 (7)	8 (9)
Intermediate	31 (22)	14 (15)	42 (33)	11 (13)
Ideal	105 (73)	72 (77)	77 (60)	67 (78)
Hypercholesterolemia n (%)	34 (24)	24 (26)	39 (30)	17 (20)
Physical activity n (%)				
Poor	66 (46)	53 (57)	73 (57)	46 (54)
Intermediate	38 (26)	21 (23)	31 (24)	21 (24)
Ideal	40 (28)	19 (20)	24 (19)	19 (22)
Diet n (%)				
Poor	71 (49)	45 (48)	72 (56)	58 (67) ‡
Intermediate	38 (26)	32 (34)	36 (28)	17 (20)
Ideal	35 (24)	16 (17)	20 (16)	11 (13)
Diabetes n (%)	8 (6)	6 (6)	11 (9)	5 (6)
High blood pressure n (%)				
Poor	51 (35)	28 (30)	48 (38)	32 (37)
Intermediate	72 (50)	50 (54)	70 (55)	49 (57)
Ideal	21 (15)	15 (16)	10 (8)	5 (6)
Body mass index (kg/m^2)	26.5 ± 3.8	26.4 ± 4.2	27.3 ± 4.6	27.5 ± 5.0

*p < 0.05 active vs. low strain; †p < 0.05 passive vs. low strain; ‡p < 0.05 high strain vs low strain.

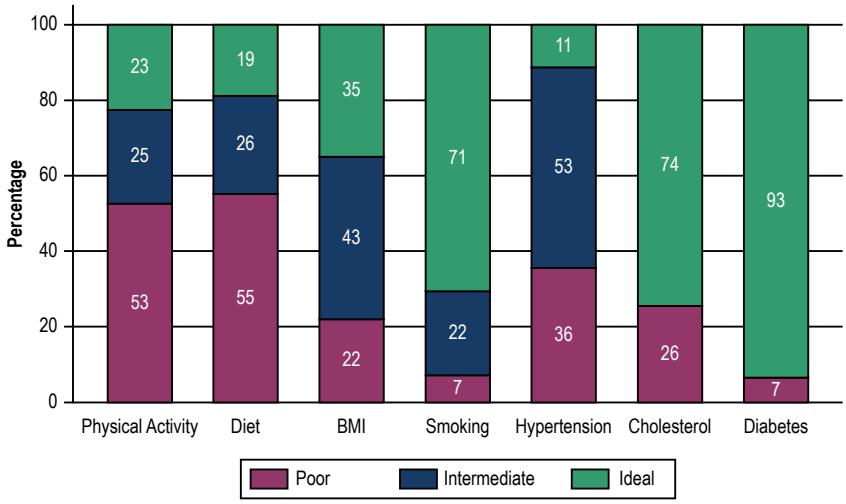

Figure 1 – *Stacked bars showing the prevalence of cardiovascular risk factors. BMI: Body mass index (kg/m²).*

Table 2 – Distribution (count) of poor cardiovascular health factors according to job strain*

Number of poor CV factors	Low strain n = 144(32%)	Active n = 93(21%)	Passive n = 128(28%)	High Strain n = 86(19%)
0	16 (11)	9 (10)	12 (9)	6 (7)
1	52 (36)	31 (33)	27 (21)	18 (21)
2	37 (26)	23 (25)	35 27)	27 (31)
3	29 (20)	17 (18)	35 (27)	25 (29)
4	5 (4)	9 (10)	13 (10)	8 (9)
5	3 (2)	4 (4)	4 (3)	2 (2)
6	2 (1)	0	2 (2)	0
7	0	0	0	0
Mean of poor CV factors (n)	1.8	2	2.2	2.2

p >0.05 for all group comparisons. CV: cardiovascular.

CV health. High job strain was associated with a poor diet and obesity. These findings highlight the influence of workplace condition in CV health of employees and the need to implement policies to improve their health.

We found no individuals in our sample that would be classified as having ideal CV health as defined by the AHA guideline. More than 90% were classified as having poor CV health. Surprisingly, these findings are worse than those from studies in developed countries. In a United States community-based study with 1933 individuals, only one individual fulfilled criteria for ideal CV health. In the same study, 17% had intermediate CV health, and 83% had poor CV health.[11] We would expect a better CV health profile in our population since we recruited employees from an academic center with wide access to health information, particularly given the presence of nutrition, medicine and other health-related disciplines on campus. Furthermore, our sampled population was approximately 10 years younger than the population of other similar studies.[11,12] In an Asian study, the prevalence of ideal CV health was 0.2%, intermediate 21% and poor 79% among hospital workers.[13] Comparing this sample with the current study participants, the main difference of CV parameters can be explained by better blood pressure control and low index of overweight and obesity in the Asian population. Importantly, this worse scenario found in our sample could not be explained by differences in methodology among studies because we used similar definitions for CV health factors as defined by the AHA.[4]

In regards to the difference in job strain and CV health, no relationship between job strain and poor CV health was demonstrated. Previous studios with larger sample size than our study demonstrated that job strain was associated with CV health scores or established CV disease.[14] The current study included 451 participants which limits the power to find small differences. Moreover, socio-cultural differences between this study sample and other studies mainly from developing

Table 3 – Association between job demand, control, or strain with poor cardiovascular health

		Poor Cardiovascular Health (Crude)		Poor Cardiovascular Health (Adjusted*)	
	n (%)	Odds Ratio (95% CI)	p	Odds Ratio (95% CI)	p
Isolated parameters					
High demand	180 (40)	1.24 (0.64-2.39)	0.52	1.49 (0.76-2.94)	0.24
Low Control	229 (49)	1.29 (0.69-2.40)	0.43	1.09 (0.54-2.20)	0.81
Combined parameters					
Low strain	144 (32)	Ref	-	Ref	-
Active	93 (21)	1.17 (0.49-2.76)	0.73	1.21 (0.49-2.97)	0.68
Passive	128 (28)	1.21 (0.55-2.66)	0.64	0.91 (0.38-2.18)	0.84
High strain	86 (19)	1.67 (0.63-4.44)	0.31	1.79 (0.65-4.92)	0.26

*CI: confidence interval; *Adjusted for age, sex, income, education and profession.*

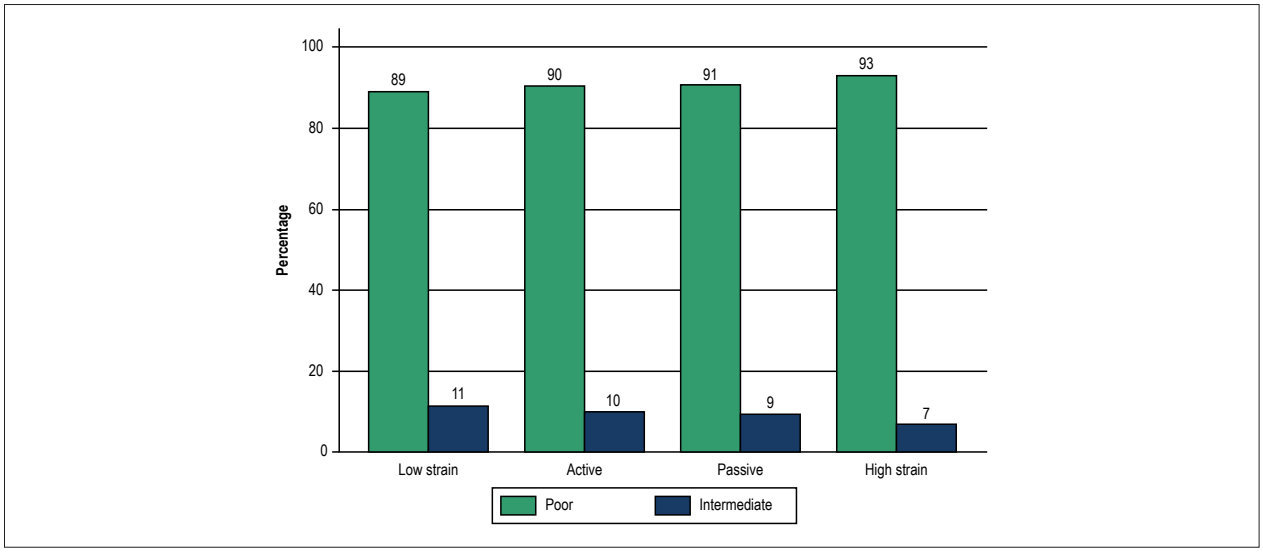

Figure 2 – *Bar graph with percentages of intermediate and poor cardiovascular health according to tob strain categories are low strain (low demand and high control), active (high demand and high control), passive (low demand and low control), and high strain (high demand and low control). Ideal cardiovascular health is not represented because none individual was in this group.*

countries might influence to change the impact of job strain in CV health. Other authors explored individual CV health factors and found association between high job strain and physical inactivity,[15,16] diabetes, smoking and obesity.[16]

In the current study, diet pattern was associated with job strain, perhaps due to the fact that people with higher demand and lower control usually have less time to prepare or buy healthy food. We also found an association between job strain and obesity, which may be a consequence of a poor diet; it is reasonable to hypothesize that a poor diet is a mediator factor for the association between job strain and obesity. However, we did not found mediator effect for this association (data not shown). In addition, the control-demand model was built to evaluate psychosocial factors that affect mental health.[7] Participants with job strain are more prone to have eating disorders resulting in weight gain, which may explain our findings. In our questionnaires, we did not explore mental health disorders to add on this discussion. In the current study, physical inactivity was not associated with job strain, which is different from a previous publication that found it as the only risk factor associated with job strain.[15] Our data showed a trend towards worse CV health factors and job strain, albeit without statistical significance. This is likely due to the lack of sample power given the relatively small sample size. In addition, it is also possible that the busiest and healthiest employees may have declined to participate in the study, introducing a bias towards the null. On the other hand, job stress might determine less influence in CV health in an academic environment in the Amazon region because employees would work in a less competitive behavior.

This study has some limitations. Data on diabetes and hypercholesterolemia were self-reported, which could introduce misclassification bias. On the other hand, self-reported questionnaires have low sensitivity for detecting these

Table 4 – Odds ratio for cardiovascular health factors according job demand, job control and job strain

	n (%)	Crude Odds Ratio (95% CI)	p	Adjusted Odds Ratio (95% CI)*	p
Poor physical activity					
Low strain	66 (46)	Ref	-	Ref	-
Active	53 (57)	1.57 (0.93-2.65)	0.09	1.67 (0.96-2.92)	0.07
Passive	73 (57)	1.57 (0.97-2.53)	0.066	1.19 (0.70-2.04)	0.52
High strain	46 (53)	1.36 (0.80-2.32)	0.26	1.40 (0.80-2.46)	0.24
Poor diet					
Low strain	71 (49)	Ref	-	Ref	-
Active	45 (48)	0.96 (0.57-1.62)	0.89	0.95 (0.55-1.65)	0.86
Passive	72 (56)	1.32 (0.82-2.13)	0.25	1.38 (0.81-2.35)	0.24
High strain	58 (67)	2.13 (1.22-3.18)	0.008	2.31 (1.29-4.13)	0.005
BMI > 30 kg/m²					
Low strain	22 (15)	Ref	-	Ref	-
Active	21 (23)	1.62 (0.83-3.15)	0.16	1.75 (0.86-3.53)	0.12
Passive	34 (26)	2.01 (1.10-3.65)	0.023	1.83 (0.94-3.57)	0.07
High strain	23 (27)	2.02 (1.05-3.91)	0.036	2.11 (1.06-4.22)	0.034
Smoking					
Low strain	8 (6)	Ref	-	Ref	-
Active	7 (8)	1.38 (0.48-3.95)	0.55	1.65 (0.53-5.11)	0.39
Passive	9 (7)	1.29 (0.48-3.44)	0.62	1.01 (0.34-3.04)	0.98
High strain	8 (9)	1.74 (0.63 (4.83)	0.29	2.06 (0.69-6.12)	0.19
High blood pressure					
Low strain	51 (35)	Ref	-	Ref	-
Active	28 (30)	0.79 (0.45-1.37)	0.4	0.82 (0.44-1.51)	0.53
Passive	48 (38)	1.09 (0.67-1.79)	0.72	0.72 (0.41-1.28)	0.27
High strain	32 (37)	1.08 (0.62-1.88)	0.78	0.93 (0.51-1.71)	0.82
Dyslipidemia					
Low strain	34 (24)	Ref	-	Ref	-
Active	24 (26)	1.13 (0.62-2.06)	0.7	1.23 (0.64-2.36)	0.53
Passive	38 (31)	1.42 (0.83-2.43)	0.2	0.92 (0.50-1.69)	0.78
High strain	17 (19)	0.80 (0.41-1.53)	0.5	0.72 (0.36-1.45)	0.35
Diabetes					
Low strain	8 (6)	Ref	-	Ref	-
Active	6 (6)	1.17 (0.39-3.49)	0.78	1.05 (0.33-3.30)	0.94
Passive	11 (9)	1.60 (0.62-4.11)	0.33	1.20 (0.42-3.49)	0.73
High strain	5 (6)	1.05 (0.33-3.32)	0.93	1.07 (0.32-3.56)	0.91

*CI: confidence interval; BMI: body mass index; *Adjusted for age, sex, income, education and profession.*

diseases[17] and the prevalence of CV risk factors may have been underestimated, which increases the concern regarding the burden of CVD among employees at the University. Importantly, this need to be addressed at a larger scale, as it may reflect a high prevalence of cardiovascular risk factors in Rio Branco, the Brazilian capital with the highest prevalence of obesity.[18] However, the prevalence of these cardiovascular factors in our study was similar to data on cardiovascular risk factors reported in the literature.[18-20] The food questionnaire used couldn't capture sodium and fiber-rich whole grains consumption, which limited the food related factors to only three items of the diet guideline proposed by the AHA.[4] Furthermore, some employees declined to respond the questionnaire, which could introduce bias, as employees who declined to fill out the survey could have different characteristics such as higher strain jobs and lower education compared to employees who filled out the survey. We considered that the current study sample is significant, since most part of

Table 5 – Association between job demand or job control with cardiovascular health factors

	Demand				Control		
	n (%)	Adjusted Odds Ratio (95% CI)	p		n (%)	Adjusted Odds Ratio (95% CI)*	p
Poor physical activity							
Low demand	99 (39)	Ref	-	High control	121 (49)	Ref	-
High demand	141 (59)	1.34 (0.90-1.98)	0.15	Low control	126 (51)	1.03 (0.68-1.56)	0.88
Poor diet							
Low demand	160 (61)	Ref	-	High control	123 (47)	Ref	-
High demand	103 (39)	1.21 (0.82-1.80)	0.34	Low control	140 (53)	1.70 (1.12-2.58)	0.012
BMI > 30 kg/m²							
Low demand	45 (44)	Ref	-	High control	59 (58)	Ref	-
High demand	58 (56)	1.49 (0.93-2.41)	0.1	Low control	43 (42)	1.50 (0.91-2.49)	0.12
Smoking							
Low demand	18 (55)	Ref	-	High control	18 (54)	Ref	-
High demand	15 (45)	1.98 (0.91-4.29)	0.085	Low control	15 (45)	1.17 (0.52-2.65)	0.71
Hypertension							
Low demand	31 (61)	Ref	-	High control	17 (32)	Ref	-
High demand	20 (39)	0.70 (0.37-1.35)	0.29	Low control	36 (68)	0.78 (0.38-1.60)	0.5
Dyslipidemia							
Low demand	74 (64)	Ref	-	High control	62 (52)	Ref	-
High demand	42 (36)	1.00 (0.62-1.59)	0.99	Low control	58 (48)	0.83 (0.51-1.34)	0.44
Diabetes							
Low demand	19 (63)	Ref	-	High control	14 (44)	Ref	-
High demand	11 (37)	1.01 (0.19-1.16)	0.98	Low control	18 (56)	1.21 (0.52-2.79)	0.66

*CI: confidence interval; BMI: body mass index; *Adjusted for age, sex, income, education and profession.*

employees responded the questionnaire (still representative of our community as most people invited to participate responded to the questionnaire). Moreover, unmeasured and residual confounding of the relationship between change job stress and CV health could not be completely addressed by multivariate modeling. Finally, as the design of the study is cross-sectional, only associations can be established. A further study with a longitudinal design would explore causality between job strain and CV health factors.

Conclusion

The findings of high prevalence of poor CV health provide important information to public health officials in middle-income countries. Furthermore, a trend to worse CV health in high strain jobs is of interest as these factors could potentially worsen overtime with poor working conditions in developing countries. Strategies for promoting healthy behaviors such as healthier foods offered on campus restaurants, fitness projects, education campaigns, in conjunction with good primary care on campus could potentially have a great impact on life expectancy and improved CV health in this population.

Author contributions

Conception and design of the research: Muniz DD, Siqueira KS, Muniz PT, Silvestre OM; acquisition of data: Muniz DD, Siqueira KS, Muniz PT; analysis and interpretation of the data: Muniz DD, Cornell CT, Silva MMF, Silvestre OM; statistical analysis: Silva MMF, Silvestre OM; writing of the manuscript: Muniz DD, Cornell CT, Silvestre OM; critical revision of the manuscript for intellectual content: Muniz DD, Siqueira KS, Cornell CT, Silva MMF, Muniz PT, Silvestre OM.

Potential Conflict of Interest

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

Sources of Funding

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Study Association

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

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Universidade Federal do Acre under the protocol number 23107.017363/2011-52. 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. Pagidipati NJ, Gaziano TA. Estimating deaths from cardiovascular disease: a review of global methodologies of mortality measurement. Circulation. 2013;127(6):749-56.
2. Santulli G. Epidemiology of cardiovascular disease in the 21st century: updated numbers and updated facts. J Cardiovasc Dis. 2013;1(1):1-2.
3. Stevens G, Mascarenhas M, Mathers C. Global health risks: progress and challenges. Bull World Health Organ. 2009;87(9):646.
4. Lloyd-Jones DM, Hong Y, Labarthe D, Mozaffarian D, Appel LJ, Van Horn L, et al. Defining and setting national goals for cardiovascular health promotion and disease reduction: the American Heart Association's strategic impact goal through 2020 and beyond. Circulation. 2010;121(4):586-613.
5. Stamler J, Stamler R, Neaton JD, Wentworth D, Daviglus ML, Garside D, et al. Low risk-factor profile and long-term cardiovascular and noncardiovascular mortality and life expectancy: findings for 5 large cohorts of young adult and middle-aged men and women. Jama. 1999;282(21):2012-8.
6. Yang Q, Cogswell ME, Flanders WD, Hong Y, Zhang Z, Loustalot F, et al. Trends in cardiovascular health metrics and associations with all-cause and CVD mortality among US adults. Jama. 2012;307(12):1273-83.
7. Karasek RA. Job demands, job decision latitude, and mental strain: Implications for job redesign. Adm Sci Q. 1979;24(2):285-308.
8. Karasek R, Baker D, Marxer F, Ahlbom A, Theorell T. Job decision latitude, job demands, and cardiovascular disease: a prospective study of Swedish men. Am J Public Health. 1981;71(7):694-705.
9. Alves MG, Chor D, Faerstein E, Lopes CS, Werneck GL. Short version of the "job stress scale": a portuguese-language adaptation. Rev Saude Publica. 2004;38(2):164-71.
10 Molina MC, Benseñor IM, Cardoso LO, Velasquez-Melendez G, Drehmer M, Pereira TS, et al. Reproducibility and relative validity of the Food Frequency Questionnaire used in the ELSA-Brasil. Cad Saude Publica. 2013;29(2):379-89.
11. Folsom AR, Yatsuya H, Nettleton JA, Lutsey PL, Cushman M, Rosamond WD, et al. Community prevalence of ideal cardiovascular health, by the American Heart Association definition, and relationship with cardiovascular disease incidence. J Am Coll Cardiol. 2011;57(16):1690-6.
12. Wu S, Huang Z, Yang X, Zhou Y, Wang A, Chen L, et al. Prevalence of ideal cardiovascular health and its relationship with the 4-year cardiovascular events in a northern chinese industrial city. Circ Cardiovasc Qual Outcomes. 2012;5(4):487-93.
13. Chou LP, Tsai CC, Li CY, Hu SC. Prevalence of cardiovascular health and its relationship with job strain: a cross-sectional study in taiwanese medical employees. BMJ Open. 2016;6(4):e010467.
14. Rocco PTP, Bensenor IM, Griep RH, Moreno AB, Alencar AP, Lotufo PA, et al. Job Strain and Cardiovascular Health Score (from the Brazilian Longitudinal Study of Adult Health [ELSA-Brasil] Baseline). Am J Cardiol. 2017;120(2):207-12.
15. Griep RH, Nobre AA, Alves MGDM, Da Fonseca MDJM, Cardoso LDO, Giatti L, et al. Job strain and unhealthy lifestyle: results from the baseline cohort study, Brazilian Longitudinal Study of Adult Health (ELSA-Brasil). BMC Public Health. 2015;15:309.
16. Nyberg ST, Fransson EI, Heikkilä K, Alfredsson L, Casini A, Clays E, et al. Job strain and cardiovascular disease risk factors: meta-analysis of individual-participant data from 47,000 men and women. PLoS One. 2013;8(6): e67323.
17. Ning M, Zhang Q, Yang M. Comparison of self-reported and biomedical data on hypertension and diabetes: findings from the China Health and Retirement Longitudinal Study (CHARLS). BMJ Open. 2016;6(1):e009836.
18. Brasil. Ministério da Saúde. Vigilância De Fatores De Risco E Proteção Para Doenças Crônicas Por Inquérito Telefônico. VIGITEL. Brasilia;2016. [Citado 10 jun 2018]. Disponível em: http://portalsaude.saude.gov.br/images/pdf/2015/ab.
19. Shaw JE, Sicree RA, Zimmet PZ. Global estimates of the prevalence of diabetes for 2010 and 2030. Diabetes Res Clin Pract. 2010;87(1):4-14.
20. Carroll MD, Kit BK, Lacher DA. Total and high-density lipoprotein cholesterol in adults: National Health and Nutrition Examination Survey, 2009-2010. NCHS Data Brief. 2012;92:1-8.

Job Stress and Cardiovascular Health: Is There a Connection?

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Short Editorial related to the article: Ideal Cardiovascular Health and Job Strain: A Cross-Sectional Study from the Amazon Basin

The relationship between psychological stress and cardiovascular (CV) disease has been studied for a long time. In particular, the link between job stress and CV outcomes has been a matter of debate. While there are data supporting that job stress increases CV risk, some experts believe that this association is not truly relevant or the results may be biased.[1]

There are many plausible mechanisms by which job stress may increase the likelihood of CV events, including augmentation of autonomic tonus and predisposition to risk behaviors, such as physical inactivity, unhealthy diet, and smoking.[2]

In this context, the study by Muniz e al.[3] published in this issue of Arquivos Brasileiros de Cardiologia is very welcome. The authors sought to investigate, in a cross-sectional study, the prevalence of ideal CV health and the influence of job stress on CV health among 478 employees from a university in Rio Branco, Acre, Brazil.

CV health was determined by a standard method proposed by the American Heart Association,[4] which considers variables related to lifestyle and traditional risk factors. Job stress was assessed by the classic model proposed by Karasek,[5] which is the method most frequently used in similar studies. According to this model, high job strain occurs when there is a high psychological demand associated with low control over the demands.

Three main aspects of the study by Muniz et al.[3] can be highlighted.

First, it is always good and enriching to see scientific data from a remote place, underrepresented in the cardiological literature, being reported in a medical journal.

Second, and this is alarming, the vast majority of individuals (91%) were considered to have poor CV health, and no one had ideal CV health.[3] One can say that criteria for ideal CV health are too stringent. It can also be said that CV health was not properly evaluated (for instance, information on high blood cholesterol and diabetes was self-reported). Also, the study has limited external validation, as it recruited employees from a single university (65% men), not really representing the general population. Even though, the overall poor CV health reported in this study surpassed the expectations, as the authors pointed out.[3] This finding is, *per se*, a headline to be carefully interpreted by the general population, healthcare providers, and health authorities.

Third, the study brings some insights into the relationship between work stress and CV health. The authors report an association between job strain and poor CV health that did not reach statistical significance. However, high job strain was related to obesity and poor diet.[3]

It must be acknowledged, as the authors do, that cross-sectional studies can only establish an association and not causality. Therefore, the present study has limited ability to add relevant contribution to the knowledge about the causal relationship between job stress and CV disease. This issue is better assessed by prospective cohort studies, once randomized controlled trials with job stress as an intervention are not feasible or ethical. In this regard, although many cohort studies failed to find a positive association between work stress and coronary heart disease (CHD),[2] many other studies and meta-analyses did find a significant relationship between job strain and CV outcomes,[1,6] as well as with diabetes, smoking, physical inactivity, and obesity.[7,8]

For instance, Kivimäki et al. reported that job strain increased the risk of CHD by 23% in a meta-analysis including almost 200,000 individuals from published and unpublished studies, an attempt to avoid publication bias.[6]

Long working hours (≥ 55 hours a week), a pattern frequently correlated with job stress, were also shown to increase the risk of CHD by 1.12-fold and the risk of stroke by 1.21-fold in a large meta-analysis.[9]

Therefore, it seems reasonable to accept job strain as a risk factor for CV disease or, at least, a factor that may increase the risk of CV events by exacerbating traditional risk factors or by facilitating an unhealthy lifestyle.

Efforts should be made to deepen knowledge in this field. Future research should focus on the nuances of the relationship between job stress and CV health. Identifying types and patterns of work more closely related to CV disease may reveal targets for preventive interventions, that can be tested in clinical trials or implemented in the workplace.

The study by Muniz et al.[3] has the merit of shedding light on a relevant, frequently underappreciated aspect of CV prevention. In the contemporary world characterized by a highly competitive professional environment, job stress is very prevalent and its relevance increases in times of economic crisis. Both employers and employees should be aware of the potential unhealthy consequences of job strain. Healthcare providers should address this issue when talking with patients about lifestyle and CV prevention. Health authorities should not neglect this topic. The ultimate goal is to reduce the burden of job stress on CV disease.

Keywords

Cardiovascular Diseases; Occupational Stress; Stress, Psychological, Risk Factors.

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References

1. Kivimäki M, Kawachi I. Work Stress as a risk factor for cardiovascular disease. Curr Cardiol Rep. 2015;17(9):630.
2. Sara JD, Prasad M, Eleid MF, Zhang M, Widmer RJ, Lerman A. Association between work-related stress and coronary heart disease: a review of prospective studies through the Job Strain, Effort-Reward Balance, and Organizational Justice Models. J Am Heart Assoc. 2018;7(9):pii.e008073
3. Muniz DD, Siqueira KS, Cornell CT, Fernandes-Silva MM, Muniz PT, Silvestre OM. Ideal cardiovascular health and job strain: a cross-sectional study from the Amazon Basin. Arq Bras Cardiol. 2019; 112(3):260-268.
4. Lloyd-Jones DM, Hong Y, Labarthe D, Mozaffarian D, Appel LJ, Van Horn L, et al. Defining and setting national goals for cardiovascular health promotion and disease reduction: the American Heart Association's strategic Impact Goal through 2020 and beyond. Circulation. 2010;121(4):586-613.
5. Karasek R, Baker D, Marxer F, Ahlbom A, Theorell T. Job decision latitude, job demands, and cardiovascular disease: a prospective study of Swedish men. Am J Public Health. 1981;71(7):694-705.
6. Kivimäki M, Nyberg ST, Batty GD, Fransson EI, Heikkilä K, Alfredsson L, et al. Job strain as a risk factor for coronary heart disease: a collaborative meta-analysis of individual participant data. Lancet. 2012;380(9852):1491-7.
7. Nyberg ST, Fransson EI, Heikkilä K, Alfredsson L, Casini A, Clays E, et al. Job strain and cardiovascular disease risk factors: meta-analysis of individual-participant data from 47,000 men and women. PLoS One. 2013;8(6):e67323.
8. Nyberg ST, Fransson EI, Heikkilä K, Ahola K, Alfredsson L, Bjorner JB, et al. Job strain as a risk factor for type 2 diabetes: a pooled analysis of 124,808 men and women. Diabetes Care. 2014;37(8):2268-75.
9. Virtanen M, Kivimäki M. Long Working Hours and Risk of Cardiovascular Disease. Curr Cardiol Rep. 2018;20(11):123.

Hypertension Prevalence, Treatment and Control in Older Adults in a Brazilian Capital City

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Abstract

Background: The diagnosis, treatment and control of arterial hypertension are fundamental for a reduction in cardiovascular outcomes, especially in the elderly. In Brazil, there are few studies that specifically identified these rates in the elderly population.

Objective: To verify rates of prevalence, treatment and control of hypertension in elderly people living in the urban area of a Brazilian capital city.

Methods: A cross-sectional, population-based, randomized, cluster-based study with 912 non-institutionalized elderly individuals (≥ 60 years), living in urban areas in the city of Goiania, Midwest Brazil. Predictor variables were: age, gender, socioeconomic and lifestyle aspects. Blood pressure measurements were performed at home; patients were considered as having arterial hypertension when SBP and/or DBP ≥ 140/90 mmHg or when using antihypertensive drugs (dependent variable). Rates of hypertension treatment and control were evaluated. Variable association analyses were performed by multivariate logistic regression and level of significance was set at 5%.

Results: The prevalence of arterial hypertension was 74.9%, being higher (78.6%) in men (OR 1.4, 95% CI: 1.04-1.92); the treatment rate was 72.6%, with higher rates being observed in smokers (OR 2.06, 95% CI: 1.28-3.33). The rate of hypertension control was 50.8%,being higher in women (OR 1.57, 95% CI: 1.19-2.08).

Conclusion: The prevalence rates were high. Treatment and control rates were low and associated with gender, age and lifestyle, indicating the need for early and individual interventions. (Arq Bras Cardiol. 2019; 112(3):271-278)

Keywords: Hypertension/epidemiology; Hypertension/prevention and control; Prevalence; Aging; Blood Pressure; Cross-Sectional Studies.

Introduction

Despite the easy diagnosis and available treatments, arterial hypertension (AH) is still an underdiagnosed disease, with low control rates.[1,2] Information on the prevalence, knowledge of diagnosis, treatment and control among the elderly is scarce in developing countries, even though they are acknowledged as necessary for the monitoring and development of effective strategies for AH control.[2]

In Brazil, starting from the 1970s, there was a change in the population's demographic profile, going from a mostly rural society with large families and young individuals to a mainly urban society, and with a larger proportion of elderly individuals.[3]

The prevalence of AH increases as the analyzed age group changes. In Brazil, the National Health Survey showed a 44.4% prevalence of AH in individuals aged 60 to 64 years; 52.7% from 65 to 74 years and 55.5% for those aged 75 years or older.[4] A study carried out in Tibet identified a progressive increase in this rate, with a 19% variation in the 40-year age range and 78.1% in the 70-year age range.[5] On the other hand, the rates of knowledge of diagnosis, treatment and control were low.[6]

It can be observed that in the Brazilian elderly population, little has been analyzed beyond the prevalence data.[7-10] Brazilian population surveys carried out in the last 20 years, considering the adult population aged > 20 years, showed a prevalence of AH varying from 28.5% in the Southeast region[11] to up to 53.2% in the Northern region of the country.[12] In this latter study, the rate of knowledge of the diagnosis was 63.1% and the treatment rate was 85.4%,[12] albeit not specifically among the elderly. No population-based studies that analyzed all these rates in the elderly population in Brazil have been identified and this lack of information has been a barrier to the development of public health policies for this population.

The aim of this study was to analyze the prevalence, treatment and control of AH and the association with life habits among the elderly, living in the urban area of a capital city in Midwest Brazil.

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Methods

This is a cross-sectional population-based study, carried out through a household survey and randomized cluster sampling, from the matrix project "*Situação de saúde da população idosa do município de Goiânia-GO*" (Health Status of the Elderly Population of the Municipality of Goiânia-GO), linked to the *Rede de Vigilância à Saúde do Idoso* (REVISI) (Health Surveillance Network of the Elderly) in the State of Goiás. The methodological and sample calculation details were described in previous publications.[13,14]

This study was developed by Universidade Federal de Goiás, the Municipal Health Secretariat of Goiânia and State Health Secretariat of the state of Goiás, through REVISI, after being approved by the Research Ethics Committee of Universidade Federal de Goiás (Protocol number 050/2009), in agreement with the Declaration of Helsinki.

An epidemiological survey was carried out, with the participation of people aged 60 and over, living in their homes and in the urban area of Goiânia. The sample was calculated considering the elderly population as 7% of the total 1,249,645 inhabitants, based on the year 2007,[15] an estimated frequency of 30% (lowest expected frequency among the variables investigated in the matrix project), a 95% confidence interval (CI), a 5% significance level, and 5% absolute precision. To the calculated sample (n = 823), 11% were added to compensate for losses, and 934 elderly were assessed. Of the total of 934 questionnaires, 22 were excluded due to data inconsistency, and the final sample consisted of 912 elderly individuals.

The study area was defined based on census sectors (CS). The sample units were the households and the elderly in elementary observation units. Firstly, the CS were identified using the Basic Urban Digital Map of Goiânia as the basic layer. The sampling process was based on the maps of blocks and allotments of the selected regions and was carried out in multiple stages starting from the identification of CS defined by the Instituto Brasileiro de Geografia e Estatística (IBGE - Brazilian Institute of Geography and Statistics).[16] A total of 56 CS were selected, with an estimate of reaching, on average, 17 elderly individuals in each CS.

The data were collected from residents who were at home at the time of the interviewer's visit and who accepted to participate in the study by signing the Free and Informed Consent Form. If, during data collection, two consecutive households with elderly residents were identified, the second house was excluded to minimize the conglomerate and neighborhood effect. The following inclusion criteria were considered in the study: age older than 60 years and being a resident of the household. Elderly individuals who were at the household at the time of the interview but were not residents or were unable to answer for any reason (dementia, unconsciousness) were excluded. In those cases, that household was disregarded, and the next house was considered.

The interviews were carried out by researchers properly trained to apply the study forms and also for the standardization of the procedures to be performed in data collection. The interviews were carried out from November 2009 to April 2010, considering the baseline for the *Rede de Vigilância à Saúde do Idoso* (Health Surveillance Network of the Elderly) in the capital city. Further details on the method can be verified in a previous publication.[17]

At the time of data collection, information were obtained on age, gender, socioeconomic status (level of schooling, marital status and family income), modifiable risk factors (physical activity, smoking, alcohol consumption) and information on AH treatment. Blood pressure (BP) levels were also measured.

BP was measured using an OMRON automatic device, model HEM-705CP, following the protocol of the Brazilian Guidelines.[18] Three measurements were performed in the same arm with the person in the sitting position, following a 3-to-5 minute interval, using the last two measurements for the calculation of the mean value, providing the difference between them was not greater than 4 mmHg. This was done to reduce data dispersion. It is worth noting that appropriate cuff sizes were used according to the arm circumference, using adequate sizes (standard, obese, pediatric) that covered two-thirds of arm extension.[18]

To identify AH prevalence, the elderly were considered hypertensive if they, during data collection, had systolic pressure values ≥ 140 mmHg or diastolic pressure ≥ 90 mmHg, or if they reported regular use of antihypertensive drugs, regardless of the BP value at the time of the interview.[18]

All patients who reported antihypertensive medication use at the time of data collection and who were able to show the prescription, or the medication boxes to be verified, were considered as undergoing treatment for AH.

The individual was considered to have controlled BP when he/she reported AH treatment and the mean BP value was lower than 140/90 mmHg.

Smoking status was classified into three groups: ex-smokers, regardless of the time since they had stopped smoking, non-smokers, for those who never smoked, and smokers. Alcohol consumption was identified according to the elderly individual's response into two groups: those who reported consuming alcohol, even occasionally, and those who reported not consuming it at all. Individuals who reported regular physical activity (three or more times a week) were classified as non-sedentary, and those who practiced physical activity less than three times a week or did not practice any physical activity were classified as sedentary.

Statistical analysis

The quantitative variables were shown with their means and medians, standard deviations and 95%CI; the categorical variables were shown, according to their frequencies, as absolute numbers and percentages. The analysis of the normal distribution of data was performed using the Kolmogorov-Smirnov test.

The software SPSS-IBM version 23 was used to analyze the data, and the odds ratios, AH prevalence, treatment and control rates were calculated, with 95%CI. The chi-square test was used to analyze the association between AH and categorical variables, and the Mann Whitney-U test of independent samples was used to analyze the association between non-parametric, continuous quantitative variables.

Multiple logistic regression analysis was used to estimate the independent effect of variables on outcomes such as AH prevalence, treatment and disease control. The variables that showed a p value < 0.20 in the bivariate analysis were tested in the multiple logistic regression models. All statistical tests were performed considering a level of significance of 5%.

Results

Of the 912 elderly, 683 (74.9%) were hypertensive, of which 72.6% were treated for AH and, among the treated ones, 50.8% had controlled BP (Figure 1).

Of the total sample (n = 912), 62.1% were females. The mean age was 71.5 years (SD ± 8.3), and the median age was 70 years (Table 1).

The AH prevalence was 74.9% (n = 683), of which 431 elderly individuals were identified as having BP ≥140 and/or 90 mmHg, whereas 252 elderly individuals had BP values within the normal range but used hypertensive medication. There was a difference in prevalence between genders, being 39.8% in men and 60.2% in women.

The prevalence of isolated systolic hypertension (ISH) was 29.2% in total, with no difference between genders, being significantly higher in the age group of 70 to 80 years (112; 42.1%) when compared with the age group of 60 to 70 years (94; 35.3%), with a prevalence ratio of 1.75 (95%CI: 1.38–2.20).

Lifestyle-related variables, such as smoking status, alcohol consumption, overweight/obesity, sedentary lifestyle, level of schooling, income and marital status showed no association with AH prevalence (Table 2).

Of the 431 individuals who were identified as having altered BP levels, 187 (43.4%) were unaware of the probable AH diagnosis and were not being treated for the disease. Of the 683 patients considered hypertensive, 496 (72.6%) reported regular use of antihypertensive medication, with lower rates (67.6%) being observed in men when compared to women (75.9%) (Table 2).

Among those who received treatment for the disease, 252 (50.8%) showed BP control (SBP/DBP < 140/90mmHg), also with a difference between genders; the control rates were higher among those aged 60 to 70 years (Table 2).

As for alcohol consumption, there was an association with the control rate, with lower control rates being observed among those who consumed alcohol (Table 2).

The multiple logistic regression analysis showed there was a significant association between the prevalence rate and the male gender, with a higher probability of AH (OR = 1.39, 95%CI 1.04-1.92). Current smoker was associeted with the treatment rate (OR = 2.06, 95%CI: 1.28-3.33). Female gender (OR = 1.57, 1.19-2.08) and alcohol consumption (OR = 1.41, 95%CI 1.00-1.99) were associated with the control rate (Table 3).

Discussion

The present study analyzed the prevalence, treatment and control rates of AH in a representative sample of the urban elderly population in the city of Goiânia, Brazil. The prevalence of AH was 74.9%, higher than observed in the country's adult population shown by other studies carried out in different regions.[8,11,12,19-21] The prevalence of AH in individuals aged between 50 and 70 years is approximately 6 to 8-fold higher than that in young adults, aged between 18 and 29 years,[19-22] consistent with 16 studies carried out in the country between 1989 and 2007, which reported prevalence rates of AH higher than 60% in the elderly population.[10]

Similar prevalence rates were also shown in a study carried out in Poland, with lower values being observed in men (69.9%; 95%CI: 65.2–74.2) than in women (80.2%, 95%CI: 75.7–84.1), at the age range of 80 years old or older. The prevalence for Polish individuals older than 65 years (BP140/90 mmHg) was 78.2% (95%CI: 76.44–79.8) in women

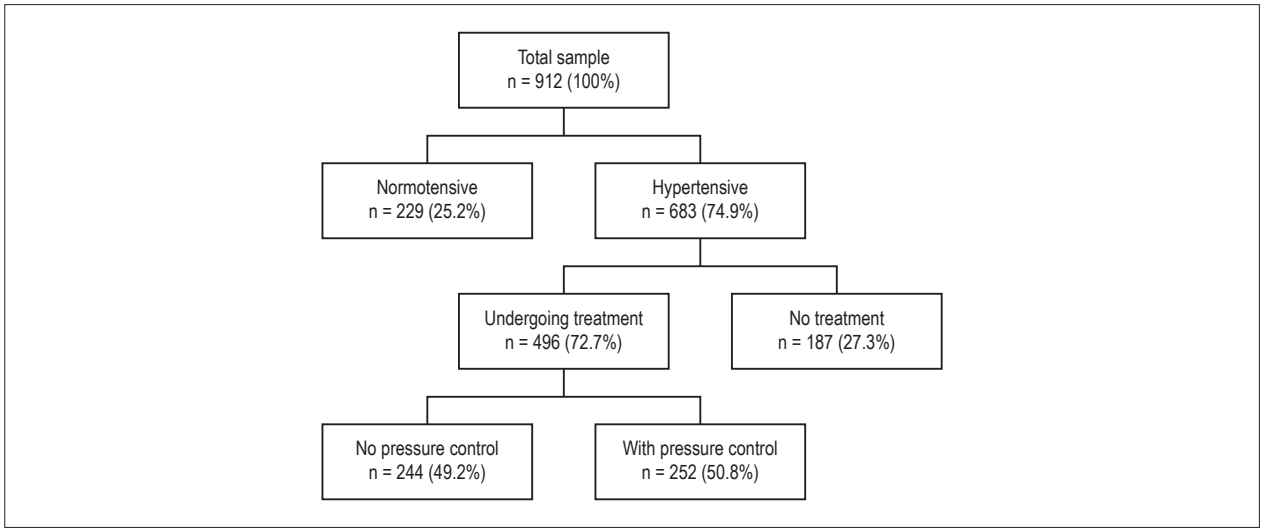

Figure 1 – *Flowchart of the assessed sample identifying normotensive and hypertensive participants; those undergoing treatment and the ones without treatment for hypertension; and with and without pressure control. Goiânia, Goiás, 2010.*

Table 1 – General characteristics of elderly individuals according to the arterial hypertension status. Goiânia, Goiás, Brazil, 2010

Variables	Hypertensive n = 683	Non-hypertensive n = 229	p	Total n = 912
	Median (Interquartile range)	Median (Interquartile range)		Median (Interquartile range)
Age (years)	70.0 (64.0 – 77.0)	70.0 (66.0 – 77.5)	0.275**	70.0 (65.0 – 77.0)
SBP (mmHg)	144.0 (126.0 – 158.0)	124.0 (114.0 – 132.5)	< 0.001**	136.5 (123.0 – 152.0)
DBP(mmHg)	81.0 (73.0 – 89.0)	73.0 (66.5 – 79.4)	< 0.001**	79.4 (70.0 – 87.0)
	n(%)	n(%)		n(%)
Gender			**0,043†**	
Male	272 (39.8)	74 (32.3)		346 (37.9)
Female	411 (60.2)	155 (67.7)		566 (62.1)
Age range			**0.906†**	
60 |-- 70	335 (49.0)	106 (46.3)		441 (48.4)
70 |-- 80	222 (32.5)	79 (34.5)		301 (33.0)
80 |-- 90	110 (16.1)	38 (16.6)		148 (16.2)
90 +	16 (2.3)	6 (2.6)		22 (2.4)
Marital status			**0.730†**	
Married	330 (48.3)	118 (51.5)		448 (49.1)
Single	69 (10.1)	19 (8.3)		88 (9.6)
Widowed	220 (32.2)	73 (31.9)		293 (32.1)
Divorced	61 (8.9)	19 (8.3)		80 (8.8)
Level of schooling			**0.831†**	
Illiterate	107 (15.7)	34 (14.8)		141 (15.5)
Never attended school/Can read	34 (5.0)	10 (4.4)		44 (4.8)
Complete/incomplete Elementary School	324 (47.4)	106 (46.3)		430 (47.1)
Complete/incomplete High School	144 (21.1)	50 (21.8)		194 (21.3)
Complete/incomplete College/University	67 (9.8)	24 (10.5)		91 (10.0)
Income (in MW*)			**0.173†**	
< 1MW	210 (30.8)	54 (23.6)		264 (29.0)
1MW |--- 2MW	284 (41.6)	110 (48.0)		394 (43.2)
2MW|--- 4MW	118 (17.3)	43 (18.8)		161 (17.7)
4MW +	70 (10.3)	22 (9.6)		92 (10.1)
Smoker			**0.240†**	
Yes	73 (10.7)	16 (7.0)		89 (9.8)
No	368 (54.1)	132 (57.9)		500 (55.1)
Ex-smoker	239 (35.1)	80 (35.1)		319 (35.1)
Alcoholism			**0.243†**	
Yes	147 (21.8)	38 (16.7)		185 (20.5)
No	459 (68.0)	162 (71.4)		621 968.8)
Ex-alcoholic	69 (10.2)	27 (11.9)		96 (10.6)
Physical activity			**0.374†**	
Yes	206 (30.2)	73 (31.9)		279 (30.6)
No	466 (68.2)	155 (67.7)		621 (68.1)
Did not answer	11 (1.6)	1 (0.4)		12 (1.3)

**MW: minimum wage (value R$ 510.00 - year 2010); † Chi-Square Test; **Mann Whitney U-test of independent samples.*

Table 2 – Hypertension prevalence, treatment and control in elderly individuals from a Brazilian capital city. Goiânia, Goiás, 2010

Variables	Prevalence rate (n = 683) (95%CI)	Treatment rate (n = 496) (95%CI)	Control rate (n = 252) (95%CI)
Total	74.9 (69.2 – 75.9)	72.6 (69.2 – 75.9)	50.8 (44.8 – 53.6)
Gender			
Male	78.6 (74.1 – 82.7)	67.6 (61.9 – 73.0)	44.0 (37.0 – 51.3)
Female	72.6 (68.8 – 76.2)	75.9 (71.6 – 79.9)	54.8 (49.2 – 60.3)
p value	0.043	0.018	0.020
Age range (years)			
60 |-- 70	76.0 (71.8 – 79.8)	74.9 (70.1 – 79.4)	57.8 (51.6 – 63.8)
70 |-- 80	73.8 (68.6 – 78.5)	68.9 (62.6 – 74.8)	39.2 (31.7 – 47.1)
80 |-- 90	74.3 (66.8 – 80.9)	70.9 (61.9 – 78.8)	51.3 (40.2 – 62.2)
90 +	72.7 (51.7 – 88.1)	87.5 (64.5 – 97.8)	50.0 (25.1 – 74.9)
p value	0,906	0,224	0,004
Marital status			
Married	73.7 (69.4 – 77.6)	73.6 (68.7 – 78.2)	51.4 (45.2 – 57.7)
Single	78.4 (68.9 – 86.1)	72.5 (61.1 – 82.0)	50.0 (36.3 – 63.7)
Widowed	75.1 (69.9 – 79.8)	70.9 (64.6 – 76.6)	46.8 (39.1 – 54.6)
Divorced	76.3 (66.0 – 84.6)	72.1 (59.9 – 82.3)	63.6 (48.7 – 76.8)
p value	0.730	0.803	0.364
Level of schooling			
Illiterate	75.9 (68.3 – 82.4)	68.2 (59.0 – 76.5)	46.6 (35.4 – 58.0)
Never attended school/Can read	77.3 (63.2 – 87.8)	55.9 (39.1 – 71.8)	31.6 (13.9 – 54.5)
Complete/incomplete Elementary School	75.3 (71.1 – 79.2)	73.8 (68.8 – 78.3)	53.6 (47.2 – 59.8)
Complete/incomplete High School	74.2 (67.7 – 80.0)	74.3 (66.7 – 80.9)	50.5 (41.0 – 59.9)
Complete/incomplete College/University	73.6 (63.9 – 81.9)	79.1 (68.2 – 87.6)	54.7 (41.2 – 67.7)
p value	0.986	0.104	0.359
Income (in MW)			
< 1 SMW	79.5 (74.4 – 84.1)	74.3 (68.1 – 79.8)	55.8 (47.9 – 63.4)
1MW |--- 2MW	72.1 (67.5 – 76.3)	72.9 (67.5 – 77.8)	44.9 (38.2 – 51.8)
2 MW|--- 4MW	73.3 (66.1 – 79.7)	70.3 (61.6 – 78.1)	51.8 (41.1 – 62.4)
4MW +	76.1 (66.6 – 83.6)	71.4 (60.1 – 81.1)	58.0 (44.1 – 71.0)
p value	0.173	0.883	0.141
Smoker			
Yes	82.0 (73.0 – 89.0)	84.9 (75.3 – 91.8)	46.8 (34.6 – 59.2)
No	73.6 (69.6 – 77.3)	72.8 (68.11 – 77.2)	51.5 (45.5 – 57.4)
Ex-smoker	74.9 (69.9 – 79.4)	68.6 (62.5 – 74.3)	51.8 (44.2 – 59.4)
p value	0.240	0.024	0.773
Alcoholism			
Yes	79.5 (73.2 – 84.8)	75.5 (68.1 – 81.9)	38.7 (30.2 – 48.0)
No	73.9 (70.4 – 77.2)	71.2 (67.0 – 75.2)	53.2 (47.8 – 58.6)
Ex-alcoholic	71.9 (62.3 – 80.2)	73.9 (62.6 – 83.2)	58.8 (45.0 – 71.7)
p value	0.243	0.577	0.014
Physical activity			
Yes	73.8 (68.4 – 78.7)	75.2 (69.0 – 80.8)	51.0 (43.1 – 58.8)
No	75.0 (71.5 – 78.3)	71.2 (67.0 – 75.2)	50.6 (45.2 – 56.0)
p value	0.374	0.285	0.940

MW: minimum wage (value R $ 510.00 - year 2010).

Table 3 – Multivariate logistic regression analysis of the factors associated with the analyzed rates

Variables	Adjusted Odds Ratio (95%CI)	Wald test	p value
Prevalence of arterial hypertension			
Age (years)	1.01 (0.99 – 1.02)	0.25	0.614
Gender			
Female	1		
Male	1.39 (1.04 – 1.92)	4.16	0.041
Income (in MW)			
< 1MW	1		
1MW |--- 2MW	0.79 (0.45 – 1.4)	0.64	0.423
2 MW|--- 4MW	1.17 (0.69 -- 2.00)	0.34	0.559
4MW +	1.12 (1.00 – 1.02)	0.25	0.614
Treatment rate			
Age (years)	1,00 (0,99 – 1,02)	0,11	0,740
Gender			
Female	1		
Male	1.12 (0.85 – 1.47)	0.66	0.417
Smoker			
Non/ex-smoker	1		
Yes	2.06 (1.28 – 3.33)	3.22	0.003
Control rate			
Age (years)	0.99 (0.97 – 1.00)	2.30	0.130
Gender			
Male	1		
Female	1.57 (1.19 – 2.08)	9.93	0.002
Alcohol consumption			
Yes	1		
No	1.41 (1.00 – 1.99)	3.88	0.049

Other studies carried out with the elderly found a greater proportion of women undergoing treatment.

and 70.1% (95%CI 68.2–71.8) in men,[22] in opposition to our study, where women showed lower rates. The difference in AH prevalence between genders has been previously described in several studies carried out in different countries, as well as the association with age.[23-26] Until the age of 60 years, the proportion of hypertensive women is lower because they rely on the hormonal protection of estrogens, whereas it is predicted that these rates will be equal between men and women after the latter go through menopause.[24]

Similarly, our study showed that ISH had higher prevalence rates among those aged 70 years and older, with no difference between genders, which contrasts with the Polish study that found higher ISH rates in men older than 85 years.[22]

The treatment rate found in our study was higher among women and showed no association with the different age groups. Other studies carried out with the elderly found a greater proportion of women undergoing treatment. Treatment is related to the access to health services, as well as the level of knowledge of AH diagnosis and the prevalence.[28,29] In our country, the identification of these rates, whether among the general population or in specific age groups, comes from population-based surveys or specific studies under certain conditions, such as implemented programs.[30] The difficulty of having access to and receiving care at health services do not allow the opportunity for diagnosis and treatment. This is even more serious when it is related to elderly individuals with AH who are unaware of their diagnosis.

The blood pressure control rates found in our study among those who received treatment for AH were low and significantly lower in men. According to data from the PURE study, which analyzed data from 17 countries representing five continents, AH treatment and control rates in South American countries were lower than those found in our study, even when considering the specific age range of the elderly.[2]

Despite the efforts of health professionals at all levels, blood pressure control rates worldwide are only reasonable. Canada has a rate of 64.6%,[31] Switzerland has 59.4%,[32] the United States has 57%[33] and England, 37%.[34] In Brazil, these rates vary between 22.5% in the North region[11] and 24.2% in the Midwest.[20]

Ignoring a high BP rate is a risk to one's cardiovascular and renal health, as it increases the chances of life-threatening complications, and the higher the BP, the greater the risk of consequences for the heart and blood vessels in the major organs, such as the brain and kidneys, regardless of the age range.[29]

Conclusions

The prevalence and treatment rates of AH found in this study's population were high, 74.9% and 72.6%, respectively. However, only 50.8% of the individuals achieved their blood pressure control targets. Women showed higher rates of treatment and control when compared to men.

Author contributions

Conception and design of the research: Sousa ALL, Batista SR, Pagotto V; acquisition of data and statistical analysis: Sousa ALL; analysis and interpretation of the data: Sousa ALL, Batista SR, Vitorino PVO, Pagotto V; writing of the manuscript: Sousa ALL, Batista SR, Sousa AC, Pacheco JAS, Vitorino PVO, Pagotto V; critical revision of the manuscript for intellectual content: Sousa ALL, Batista SR, Sousa AC, Pacheco JAS, Vitorino PVO, Pagotto V.

Potential Conflict of Interest

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

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Study Association

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

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Universidade Federal de Goiás under the protocol number 050/2009. 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. Supiyev A, Nurgozhin T, Zhumadilov Z, Peasey A, Hubacek JA, Bobak M. Prevalence, awareness, treatment and control of dyslipidemia in older persons in urban and rural population in the Astana region, Kazakhstan. BMC Public Health. 2017;17(1):651.
2. Chow CK, Teo KK, Rangarajan S, Islam S, Gupta R, Avezum A, et al. Prevalence, awareness, treatment, and control of hypertension in rural and urban communities in high-, middle-, and low-income countries. JAMA. 2013;310(9):959-68.
3. Vasconcelos AM, Gomes MM. Transição demográfica: a experiência brasileira. Epidemiol Serv Saúde. 2012;21(4):539-48.
4. Instituto Brasileiro de Geografia e Estatística. IBGE. Pesquisa Nacional de Saúde 2013. Percepção do Estado de Saúde, Estilos de Vida e Doenças Crônicas. Rio de Janeiro, 2013.
5. Huang X, Zhou Z, Liu J, Song W, Chen Y, Liu Y, et al. Prevalence, awareness, treatment, and control of hypertension among China's Sichuan Tibetan population: A cross-sectional study. Clin Exp Hypertens. 2016;38(5):457-63.
6. Huang G, Xu JB, Zhang TJ, Li Q, Nie XL, Liu Y, et al. Prevalence, awareness, treatment, and control of hypertension among very elderly Chinese: results of a community-based study. J Am Soc Hypertens. 2017;11(8):503-12 e2.
7. Tortorella C, Corso ACT, Gonzales-Chica DA, Melhen ARF. Time trends of hypertension and diabetes mellitus prevalence among adults registered in the Brazilian National Health System, in Florianopolis, Santa Catarina State, Brazil, 2004-2011. Epidemiol Serv Saude. 2017;26(3):469-80.
8. Lobo LAC, Canuto R, Dias-da-Costa JS, Pattussi MP. Time trend in the prevalence of systemic arterial hypertension in Brazil. Cad Saude Publica. 2017;33(6):e00035316.
9. Mendes TA, Goldbaum M, Segri NJ, Barros MB, Cesar CL, Carandina L. Factors associated with the prevalence of hypertension and control practices among elderly residents of Sao Paulo city, Brazil. Cad Saude Publica. 2013;29(11):2275-86.
10. Picon RV, Fuchs FD, Moreira LB, Fuchs SC. Prevalence of hypertension among elderly persons in urban Brazil: a systematic review with meta-analysis. Am J Hypertens. 2013;26(4):541-8.
11. Ribeiro TS, Carvalho DP, Guimaraes MT, Campina NN, Lobarinhas MR, Lopes AL, et al. Prevalence of hypertension and its associated factors in contaminated areas of the Santos-Sao Vicente Estuarine region and Bertioga, Brazil: 2006-2009. Environ Sci Pollut Res Int. 2016;23(19):19387-96.
12. Almeida RC, Dias DJ, Deguchi KT, Spesia CH, Coelho OR. Prevalence and treatment of hypertension in urban and riverside areas in Porto Velho, the Brazilian Amazon. Postgrad Med. 2015;127(1):66-72.
13. Vera I, Lucchese R, Nakatani AYK, Pagotto V, Montefusco SRA, Sadoyama G. Funcionalidade familiar em longevos residentes em domicílio. Rev Bras Enferm. 2015;68(1):68-75.
14. Pimentel W, Pagotto V, Nakatani A, Pereira L, Menezes R. Quedas e qualidade de vida: associação com aspectos emocionais em idosos comunitários. Geriatr Gerontol Aging. 2015;9(2):42-8.
15. Instituto Brasileiro de Geografia e Estatística. IBGE.Contagem da População 2007. Rio de Janeiro; 2007.
16. Instituto Brasileiro de Geografia e Estatística. IBGE. Contagem da População 1996. Rio de Janeiro;1997.
17. Castro DC, Nunes DP, Pagotto V, Pereira LV, Bachion MM, Nakatani AYK. Incapacidade funcional para atividades básicas de vida diária de idosos: estudo populacional. Cienc Cuid Saude. 2016;15(1):9.

18. Malachias M, Souza W, Plavnik F, Rodrigues C, Brandão A, Neves M; Sociedade Brasileira de Cardiologia. 7ª Diretriz brasileira de hipertensão arterial. Arq Bras Cardiol. 2016;107(3):1-103.

19. James PA, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler J, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: Report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA. 2014;311(5):507-20.

20. Rosario TM, Scala LN, Franca GA, Pereira MG, Jardim PB. Prevalência, controle e tratamento da hipertensão arterial sistemica em Nobres, MT. Arq Bras Cardiol. 2009;93(3):672-8.

21. Jardim PC, Gondim MR, Monego ET, Moreira HG, Vitorino PV, Souza WK, et al. Hipertensão Arterial e alguns fatores de risco em uma capital brasileira. Arq Bras Cardiol. 2007;88(4):452-7.

22. Zdrojewski T, Wizner B, Wiecek A, Slusarczyk P, Chudek J, Mossakowska M, et al. Prevalence, awareness, and control of hypertension in elderly and very elderly in Poland: results of a cross-sectional representative survey. J Hypertens. 2016;34(3):532-8.

23. Choi HM, Kim HC, Kang DR. Sex differences in hypertension prevalence and control: Analysis of the 2010-2014 Korea National Health and Nutrition Examination Survey. PLoS One. 2017;12(5):e0178334.

24. Chu SH, Baek JW, Kim ES, Stefani KM, Lee WJ, Park YR, et al. Gender differences in hypertension control among older korean adults: Korean social life, health, and aging project. J Prev Med Public Health. 2015;48(1):38-47.

25. Xu T, Zhu G, Liu J, Han S. Gender-specific prevalence and associated risk factors of high normal blood pressure and hypertension among multi-ethnic Chinese adolescents aged 8-18 years old. Blood Press. 2015;24(3):189-95.

26. Shirani S, Gharipour M, Khosravi A, Kelishadi R, Habibi HR, Abdalvand A, et al. Gender differences in the prevalence of hypertension in a representative sample of Iranian population: the Isfahan Healthy Heart Program. Acta Biomed. 2011;82(3):223-9.

27. Kiau BB, Kau J, Nainu BM, Omar MA, Saleh M, Keong YW, et al. Prevalence, awareness, treatment and control of Hypertension among the elderly: the 2006 National Health and Morbidity Survey III in Malaysia. Med J Malaysia. 2013;68(4):332-7.

28. Malhotra R, Chan A, Malhotra C, Ostbye T. Prevalence, awareness, treatment and control of hypertension in the elderly population of Singapore. Hypertens Res. 2010;33(12):1223-31.

29. World Health Organization.WHO. Global status report on noncommunicable diseases Géneve; 2014.

30. Minelli C, Borin LA, Trovo M de C, Reis GC. Hypertension Prevalence, Awareness and Blood Pressure Control in Matao, Brazil: A Pilot Study in Partnership With the Brazilian Family Health Strategy Program. J Clin Med Res. 2016;8(7):524-30.

31. McAlister FA, Wilkins K, Joffres M, Leenen FH, Fodor G, Gee M, et al. Changes in the rates of awareness, treatment and control of hypertension in Canada over the past two decades. CMAJ. 2011;183(9):1007-13.

32. Guessous I, Bochud M, Theler JM, Gaspoz JM, Pechere-Bertschi A. 1999-2009 Trends in prevalence, unawareness, treatment and control of hypertension in Geneva, Switzerland. PLoS One. 2012;7(6):e39877.

33. Olives C, Myerson R, Mokdad AH, Murray CJ, Lim SS. Prevalence, awareness, treatment, and control of hypertension in United States counties, 2001-2009. PLoS One. 2013;8(4):e60308.

34. Falaschetti E, Mindell J, Knott C, Poulter N. Hypertension management in England: a serial cross-sectional study from 1994 to 2011. Lancet. 2014;383(9932):1912-9.

The Challenges of Controlling Arterial Hypertension in the Elderly

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Short Editorial related to the article: Hypertension Prevalence, Treatment and Control in Older Adults in a Brazilian Capital City

This issue of the "Archives" brings the study "Hypertension Prevalence, Treatment and Control in Older Adults in a Brazilian Capital City", by Souza ALL et al.,[1] disclosing data about this important cardiovascular risk factor in Goiânia, state of Goiás, Brazil, depicting the situation in our coutry.[1] In this mini-editorial, we review the epidemiology of arterial hypertension (AH) in Brazil and worldwide.

AH is the leading preventable cause of premature death.[2] A report by the US Institute of Medicine considers AH as a neglected disease, because it is often overlooked by the population and underestimated by the medical community.[3] Although AH is relatively easy to prevent, simple to diagnose and considerably less expensive to treat, it remains one of the most important causes of death.[4] More than 50% of deaths from coronary artery disease and cerebrovascular accidents in the US occur in individuals with AH.[5]

A survey concluded that the estimated global prevalence of AH is increasing.[6] Globally, 31.1% of the adult population had AH in 2010. The prevalence of AH is higher in low- and middle-income countries (31.5%) when compared to high-income countries (28.5%).[6] From 2000 to 2010, the AH prevalence in high-income countries decreased by 2.6%, and awareness, treatment and control substantially improved. However, in low- and middle-income countries, there was an increase in prevalence of 7.7%.[6]

However, a more recent analysis showed that the overall prevalence of age-standardized AH was 24.1% in men and 20.1% in women by 2015.[7] The worldwide number of adults with AH increased from 594 million in 1975 to 1.13 billion in 2015, increasing mainly in low- and middle-income countries.[7]

In relation to the elderly population, the International Mobility In Aging Study (IMIAS) showed that the prevalence of AH ranged from 53.4% to 83.5% in five assessed cities: Kingston (Canada), Saint-Hyacinthe (Canada), Tirana (Albania), Manizales (Colombia) and Natal (Brazil).[8] More than 2/3 of the hypertensive participants were aware of the diagnosis (of 67.3% in Saint-Hyacinthe to 85.4% in Tirana), especially among women.[8] Although more than 80% of the patients were receiving treatment, the control rates were low: 37.6% in Manizales; 29.5% in Kingston; 26.5% in Saint-Hyacinthe; 24% in Tirana and 22% in Natal, with the Brazilian city showing the least effective disease control.[8]

Currently, Canada has the world's best rates of AH control, estimated at 68% of the affected population.[9] That country has achieved a dramatic reduction regarding the lack of diagnosis knowledge (43% in 1991 *versus* 17% in 2013), with the percentage of patients being treated increasing from 34% to 80% in the same period.[9]

The US has shown better AH control in women than in men (55.3% *versus* 38.0% in 2009-2012); as well as among Whites compared to Blacks and Hispanics (41.3% *versus* 31.1% and 23.6%).[10] In that country, there is a better AH control among the elderly than in young individuals (50.5%, in adults aged 60 to 70 years, *versus* 34.4% in patients aged 18 to 39 years in 2011-2012).[11,12] As for the population aged 75 years or older, there was a slight decline in control (46%), which continues to decline from 80 years onward (39.8%).[12]

In Brazil, data from the "Surveillance System for Risk and Protective Factors for Chronic Diseases by Telephone Survey (Vigitel)" (2006 to 2014), indicate that self-reported AH in adults living in capitals ranged from 23% to 25%.[13,14] Among adults aged 60 to 64 years, the prevalence was 44.4%; in those aged 65 to 74 years, 52.7%; and from 75 years onward, 55%.[13] The rates of knowledge (22% to 77%), treatment (11.4% to 77.5%) and control (10.1% to 35.5%) varied widely, depending on the assessed population.[15] Data from VIGITEL 2017, related to 2016, showed that 60.9% of adults aged 65 years and older reported the diagnosis of AH in a telephone survey.[16]

The first Brazilian Registry of AH reveals encouraging data, demonstrating a significant improvement in AH control in the country, when considering the population treated in referral centers.[17] Based on the population treated in 45 centers distributed throughout all Brazilian regions, with a mean age of 61 years, blood pressure (BP) control was observed below 140/90 mmHg in 59.6% of the patients, considering the stabilization of BP in all visits, and 60.6% when considering the measurements in the one-year follow-up consultation.[17] Such rates, however, do not reflect the overall situation of AH control in the country.

In the article by Souza ALL et al.,[1] published in this issue, the total prevalence of AH in the assessed elderly was 74.9%, being higher among men (78.6%). The treatment rate was 72.6% and the percentage of AH control was 50.8%, being higher among women.[1] These data show that, although there is still need for improvement, there has been an important increase in the rates of diagnosis, knowledge, treatment and control of AH in our country, especially among the elderly population.

Keywords

Hypertension/epidemiology; Aged; Hypertension/prevention and control; Prevalence; Arterial Pressure.

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References

1. Sousa ALL, Batista SR, Sousa AS, Pacheco JAS, Vitorino Pv, Pagotto V. Prevalência, tratamento e controle da hipertensão arterial em idosos de uma capital brasileira. Arq Bras Cardiol. 2019; 112(3):271-278.
2. Lim SS, Vos T, Flaxman AD,Danali G, Shibuya K, Adair-Rohani H, et al., A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380(9859):2224-60.
3. Institute of Medicine (US) Committee on Public Health Priorities to Reduce and Control Hypertension. A Population-Based Policy and Systems Change Approach to Prevent and Control Hypertension. Washington (DC): National Academies Press (US); 2010.
4. Mitka M. IOM urges more attention by physicians, public on "neglected" hypertension. JAMA. 2010;303(14):1354-5.
5. Ford ES. Trends in mortality from all causes and cardiovascular disease among hypertensive and nonhypertensive adults in the United States. Circulation. 2011; 123(16):1737-44.
6. Mills KT, Bundy JD, Kelly TN,Reed JE, Kearney PM, Reynolds K, et al. Global disparities of hypertension prevalence and control: a systematic analysis of population-based studies from 90 countries. Circulation. 2016; 134(6):441-50.
7. NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in blood pressure from 1975 to 2015: a pooled analysis of 1479 population-based measurement studies with 19·1 million participants. Lancet. 2017; 389(10064):37-55.
8. Doulougou B, Gomez F, Alvarado B, Guerra RO, Ylli A, Guralnik J, et al. Factors associated with hypertension prevalence, awareness, treatment and control among participants in the International Mobility in Aging Study (IMIAS). J Hum Hypertens. 2016;30(2):112-9.
9. Schiffrin EL, Campbell NR, Feldman RD,Kaczorowski J, Lewanczuck R, Padwal R, et al. Hypertension in Canada: past, present, and future. Ann Glob Health. 2016; 82(2):288-99.
10. National Center for Health Statistics (U.S.). Health, United States, 2013: With Special Feature on Prescription Drugs. Hyattsville, MD: National Center for Health Statistics (US); 2014.
11. Nwankwo T, Yoon SS, Burt V, Gu Q. Hypertension among adults in the United States: National Health and Nutrition Examination Survey, 2011-2012. NCHS Data Brief. 2013 Oct (133):1-8.
12. Bromfield SG, Bowling CB, Tanner RM, Peralta CA, Odden MC, Oparil S, et al. Trends in hypertension prevalence, awareness, treatment, and control among US adults 80 years and older, 1988-2010. J Clin Hypertens (Greenwich). 2014; 16(4):270-6.
13. VIGITEL Brasil 2014. Vigilância de fatores de risco e proteção para doenças crônicas por inquérito telefônico. [Internet]. Disponível em: http://portalsaude.saude.gov.br/images/pdf/2015/abril/15/PPT-Vigitel-2014-.pdf . Acesso em: 21/12/2018.
14. Malachias M, Plavnik FL, Machado CA, Malta D, Scala LCN, Fuchs S. 7th Brazilian Guideline of Arterial Hypertension: Chapter 1 - Concept, Epidemiology and Primary Prevention. Arq Bras Cardiol. 2016; 107(3 Suppl 3):1-6.
15. Scala LC, Magalhães LB, Machado A. Epidemiologia da hipertensão arterial sistêmica. In: Moreira SM, Paola AV; Sociedade Brasileira de Cardiologia. Livro Texto da Sociedade Brasileira de Cardiologia. 2ª. ed. São Paulo: Manole; 2015. p. 780-5.
16. Brasil. Ministério da Saúde (MS). Secretaria de Vigilância em Saúde. Departamento de Vigilância de Doenças e Agravos não Transmissíveis e Promoção da Saúde. VIGITEL Brazil 2017: surveillance of risk and protective factors for chronic diseases by telephone survey: estimates of Frequency and sociodemographic distribution of risk and protective factors for chronic diseases in the capitals of the 26 Brazilian states and the Federal District in 2017 – Brasília; 2018.[Citado em 218 out 12) Disponível em http://bvsms.saude.gov.br/bvs/publicacoes/vigitel_brasil_2017_vigilancia_fatores_risco.pdf. Acesso em 21/12/2018.
17. Lopes RD, Barroso WKS, Brandão AA, Barbosa EC, Malachias MVB, Gomes MM, et al. First Brazilian Registry of Hypertension. Am Heart J. 2018 Nov; 205:154-7.

Role of Myocardial Fibrosis in Hypertrophic Cardiomyopathy: A Systematic Review and Updated Meta-Analysis of Risk Markers for Sudden Death

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Abstract

Background: Hypertrophic cardiomyopathy (HCM) is associated with sudden death (SD). Myocardial fibrosis is reportedly correlated with SD.

Objective: We performed a systematic review with meta-analysis, updating the risk markers (RMs) in HCM emphasizing myocardial fibrosis.

Methods: We reviewed HCM studies that addressed severe arrhythmic outcomes and the certain RMs: SD family history, severe ventricular hypertrophy, unexplained syncope, non-sustained ventricular tachycardia (NSVT) on 24-hour Holter monitoring, abnormal blood pressure response to exercise (ABPRE), myocardial fibrosis and left ventricular outflow tract obstruction (LVOTO) in the MEDLINE, LILACS, and SciELO databases. We used relative risks (RRs) as an effect measure and random models for the analysis. The level of significance was set at $p < 0.05$.

Results: Twenty-one studies were selected (14,901 patients aged 45 ± 16 years; men, 62.8%). Myocardial fibrosis was the major RISK MARKER (RR, 3.43; 95% CI, 1.95-6.03). The other RMs, except for LVOTO, were also predictors: SD family history (RR, 1.75; 95% CI, 1.39-2.20), severe ventricular hypertrophy (RR, 1.86; 95% CI, 1.26-2.74), unexplained syncope (RR, 2.27; 95% CI, 1.69-3.07), NSVT (RR, 2.79; 95% CI, 2.29-3.41), and ABPRE (RR, 1.53; 95% CI, 1.12-2.08).

Conclusions: We confirmed the association of myocardial fibrosis and other RMs with severe arrhythmic outcomes in HCM and emphasize the need for new prediction models in managing these patients. (Arq Bras Cardiol. 2019; 112(3):281-289)

Keywords: Cardiomyopathy, Hypertrophic, Familial;Endomyocardial Fibrosis; Risk Factors; Death, Sudden,Cardiac; Review; Meta-Analsis.

Introduction

Hypertrophic cardiomyopathy (HCM) is an autosomal dominant disease characterized by ventricular hypertrophy in the absence of other conditions that cause heart overload.[1-3] It is the most common genetic disease, with a prevalence rate estimated at 1:500, affecting both men and women. Its presentation can vary from asymptomatic to more severe complications, such as sudden death (SD), which has an incidence rate of 1% per year. HCM is mainly responsible for SD in young and competitive athletes.[5-7] There is a discussion regarding how we should stratify SD and indicate implantable cardioverter-defibrillator (ICD) for the purpose of primary prevention of this disease. Strategies have been proposed to identify these patients, and classic risk markers (RMs), such as family history of SD, severe ventricular hypertrophy, unexplained syncope, non-sustained ventricular tachycardia (NSVT) on 24-hour Holter monitoring, and abnormal blood pressure response to exercise (ABPRE), have been evaluated in several clinical studies.[13] As such, the pathophysiology of SD in HCM is not fully understood. Some factors seem to be involved, including the development of myocardial fibrosis. Studies that investigated myocardial fibrosis using magnetic resonance imaging (MRI) have shown correlations with severe outcomes. In a recent study, Chan et al.[14] found that a percentage of fibrosis > 15% of the left ventricular mass was associated with a twofold increase in the risk of SD in patients considered initially at low risk.[1] However, the detection of myocardial fibrosis using cardiac MRI continues to generate discussions among experts and is now considered only a risk modifier, as evidenced by the American College of Cardiology Foundation / American Heart Association Task Force on Practice Guidelines.[1] The reassessment of RMs, considering the presence of myocardial fibrosis, is fundamental to improve risk stratification. We performed a systematic review and meta-analysis of observational studies that examined RMs in HCM, emphasizing the presence of fibrosis using cardiac MRI, to evaluate their statistical power in predicting SD.

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Methods

Study design

Systematic review with meta-analysis of observational studies of the natural history of HCM that reported RMs of SD and severe arrhythmic outcomes.

Search strategy

The search used 3 databases - MEDLINE, LILACS and SciELO - contemplating prospective or retrospective studies conducted between 1980 and 2016, which analyzed the natural history of patients with HCM, regardless of sex or ethnicity. We used the PRISMA statement checklist to conduct the systematic review and meta-analysis. The detailed research adapted for each database was conducted using the following keywords of Medical Subject Heading (MeSH) and DECS: Cardiomyopathy, Hypertrophic, Familial [MeSH] OR "Cardiomyopathy, Hypertrophic" [Mesh] OR "cardiomyopathies" [MeSH] OR cardiomyopathy [MEASURE] OR "risk factors" [MeSH] Death [Text Word] OR "defibrillators, implantable" [MeSH] OR "cardioverter defibrillator, implantable" [Text Word]. Only the articles published in English, Portuguese, and Spanish were considered for the full-text review.

Selection criteria

We have included only observational studies (prospective or retrospective cohorts) that had a severe arrhythmic outcome equivalent to SD. The studies that also analyzed at least one of the following RMs were included: a) family history of SD, b) severe left ventricular hypertrophy, c) unexplained syncope, d) NSVT on 24-hour Holter monitoring, e) ABPRE, f) presence of left ventricular outflow tract obstruction (LVOTO), and g) presence of myocardial fibrosis on cardiac MRI. The exclusion criteria were (1) studies that were case reports or review articles, (2) studies that did not meet the previously described inclusion criteria, and (3) duplicate studies.

Definitions

The studies included in our meta-analysis often used variable concepts, but fit the definitions listed in Table 1.

Data extraction

The eligibility (using inclusion and exclusion criteria) of each study was systematically analyzed by two reviewers (MIB and SAC), initially by reading the titles and abstracts. Selected articles were read and analyzed in full to assess their eligibility and methodological quality; all references were revised to identify additional studies. Differences in opinion between the two main reviewers were independently resolved by a third reviewer (DV). After this phase, the data were extracted. The information collected from each study included study design, number of patients, demographic data, follow-up, RMs for SD, and severe arrhythmic outcomes. Authors were contacted when any additional information was needed. There was no time restriction for the severe arrhythmic outcomes.

Statistical analysis

The statistical analysis used relative risks (RRs) as a measure of effect with 95% confidence intervals (CIs). The meta-analysis was performed using the DerSimonian and Laird method in case of heterogeneity and the Mantel-Haenszel method in case of homogeneity. The heterogeneity was analyzed using Cochran's Q and I^2 Higgins/Thompson tests. The risk of bias was tested using funnel plots and Egger's linear regression test. The software used for the analysis was R 3.4.1. The level of significance was set at $p < 0.05$.

Ethical and legal aspects

The study protocol was submitted to the Medical Ethics Committee of Pedro Ernesto University Hospital and received a final opinion on November 14, 2013.

Results

Search results

The search strategy identified 809 potentially relevant articles (Figure 1). After reading the titles and abstracts, 123 remained for the eligibility analysis. After detailed evaluation, 103 articles were excluded, and 1 article was added after reviewing the references. Thus, 21 observational studies

Table 1 – Definitions of outcomes and risk markers used in the meta-analysis

Severe arrhythmic outcomes	SD, aborted SD, documented sustained ventricular tachycardia, or appropriate shock in patients with ICD
Family history of SD	Family history of SD in the first-degree relatives of patients
Severe left ventricular hypertrophy	Ventricular thickness > 30 mm measured using echocardiography in any left ventricular segment
Unexplained syncope	A history of unexplained and transient loss of consciousness with spontaneous recovery
NSVT on 24-hour Holter monitoring	≥ 3 consecutive ventricular extrasystoles with heart rates of ≥ 120 bpm for < 30 seconds
LVOTO	Peak gradient of ≥ 30 mmHg in the left ventricular outflow tract detected on echocardiography
ABPRE	Increased (< 20 mmHg) or decreased (> 10 mmHg) systolic blood pressure with peak exercise
Myocardial fibrosis	Detection of late enhancement on MRI with gadolinium

SD: sudden death; ICD: implantable cardioverter-defibrillator; NSVT: non-sustained ventricular tachycardia; LVOTO: left ventricular outflow tract obstruction; ABPRE: abnormal blood pressure response to exercise; MRI: magnetic resonance imaging.

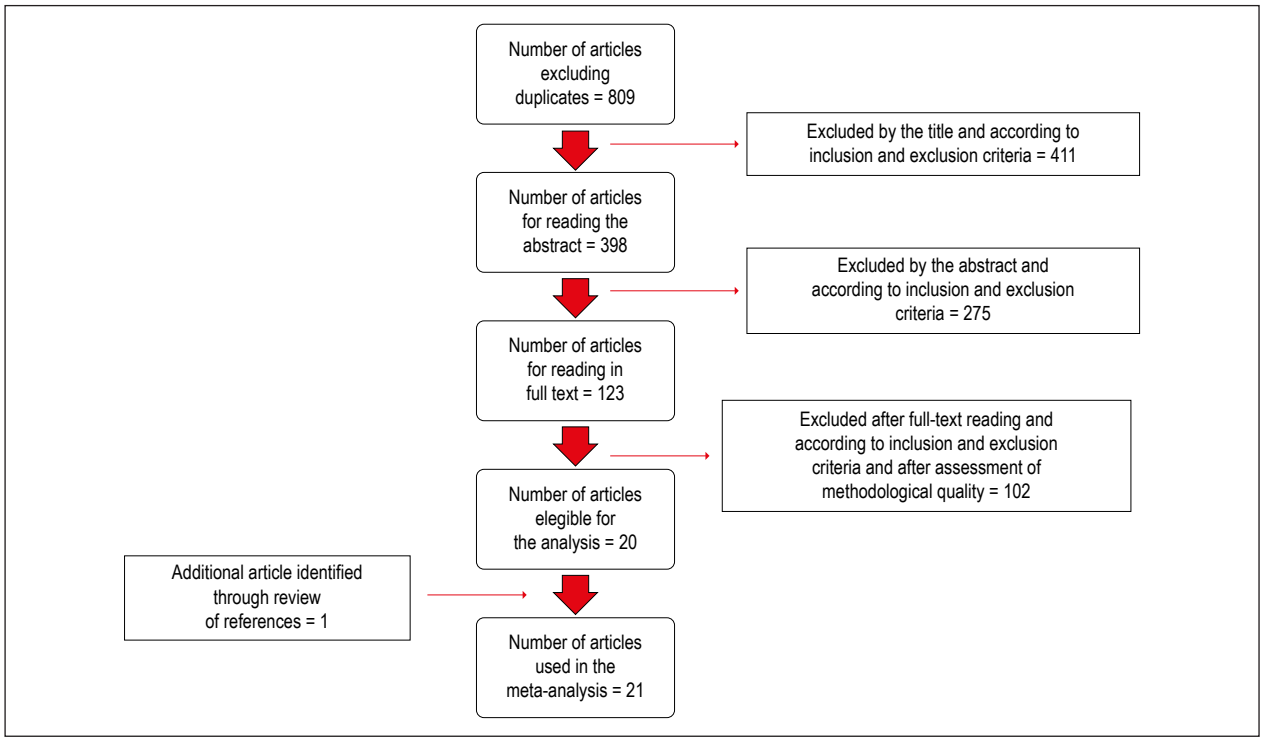


Figure 1 – *Flowchart of the systematic review.*

were selected, including 14 prospective and 7 retrospective studies, comprising 14,901 patients (age, 45 ± 16 years; 62.8% males).[11-14,17-33] The main characteristics of the included studies are shown in Table 2.

Myocardial fibrosis

The systematic review selected 5 articles that correlated the presence of fibrosis on cardiac MRI with severe arrhythmic outcomes. One of them was excluded from the meta-analysis because all the patients who had events had myocardial fibrosis using the MRI, making it impossible to calculate the measure of effect.[24] Among the four remaining studies involving 2549 patients, the presence of fibrosis was correlated with events equivalent to SD in two studies;[14,29] however, this only occurred in the univariate analysis of the other two.[32,33] In the meta-analysis, we found a significant probability of severe arrhythmic outcomes in the presence of this variable (RR, 3.43; 95% CI, 1.95-6.03). We highlighted the absence of heterogeneity in the Forest plot and the RR, which was the highest among all the other markers evaluated (Figures 2A and 3). The funnel plot for myocardial fibrosis is shown in figure 2B.

Meta-analysis of classic RMs

As shown in Figure 3, the following classic RMs demonstrated an association with the outcomes studied: family history of SD (13 studies – 9815 patients; RR, 1.75; 95% CI, 1.39-2.20); severe left ventricular hypertrophy (11 studies – 5501 patients; RR, 1.86; 95% CI, 1.26-2.74); unexplained syncope (12 studies – 10064 patients; RR, 2.27; 95% CI, 1.69-3.07); NSVT on 24-hour Holter monitoring (14 studies – 9421 patients; RR, 2.79; 95% CI, 2.29-3.41); and ABPRE (6 studies – 3061 patients; RR, 1.53; 95% CI, 1.12-2.08).

In our analysis, the only RISK MARKER that showed no correlation with serious arrhythmic outcomes was LVOTO (5 studies – 4762 patients; RR, 1.72; 95% CI, 0.97-3.02). This may have been influenced by the small number of studies involved in the combined analysis. It should be emphasized that the inclusion of this marker in the stratification of SD has always been a matter of debate.

When we evaluated the heterogeneity in all the RMs, we observed that only severe left ventricular hypertrophy was significant ($I^2 = 75\%$, $p < 0.01$), although we emphasize that the random effect model used in the meta-analysis already had mitigated this aspect. The Egger´s test also points to a publication bias for this RISK MARKER ($p = 0.002$)

We did not observe any publication bias by Egger's test or by the funnel plot for the other classic RMs.

Based on these results, it seems plausible that all classic RMs can still be used in SD stratification in HCM, except for LVOTO.

Discussion

This systematic review and meta-analysis shows the importance of a broad approach in SD risk stratification in patients with HCM, including myocardial fibrosis assessment.

The evaluation of patients with HCM may include multiple complementary examinations in an attempt to predict SD.

Table 2 – Characteristics of the observational studies involving RMs of SD in HCM

Author / year of publication	Country	N. of patients	Age (years)	% males	Follow-up (months)	Severe arrhythmic outcomes
Elliott et al. 2006[17]	UK ;1988-2002	917	43	60.4	61	54
Elliott et al. 2000[18]	UK; 1988-1998	368	37	64.9	43.2	22
Gimeno et al. 2009[13]	UK; 1988 – 2004	1380	42	61.8	54	NI
Kofflard et al. 2003[19]	Netherlands; 1970-1999	225	41	57.7	96	20
Kofflard et al. 1993[20]	Netherlands; 1970-1990	113	38	53.09	87.6	9
Maron B et al. 2007[21]	Multicentric; 1983-2005	383	41	62.9	44.4	51
Maron M et al. 2003[22]	USA and Italy; 1983- 2001	1101	45	59.4	75.6	71
Michaelides et al. 2009[23]	Greece; 1999-2001	81	42	70.3	63.6	8
Monserrat et al. 2003[12]	UK; 1988-2000	531	39	60.8	70	32
Rubinshtein et al. 2010[24]	USA; 2001-2007	424	55	59.1	43	8
Spirito et al. 2009[25]	USA and Italy; 1983-2005	1511	46	61.3	67.2	74
Spirito et al. 2000[11]	USA and Italy; 1983-1997	480	47	60	78	23
Syska et al. 2010[26]	Poland; 1996-2006	78	36.4	47.4	55.2	13
Chan et al. 2014[14]	USA and Italy: 2001-2010	1293	46	63	39.6	37
Spirito et al. 2014[27]	Multicentric; 1990-2009	653	44.4	70.5	63.6	24
Magnusson et al. 2016[28]	Sweden; 1995-2002	237	52	69.2	64.8	77
Klopotowski et al. 2015[29]	Poland; 2008-2013	328	45	58.5	37	14
Mahony et al. 2014[30]	Multicentric	3675	48	63.9	68.4	198
Debonmaire et al. 2015[31]	Netherlands and Belgium	195	52	61	68.4	26
Ismail et al. 2014[32]	UK; 2000-2011	711	55	70.4	42	22
O´Hanlon et al. 2010[33]	UK; 2000-2006	217	53.2	70.5	37.2	12

RMs: risk markers; SD: sudden death; HCM: hypertrophic cardiomyopathy; UK: United Kingdom; USA: United States of America; NI: Not informed.

Obviously, this has several effects, including economic burdening. Thus, knowing how to select the more important RMs is essential. Although primary prevention has been the object of research in several studies in the last decades, attempting to predict which patients with HCM have a higher risk of SD remains challenging. Therefore, systematic reviews and meta-analyses of such a controversial topic becomes important. The presence of the RMs studied here may define the need for ICD placement, considering that it is the only safe and effective tool in preventing SD.[36] Some RMs have been reported to be more relevant, such as family history of SD, which was highlighted in the study by Dimitrow et al.,[10] however, its low positive predictive values is a limitation. In the event of syncope, it is only indicative of the risk when unexplained. Thus, all RMs have their limitations.

Strategies using the sum of classic RMs were not feasible. In the multicenter registry performed by Maron et al.[8] in patients with HCM who were treated with ICD placement, it was observed that 35% who received an appropriate shock had only 1 RM. These data were reinforced by a recent meta-analysis of patients with HCM and ICD who had 1.8 RISK MARKERS for SD on average, with a rate of 3.3% appropriate shocks per year. We also emphasize that the analysis did not include studies that had myocardial fibrosis as an RM.

Among the more recently studied markers aiming to establish correlations with an increased risk of SD in HCM, the most important was myocardial fibrosis. The mechanism suggested for this predisposition is that the presence of myocardial fibrosis could be a substrate for ventricular reentry areas. A classic study demonstrated that this finding correlates with the presence of NSVT in the 24-hour Holter monitoring. Shiozaki et al.[39] in a recent national experience with 26 patients with HCM and ICD, assessed myocardial fibrosis by another method, the contrast-enhanced computed tomography, and found a higher rate of appropriate shocks in patients who had a fibrosis mass ≥ 18 g. Most of the studies that evaluated myocardial fibrosis in this population used cardiac MRI, and these were the experiences we analyzed with the focus on outcomes associated with MS.

Putting the results into context, this meta-analysis of observational studies reports a statistically significant association between myocardial fibrosis detected on cardiac MRI and outcomes equivalent to SD. Although we have assessed few articles, this is the most important finding in this study, showing the highest RR among all RMs studied with a very reliable CI. And even if the funnel plot has revealed discrete asymmetry suggesting a publication bias for myocardial fibrosis, it is important to note that the small number of articles does not allow one to conclude this assertion.

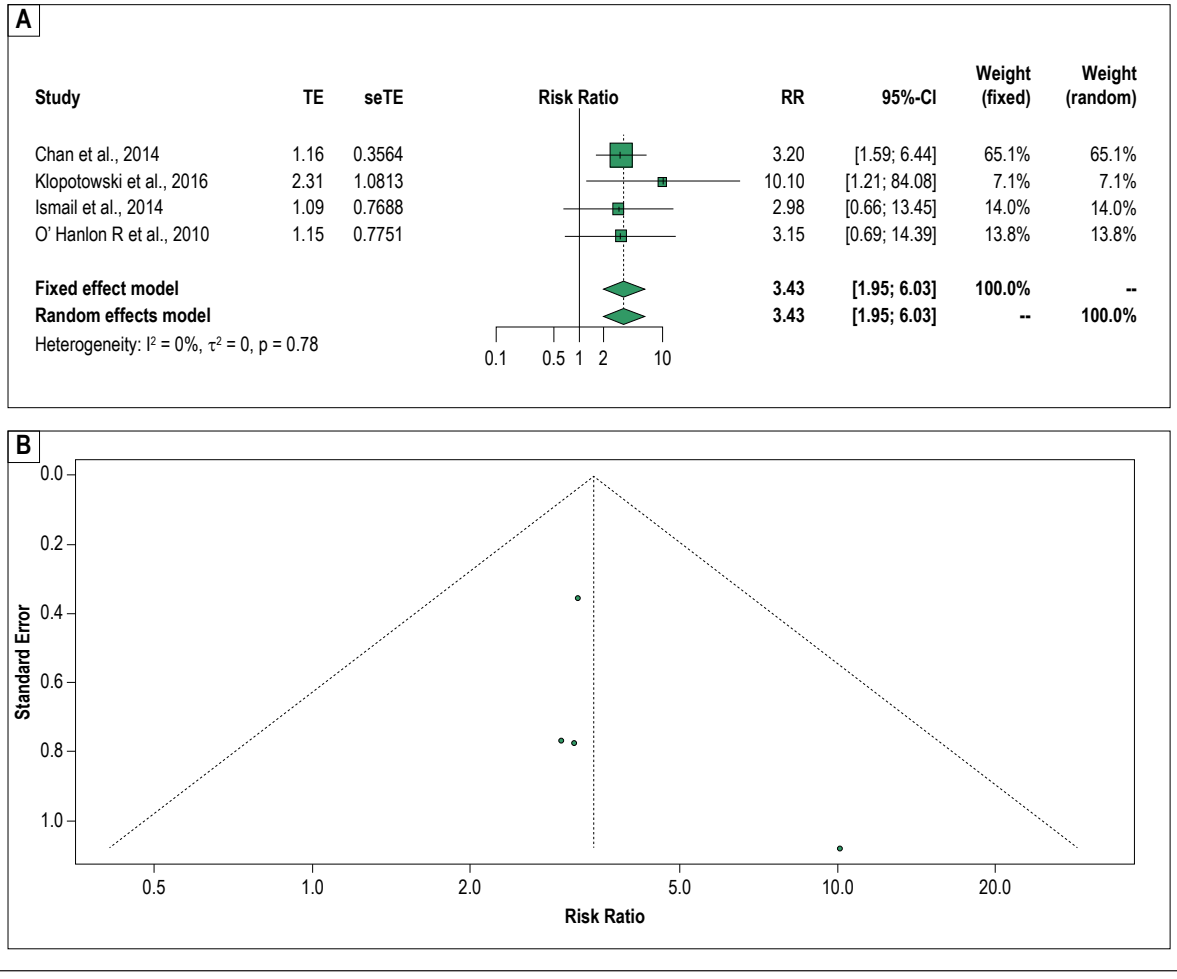


Figure 2 – *A. Forest plot of myocardial fibrosis and relative risk of the severe arrhythmic outcomes. B. Funnel plot of myocardial fibrosis to evaluate for publication bias. TE: estimated treatment effect; seTE: standard error of treatment estimate; RR: relative risk; 95%CI: 95% confidence interval.*

A meta-analysis published by Briasoulis et al.,[40] addressing only myocardial fibrosis, found similar results. However, one article used in the analyses did not allow a precise calculation of an effect measure because the group without fibrosis did not have any event.[24] Our option was to remove it, because we understood this would compromise the statistical analysis. It stands out that this meta-analysis included the article of Klopotowski et al.[29] with 328 patients and updated other RMs.

We consider that this finding is of much clinical relevance, as the latest guidelines on the subject do not address the presence of fibrosis as an RM. In its latest document regarding the disease, the European Society of Cardiology based the indication of ICD placement on using a risk calculator (HCM-Risk SCD) created to provide more accurate stratifications.[2] Based on a cohort, the derived model used the parameters of age, maximum ventricular thickness, LVOTO, left atrial diameter, family history of SD, presence of NSVT, and unexplained syncope.[30] Subsequent studies showed conflicting results regarding the calculator., Perhaps, the fact that it does not assess fibrosis may be a limitation.

Regarding the other findings, we observed that all classic RMs correlated with the occurrence of the outcomes studied, except for LVOTO. In contrast to what has been observed in a previously published meta-analysis, our findings do not indicate that LVOTO may be associated with severe arrhythmic outcomes. This was probably because of the smaller number of patients used in our analysis and the inclusion of two recent studies of which results do not indicate the association between this marker and SD.

The methods that investigated possible publication bias only found significant result for severe left ventricular hypertrophy. However, the clinical relevance of this risk marker has already been documented in several studies and emphasized in the last guidelines.[1,2,11,18,43]

The limitations of our study include: (1) the inclusion and exclusion criteria, diagnostic methods, and definitions varied discreetly among the different studies; (2) the data of the patients from the same institution may have overlapped, although this did not occur in most of the analyses; (3) the absence of randomized trials may also be considered a relative

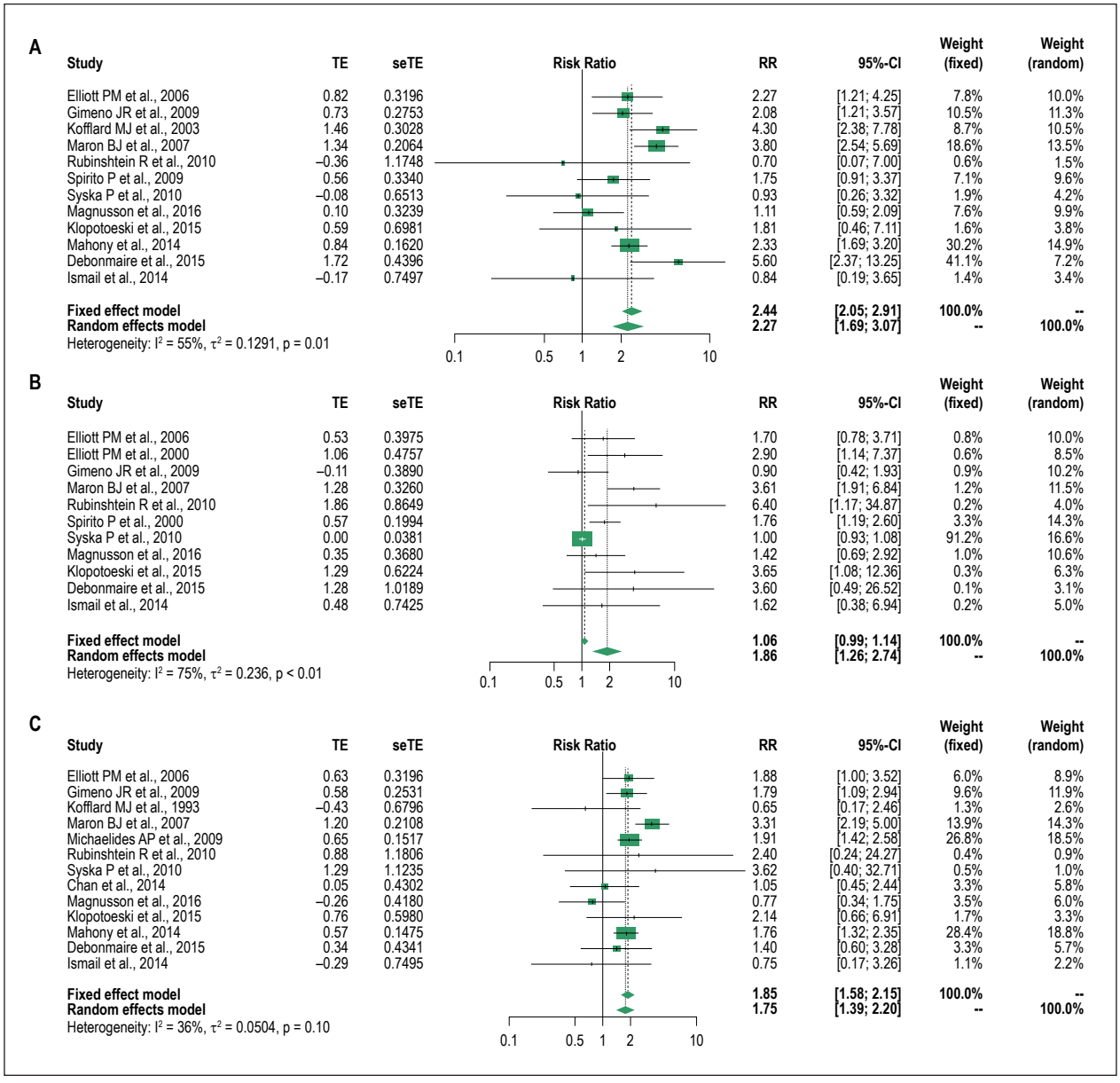


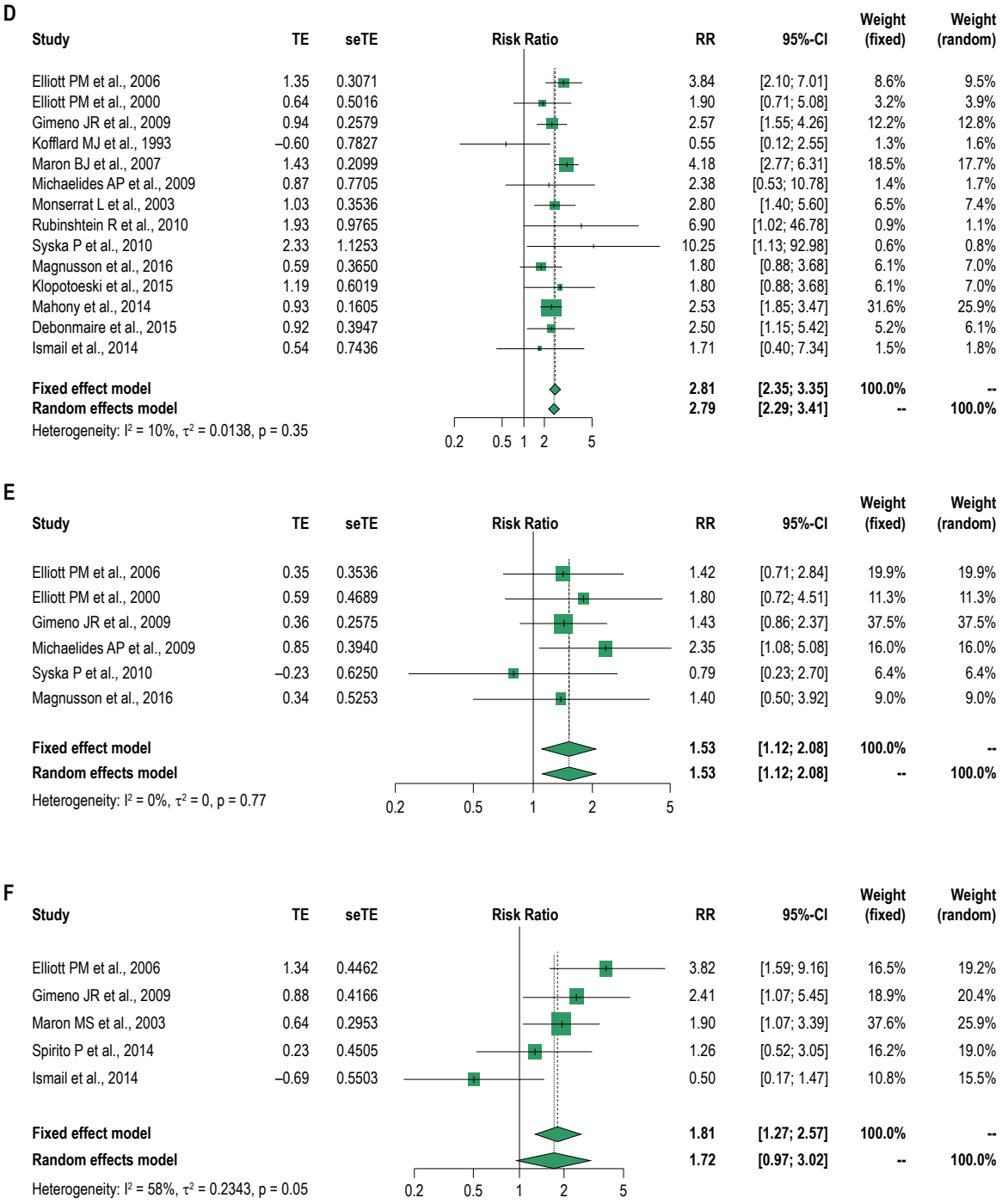
Figure 3 – *Forest plot of the risk markers and the relative risk of severe arrhythmic outcomes: A: unexplained syncope; B: severe ventricular hypertrophy; C: family history of sudden death; D: non-sustained ventricular tachycardia; E: abnormal blood pressure response to exercise; F: left ventricular outflow tract obstruction. TE: estimated treatment effect; seTE: standard error of treatment estimate; RR: relative risk; 95%CI: 95% confidence interval.*

limitation, but it is important to remember that the systematic review with meta-analysis has the capacity of minimizing this problem, bringing information from observational studies to a higher level of evidence; (4) myocardial fibrosis was analyzed in a few studies and in a binary manner, not quantitatively, although the latter has been gaining attention in recent publications.[14] Although the study of Chan et al.,[14] which was used in this meta-analysis, provided quantitative information, we used only the RR for the presence or absence of fibrosis.[14] Another relevant issue for discussion, although not addressed in this study, which can be considered a limitation, is the cost of cardiac MRI. No cost-effectiveness analysis aimed at the investigation of fibrosis using MRI in patients with HCM has been conducted yet.

Despite these limitations, we rely on the findings of our study because of its methodology, consistency of results (absence of heterogeneity in most analyses), and especially the close and well-known association between myocardial fibrosis and arrhythmias. And with the purpose of studying this association, it is important to emphasize that we chose to include only studies that evaluated outcomes equivalent to SD.

Conclusions

In summary, although it is very difficult to make clinical decisions of great relevance to patients based solely on information from observational studies, it is important to



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weigh the risks and benefits of ICDs with patients and their families. Nevertheless, this meta-analysis of observational studies emphasizes the importance of cardiac MRI in the detection of myocardial fibrosis for the risk stratification of SD in HCM and confirms the role of traditional RMs, with a doubtful role for LVOTO. Thus, new clinical prediction models using myocardial fibrosis should be considered as a primary prevention strategy for SD in these patients in the future.

Author contributions

Conception and design of the research and analysis and interpretation of the data: Bittencourt MI, Cader SA, Araújo DV, Mourilhe-Rocha R; acquisition of data: Bittencourt MI, Cader AS; statistical analysis: Bittencourt MI, Araújo DV; writing of the manuscript: Bittencourt MI, Cader SA, Mourilhe-Rocha R; critical revision of the manuscript for intellectual content: Bittencourt MI, Cader SA, Araújo DV, Salles ALF, Albuquerque FN, Spineti PPM, Albuquerque DC, Mourilhe-Rocha 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 Hospital Universitário Pedro Ernesto under the protocol number 457893. 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. Chan RH, Maron BJ, Olivotto I, Pencina MJ, Assenza GE, Haas T, et al. Prognostic value of quantitative contrast-enhanced cardiovascular magnetic resonance for the evaluation of sudden death risk in patients with hypertrophic cardiomyopathy. Circulation. 2014;130(6):484-95.
2. Bittencourt MI, Cader SA, Araújo DV, Salles ALF, Albuquerque FN, Spineti PPM, et al. Sudden death in hypertrophic cardiomyopathy. Int J Cardiovasc Sci. 2016;29(6):504-11.
3. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med. 2009;151(4):264-9.
4. Elliott PM, Gimeno JR, Tomé MT, Shah J, Ward D, Thaman R, et al. Left ventricular outflow tract obstruction and sudden death risk in patients with hypertrophic cardiomyopathy. Eur Heart J. 2006;27(16):1933-41.
5. Elliott PM, Poloniecki J, Dickie S, Sharma S, Monserrat L, Varnava A, et al. Sudden death in hypertrophic cardiomyopathy: identification of high risk patients. J Am Coll Cardiol. 2000;36(7):2212-8.
6. Kofflard MJ, Ten Cate FJ, van der Lee C, van Domburg RT. Hypertrophic cardiomyopathy in a large community-based population: clinical outcome and identification of risk factors for sudden cardiac death and clinical deterioration. J Am Coll Cardiol. 2003;41(6):987-93.
7. Kofflard MJ, Waldstein DJ, Vos J, ten Cate FJ. Prognosis in hypertrophic cardiomyopathy observed in a large clinic population. Am J Cardiol. 1993;72(12):939-43.
8. Maron BJ, Spirito P, Shen WK, Haas TS, Formisano F, Link MS, et al. Implantable cardioverter-defibrillators and prevention of sudden cardiac death in hypertrophic cardiomyopathy. JAMA. 2007;298(4):405-12.
9. Maron MS, Olivotto I, Betocchi S, Casey SA, Lesser JR, Losi MA, et al. Effect of left ventricular outflow tract obstruction on clinical outcome in hypertrophic cardiomyopathy. N Engl J Med. 2003;348(4):295-303.
10. Michaelides AP, Stamatopoulos I, Antoniades C, Anastasakis A, Kotsiopoulou C, Theopistou A, et al. ST segment "hump" during exercise testing and the risk of sudden cardiac death in patients with hypertrophic cardiomyopathy. Ann Noninvasive Electrocardiol. 2009;14(2):158-64.
11. Rubinshtein R, Glockner JF, Ommen SR, Araoz PA, Ackerman MJ, Sorajja P, et al. Characteristics and clinical significance of late gadolinium enhancement by contrast-enhanced magnetic resonance imaging in patients with hypertrophic cardiomyopathy. Circ Heart Fail. 2010;3(1):51-8.
12. Spirito P, Autore C, Rapezzi C, Bernabò P, Badagliacca R, Maron MS, et al. Syncope and risk of sudden death in hypertrophic cardiomyopathy. Circulation. 2009;119(13):1703-10.
13. Syska P, Przybylski A, Chojnowska L, Lewandowski M, Sterliński M, Maciag A, et al. Implantable cardioverter-defibrillator in patients with hypertrophic cardiomyopathy: efficacy and complications of the therapy in long-term follow-up. J Cardiovasc Electrophysiol. 2010;21(8):883-9.
14. Spirito P, Autore C, Formisano F, Assenza GE, Biagini E, Haas TS, et al. Risk of sudden death and outcome in patients with hypertrophic cardiomyopathy with benign presentation and without risk factors. Am J Cardiol. 2014;113(9):1550-5.
15. Magnusson P, Gadler F, Liv P, Mörner S. Risk markers and appropriate implantable defibrillator therapy in hypertrophic cardiomyopathy. Pacing Clin Electrophysiol. 2016;39(3):291-301.
16. Klopotowski M, Kukula K, Malek LA, Spiewak M, Polanska-Skrzypczyk M, Jamiolkowski J, et al. The value of cardiac magnetic resonance and distribution of late gadolinium enhancement for risk stratification of sudden cardiac death in patients with hypertrophic cardiomyopathy. J Cardiol. 2016;68(1):49-56.
17. O'Mahony C, Jichi F, Pavlou M, Monserrat L, Anastasakis A, Rapezzi C, et al. A novel clinical risk prediction model for sudden cardiac death in hypertrophic cardiomyopathy (HCM risk-SCD). Eur Heart J. 2014;35(30):2010-20.
18. Debonnaire P, Katsanos S, Joyce E, VAN DEN Brink OV, Atsma DE, Schalij MJ, et al. QRS fragmentation and QTc duration relate to malignant ventricular tachyarrhythmias and sudden cardiac death in patients with hypertrophic cardiomyopathy. J Cardiovasc Electrophysiol. 2015;26(5):547-55.
19. Ismail TF, Jabbour A, Gulati A, Mallorie A, Raza S, Cowling TE, et al. Role of late gadolinium enhancement cardiovascular magnetic resonance in the risk stratification of hypertrophic cardiomyopathy. Heart. 2014;100(23):1851-8.

20. O'Hanlon R, Grasso A, Roughton M, Moon JC, Clark S, Wage R, et al. Prognostic significance of myocardial fibrosis in hypertrophic cardiomyopathy. J Am Coll Cardiol. 2010;56(11):867-74.

21. Almquist AK, Montgomery JV, Haas TS, Maron BJ. Cardioverter-defibrillator implantation in high-risk patients with hypertrophic cardiomyopathy. Heart Rhythm. 2005;2(8):814-9.

22. Jayatilleke I, Doolan A, Ingles J, McGuire M, Booth V, Richmond DR, et al. Long-term follow-up of implantable cardioverter defibrillator therapy for hypertrophic cardiomyopathy. Am J Cardiol. 2004;93(9):1192-4.

23. Maron BJ, Spirito P. Implantable defibrillators and prevention of sudden death in hypertrophic cardiomyopathy. J Cardiovasc Electrophysiol. 2008;19(10):1118-26.

24. Schinkel AF, Vriesendorp PA, Sijbrands EJ, Jordaens LJ, ten Cate FJ, Michels M. Outcome and complications after implantable cardioverter defibrillator therapy in hypertrophic cardiomyopathy: systematic review and meta-analysis. Circ Heart Fail. 2012;5(5):552-9.

25. Adabag AS, Maron BJ, Appelbaum E, Harrigan CJ, Buros JL, Gibson CM, et al. Occurrence and frequency of arrhythmias in hypertrophic cardiomyopathy in relation to delayed enhancement on cardiovascular magnetic resonance. J Am Coll Cardiol. 2008;51(14):1369-74.

26. Shiozaki AA, Senra T, Arteaga E, Martinelli Filho M, Pita CG, Ávila LF, et al. Myocardial fibrosis detected by cardiac CT predicts ventricular fibrillation/ventricular tachycardia events in patients with hypertrophic cardiomyopathy. J Cardiovasc Comput Tomogr. 2013;7(3):173-81.

27. Briasoulis A, Mallikethi-Reddy S, Palla M, Alesh I, Afonso L. Myocardial fibrosis on cardiac magnetic resonance and cardiac outcomes in hypertrophic cardiomyopathy: a meta-analysis. Heart. 2015;101(17):1406-11.

28. Vriesendorp PA, Schinkel AF, Liebregts M, Theuns DA, van Cleemput J, Ten Cate FJ, et al. Validation of the 2014 European Society of Cardiology guidelines risk prediction model for the primary prevention of sudden cardiac death in hypertrophic cardiomyopathy. Circ Arrhythm Electrophysiol. 2015;8(4):829-35.

29. Maron BJ, Casey SA, Chan RH, Garberich RF, Rowin EJ, Maron MS. Independent assessment of the European Society of Cardiology sudden death risk model for hypertrophic cardiomyopathy. Am J Cardiol. 2015;116(5):757-64.

30. Christiaans I, van Engelen K, van Langen IM, Birnie E, Bonsel GJ, Elliott PM, et al. Risk stratification for sudden cardiac death in hypertrophic cardiomyopathy: systematic review of clinical risk markers. Europace. 2010;12(3):313-21.

31. Oliveira DC, Assunção FB, Santos AA, Nacif MS. Cardiac magnetic resonance and computed tomography in hypertrophic cardiomyopathy: an update. Arq Bras Cardiol. 2016;107(2):163-72.

Myocardial Fibrosis in Hypertrophic Cardiomyopathy: What Remains to be Proven?

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Short Editorial related to the article: Role of Myocardial Fibrosis in Hypertrophic Cardiomyopathy: A Systematic Review and Updated Meta-Analysis of Risk Markers for Sudden Death

Hypertrophic cardiomyopathy (HCM) is a complex and well-characterized disease. Its prevalence in the general population is 1 in 500 individuals, with some data suggesting an even higher prevalence when using associated genetic criteria.[1] This means that, based on a conservative estimate, cities such as Goiânia-GO or Recife-PE have approximately more than 3,000 individuals with the disease, a figure that can be as high as 25,000 individuals in a large city such as São Paulo.

Although HCM is perceived as a rare and usually very severe disease, related to dramatic episodes of sudden death (SD) in young individuals and athletes, it is a disease with low mortality. Due to advances in the diagnosis, treatment and prevention of SD, current estimates indicate a mortality rate of 0.5% a year, similar to that found in the general population, with most patients with the disease being asymptomatic or minimally symptomatic.[2] In this scenario, the correct identification of subgroups of individuals with a higher risk of unfavorable outcome and, therefore, a greater chance of benefit when submitted to specific therapeutic strategies, such as the use of implantable cardioverter defibrillators (ICD), is of utmost importance.

However, HCM is an extremely challenging disease, with variable clinical presentations and an often unpredictable natural history. SD, its most devastating clinical manifestation, occurs most often in previously healthy individuals and unaccompanied by preceding symptoms. Several clinical markers derived from observational studies were organized into risk stratification models, giving origin to the algorithms adopted by the American and European Cardiology Societies.[3,4]

However, the use of such tools has several limitations. The scarcity of randomized studies makes recommendations be based primarily on registries, retrospective or prospective small-scale studies. The accuracy of these models for SD prediction according to validation analyses was moderate (area under the ROC curve ranging from 0.60 to 0.69), with low specificity and positive predictive value and sub-optimal performance when used at the individual level. Moreover, individual traditional risk markers have low sensitivity and specificity, and their absence does not safely rule out the chance of SD.[5] Therefore, the current risk stratification tools in HCM are imperfect and imprecise, making research on new risk markers a crucial matter.

Cardiac magnetic resonance (CMR) imaging allows the precise identification of areas of myocardial replacement fibrosis through the late enhancement technique.[6,7] Analyses of prevalence and the distribution pattern of late enhancement in HCM have been widely described. There is a large body of evidence showing that the arrhythmogenic mechanism that would lead to SD in HCM patients is directly related to myocardial fibrosis and, similarly, several studies in patients with HCM evaluated by magnetic resonance showed a worse prognosis in those with late enhancement such as arrhthmias, heart failure, SD, cardiac death and death from any cause.[8]

In the present article of this issue,[9] the authors presented a systematic review and meta-analysis that included 21 studies evaluating the association of risk markers with the occurrence of SD. The authors demonstrated a strong correlation between the presence of myocardial fibrosis detected by CMR and the occurrence of arrhythmic outcomes, with a clearly higher relative risk when compared to the other identified risk markers (RR: 3.43; 95%CI: 1.95–6.03). This result is in accordance with another meta-analysis evaluating HCM and myocardial fibrosis, totaling 1,063 patients (mean follow-up of 43 ± 14 months), in which the presence of late enhancement in these patients resulted in a 9-fold higher chance of ventricular fibrillation / tachycardia and a 3.3-fold higher chance of SD.[10] These results suggest that late enhancement may be very useful as a high-risk prognostic marker.

About this subject, it should be noted that some considerations are important. Myocardial fibrosis detected by CMR is very common in HCM and is observed in approximately 2/3 of the patients.[8] Therefore, its presence alone does not allow adequate selection of patients candidates for ICD.

Recently, studies have been published establishing a positive and linear association between late enhancement extent and worse prognosis, with the presence of more than 15% of myocardial fibrosis mass, giving a roughly 2-fold higher chance of SD when compared to individuals without late enhancement, regardless of other risk markers.[11,12] However, this approach also has significant limitations. First, there is no universal standardization of the late enhancement quantification technique, leading to the great heterogeneity of results (currently, the most often used techniques are the 6 standard deviation method, the full-with half maximum technique and the Rayleigh Curve Method).[8]

Keywords

Cardiomyopathy, Hypertrophic; Prevalence; Death, Sudden, Cardiac/prevention & control; Heart Failure; Magnetic Resonance Spectroscopy/methods.

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Moreover, there is still some controversy over whether late enhancement provides clinically relevant incremental information to traditional risk factors, mostly because of the small number of primary outcomes observed in the studies. Additionally, there are no large-scale prospective studies evaluating the late enhancement quantification incorporated into the ACC/AHA and European Cardiology Society algorithms for the prediction of SD in HCM.

CMR is an extremely valuable tool in the evaluation of HCM and its application for diagnostic purposes has been very well established. Similarly, the evaluation of myocardial fibrosis by the late enhancement technique is a strong prognostic marker of the disease and will probably have a great impact as a risk stratification tool.

Nevertheless, according to the main guidelines on HCM, currently the clinical use of the technique for primary prophylaxis of SD is restricted to ambiguous cases, when the ICD indication is uncertain when using the traditional algorithms.[3,4] Therefore, to take one step further and for myocardial fibrosis screening to be formally incorporated into the risk stratification routine in HCM, some gaps still need to be addressed.

I think it is a matter of time!

References

1. Maron BJ. Clinical Course and Management of Hypertrophic Cardiomyopathy. N Engl J Med. 2018;379(7):655–68.
2. Maron BJ, Maron MS, Rowin EJ. Perspectives on the Overall Risks of Living with Hypertrophic Cardiomyopathy. Circulation. 2017;135:2317-9.
3. 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 Developed in Collaboration with the American Ass. J Am Coll Cardiol. 2011;58(25):212–60.
4. Zamorano JL, 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). Vol. 35, European Heart Journal. 2014. p. 2733–79.
5. Sen-Chowdhry S, Jacoby D, Moon JC, McKenna WJ. Update on hypertrophic cardiomyopathy and a guide to the guidelines. Nat Rev Cardiol. 2016;13(11):651–75.
6. Moon JCC, McKenna WJ, McCrohon JA, Elliott PM, Smith GC, Pennell DJ. Toward clinical risk assessment in hypertrophic cardiomyopathy with gadolinium cardiovascular magnetic resonance. J Am Coll Cardiol. 2003;41(9):1561–7.
7. Choudhury L, Mahrholdt H, Wagner A, Choi KM, Elliott MD, Klocke FJ, et al. Myocardial scarring in asymptomatic or mildly symptomatic patients with hypertrophic cardiomyopathy. J Am Coll Cardiol.2002;40(12):2156–64.
8. Quarta G, Aquaro GD, Pedrotti P, Pontone G, Dellegrottaglie S, Iacovoni A, et al. Cardiovascular magnetic resonance imaging in hypertrophic cardiomyopathy: The importance of clinical context. Eur Heart J Cardiovasc Imaging. 2018;19:601-10.
9. Bittencourt MI, Cader SA, Araújo DV, Salles ALF, Albuquerque FN, Spineti PPM, et al. Papel da fibrose miocárdica na cardiomiopatia hipertrófica: Revisão sistemática e metanálise atualizada de marcadores de risco para morte súbita. Arq Bras Cardiol. 2019;112(3):281-289.
10. Reddy ST, Tito A, Filho P, Silva NJ, Doyle M, Yamrozik J, et al. A Systematic review for sudden cardiac death in hyoetrophic cardiomyopathy patients with myocardial fibrosi: a CMR LGE Study. J Am Coll Cardiol. 2012;59(13):E1228.
11. Chan RH, Maron BJ, Olivotto I, Pencina MJ, Assenza GE, Haas T, et al. Prognostic value of quantitative contrast-enhanced cardiovascular magnetic resonance for the evaluation of sudden death risk in patients with hypertrophic cardiomyopathy. Circulation. 2014;130(6):484–95.
12. Weng Z, Yao J, Chan RH, He J, Yang X, Zhou Y, et al. Prognostic Value of LGE-CMR in HCM: A Meta-Analysis. JACC Cardiovasc Imaging. 2016;9(12):1392–402.

Comparison of Biological and Mechanical Prostheses for Heart Valve Surgery: A Systematic Review of Randomized Controlled Trials

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Abstract

Background: The choice of a mechanical (MP) or biological prosthesis (BP) for patients with valvular heart disease undergoing replacement is still not a consensus.

Objective: We aimed to determine the clinical outcomes of MP or BP placement in those patients.

Methods: We conducted a systematic review and meta-analysis of randomized controlled trials (RCTs) that compared biological prostheses and mechanical prostheses in patients with valvular heart diseases and assessed the outcomes. RCTs were searched in the MEDLINE, EMBASE, LILACS, CENTRAL, SCOPUS and Web of Science (from inception to November 2014) databases. Meta-analyses were performed using inverse variance with random effects models. The GRADE system was used to rate the quality of the evidence. A P-value lower than 0.05 was considered significant.

Results: A total of four RCTs were included in the meta-analyses (1,528 patients) with follow up ranging from 2 to 20 years. Three used old generation mechanical and biological prostheses, and one used contemporary prostheses. No significant difference in mortality was found between BP and MP patients (risk ratio (RR = 1.07; 95% CI 0.99-1.15). The risk of bleeding was significantly lower in BP patients than MP patients (RR = 0.64; 95% CI 0.52-0.78); however, reoperations were significantly more frequent in BP patients (RR = 3.60; 95% CI 2.44-5.32). There were no statistically significant differences between BP and MP patients with respect to systemic arterial embolisms and infective endocarditis (RR = 0.93; 95% CI 0.66-1.31, RR = 1.21; CI95% 0.78-1.88, respectively). Results in the trials with modern and old prostheses were similar.

Conclusions: The mortality rate and the risk of thromboembolic events and endocarditis were similar between BP and MP patients. The risk of bleeding was approximately one third lower for BP patients than for MP patients, while the risk of reoperations was more than three times higher for BP patients. (Arq Bras Cardiol. 2019; 112(3):292-301)

Keywords: Heart Valve Prosthesis; Bioprosthesis; Metal-on-Metal Joint Prosthesis; Heart Valve Prosthesis Implantation/trends; Review.

Introduction

In the early 1960's, valve replacement surgery using prostheses completely changed the natural history of patients with valvular heart disease. Approximately 90,000 valve prostheses are implanted in the United States, and 280,000 are implanted worldwide each year.[1] Currently, the total number of biological valve prosthesis implants surpasses that of mechanical prosthesis implants.[2-4]

The factors that seem to affect the increased use of biological prostheses include advances in their construction, leading to increased durability, and the fact that they do not require permanent use of oral anticoagulants.[5] However, biological prostheses still present an increased risk of structural deterioration and the need for reoperation, although the surgical risk involved in reoperation has decreased substantially in recent years.[6] Furthermore, in the event of a stenosis disorder, patients with aortic bioprosthesis impairment can be treated with a catheter-implanted prosthesis.[7]

A systematic review of randomized trials published in 2000 comparing mechanical and biological valve prostheses suggested that no difference in mortality existed between the two implant types.[8] There was, however, less risk of reoperation with mechanical prostheses but increased risk of bleeding compared to biological prostheses. There are no recent systematic reviews comparing the performance of biological valve prostheses with that of mechanical prostheses. Since the publication of the last review, further randomized studies may have been published that better reflect progress in prosthesis development, surgical techniques and clinical treatments during that time period. The objective of the present systematic review of randomized studies was to compare the effect of biological valve prosthesis use with

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that of mechanical prosthesis use in terms of mortality, reoperations, the incidence of thromboembolic events, bleeding, and endocarditis.

Methods

Search strategy and sources

The literature search included the following electronic databases: MEDLINE/PubMed, (from 1950 to 04 November 2014), CENTRAL/Cochrane Library, EMBASE/Elsevier (from 1966 to November 4, 2014), SCOPUS/Elsevier (from 1960 to November 4 2014), Web of Science/Thomson Reuters (from 1898 to November 4, 2014), and LILACS/BVS (from 1980 to November 4, 2014), without language and publication date restrictions. Previous systematic reviews and guidelines were consulted to identify and include relevant studies. Other sources were also consulted to identify relevant studies including Clinicaltrials.gov, conference abstracts; lists of text references related to the topic; review articles; and information letters concerning unpublished or incomplete studies.

The search strategies were developed by defining descriptors, synonyms and the use of Boolean logical operators (AND, OR, and AND NOT) for each database (MeSH/Medline, Emtree/Embase, and DeCs/BVS).[9] The MeSH/Medline subject descriptors were sensitised by the strategy of adding "entry terms" (synonyms). In Medline, the Cochrane Handbook Filter[10] was used, which has high sensitivity for recovery of indexed randomized controlled trials (RCTs).

Study Selection

We included randomized trials in any language that compared native valve replacement with the biological and mechanical prosthesis, regardless of the follow-up period. Observational studies, studies with children or patients under 18 years of age, and studies with patients who required tricuspid valve replacement were excluded. The study eligibility evaluation process consisted of two steps, both performed independently by pairs of reviewers. The first author (ATK) participated in all pairs. The first step consisted of screening articles by reading the title and abstract. In this step, the article was selected for the next step if at least one of the reviewers deemed the article eligible. In the second step, the full article texts were evaluated and selected based on an eligibility form. The final eligibility of the article was decided by agreement between the reviewers or by the judgment of a third reviewer in the event of a disagreement. In the case of multiple publications of the same study, we considered the manuscript reporting the longest follow-up.

Data extraction and risk of bias

For the data extraction process, we developed a standard form with the clinical information of each patient, including gender, age, functional class, affected valve, type of implanted prosthesis, follow-up period, and methodological characteristics, for further evaluation of evidence quality.

An assessment of the risk of bias of the included studies was based on an evaluation of the following domains: random sequence generation, allocation concealment, blinding of outcome assessors, and incomplete outcome data. Blinding of patients and the healthcare team regarding the prosthesis type was not feasible, and these items were therefore not evaluated. We generated a descriptive table to compare the selected studies by classifying the risk of bias as low, moderate, high, or unclear for each risk of bias domain.

Outcomes

The outcomes measured included total mortality, defined as death from any cause; embolic events, defined as a systemic embolism; bleeding events (of any magnitude); new surgery, defined as the need to replace the prosthesis implanted in the initial procedure; and episodes of infectious endocarditis.

Data synthesis and analysis

We determined the risk ratios (RRs) and their respective 95% confidence intervals (CIs) for binary outcomes of each trial. Meta-analyses were performed with random effects models using inverse variance. Subgroup analyses were conducted based on the position of valve replacement (aortic, mitral or combined aortic-mitral).

Most trials did not report the number of events, only probabilities of events and their standard errors. Thus we calculated the variance of the logarithm of the RR with the formula used by Kassai et al.[8]

$$\frac{SE_1^2}{p_1^2} + \frac{SE_2^2}{p_2^2}$$

Where:

p_1 = the probability of an event for a mechanical heart valve

p_2 = the probability of an event for a bioprosthesis

SE_1 = standard error of p_1

SE_2 = standard error of p_2

We assessed the statistical heterogeneity across trials or subgroups using Cochrane's chi-squared test. The Higgins inconsistency test (I^2) was used to quantify the percentage of the variability in the effect estimates that was due to heterogeneity rather than by chance;[11] we considered values of $I^2 \leq 25\%$ as low heterogeneity and values $\geq 50\%$ as high heterogeneity. We conducted these analyses using Review Manager Version 5.2 software (Cochrane IMS, Oxford, UK). A p-value lower than 0.05 was considered significant.

Quality of evidence assessment

We assessed the confidence in the estimates of effect (quality of evidence) using the GRADE (Grades of Recommendation, Assessment, Development, and Evaluation) system.[12]

Results

Characteristics of included studies

The electronic database search resulted in 7,725 citations (Figure 1). After evaluation of the articles, we identified four original studies including 1,528 patients in total. The clinical characteristics of the four included studies are presented in Table 1.

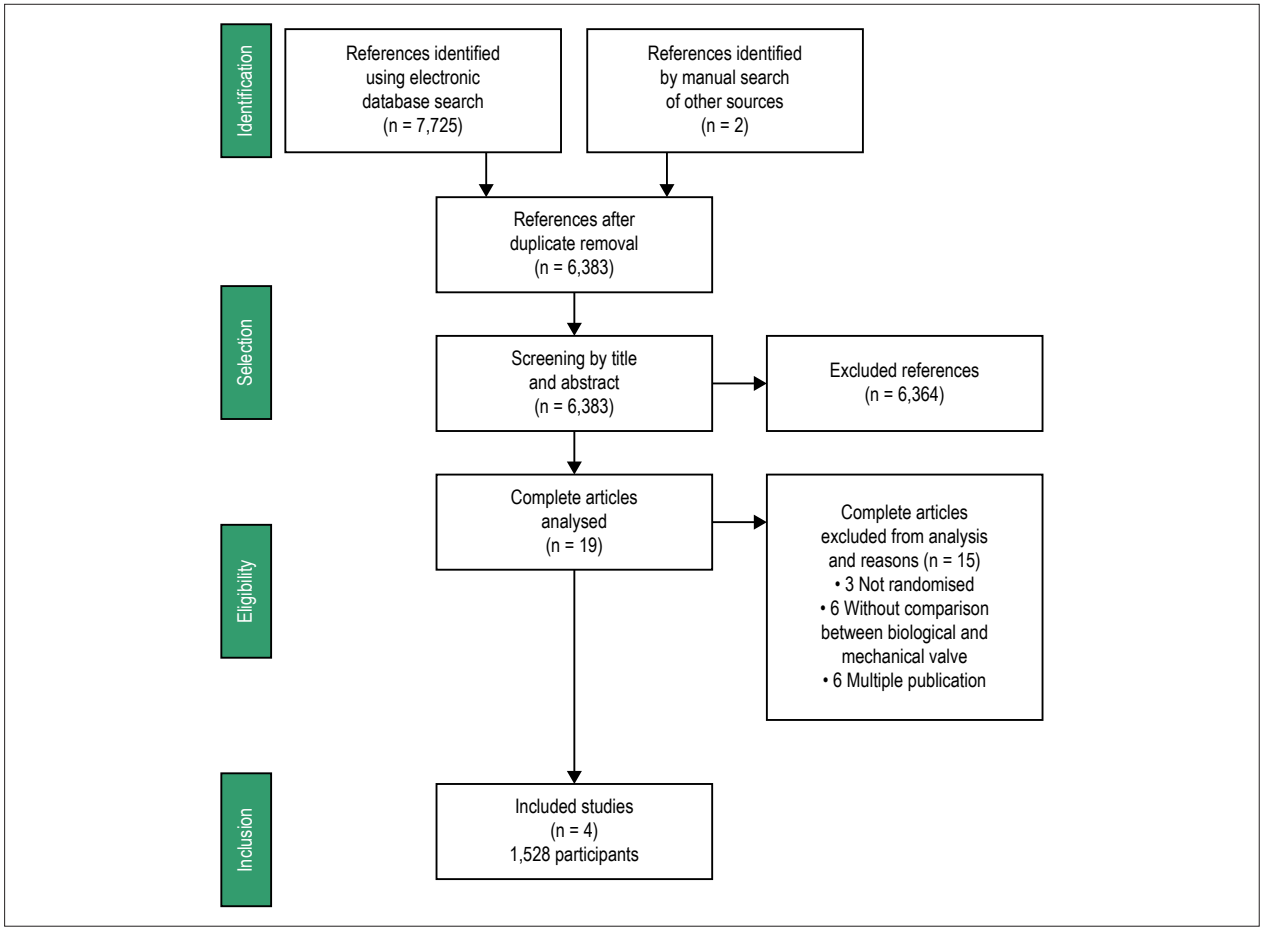


Figure 1 – *Study search and selection processes.*

Vallejo et al.[13] randomized 110 mitral valve replacement candidates, from 1975 to 1979, into one of three groups: Angell-Shiley porcine bioprosthesis, Björk-Shiley mechanical prosthesis, and Lillehei-Kaster mechanical prosthesis. The mean follow-up time was approximately two years.[13]

The Veterans Affairs Cooperative Study randomized 575 patients between 1977 and 1982.[14-17] This study included men who received a Hancock first generation porcine bioprosthesis or Björk-Shiley mechanical single spherical 60 degrees disc prosthesis. Most patients (70%) underwent aortic valve replacement. The mean follow-up time was 15 years.

Bloomfield et al randomized 533 patients of both genders to receive either a mechanical Byork-Schiley 60 degrees spherical tilting disk or a porcine bioprosthetic valve. Between 1975 and 1977 the patients assigned to a bioprosthesis received a Hancock prosthesis and after January 1977 to 1979 such patients received a Carpentier- Edwards prosthesis.[18-20] Approximately half of the patients underwent aortic valve replacement, and half underwent mitral valve replacement. The mean follow-up time was 20 years.

Stassano et al.[21] randomized 310 patients, who required aortic valve replacement between 1995 and 2003, into a biological prosthesis group and a mechanical prosthesis group.[21] Carpentier-Edwards porcine or Carpentier-Edwards bovine pericardial prostheses were used in the bioprosthesis group. In the group allocated to mechanical prostheses, Carbomedics or St. Jude double disc prostheses were used. The mean follow-up time was 8.8 years.

Risk of Bias

Characteristics related to the risk of bias of the studies are presented in Table 2. None of the studies described how the random list was generated. The trials were at low risk of bias for all the other domains including allocation concealment, blinding of outcome assessors, and incomplete outcome data. None of the studies used blinding of patients and health professionals, which is not feasible in this scenario.

Clinical outcomes

There was no statistically significant difference in the risk of death between biological or mechanical prosthesis, although most of the confidence interval favours the latter (RR = 1.07; 95% CI 0.99-1.15) (Figure 2). In addition, mortality was similar in the subgroups of patients receiving prostheses in the aortic or mitral positions or in both positions simultaneously. The effect estimates from different studies were reasonably homogeneous (I^2 = 22%).

Table 1 – Characteristics of included studies

Trials	Year of publication	Total randomised	Type of valves	Number Randomised	Patients Characteristics	Local of prosthesis implantation	Follow-up (m/y)
Vallejo	1981	110	Bioprosthesis: Angell-Shiley	38	7% NYHA II; 27% NYHA III; 4% NYHA IV 66% Male, Mean age: 39.7 ± 11 .2	MVR	Mean 24.13 ±11.16 m
			Mechanical prosthesis *: Bjork-Shiley	35	7% NYHA II; 24% NYHA III; 4% NYHA IV 69% Male, 40.7 ± 11.3	MVR	Mean 31.61 ± 13.02 m
			Lillehei-Kaster	37	4% NYHA II; 30% NYHA III; 3% NYHA IV 76% Male, 41.9 ± 10.4	MVR	Mean 30.4 ± 15.9 m
Veterans Affairs (Hammermeister)	2000	575	Bioprosthesis: Hancock porcine	289	100% Male	67% AVR; 33% MVR	Maximum 18 y
			Mechanical prosthesis: Bjork-Shiley	286	100% Male	69% AVR; 31% MVR	Maximum 18 y
Edinburgh (Oxenham, Bloomfield)	2003	533	Bioprosthesis: Hancock porcine Carpentier-Edwards	107 159	53% NYHA III or IV AF † 76% Female mitral valve	38% AVR, 50% MVR, 12% AVR+MVR	Mean 20.4 y
			Mechanical prosthesis: Bjork-Shiley	267	57% NYHA III or IV 74% Female mitral valve	41% AVR, 48% MVR, 11% AVR+MVR	Mean 20.4 y
Stassano	2009	310	Bioprosthesis: Carpentier-Edwards SAV	93	75.5% NYHA III or IV Male 50.3% Age 63.5 ± 3.9	100% AVR	Mean 106 ± 28 m
			Carpentier-Edwards Pericardial	62			
			Mechanical prosthesis: St. Jude Medical	107	76,8% NYHA III or IV Male 42,5% Age 64.0 ± 7.6		
			Carbomedics	48			

**Tilting disc valve. 37.8% previous surgery in mitral valve with LK ($p < 0.005$); † 67% Bioprosthesis in atrial fibrillation.*

The need for reoperation was more frequent among patients who received biological prostheses than among those who received mechanical prostheses (RR = 3.60; 95% CI 2.44-5.32; I^2 = 0%). The effect was similar in patients who received prostheses in the aortic or mitral position or both simultaneously (Figure 3).

The risk of bleeding was lower in patients treated with biological prostheses than in those treated with mechanical prostheses (RR = 0.64; 95% CI 0.52-0.78; I^2 = 0%). There was a trend toward a distinct effect between the subgroups according to the position of the implant, but that was not statistically significant (P for subgroup differences = 0.09) (Figure 3). It should be noted that the definitions of bleeding were not equal across studies. Vallejo et al.[13] considered only bleeding that required hospitalisation or that was a direct cause of death.[13] In their study, Bloomfield et al.[20] included all major (65%) and minor bleeding.[20] The Veterans Affairs study included clinically important bleeding.[17] Stassano et al.[21] made no reference to the magnitude of the bleeding.[21]

There were no significant differences in the risk of endocarditis (RR = 1.21, 95% CI 0.78-1.88; I^2 = 4%) or systemic arterial embolism (RR = 0.93, 95% CI 0.66-1.31; I^2 = 31%) between the group that received bioprostheses and the group that received mechanical prostheses (Figure 4).

Discussion

This systematic review and meta-analysis of randomized studies involving patients requiring cardiac valve replacement revealed similar mortality between patients who underwent implantation of biological prostheses and those who underwent implantation of mechanical prostheses. There were also no differences regarding the risk of thromboembolism and endocarditis. However, the risk of bleeding was approximately one third lower among patients treated with biological prostheses than in those treated with mechanical prostheses. In contrast, the need for reoperation among patients treated with bioprostheses was more than three times greater that of patients treated with mechanical prostheses.

Table 2 – Risk of bias in included studies

	Vallejo 1981	Veterans 2000	Edinburgh 2003	Stassano 2009
Random sequence generation	Unclear	Unclear	Unclear	Unclear
Allocation concealment	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Blinding of outcome assessors	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Complete outcome data	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias

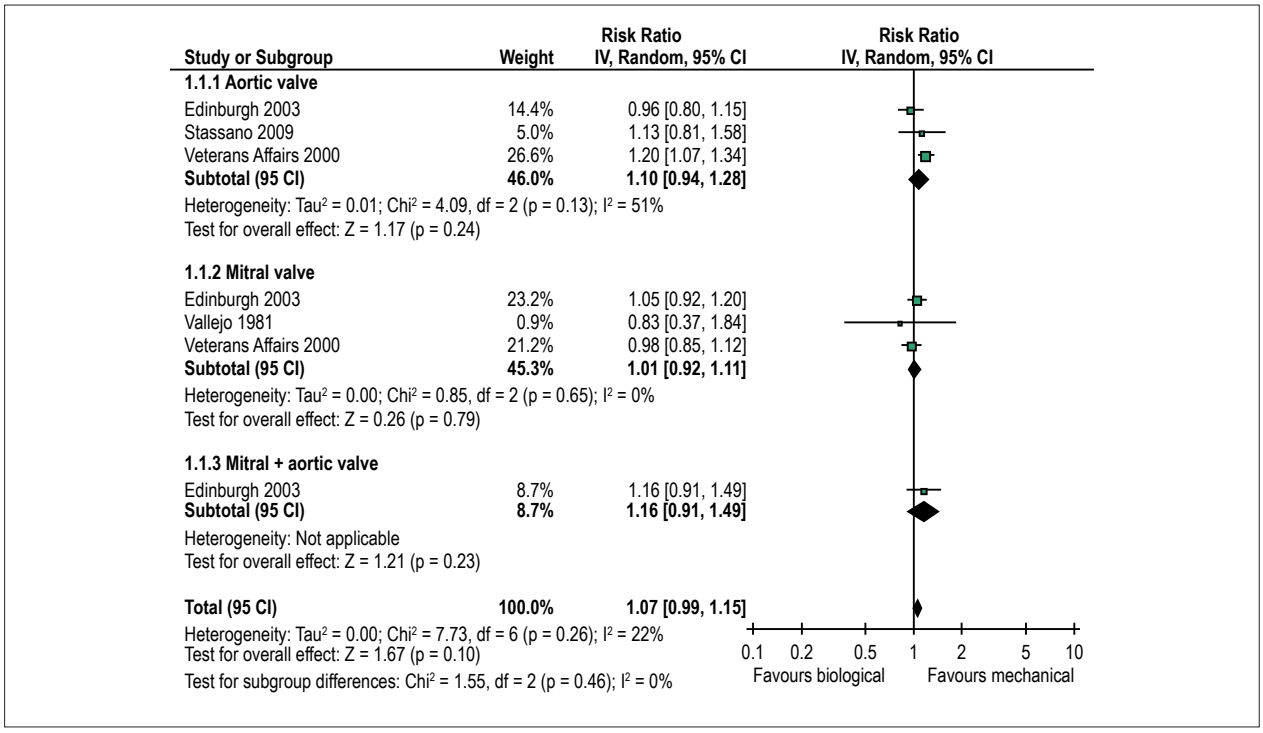
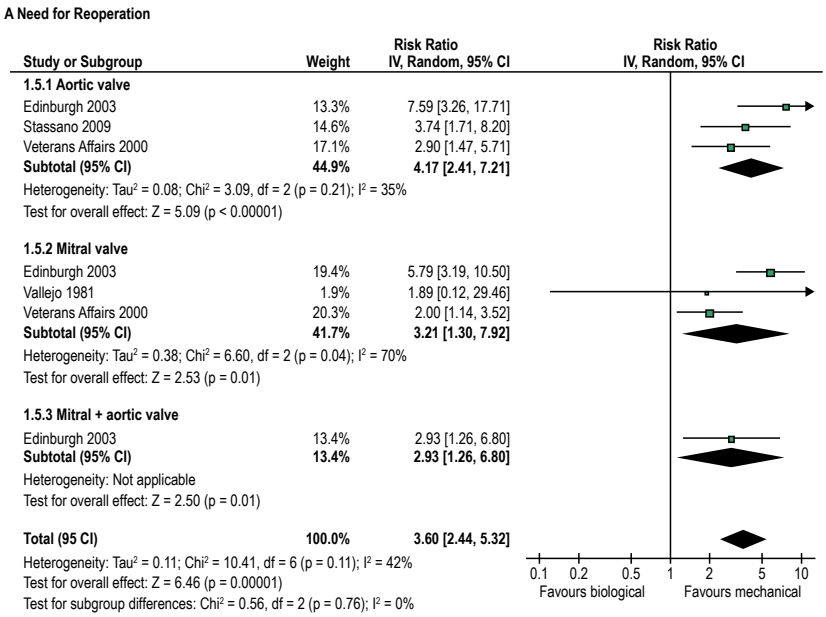


Figure 2 – *Forest plot showing the effects of biological versus mechanical prostheses on mortality.*

Currently, the decision between a biological and mechanical prosthesis is based on medical assessment and patient preference. The following are important factors in this decision: biological and chronological age, life expectancy, and absolute or relative contraindications to the use of oral anticoagulants after surgery, e.g., comorbidities or intense sport activity. The 2014 American Guidelines[22] recommend a mechanical prosthesis for mitral or aortic valve implantation in patients less than 60 years old who have no contraindication to the use of oral anticoagulants (recommendation IIa, evidence level B); a bioprosthesis is recommended for those aged over 70 years, and biological or mechanical prostheses are recommended for patients between 60 and 70 years of age (both with recommendation IIa and evidence level B).[22] The 2012 European directive recommends the use of a mechanical prosthesis in patients less than 60 years old in the aortic position and in those under 65 in the mitral position (recommendation IIa, evidence level C).[23] Therefore, there is currently no exact recommendation for the choice of prosthesis in the 60-70 year age range, and there is no solid evidence upon which the choice of one prosthesis over another can be made. Thus, variability in preferences will likely occur among patients, in special for those aged between 60 and 70 years, and the data from this systematic review should be useful to inform the decision.[24]

Randomized studies to assess treatments for valvular heart disease pose unique clinical challenges in cardiology for several reasons. First, the disease is of relatively low prevalence. Second, comparing surgical complex interventions in randomized controlled trials is difficult. Third, important clinical endpoints are assessed only after decades of follow-up. Fourth, continuing advances in prosthetic heart valve technology make follow-up a moving target because long-term data by definition are available only for older prostheses. Newer tissue and mechanical prostheses afford superior hemodynamics compared with their older counterparts, and data suggest that durability and patient mortality are superior with newer compared with older bioprostheses. In parallel, the mechanical prosthesis has also evolved. Nevertheless, important advances have been made through the results of randomized trials in equally challenging fields in cardiology, for instance, assessment of CABG vs medical treatment or percutaneous treatment. It is in the public interest, both in health and financial terms,



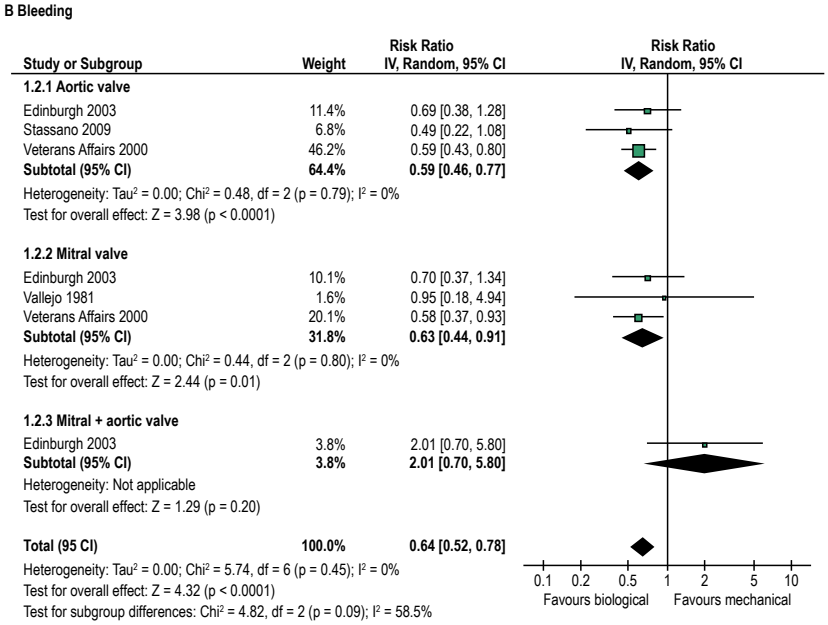


Figure 3 – *Forest plots showing the effects of biological versus mechanical prostheses on a need for reoperation (A) and risk of bleeding (B).*

to have access to high-quality data to inform decisions regarding the use of health technologies. Therefore, more and better trials comparing technologies for patients with valvular heart disease are needed and feasible. Funding for those trials might be provided by the prosthesis industry had the regulatory environment enforced formal comparative testing, as is currently done with drugs. Alternatively, public funding agencies might support these trials.

Evidence Applicability

Bleeding was more common in the mechanical prosthesis group than in the biological prosthesis group. However, the studies included in the present review were conducted at a time predating the International Normalised Ratio (INR) and the International Sensitivity Index (ISI). The INR was introduced in the 1980s, and the ISI was introduced in the 1990s. It is possible that with the improved anticoagulation

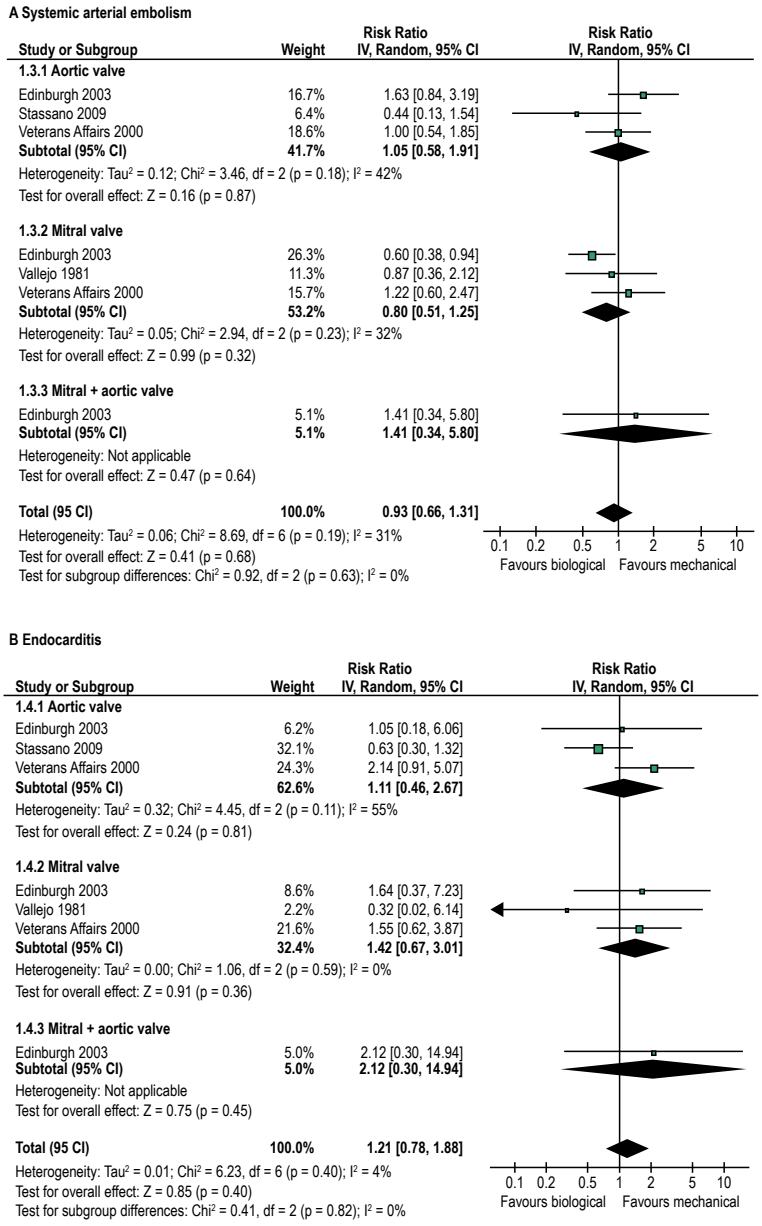


Figure 4 – *Forest plots showing the effects of biological versus mechanical prostheses on the risk of systemic arterial embolism (A) and the risk of endocarditis (B).*

monitoring processes currently available, the difference in the risk of bleeding for patients treated with mechanical versus biological prostheses may be lower than that found in this review.

In our systematic review, three of the four trials considered used the first generation biological prostheses and single disc mechanical prostheses.[13,17,20] Although uncontrolled studies suggest that second and third generation biological prostheses have greater durability,[24] in the study by Stassano et al.,[21] which included both modern biological and modern mechanical prostheses, the increased risk of reoperation was similar to that observed in the other trials.

Concordance and discordance in relation to other studies

We found a single meta-analysis that included three trials comparing old generation biological and mechanical prostheses, which was published by Kassai et al.[13] 15 years ago. In the current review, we identified an additional study[21] that compared modern prostheses. In addition, the randomized studies of the Veterans Affairs group[14] and the Edinburgh group[18] presented new publications with extended follow-up periods of 15 and 20 years, respectively.[17,20] Our results, as well as adding an additional study, reflect long-term follow-up, which is fundamental for better characterising the clinical progress of patients undergoing prosthetic valve implantation.

Table 3 – Assessment of the quality of evidence and summary of findings

	Quality assessment					Summary of findings	
No of studies (No. of participants)	Study limitations	Inconsistency	Indirectness	Imprecision	Publication bias	Relative risk (95% CI)	Quality
Mortality							
4 (1,535)	No serious limitations	No serious inconsistency	Direct	No serious imprecision	Unlikely	1.07 (0.99, 1.15)	⊕⊕⊕⊕ HIGH
Reoperation							
4 (1,535)	No serious limitations	No serious inconsistency	Direct	No serious imprecision	Unlikely	3.60 (2.44, 5.32)	⊕⊕⊕⊕ HIGH
Bleeding							
4 (1,535)	No serious limitations	No serious inconsistency	Direct	No serious imprecision	Unlikely	0.64 (0.52, 0.78)	⊕⊕⊕⊕ HIGH
Embolism							
4 (1,535	No serious limitations	No serious inconsistency	Direct	Imprecision†	Unlikely	0.93 (0.66, 1.31)	⊕⊕⊕O MODERATE
Endocarditis							
4 (1,535)	No serious limitations	No serious inconsistency	Direct	Imprecision*	Unlikely	1.21 (0.78, 1.88)	⊕⊕⊕O MODERATE

** Effect estimate compatible with either no effect or harm; † Effect estimate compatible with either substantial benefit or harm.*

Indeed a number of observational studies have shown the extended durability of biological prostheses, with a decrease in mortality of reoperation.[5] In parallel, use of biological prostheses has increased substantially.[6] However, the evidence provided by observational studies is weak due to the high risk of selection bias. Conversely, observational studies have also suggested increased mortality with biological prosthesis for mitral valve replacement. Our results showed a nonsignificant trend towards increased mortality with biological valves irrespective of position.

Quality of evidence (GRADE)

The included randomized studies present a low risk of bias and directly evaluate whether differences in clinical outcomes exist between biological and mechanical prostheses. Reporting bias is also unlikely. Regarding the mortality, reoperation and bleeding outcomes, the estimated effect of biological versus mechanical prostheses exhibited good precision and absence of serious inconsistency. We, therefore, consider that the evidence is of high quality (Table 3). For the systemic arterial embolism and endocarditis outcomes, although there was no serious inconsistency, the estimated effect is imprecise (i.e., the 95% CI is compatible with an unfavourable outcome of both the bioprosthesis and the mechanical prosthesis).

Strengths and weaknesses

Our systematic review has strengths and limitations. The development of the search strategy may be cited as a strength, as it was very sensitive and offered little likelihood of not identifying any relevant evidence. The main databases were searched along with unpublished evidence sources, and a manual evidence search was performed. All systematic review procedures were directed by guidelines and literature specific to this type of study, including all methodological characteristics necessary for proper execution of the review.[10] The included trials conducted extended follow-up of patients (from 2 to 20 years), allowing adequate evaluation of the effect of biological versus mechanical prostheses in clinical outcomes, particularly those with late incidence of outcomes such as the need for reoperation.

With regard to limiting factors, the inherent limitations of systematic reviews should be considered, such as slight differences in the populations of trial studies. For example, patients with a small aortic annulus were excluded in the Bloomfield study,[20] those with a small mitral annulus or significant coronary artery disease were excluded from the Veterans study,[17] and patients with aortic valve lesions were excluded from Vallejo's study.[13]

A major weakness of our systematic review is the age of available trials. Three of the 4 trials included are old and used first generation biological prostheses and single-disk mechanical prostheses. As both prostheses and ancillary care have evolved, it is possible that the results we have observed would not be currently applicable. Indeed a number of observational studies have shown the higher durability of biological prostheses and a trend towards its use in younger patients.[6] However, the evidence provided by observational studies is weak due to the high risk of selection bias. Furthermore, the results of the randomized trial by Stassano et al.[21] comparing modern biological to mechanical prosthesis are completely consistent with those of previous trials. In special, there was an important increase in the need of reoperation and a decreased risk of bleeding with biological prostheses. Thus, although more evidence from new trials comparing biological to mechanical is urgently needed, the best available evidence does not support the increasing preference for biological prostheses.

Conclusion

Our systematic review of randomized studies, which evaluated the outcomes of patients who randomly received biological and mechanical valve prostheses, showed that although there are no differences in mortality, there is a significant increase in the risk of new valve replacement surgery when opting for biological prostheses.

In contrast, the risk of bleeding is lower with bioprostheses. There were no differences in mortality, the risk of endocarditis or systemic embolism between the two prosthesis types. Although three of the four trials included in our meta-analysis used old generation biological and mechanical prostheses, the trial which evaluated currently used prostheses for aortic valve replacement showed the same results. Nevertheless, evidence to inform the choice between currently available prostheses is very limited and mostly based on observational studies. Randomized comparisons are utterly necessary.

Author contributions

Conception and design of the research: Kiyose AT, Moises VA, Cavalcanti AB; acquisition of data: Kiyose AT, Suzumura EA, Laranjeira L, Buehler AM, Santo JAE, Moises VA, Cavalcanti AB; analysis and interpretation of the data and writing of the manuscript: Kiyose AT, Moises VA, Cavalcanti AB; statistical analysis: Kiyose AT, Buehler AM, Moises VA, Cavalcanti AB; obtaining funding: Moises VA; critical revision of the manuscript for intellectual content: Kiyose AT, Berwanger O, Carvalho ACC, Paola AA, Moises VA, Cavalcanti AB.

Potential Conflict of Interest

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

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Ethics approval and consent to participate

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

References

1. Pibarot P, Dumesnil JG. Prosthetic heart valves: selection of the optimal prosthesis and long-term management. *Circulation.* 2009;19(7):1034-48.
2. Bonow RO, Carabello B, de Leon AC, Henry EL, Fedderly BJ, Freed MD, et al. Guidelines for the management of patients with valvular heart disease executive summary a report of the American College of Cardiology/ American Heart Association Task Force on Practice Guidelines (Committee on Management of Patients With Valvular Heart Disease). *Circulation.* 1998;98(18):1949-84.
3. Vahanian A, Baumgartner H, Bax J, Butchart E, Dion R, Filippatos G, et al. Guidelines on the management of valvular heart disease: The task force on the management of valvular heart disease of the European Society of Cardiology. *Eur Heart J.* 2007;28(2):230-68.
4. Dagenais F, Cartier P, Voisine P, Desaulniers D, Perron J, Baillot R,et al. Which biologic valve should we select for the 45- to 65-year-old age group requiring aortic valve replacement? *J Thorac Cardiovasc Surg.* 2005;129(5):1041-9.
5. Hoffmann G, Lutter G, Cremer J. Durability of bioprosthetic cardiac valves. *Deutsches Arzteblatt Int.* 2008;105(8):143-8.
6. El Oakley R, Kleine P, Bach DS, Bach MD. Choice of prosthetic heart valve in today's practice. *Circulation.* 2008;117(2):253-6.
7. Wood DA, Gurvitch R, Cheung A, Ye J, Leipsic J., Horlick E, et al. Transcatheter valve in valve implantation for failed bioprosthetic heart valves. *J Am Coll Cardiol.* 2010;55(10 Suppl):A147-E1385.
8. Kassai B, Gueyffier F, Cucherat M, Boissel J P. Comparison of bioprosthesis and mechanical valves, a meta-analysis of randomised clinical trials. Cardiovasc Surg.2000; 8(6):477-83.
9. Brandau R, Monteiro R, Braile DM. Importância do uso correto dos descritores nos artigos científicos. *Rev Bras Cir Cardiovasc.* 2005;20(1):7-9.
10. Higgins JP. Cochrane handbook for systematic reviews of interventions. Chichester: Wiley-Blackwell;2008. V.5.
11. Higgins JPT, Altman DG. Assessing risk of bias in included studies. In: Higgins JPT, Green G, editors. Cochrane Handbook for Systematic Reviews of Interventions. England: Wiley-Blackwell;2009. p.187-241.
12. Balshem H, Helfand M, Schunemann HJ, Oxman AD, Kunz R, Brozek J, et al. GRADE guidelines: 3. Rating the quality of evidence. *J Clin Epidemiol.* 2011;64(4):401-6.
13. Vallejo JL. Randomised, prospective, clinical study comparing the Björk-Shiley, Lillehei-Kaster and Angell-Shiley prostheses in the mitral position. *Rev Esp Cardiol.* 1981;34(6):457-63.
14. Khuri, SF, Sethi GK, Souchek J, Oprian C, Wong M, Burchfiel C, et al. Six month postoperative hemodynamics of the Hancock heterograft and the Björk-Shiley prosthesis: results of a Veterans Administration cooperative prospective randomized trial. *J Am Coll Cardiol.* 1998;12(1):8-18.
15. Hammermeister KE, Henderson WG, Burchfiel CM, Sethi GK, Souchek J, Oprian C, et al. Comparison of outcome after valve replacement with a bioprosthesis versus a mechanical prosthesis: initial 5 year results of a randomized trial. *J Am Coll Cardiol.* 1987;10(4):719-32.
16. Hammermeister KE, Sethi GK, Henderson WG, Oprian C, Kim T, Rahimtoola S. A comparison of outcomes in men 11 years after heart-valve replacement with a mechanical valve or bioprosthesis. *N Engl J Med.* 1993;328(18):1289-96.
17. Hammermeister K, Sethi GK, Henderson WG, Grover FL, Oprian C, Rahimtoola SH. Outcomes 15 years after valve replacement with a mechanical versus a bioprosthetic valve: final report of the Veterans Affairs randomized trial. *J Am Coll Cardiol.* 2000;36(4):1152-8.

18. Bloomfield P, Kitchin AH, Wheatley DJ, Walbaum PR, Lutz W, Miller HC. A prospective evaluation of the Björk-Shiley, Hancock, and Carpentier-Edwards heart valve prostheses. *Circulation.* 1986;73(6):1213-22.

19. Bloomfield P, Wheatley DJ, Prescott RJ, Miller HC. Twelve-year comparison of a Bjork-Shiley mechanical heart valve with porcine bioprostheses. *N Engl J Med* .1991;324(9):573-9.

20. Oxenham H, Bloomfield P, Wheatley DJ, Lee RJ, Cunningham J, Prescott RJ, et al. Twenty year comparison of a Bjork-Shiley mechanical heart valve with porcine bioprostheses. Heart. 2003;89(7):715-21.

21. Stassano P, Di Tommaso L, Monaco M, Iorio F, Pepino P, Spampinato N, et al. Aortic valve replacement: a prospective randomized evaluation of mechanical versus biological valves in patients ages 55 to 70 years. *J Am Coll Cardiol.* 2009;54(20):1862-8.

22. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP 3rd, Guyton RA, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol.* 2014;63(22):e57-e185.

23. Vahanian A, Alfieri O, Andreotti F, Antunes MJ, Baron-Esquivias G, Baumgartner H, et al. [Guidelines on the management of valvular heart disease (version 2012). The Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)]. *G Ital Cardiol (Rome).* 2013;14(3):167-214.

24. Suri RM., Schaff HV. Selection of aortic valve prostheses: contemporary reappraisal of mechanical versus biologic valve substitutes. *Circulation.* 2013;128(12):1372-80.

How to Choose the Right Valve Prosthesis for My Patient?

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Short Editorial related to the article: Comparison of Biological and Mechanical Prostheses for Heart Valve Surgery: A Systematic Review of Randomized Controlled Trials

The manuscript: "Comparison of Biological and Mechanical Prostheses for Heart Valve Surgery: Systematic Review of Randomized Controlled Trials"[1] addresses a controversial issue. The authors conducted a meta-analysis of randomized trials involving long-term follow-up of patients requiring cardiac valve replacement revealing similar mortality among patients who underwent implantation of biological prostheses and those who underwent implantation of mechanical prosthesis. There were no significant differences in the risk of thromboembolism and endocarditis. However, the risk of bleeding was approximately one-third lower among patients treated with biological prostheses than those treated with mechanical prostheses. In contrast, the need for reoperation among patients treated with bioprostheses was at least three times greater than that of patients treated with mechanical prostheses.

The authors selected "randomized" trials to avoid evaluation bias. The trial is interesting, as it seeks to be faithful to randomized evaluations, which are very unusual in the literature on valve diseases, especially at the time when the trials were conducted.

The choice of the valve prosthesis that is most appropriate for our patients should consider classic factors such as age (young adults: most likely, mechanical prosthesis/elderly: biological prosthesis), sex (women of childbearing age: most likely, biological prosthesis), number of previous cardiac surgeries (two or more surgeries: mechanical prostheses are the preferred ones), need for permanent anticoagulation (mechanical prostheses), social and educational factors (difficulty in accepting or controlling anticoagulation and/or contraindication to anticoagulation: biological prostheses), and, more importantly, the patient's preference should be respected.[2]

Considering the age factor alone, the guidelines on valve diseases have recommended choosing mechanical prostheses for younger patients, that is, under the age of 50 (AHA/ACC/ESC) and biological prostheses for patients older than 65-70.[3,4] However, the best prosthesis for those between 50 and 70 years of age remains controversial.[3-5]

Keywords

Heart Valve Prosthesis; Bioprosthesis, Metal on Metal Joint Prostheses; Heart Valve Prosthesis Implantation/trends.

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Recent evaluations have demonstrated a potentially longer durability of the most modern biological prostheses and a worldwide tendency to choose this prosthesis for increasingly younger. From the decade of 1990 to 2013, there was a three to four-fold increase in the implantation of biological prostheses in both aortic and mitral positions.[6] New medical techniques, such as the possibility of implanting a prosthesis in another prosthesis (valve-in-valve),[7] has also been promising, to avoid the use of mechanical prostheses and mandatory anticoagulation and their known risks, that is, bleeding and/or thromboembolic events.

The study by Takeshi et al.[1] found that "both prostheses have similar late mortality." However, we know that these findings may have occurred due to evaluation bias due to inadequate follow-up time in most randomized or observational trials.[8,9] Besides, valve prostheses evaluated in these studies are mostly outdated or even not available for purchase. The information is "historical," but continuous evaluation is still required to identify the actual durability of the prostheses, which vary greatly. The structural deterioration of biological prostheses correlates with the age of implant, so in 15 years' time, 50% of the prostheses implanted at the age of 20 will have structural deterioration, dropping to 30% if implanted at 40 and 10% if after 70.[3]

The relevance of this study is that it calls attention to an underdiscussed topic. Biological prostheses with the latest technology may last longer, compromising the main reason for using mechanical prostheses, which is to prevent further cardiac surgeries. However, the same can occur with mechanical prostheses with a better technological profile, thus reducing the need for anticoagulation with high INR values. It is also known that compliant patients, with excellent anticoagulation monitoring, have reduced bleeding or thromboembolic events.

Endoprostheses implanted by catheter have contributed to changes in this scenario, and we believe that the trend of implanting biological prostheses in increasingly younger patients should become usual in the near future.

In conclusion, it seems reasonable to admit the choice of biological prostheses in patients who do not need permanent anticoagulation, aged over 60-65 years, for women who wish to get pregnant and patients with difficulty in monitoring or with contraindication to anticoagulation. On the other hand, mechanical prostheses should be reserved for younger patients, chronic users of anticoagulants and patients with multiple surgeries. Note that the final decision should be the patient's, after detailed explanation of the benefits and drawbacks of each prosthesis, by their clinical cardiologist and surgeon.

References

1. Kiyose AT, Suzumura EA, Laranjeira L, Buehler AM, Espirito Santo JA, Berwanger O, et al. Comparação de próteses biológicas e mecânicas para cirurgia de valvula cardíaca:revisão sistemática de estudos controlados randomizados. Arq Bras Cardiol. 2019; 112(3):292-301.
2. Tarasoutchi F, Montera MW, Ramos AIO, Sampaio RO, Rosa Vee, Accorsi TAD, et al. Atualização das Diretrizes Brasileiras de Valvopatias: abordagem das lesões anatomicamente importantes. Arq Bras Cardiol 2017: 109(6 supl 2):1-34.
3. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP 3rd, Fleister LA, et al. 2017 AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2017;135(25):e1159–e1195.
4. Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease The Task Force for the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio- Thoracic Surgery (EACTS). Eur Heart J. 2017;38(36):2739-91.
5. Head SJ, Çelik M, Kappetein AP. Mechanical versus bioprosthetic aortic valve replacement. Eur Heart J. 2017; 38(28):2183-91
6. Goldstone AB, Chiu P, Baiocchi M, Lingala B, Patrick WL, FischbeinMP, Woo YJ. Mechanical or biologic prostheses for aortic-valve and mitral-valve replacement. N Engl J Med. 2017; 377(19):1847-57.
7. Sampaio RO, Paixão MR, Miranda TT, Veronese ET, Palma JHA, Tarasoutchi F. Combined mitral and aortic valvar bioprosthesis transcatheter transapical implant: first description in Brazil. Arq Bras Cardiol. 2017;109(5):491-4.
8. Chikwe J, Chiang YP, Egorova NN, Itagaki S, Adams DH. Survival and outcomes following bioprosthetic vs mechanical mitral valve replacement in patients aged 50 to 69 years. JAMA. 2015; 313(14):1435-42.
9. Hirji AS, Kolkailah AA, Ramirez-Del Val F, Lee J,McGurk S, Pelletier M, et al. Mechanical versus bioprosthetic aortic valve replacement in patients aged 50 years and younger. Ann Thorac Surg. 2018;106(4):1113-20.

Beta-Blocker Type Effect on Substrate Oxidation during HIIE in Heart Failure Patients: Pilot Data

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Abstract

The effect of third and second-generation type of beta-blocker on substrate oxidation especially during high-intensity exercises are scarce.

The objective of the study is to explore differences of beta-blocker regimens (vasodilating vs. non-vasodilating beta-blockers) for substrate oxidation during in high-intensity intermittent exercise (HIIE) in chronic heart failure and reduced ejection fraction (HFrEF).

Eighteen CHF males (58.8 ± 9 years), 8 under use of β1 specific beta-blockers+alfa 1-blocker and 10 using β1 non-specific beta-blockers, were randomly assigned to 4 different HIIE, in a cross-over design. The 4 protocols were: 30 seconds (A and B) or 90 seconds (C and D) at 100% peak power output, with passive (A and C) or active recovery (50% of PPO; B and D). Energy expenditure (EE; kcal/min), quantitative carbohydrate (CHO) and lipid oxidation (g/min) and qualitative (%) contribution were calculated. Two-way ANOVA and Bonferroni post-hoc test were used (p-value ≤ 0.05) to compare CHO and lipid oxidation at rest and at 10min.

Total exercise time or EE did not show differences for beta-blocker use. The type of beta-blocker use showed impact in CHO (%) and lipid (g/min and %) for rest and 10 min, but absolute contribution of CHO (g/min) was different just at 10min (Interaction p = 0.029). Higher CHO oxidation was found in vasodilating beta-blockers when comparing to non-vasodilating.

According to our pilot data, there is an effect of beta-blocker type on substrate oxidation during HIIE, but no influence on EE or exercise total time in HFrEF patients.

Introduction

To reduce sympathetic nervous system activation and improve myocardium contractility, morbidity and mortality, most of the chronic heart failure (CHF) patients are under beta-blocker use.[1] Besides all benefits, there is some evidence showing reduced glycemic control, weight gain, insulin secretion inhibition and resistance and dyslipidemia in resting states in patients under beta-blocker regimen.[2,3] Also, it was showed that the use of beta blockers could remodel substrate use during moderate-intensity continuous exercise.[4]

The third generation of beta-blockers, described as vasodilating β- blockers (i.e. β non-selective + α-1 blocker), seem to have a beneficial effect comparing to previous ones (β –selective). Because of its lack of effect on α1- adrenergic receptors, non-vasodilating beta blockers can induce vasoconstriction, reducing blood flow and glucose uptake at muscular level.[2,3] But when comparisons between carvedilol vs. metoprolol were made concerning NYHA no changes were found.[5] However, there is a lack of evidence of comparison of the type of beta-blocker during exercise, especially during high-intensity exercises (i. e. vasodilating vs. non-vasodilating).

Regarding exercise intensity, there is an increasing use of high-intensity interval training programs in cardiac rehabilitation sites. Enough evidence is provided about the superior benefits of this modality for maximal oxygen uptake (VO_2max) and quality of life when compared to moderate continuous training.[6] However, still a lack of evidence about different high-intensity interval exercise (HIIE) prescriptions in terms of optimal intensity, duration of bouts, recovery time and type (passive or active).[7] Also, not enough evidence about substrate utilization in cardiac rehabilitation context, especially what concerns to medication use.[4,8] We believe that vasodilating beta-blockers could especially influence carbohydrate (CHO) oxidation, and this may reflect in total time of exercise session.

Therefore, for this study, we compared substrate oxidation, energy expenditure (EE) and total time of HIIE protocols performed by CHF with reduced left ejection fraction (HFrEF), under two different beta-blocker regimens (vasodilating vs. non-vasodilating).

Keywords

Heart Failure, Adrenergic beta-Antagonists; Stroke Volume, Chemical Oxidation, Exercise.

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Methods

Participants

Twenty stable HFrEF were recruited from the heart failure ambulatory at the Montreal Heart Institute. This is a sub-study, inclusion criteria and exclusion criteria have been detailed in the previous publication,[7] and clinical information was

obtained from medical records. The study was performed in a cross-over design, all patients participated in the same exercise sessions in random order (generated by randomizer.org), and every single session being separated by one week (5 weeks for complete protocol). No changes in medication were made during the evaluations. The protocol was accepted by the Ethics Committee of the Montreal Heart Institute (08-1023), all procedures in agreement with Helsinki declaration and written informed consent was obtained from all patients.

Maximal cardiopulmonary exercise test

Maximal cardiopulmonary exercise testing was performed according to previously published methodology.[7-9] In short, the maximal exercise protocol was performed on a cycle ergometer (Ergoline 800S, Bitz, Germany), speed was settled at 60 RPM, and the power was increased by 10 W every minute until exhaustion. Gas exchanges variables were measured breath by breath during testing and then averaged every 15s. Peak power output (PPO) was defined as the power output reached the last fully completed stage. Electrocardiographic activity was monitored continuously using an 8-lead ECG (Marquette, Missouri, USA).

HIIE sessions

The exercise sessions were based on previously published methodology in patients with HFrEF.[7] HIIE protocols were all prescribed at 100% PPO, based on CPET and differed in interval duration (30 seconds for protocols A and B vs 90 seconds for protocols C and D) and type of recovery (active recovery at 50% of PPO for protocols B and D vs passive recovery [0% of PPO] for protocols A and C). The exercise time and recovery were designed as 1:1 ratio. Each patient exercised for a maximal time of 30 min or until exhaustion due to fatigue, dyspnea, dizziness, or inability to maintain pedal cadence at 60 rpm.[7]

Substrate oxidation and energy expenditure calculation

EE was calculated using Weir equation.[10] Substrate oxidation (CHO and lipid) was calculated from gas exchange using the Frayn equation[11] (in g/min) and with a respiratory exchange ratio values (in %) using a table of non-protein respiratory quotient.[12]

Statistical analysis

Results are expressed as mean ± SD for clinical characteristics and described as n (%) for beta blocker regimen (Table 1). This is an exploratory analysis from our previous studies,[7-9] all HIIE sessions that lasted more than 10 min of exercise were included. The substrates were compared in two time-points: rest and end of 10 min, both averages of 3 min measurements. EE (Kcal/min; EE), CHO and lipid oxidation, in g/min and total contribution (%), were compared during HIIE protocols using a two-way ANOVA for beta-blocker type and time factors. The Bonferroni *post-hoc* test with a p value ≤ 0.05 was used. Student`s t-test was used to compare the exercise total time between types of beta-blocker. All analyses were performed using IBM SPSS Statistics software, version 21 and Statview.

Results

The patients' characteristics are described in Table 1, two patients were excluded for this analysis because did not achieve the minimum of 10 min exercise. Both groups were similar for clinical characteristics, except for systolic and diastolic blood pressures. Total exercise time was not different between the beta-blockers types (non-vasodilating group = 1377 ± 505 s; vasodilating group = 1371 ± 503 s; p = 0.962). Also, no differences were found for EE for group or interaction (group p = 0.203; time p < 000.1 and interaction p = 0.867). Differences in CHO (mg/min*Kg^{-1} and %; p =0.012 and p = 0.0006) and lipids (mg/min*Kg^{-1} and %; p = 0.0017 and p = 0.0083) were found for group and time analysis, and interaction was found just for CHO (mg/min*Kg^{-1}; p = 0.03) (Figure 1).

Discussion

Our results showed a different effect on substrate oxidation depending on the type of beta-blocker generation. We believe that the decision of beta-blocker use can benefit the substrate oxidation during exercise and can be chosen accordingly with patients' necessity. Because of their effect on alfa1 – adrenergic receptors, vasodilating beta-blockers like carvedilol could benefit CHO oxidation, as shown in our results for absolute and relative values, comparing to non-vasodilation beta-blockers. Because these blocking agents can have a different effect on the circulatory and respiratory systems, previously they were known to potentially reduce exercise capacity in heart failure patients.[13] Recent evidence has shown some improvement, with a different combination of drugs, vasodilating beta-blockers demonstrated positive effect increasing insulin sensitivity comparing to non-vasodilating ones[14] and probably remodelling substrate oxidation.

According to literature, HIIE requires greater energetic demand from the muscular system,[15] and therefore should be accompanied by higher CHO oxidation. The increasing use of HIIE in a clinical context is due to its superiority compared to continuous exercise training to improve VO_{2peak}, with similar effects on left ventricular function, safety and exercise compliance.[6,16] In our previous work,[9] we showed substrate oxidation differences between HIIE protocols, and the individual variances lead us to explore the potential muscle metabolism differences that could be related to beta-blocker use. Also, there is still little data available on substrate oxidation and the effect of pharmacological agents in heart failure patients,[3] especially during high-intensity exercise, so we believe we are providing interesting initial data to raise interest on the subject.

The major limitation of our study is the sample size, but we believe appropriate for a pilot study to encourage further investigation. Also, because of the lack of a placebo group, we cannot investigate the actual effect of beta-blocker on substrate oxidation, but differences between different regimens. Since more than 90% of our HFrEF patients are under some beta-block medication, we did not consider the possibility to suspend or change patients' medication.

Table 1 – Baseline Clinical Characteristics according to the type of beta-blocker class

Clinical Variables	Beta-blocker class	
	Non-vasodilating n = 10	Vasodilating n = 8
Age (years)	59.3 ± 9.8	58.0 ± 8.5
BMI (kg/m^2)	30.0 ± 4.0	28.0 ± 3.7
LVEF (%)	29 ± 7	27 ± 6
SBD (mmHg)	129 ± 20	108 ± 17*
DBP (mmHg)	75 ± 10	61 ± 15*
NYHA functional class		
I	1 (10%)	4 (50%)
II	9 (90%)	3 (37.5%)
III	0	1 (12.5%)
Etiology of heart failure		
Ischemic heart disease	6 (60%)	4 (50%)
Idiopathic dilated cardiomyopathy	4 (40%)	4 (50%)
Medical history		
Diabetes mellitus	1 (10%)	3 (37.5%)
Hypertension	6 (60%)	4 (50%)
Medications		
ACE inhibitors or ARBs	10 (100%)	8 (100%)
Digoxin	2 (20%)	4 (50%)
Furosemide	8 (80%)	6 (75%)
Spironolactone	4 (40%)	4 (50%)
Devices		
ICD	7 (70%)	6 (75%)
CRT	1 (10%)	3(37.5%)
Maximal exercise variables		
Peak power output (Watts)	108 ± 33	110 ± 31
VO_{2peak} (L/min)	1598 ± 507	1478 ± 422
VO_{2peak} (% predicted)	63 ± 13	59 ± 12
VO_{2peak} (mL/min/kg)	17.3 ± 4.6	18.3 ± 4.6

*Values are presented as means ± SDs, or numbers of patients (percentages). BMI: body mass index; LVEF: left ventricle ejection fraction; SBP: systolic blood pressure; DBP: diastolic blood pressure; ACE: angiotensin-converting enzyme; ARBs: angiotensin II receptor blockers; ICD: implantable cardioverter-defibrillator; CRT: cardiac resynchronization therapy; VO_2: oxygen uptake; VO_{2peak}: peak oxygen uptake. * $p < 0.05$.*

Conclusion

In short, according to our pilot data, carvedilol seems to facilitate CHO oxidation during HIIE and should be considered when possible, for patients under high-intensity exercise programs. However, how the use of different beta-blockers agents (ex: vasodilating) could impact muscle metabolism during various acute and chronic exercise training programs in these patients need to be better explored.

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Author contributions

Conception and design of the research: Ribeiro PAB, Juneau M, White M, Nigam A, Gayda M; acquisition of data: Normandin E, Meyer P; analysis and interpretation of the data: Ribeiro PAB, Normandin E, Meyer P, White M, Nigam A, Gayda M; statistical analysis: Ribeiro PAB; obtaining funding: Ribeiro PAB, Juneau M, Gayda M; writing of the manuscript: Ribeiro PAB, Gayda M; critical revision of the manuscript for intellectual content: Ribeiro PAB, Normandin E, Meyer P, Juneau M, White M, Nigam A, Gayda M.

Potential Conflict of Interest

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

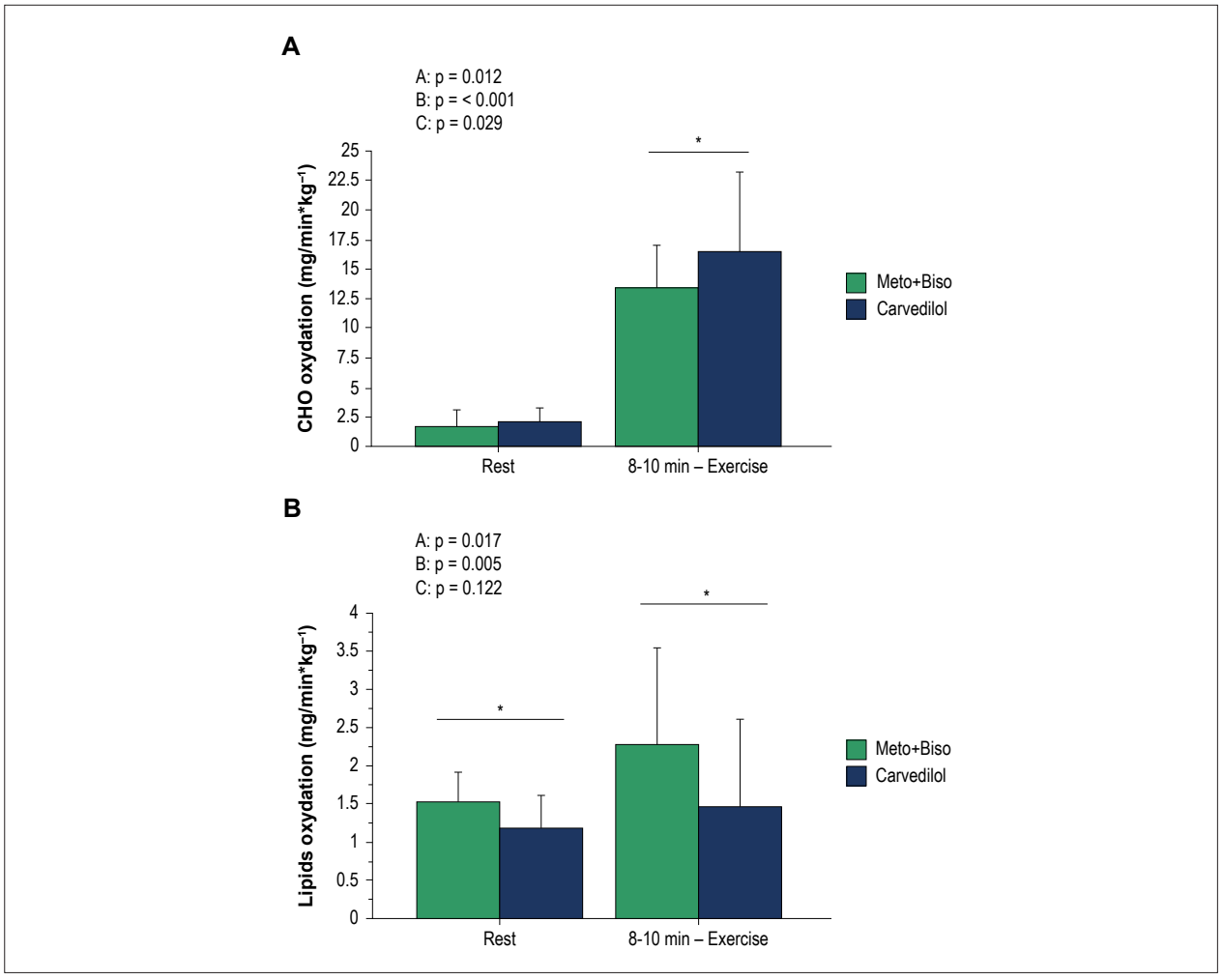

Figure 1 – *A) Carbohydrate oxidation by group at rest and 8-10 minutes high-intensity interval exercise. B) Lipids oxidation by groups at rest and 8-10 minutes high-intensity interval exercise. *p < 0.05 for groups; ANOVA p value results: A: group; B: time; C: interaction.*

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References

1. Naegele M, Flammer AJ, Enseleit F, Ruschitzka F. Medical therapy of heart failure with reduced ejection fraction: current evidence and new developments. Swiss Med Wkly. 2016 Mar;146:w14295.
2. Ladage D, Schwinger RH, Brixius K. Cardio-selective beta-blocker: pharmacological evidence and their influence on exercise capacity. Cardiovasc Ther. 2013;31(2):76-83.
3. Fonseca VA. Effects of beta-blockers on glucose and lipid metabolism. Curr Med Res Opin. 2010;26(3):615-29.
4. Smith J, Ferland A, Methot J, Brassard P, Lacroix S, Poirier P, et al. The beta-1 adrenergic antagonist, atenolol, decreases acylation stimulating protein, exercise capacity and plasma free fatty acids in men with type 2 diabetes. Nutr Metab Cardiovasc Dis. 2012;22(6):495-502.
5. Blanchet M, Ducharme A, Racine N, Rouleau JL, Tardif JC, Juneau M, et al. Effects of cold exposure on submaximal exercise performance and adrenergic activation in patients with congestive heart failure and the effects of beta-adrenergic blockade (carvedilol or metoprolol). Am J Cardiol. 2003;92(5):548-53.
6. Ismail H, McFarlane JR, Nojoumian AH, Dieberg G, Smart NA. Clinical outcomes and cardiovascular responses to different exercise training intensities in patients with heart failure: a systematic review and meta-analysis. JACC Heart Fail. 2013;1(6):514-22.
7. Meyer P, Normandin E, Gayda M, Billon G, Guiraud T, Bosquet L, et al. High-intensity interval exercise in chronic heart failure: protocol optimization. J Card Fail. 2012;18(2):126-33.
8. Kraal JJ, Sartor F, Papini G, Stut W, Peek N, Kemps HM, et al. Energy expenditure estimation in beta-blocker-medicated cardiac patients by combining heart rate and body movement data. Eur Prev Cardiol. 2016;23(16):1734-42.
9. Ribeiro PA, Normandin E, Meyer P, Juneau M, Nigam A, Gayda M. Comparison of carbohydrate and lipid oxidation during different high-intensity interval exercise in patients with chronic heart failure. Am J Phys Med Rehabil. 2017;96(1):50-4.
10. Weir JB. New methods for calculating metabolic rate with special reference to protein metabolism. 1949. Nutrition. 1990;6(3):213-21.
11. Frayn KN. Calculation of substrate oxidation rates in vivo from gaseous exchange. J Appl Physiol Respir Environ Exerc Physiol. 1983;55(2):628-34.
12. Peronnet F, Massicotte D. Table of nonprotein respiratory quotient: an update. Can J Sport Sci 1991;16(1):23-9.
13. Beauvais F. [Physical training with beta-blockers in chronic heart failure]. Ann Cardiol Angeiol (Paris). 2010;59(4):229-33.
14. Jacob S, Rett K, Wicklmayr M, Agrawal B, Augustin HJ, Dietze GJ. Differential effect of chronic treatment with two beta-blocking agents on insulin sensitivity: the carvedilol-metoprolol study. J Hypertens. 1996;14(4):489-94.
15. Gayda M, Normandin E, Meyer P, Juneau M, Nigam A. Comparison of carbohydrate and lipid oxidation during continuous and intermittent exercise in patients with chronic heart failure. Can J Cardiol. 2013;29(8):990-2.
16. Haykowsky MJ, Timmons MP, Kruger C, McNeely M, Taylor DA, Clark AM. Meta-analysis of aerobic interval training on exercise capacity and systolic function in patients with heart failure and reduced ejection fractions. Am J Cardiol. 2013;111(10):1466-9.

Early Detection and Monitoring of Cancer Chemotherapy-Related Left Ventricular Dysfunction by Imaging Methods

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Introduction

Cancer has been the second leading cause of death in Brazil since 2006, and it is predicted to surpass cardiovascular disease (CVD) as the leading cause of death between 2020 and 2025.[1] Cancer and CVD have risk factors in common, such as obesity, sedentarism, arterial hypertension, tobacco use, diabetes mellitus, advanced age, and dietary pattern. The co-prevalence of cancer and CVD is therefore elevated. The diagnosis and prevention of both diseases may be carried out in an integrated manner.[2] Oncological treatment with chemotherapy (CT) has led to an increase in survival, but it has also led to the risk of cardiotoxicity (CTX), the incidence of asymptomatic ventricular dysfunction or even cardiomyopathy.[3] Early diagnosis of CTX is important, given that the sooner this myocardial event is diagnosed, the higher the chances of recovering systolic function.[4]

The objective of monitoring left ventricular (LV) function during cancer treatment is to detect cardiac dysfunction during the subclinical phase, rather than when a symptomatic patient already has reduced ejection fraction. The groups of chemotherapeutic medications that most frequently cause myocardial aggression are anthracyclines (ANT), widely used in the treatment of solid tumors and hematological malignancies, and monoclonal antibodies, the typical example of which is trastuzumab (TZU).[5,6] The CTX of ANT was initially described as dose-cumulative, irreversible, and caused by mitochondrial injury. In contrast, TZU-related CTX, which is not dose dependent, is irreversible and does not cause mitochondrial injury. In both aggressions, however, the possibility of reverse remodeling and recovery of ventricular function has been reported. Case series of patients undergoing treatment with ANT reported an incidence of 15% to 17% of some degree of decrease in LV ejection fraction (LVEF), calculated by Simpson's method, and 2% to 3% of severe heart failure (HF).[7] More recent case series, however, have related lower incidences.

There are different definitions used for the diagnosis of ventricular dysfunction related to cancer treatment, which are extrapolated from diverse clinical situations and which have little specific validation. Currently, one of the most used definitions is as a decrease in LVEF of more than 10% of the baseline value, to values below the cutoff of 53%, with or without symptoms, it being necessary to repeat the exam 2 or 3 weeks after the initial measurement.[8] According to Zamorano et al.[9] this lower limit for LVEF normality is 50%, also with a 10% reduction. Other definitions quantify a decrease in LVEF of more than 10% to LVEF below 55%, in asymptomatic patients, or a decrease of more than 5% to LVEF below 55% in symptomatic patients.[10] Initially, endomyocardial biopsy was the gold standard used for cardiotoxicity, but its invasive character and risk of complications led to its progressive replacement by imaging methods. Various techniques have been proposed as tools for diagnosis and prognosis of CTX associated with CT, with emphasis on serum biomarkers, conventional echocardiography, two-dimensional strain echocardiography, radionuclide ventriculography (RNV), and cardiac magnetic resonance imaging (CMRI). The objective of this review is to present clinicians with the main advantages and disadvantages of different imaging methods for diagnosing and monitoring chemotherapy-related left ventricular dysfunction, regarding critical analysis, accuracy, limitations, and clinical perspectives.

Keywords

Neoplasms/mortality; Antineoplastic Agents/adverse effects; Ventricular Dysfunction, Left/diagnostic imaging; Anthracyclines/adverse effects; Trastuzumab/radiation effects.

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Methods

This review followed adaptations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) methodology principles. The bibliographic search included the databases MEDLINE, SciELO, and LILACS. The descriptors used were *cardiotoxicity*; *left ventricular dysfunction*; *antineoplastics*; *anthracyclines*; *diagnostic techniques and procedures*; *echocardiography*; *Doppler echocardiography*; *two-dimensional/three-dimensional/contrast echocardiography*; *scintigraphy*; *nuclear medicine*; *computed tomography*; *magnetic resonance*. The reference lists of the articles found in the electronic search were also consulted and relevant articles were, thus, identified. The objective was to answer the question which is the most appropriate imaging method for the early detection of ventricular dysfunction in patients submitted to cancer CT within the context of clinical practice. Two independent researchers independently analyzed all abstracts. The review considered original articles with the following study designs: clinical trial, cohort, case-control, meta-analysis, and reviews that had expert consensus; considering articles published in the period between January 1998 and June 2017, whose full texts were available in English, Spanish, or Portuguese. The studies were selected in accordance with the following criteria: (a) the underlying disease was cancer, with a diagnosis confirmed by histopathology; (b) treatment included CT with ANT, TZU, or other known myocardial depressants; and

(c) diagnostic methods such as echocardiography, computed tomography, nuclear medicine, or magnetic resonance imaging were used. The following were excluded: case reports, articles with other types of oncological therapy, and duplicate articles. Two hundred and twenty-one abstracts in the databases fulfilled the search criteria, and 162 articles were excluded.

Hereafter, we will critically analyze each of the methods, highlighting their advantages, disadvantages, and clinical applicability regarding the detection of CT-induced CTX. A summary of this analysis is given in Table 1.

Two-dimensional echocardiography

Two-dimensional echocardiography (2D ECHO) with Doppler is the method most frequently used before, during, and after CT, given that it is not invasive; it does not use ionizing radiation; it is highly available and cost-effective. It evaluates systolic and diastolic function, cardiac valves, and the pericardium, thus offering an analysis of diverse manifestations of CTX.[11] The quantification of LVEF is the most accepted for measuring LV systolic function, and it is an important parameter in the algorithm for monitoring CT-induced CTX, capable of diagnosis and prognosis of clinical results, supporting the decision to continue or stop antineoplastic therapy.[8] It is important that this measure be accurate, with minimal temporal variability. However, LVEF measured by 2D ECHO has an elevated temporal variability, approximately 10% [9,1%–11,8%], and in order to be able to detect a 10% alteration in LVEF safely, the measure should have a lower temporal variability. It is thus possible to affirm that LVEF measured by 2D ECHO is less reliable.[12]

Reduced LVEF following CT is considered a late finding that may indicate irreversible myocardial aggression and impede evolution with adequate therapy. Diastolic dysfunction may precede and predict late systolic dysfunction; however, no parameter of diastolic function has definitively shown to be predictive of CTX, and the studies are conflicting.[13-17]

The right ventricle (RV) is commonly affected by CT, in an early manner, with a higher number of affected segments than the LV, predominantly in the interventricular septum.[18] Its routine evaluation should follow the recommendations set forth by Lang et al.[19] In this manner, the quantification of RV systolic and diastolic function would be important for serial monitoring, but there is a significant technical difficulty which restricts its routine use in clinical practice.

In summary, a disadvantage of 2D ECHO is the elevated intra- and inter-examiner variability that compromises the method's reproducibility.

Three-dimensional echocardiography

Unlike 2D ECHO, the evaluation of LVEF volumes by 3D ECHO is not based on geometrical suppositions; it is not affected by shortened views,[20] and it is quantified by an automated edge-tracking algorithm.[21] Studies with CMRI have shown that evaluations of LVEF and LV volumes by 3D ECHO have better accuracy and reproducibility,[22,23] as well as lower temporal variability for serial monitoring of LVEF.[12]

The study by Walker et al.[23] evaluated the accuracy of measuring LVEF with 2D ECHO, RNV, and 3D ECHO with relation to CMRI, in patients who used Doxorubicin (DOX) and TZU. The left ventricle final diastolic volume (LVFDV) showed a modest correlation between 2D ECHO and CMRI (r = 0.64 baseline, r = 0.69 at 12 months); the correlation of LVFDV between 3D ECHO and CMRI was shown to be stronger (r = 0.87 baseline; r = 0.95 at 12 months); LVEF measured by 2D ECHO had a weak correlation with CMRI (r = 0.31 baseline, r = 0.42 at 12 months). Both 3D ECHO and RNV showed a strong correlation when comapred with CMRI (r = 0.91 baseline, r = 0.90 at 12 months). When compared with RNV, the serial measurement of LVEF via 3D ECHO was shown to be more viable, accurate, and reproducible for serial LVEF monitoring in these patients.

Table 1 – Advantages, disadvantages, and applicability of imaging methods for detecting chemotherapy-related cardiotoxicity

Method	Advantages	Disadvantages	Applicability
2D ECHO	• Available • Allows for serial repetition • Evaluates anatomy and function	• High variability • Late detection of alterations	• Screening exam • Established diagnosis of disease
2D ECHO + Simpson + Contrast	• Improves accuracy with respect to 2D ECHO	• Higher cost • Longer exam time	• Allows for accurate evaluation with simpler, more accessible technology
3D ECHO	• Accuracy and reproducibility close to that of CMRI	• Low availability	• Accurate detection
2D STE	• Detects subclinical dysfunction	• Low availability • Depends on echocardiographic window	• Initial screening of patients who will need monitoring
RNV	• Excellent accuracy and reproducibility	• Low availability • Does not evaluate other structures, such as valves, pericardium	• In doubts regarding ECHO measurements of LVEF • Inadequate ECHO image quality
CMRI	• Gold standard for evaluating volumes and LVEF • Allows for diagnosis of other etiologies of cardiomyopathy • Allows for tissue characterization	• Low availability • Long exam time • Cost	• In etiological doubts • In doubts regarding ECHO measurements of LVEF

2D ECHO: two-dimensional echocardiography; 3D ECHO: three-dimensional echocardiography; 2D STE: ecocardiograma bidimensional com strain; RNV: radionuclide ventriculography; CMRI: cardiac magnetic resonance imaging; LVEF: left ventricular ejection fraction

Echocardiography is the method of choice for serial evaluation of patients undergoing CT, considering availability, cost, and risk. Accurate LVEF calculation should be carried out with the best available method in the echocardiography laboratory, ideally 3D ECHO. In the event that 2D ECHO is used, Simpson's is the preferred method.[8] When utilizing 2D ECHO, contrast should be associated to improve the accuracy and reproducibility of the measurements of LVEF and volumes.[24]

Myocardial two-dimensional strain echocardiography

Two-dimensional speckle tracking echocardiography (2D STE) is an accurate technique, which is easy to perform and which has good reproducibility. It measures myocardial deformation through strain and strain rate in the three spatial planes, i.e. longitudinal, circumferential, and radial. Left ventricular systolic global longitudinal strain (LVGLS) has an intra- and inter-observer variability of 4.9% to 8.6%, which is lower than the that of the measurement of LVEF.[25] Its prognostic value is incremental to LVEF for the prediction of all-cause mortality in the general population.[26] Strain and strain rate are attributed to have the capacity to detect subclinical LV dysfunction and cardiac dysfunction related to CT, especially with the use of ANT and TZU.

In the study by Charbonnel et al.,[27] LVGLS measured before treatment and after low doses (150 mg/m^2) of ANT was shown to be a predictor of alterations in LVEF 12 months after the initial dose; CTX occurred in 6 of the 86 patients (7.0%). Pre-CT evaluation of LVGLS was observed to have a predictor value with an area under the ROC curve of 0.76, with a predictor threshold of (-)19.95% for LVGLS; in the evaluation with low doses, LVGLS provided incremental predictive information on CTX with an area under the ROC curve of 0.82, for a predictor threshold of (-)17.45% for LVGLS.

The study by Mousavi et al.[28] demonstrated that LVGLS was a strong predictor of symptomatic HF in pre-CT evaluation of patients undergoing CT with ANT. Age and LVGLS were also predictors of all-cause mortality. LVGLS greater than (-)16% was associated with a 4.7-fold increase in the occurrence of symptomatic HF.

Our cardio-oncology research group studied pre-CT LVGLS as a predictor of LV dysfunction and found data (yet to be published) similar to those of the above-cited authors.[27,28]

In 52 patients with breast cancer undergoing CT with ANT, who were studied 1 week before CT and after the complete cycle, a significant decrease in LVGLS occurred, which was not accompanied by a decrease of more than 10% in LVEF, which suggests that LVGLS is more sensitive than LVEF in detecting alterations in systolic function.[17]

In patients with non-Hodgkin's lymphoma, followed for 6 months, there was a significant reduction in LVGLS and an increase in cardiac troponin T (cTnT); LVEF, however, remained within reference values. When alterations in LVGLS and cTnT were included in the multivariate analysis, only the decrease in LVGLS between the baseline and the third cycle of CT was an independent predictor of CTX; there was, however, no long-term follow-up to determine the clinical relevance of these findings in predicting late cardiac events.[29]

Sawaya et al.[30] followed 43 patients with breast cancer treated with ANT and TZU, performing 2D STE and measuring biomarkers at baseline and at 3 and 6 months. High-sensitivity cardiac troponin I (hsTnI) and LVGLS were early markers of subsequent decreases in LVEF. Patients who presented neither a decrease of more than 10% in LVGLS nor an elevation in hsTnI during the third month had a 3% probability of a decreased LVEF in the sixth month. Patients who had a decrease of more than 10% in LVGLS and/or an elevation in hsTnI presented a risk of CTX during the sixth month 9 times greater than those without either of these alterations. The authors infer that the presence of these markers does not mandate the suspension of CT but rather alerts that there is a necessity for closer cardiac monitoring, earlier initiation of "cardioprotective" measures, or the use of alternative, less cardiotoxic therapies.[30]

Sawaya et al.[31] followed 81 patients treated with ANT, taxanes, and TZU, 26 of which developed CTX, 5 with symptoms of HF. LVGLS and hsTnI were predictors of CTX, and LVGLS greater than (-)19% was present in all of those who developed symptoms of HF.

According to Negishi et al.[32] a relative reduction in LVGLS of more than 11%, with respect to the pre-CT exam, is the best predictor of CTX. In the absence of a pre-CT exam, LVGLS greater than (-)20,5% would also be a predictor of CTX, albeit, with a lower area under the ROC curve (0.67); they thus suggest using relative reduction rather than absolute value.

Forty-two patients with ANT and TZU regimes were followed for 12 months, and 10 of them developed CTX. LVGLS, left ventricular systolic global radial strain (GRS), and S' detected a pre-clinical reduction in the third month, and all 10 who developed CTX had a reduction in LVEF at 6 months.[33]

Even though there is a consensus regarding the need for cardiac function monitoring via non-invasive imaging after exposure to CT, the method to be utilized and the monitoring time have yet to be defined. Evidence suggests that a reduction in LVGLS precedes a decrease in LVEF; however, long-term follow-up is necessary to determine the clinical relevance of these findings.

Radionuclide ventriculography

RNV was the first scintigraphic method for serial evaluation of LVEF in patients undergoing CT.[34,35] Its advantages include excellent accuracy, an estimated intra- and inter-variability of less than 5%, independence from LV geometry, and the possibility of being performed in patients with large body surfaces.[36,37] Gated single-photon emission computed tomography (SPECT) has currently been used to measure LVEF; nevertheless, the American Society of Nuclear Cardiology recommends that serial monitoring be performed by RNV as a Class I indication, whereas the gated blood-pool SPECT technique is a Class IIb indication.[36] Limitations to the routine use of nuclear imaging include patients with arrhythmias; incompleteness of information on the right ventricle, the atria, the valves, and the pericardium; repeated exposure to ionizing radiation; and higher costs compared to echocardiography. In 2016, the American Society of Clinical Oncology published guidelines on the prevention and monitoring of cardiac

dysfunction in adult cancer patients, recommending the use of RNV or CMRI in cases where echocardiography is not available or technically feasible, for example, in cases with inadequate ultrasound windows.[38] In addition to evaluating systolic function, RNV has demonstrated value in following diastolic function in patients exposed to cardiotoxic medications.

Radionuclide ventriculography versus echocardiography

RNV was more sensitive than echocardiography in detecting early decreases in LVEF.[39,40] However, in these small studies, there was a high incidence of CTX (over 48%) without long-term follow-up. This limitation did not allow for correlations to be drawn with HF incidence. In a study of breast cancer patients who received ANT and TZU, measurements of LVEF by 3D ECHO and RNV were comparable, with CMRI used as a reference.[23] A document titled "American Society of Echocardiography Expert Consensus Statement for Multimodality Imaging Evaluation of Adult Patients During and After Cancer Therapy"[8] recommends the use of 2D ECHO or 3D ECHO for evaluating LVEF before, during, and after CT. In the case of inadequate image quality, the use of CMRI is recommended; RNV is not mentioned as a routine method. The specific availability of each service certainly interferes with the choice of method. There are currently new scintigraphic methods with other markers of early myocardial injury,[35] which are capable of subclinically detecting LV dysfunction and which could predict the development of subsequent LV dysfunction or HF, such as sympathetic neural imaging with the ^{123}I-*meta*-iodobenzylguanidine (^{123}I-*m*IBG) technique, imaging of cell death (^{111}In-antimiosina), targeted therapy imaging (^{111}In-TZU), and molecular metabolic imaging of PET. All of these techniques have yet to be clinically validated for use in this CTX situation.

Studies with the adrenergic marker of neuronal integrity ^{123}I-*m*IBG carried out in patients using ANT demonstrated that scintigraphy with *m*IBG is capable of identifying patients with a higher risk of CTX with great accuracy.[41]

Cardiac magnetic resonance imaging

Functional evaluation (cine MR and tagging/strain)

CMRI is the gold standard evaluation of LVEF volumes, using the technique of cine MR with quantification by Simpson's method. Its routine utilization is limited by availability and cost.[42,43] In addition to accurately evaluating left and right ventricular function, CMRI can identify other probable causes associated with cardiomyopathy, such as myocardial invasion of the tumor, amyloidosis, sarcoidosis, myocarditis, and atherosclerotic coronary disease. CMRI should always be considered the first step before endomyocardial biopsy.[8]

Draft et al.[44] detected subclinical abnormalities in geometry and ventricular function, such as a significant increase in final systolic volume, decreased LVEF and increased average circumferential strain in patients receiving low to moderate doses of anthracyclines. These markers are not usual criteria for CTX and the relation with prediction of future events is unknown. Armstrong et al.[45] also detected subclinical cardiac dysfuntion using CMRI, analyzing LVEF and LV volume. No study of CMRI to date has demonstrated that alterations in myocardial function indexes after CT with ANT were predictors of subsequent CTX or HF. An ongoing observational study is assessing whether LV function measured by CMRI in patients using ANT, with or without TZU, will be able to predict a decrease in LVEF in 24 months.[46]

According to Plana et al.,[8] CMRI should be used to confirm alterations in LVEF reported by other techniques or when there is a conflict between measurements from different techniques. This is only justified in the event that there is a plan to modify or interrupt CT. It is of little interest to use CMRI for diastolic function analysis due to the fact that its accuracy is similar to that of echocardiography.[47,48]

There are few studies on the evaluation of myocardial strain by CMRI for evaluating CT-related CTX. In the trial by Draft et al.,[44] there was an early increase in midwall circumferential strain, after a month of therapy with ANT, associated with subclinical abnormality in ventricular function, demonstrated by a decrease in LVEF evaluated by CMRI. It is necessary to determine if these markers are associated with cardiovascular events in survivors of cancer.

Tissue characterization (myocardial enhancement/T1 mapping/T2 mapping)

Myocardial tissue characterization of CTX dates back to the 1980s, when necropsy and biopsy studies revealed that myocardial inflammation and cardiomyocyte edema are early findings of CTX, which occur prior to reduced myocardial function, as opposed to myocardial fibrosis, which is a late finding.[49,50] In addition to its functional evaluation, CMRI is capable of performing morphological and tissue evaluation in a qualitative (visual) and quantitative manner, as percentage of muscle affected.[51] Myocardial interstitial injuries may or may not be reversible, depending on different factors which include the degree of interstitial fibrosis. In this manner, CMRI is able to establish the differential diagnosis between reactive, infiltrative, and scar fibrosis.[52]

It is possible to evaluate CTX on the tissue level with early and late enhancement techniques.[52] The main disadvantage is that, in the large majority of subclinical disease cases, there is no visually detectable fibrosis to be quantified and this technique is negative.

T1 mapping has been validated for detection of interstitial fibrosis not detected by late enhancement techniques, and the results are informed through the quantification of myocardial relaxation time in milliseconds.[53] During postcontrast, the lower the myocardial T1, the higher the degree of interstitial fibrosis. T1 mapping has shown to be an independent predictor of CTX in patients treated with ANT who were followed for a period of 3 years.[54] Extracellular volume (ECV) fraction which indicates the expansion of interstitial space corrected by hematocrit was also a strong imaging biomarker.[54]

T2 mapping is responsible for the quantification of cardiomyocyte edema, and it assists in the characterization of acute, subacute, or chronic damage.[55] The results of T2 mapping are also represented by time in milliseconds. A study with 9 patients who received ANT showed that average T2 values > 59 ms were associated with CTX.[56]

Myocardial tissue characterization by CMRI may detect early myocardial injury during CT and identify subclinical myocardial alterations in cancer survivors; however, prospective studies are needed to confirm this hypothesis. The cost-effectiveness of using CMRI in comparison with other sequential follow-up techniques for patients undergoing CT still needs to be quantified.

Cardiac computed tomography (coronary angiotomography)

Coronary angiotomography is a method with growing clinical applicability that uses low doses of radiation (1–2 mSv) and iodinated contrast (50 mL).[57] In addition to its classical indications, it is possible to quantify the volumes and ejection fractions of both ventricles.[58] After the study by Nacif et al.,[59] the use of angiotomography for the quantification of myocardial interstitial fibrosis via the quantification of VEC may be of great clinical utility. VEC values greater than 35% are associated with interstitial fibrosis.

Rational approach strategy for early detection of CTX

In Figure 1, we propose a flowchart showing the rational approach for patients undergoing CT. This algorithm is based on a review of the literature and the authors' expertise. It thus lacks validation in randomized controlled clinical trials. This approach should be adapted to the reality of each service's supply and demand conditions.[8] Faced with a cancer patient, the following steps are recommended: (a) integrated actions, shared by cardiologists and oncologists, within a multidisciplinary team; (b) clinical evaluation of estimated global cardiovascular risk, previous diseases, previous chemo- or radiotherapy and, when indicated, specific intervention prior to CT; (c) within the institution's limitations, consider two-dimensional echocardiography with measurements of strain. (d) In the event that baseline cardiac evaluation is not available for all patients, prioritize those with high risks of CTX, such as those with CVD or cardiovascular risk factors; LV systolic dysfunction; over 65 years of age; a regimen with doses of ANT (DOX) greater than 350 mg/m^2; or combination CT (Figure 1).

If one the following is detected in a patient being monitored: LVEF < 53%, LVGLS below the lower limit of normality, or elevated troponins, in the absence of symptoms, the cardiologist should be consulted and the risk-benefit ratio related of CT discussed with the oncologist. Whether to continue or not is, however, the oncologist's decision. The healthcare flowcharts depend on the cardiotoxic potential of the CT regimen. In accordance with documents by the American and European societies of echocardiography, patients with cumulative doses below 240 mg/m^2 of DOX should repeat the cardiac evaluation at the conclusion of the CT regimen and 6 months later.[8] In patients with doses above 240 mg/m^2 there should be a new evaluation before each additional 50 mg/m^2 cycle. In patients receiving TZU, there should, ideally, be an echocardiogram every 3 months.[8] Owing to the unavailability of data, in patients undergoing therapy with vascular endothelial growth factor inhibitors, evaluation with echocardiography 1 month after the initial dose and, subsequently, every 3 months, is recommended.[8]

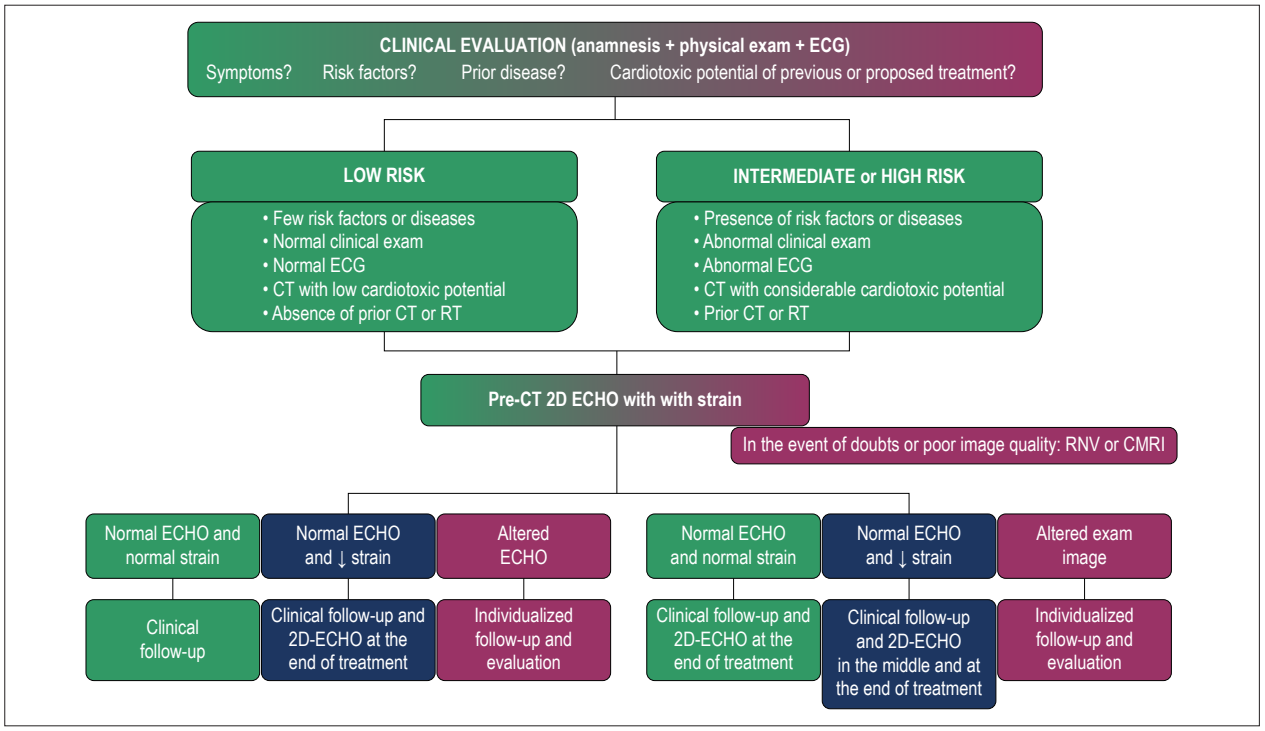

Figure 1 – *Proposal for cardiovascular monitoring of patients undergoing chemotherapy based on information in the literature and authors' expertise. ECG: electrocardiogram; CT: chemotherapy; RT: radiation therapy; 2D-ECHO: two-dimensional echocardiography; RNV: radionuclide ventriculography; CMRI: cardiac magnetic resonance imaging; ECHO: echocardiography.*

Subclinical detection of left ventricular dysfunction

To date, there is no evidence regarding the treatment of asymptomatic patients with preserved LVEF and alterations exclusively in strain. However, the rationale for measuring strain is based on the possibility of frequently monitoring patients at risk and, as soon as a decrease in LVEF is detected, initiating therapy and obtaining reverse remodeling.

For the purpose of detecting subclinical dysfunction, baseline LVGLS is the marker for comparison of post-CT measurements. A relative reduction of more than 15% can confirm the dysfunction. This altered value should be confirmed by a new exam 2 or 3 weeks later. Elevated TnI with or without alterations in LVGLS is also considered a marker of myocardial injury; there are, however, multiple causes of elevations in TnI, as well as doubts regarding its prognostic value for ventricular dysfunction. Whenever the need for suspending CT is considered in asymptomatic patients, it is necessary to measure LVEF using a more accurate method, such as RNV or CMRI.[8]

There are no studies with safe levels of evidence demonstrating the benefits of pharmacological "cardioprotective" treatment in patients undergoing CT. When considering the hypothesis of continuing CT notwithstanding alternations in LV function, echocardiographic re-evaluation is necessary before the new cycle, with the awareness that the risk of CTX will progressively increase.

Additional imaging exams are not necessary for patients who have concomitant risk factors, in the presence of normal GLS or troponins during CT and 6 months after the last CT with ANT. Following completion of the therapeutic regimen, there should be annual clinical cardiovascular examination and the use of cardiac imaging in accordance with the services available.[8]

Conclusions

Monitoring LVEF by 2D ECHO is the most executable strategy for detecting CT-related cardiovascular disease in large groups of patients; this method should, however, be considered in the context of its numerous limitations. 3D ECHO is the method of choice when considering accuracy together with availability, limitations regarding repetition, and ease of execution. When this is not available, the addition of contrast to 2D ECHO should be encouraged, seeing that this increases accuracy. LVGLS is the best parameter of myocardial deformation for subclinical detection of LV dysfunction; however, there is no solid evidence showing the benefits of initiating early "cardioprotective" therapy based on its results. RNV has a high diagnostic accuracy for ventricular dysfunction and may be an alternative in the event of doubts regarding echocardiography. CMRI assists in differential diagnoses with other causes of cardiomyopathies.

The decision to interrupt or continue a chemotherapeutic regimen is clinical, joint, and multidisciplinary, and it is based on the risk-benefit ratio for each patient.

Randomized controlled clinical trials with long-term follow-up are necessary to determine whether early detection of cardiac dysfunction is a predictor of LVEF reduction and, above all, HF and major cardiovascular events.

Author contributions

Conception and design of the research: Ribeiro ML, Martins WA; acquisition of data and analysis and interpretation of the data: Ribeiro ML; writing of the manuscript and critical revision of the manuscript for intellectual content: Jorge AJL, Ribeiro ML, Nacif MS, Martins WA.

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. Dados de Taxa de Mortalidade Específica (TME). DATASUS 2008/2009 disponível em http://tabnet.datasus.gov.br/cgi/tabcgi.exe?idb2009/c10.def. Acesso em 20/01/2011
2. Martins WA, Moço ETSM. Cardio-oncologia: o preço do envelhecimento. Rev Bras Cardiol.2012;25(3):164-6.
3. Yeh ET, Tong AT, Lenihan DJ, Yusuf SW, Swafford J, Champion C, *et al*. Cardiovascular complications of cancer therapy: diagnosis, pathogenesis, and management. Circulation.2004;109(25):3122-31.
4. Cardinale D, Colombo A, Torrisi R, Sandri MT, Civelli M, Salvatici M, *et al*. Trastuzumab-induced cardiotoxicity: Clinical and prognostic implications of troponin I evaluation. J Clin Oncol.2010;28(25):3910-6.
5. Doyle JJ, Neugut AI, Jacobson JS, Grann VR, Hershman DL. Chemotherapy and cardiotoxicity in older breast cancer patients: a population-based study. J Clin Oncol.2005; 23:8597-605.
6. Armstrong GT, Oeffinger KC, Chen Y, Kawashima T, Yasui Y, Leisenring W, *et al*. Modifiable risk factors and major cardiac events among adult survivors of childhood cancer. J Clin Oncol.2013;31(29):3673-80.
7. Mackey JR, Martin M, Pienkowski T, Rolski J, Guastalla JP, Sami A, *et al*. Adjuvant docetaxel, doxorubicin, and cyclophosphamide in node-positive breast cancer: 10-year follow-up of the phase 3 randomised BCIRG 001 trial. Lancet Oncol.2013;14:72-80.
8. Plana JC, Galderisi M, Barac A, Ewer MS, Ky B, Scherrer-Crosbie M, et al. Expert consensus for multimodality imaging evaluation of adult patients during and after cancer therapy: A report from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr.2014;27(9):911-39.
9. Zamorano JL, Lancellotti P, Munoz DR, Aboyans V, Asteggiano R, Galderisi M, *et al*. 2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines: The Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC). Eur J Heart Fail.2017;19:9-42.
10. Seidman A, Hudis C, Pierri MK, Shak S, Paton V, Ashby M, *et al*. Cardiac Dysfunction in the Trastuzumab Clinical Trials Experience. J Clin Oncol.2002; 20:1215-21.
11. Douglas OS, Garcia MJ, Haines DE, Lai WW, Manning WJ, Patel AR, *et al*. ACCF/ASE/AHA/ASNC/HFSA/HRS/SCAI/SCCM/ SCCT/ SCMR 2011 Appropriate Use Criteria for Echocardiography. J Am Soc Echocardiogr.2011;24:229-67.
12. Thavendiranathan P, Grant AD, Negishi T, Plana JC, Popovic´ ZB, Marwick TH. Reproducibility of echocardiographic techniques for sequential assessment of left ventricular ejection fraction and volumes: application to patients undergoing cancer chemotherapy. J Am Coll Cardiol. 2013;61:77-84.
13. Paraskevaidis IA, Makavos G, Tsirigotis P, Psarogiannakopoulos P, Parissis J, Gkirkas K, *et al*. Deformation Analysis of Myocardial Layers Detects Early Cardiac Dysfunction after Chemotherapy in Bone Marrow Transplantation Patients: A Continuous and Additive Cardiotoxicity Process. J Am Soc Echocardiogr. 2017;30(11):1091-102.
14. Dorup I, Levitt G, Sullivan I, Sorensen K. Prospective longitudinal assessment of late anthracycline cardiotoxicity after childhood cancer: the role of diastolic function.2004. Heart. 2004;90(10):1214-6.
15. Pellicori P, Calicchia A, Lococo F, Cimino G, Torromeo C. Subclinical anthracycline cardiotoxicity in patients with acute promyelocytic leucemia in long-term remission after the AIDA protocol. Cong Heart Fail. 2012;18:217-21.
16. Serrano JM, Gonzalez I, Del Castillo S, Muniz J, Morales LJ, Moreno F, *et al*. Diastolic Dysfunction Following Anthracycline-Based Chemotherapy in Breast Cancer Patients: Incidence and Predictors. The Oncologist. 2015;20:864-72.
17. Stoodley PW, Richards DAB, Hui R, Boyd A, Harnett PR, Meikle SR, *et al*. Two-dimensional myocardial strain imaging detects changes in left ventricular systolic function immediately after anthracycline chemotherapy. Euro J Echocardiogr. 2011;12:945-52.
18. Barendswaard EC, Prpi H, Van der Wall EE, Camps JA, Keizer HJ, Pauwels EK. Right ventricule wall motion abnormalities in patients treated with chemotherapy. Clin Nucl Med.1991;16(7):513-6.
19. Lang RM, Badano LP, MD, 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;28:1-39.
20. Jenkins C, Moir S, Chan J, Rakhit D, Haluska B, and Marwick TH. Left ventricular volume measurement with echocardiography: a comparison of left ventricular opacification, three-dimensional echocardiography, or both with magnetic resonance imaging. Eur Heart J. 2009;30(1):98-106.
21. Muraru D, Badano LP, Piccoli G, Gianfagna P, Del Mestre L, Ermacora D, *et al*. Validation of a novel automated border-detection algorithm for rapid and accurate quantitation of left ventricular volumes based on three-dimensional echocardiography. Eur J Echocardiogr. 2010;11(4):359-68.
22. Dorosz JL, Lezotte DC, Weitzenkamp DA, Allen LA, Salcedo EE. Performance of 3-dimensional echocardiography in measuring left ventricular volumes and ejection fraction: a systematic review and meta-analysis. J Am Coll Cardiol. 2012;59(20):1799-808.
23. Walker J, Bhullar N, Fallah-Rad N, Lytwyn M, Golian M, Fang T, *et al*. Role of three-dimensional echocardiography in breast cancer: comparison with two-dimensional echocardiography, multiple-gated acquisition scans, and cardiac magnetic resonance imaging. J Clin Oncol. 2010;28(21):3429-36.
24. Hoffmann R, Bardeleben S, Cate F, Borges AC, Kasprzak J, Firschke C, *et al*. Assessment of systolic left ventricular function: a multi-centre comparison of cineventriculography, cardiac magnetic resonance imaging, unenhanced and contrast-enhanced echocardiography. Eur Heart J. 2005;26:607-16.
25. Farsalinos KE, Daraban AM, Unlu S, Thomas JD, Badano LP, Voigt JU. Head-to-Head Comparison of Global Longitudinal Strain Measurements among Nine Different Vendors The EACVI/ASE Inter-Vendor Comparison Study. J Am Soc Echocardiogr. 2015;28:1171-81.
26. Stanton T, Leano R, Marwick TH. Prediction of All-Cause Mortality From Global Longitudinal Speckle Strain Comparison With Ejection Fraction and Wall Motion Scoring. Circ Cardiovasc Imaging.2009;2:356-364.
27. Charbonnel C, Convers-Domart R, Rigaudeau S, Taksin AL, Baron N, Lambert J, et al. Assessment of global longitudinal strain at low-dose anthracycline-based chemotherapy, for the prediction of subsequent cardiotoxicity.Eur Heart J Cardiovasc Imaging 2017;18:392-401.
28. Mousavi N, Tan TC, Ali M, Halpern EF, Wang L, Scherrer-Crosbie M. Echocardiographic parameters of left ventricular size and function as predictors of symptomatic heart failure in patients with a left ventricular ejection fraction of 50-59% treated with anthracyclines. Eur Heart J Cardiovasc Imaging. 2015;16:977–84.
29. Kang Y, Xu X, Cheng L, Li L, Sun M, Chen H, *et al*. Two-dimensional speckle tracking echocardiography combined with high-sensitive cardiac troponin T in early detection and prediction of cardiotoxicity during epirubicine-based chemotherapy. Eur J Heart Fail. 2014;16:300-8.
30. Sawaia H, Sebag IA, Plana JC, Januzzi JL, Ky B, Cohen V, *et al*. Early detection and prediction of cardiotoxicity in chemotherapy-treated patients. Am J Cardiol. 2011;107(9):1375-80.
31. Sawaia H, Sebag IA, Plana JC, Januzzi JL, Ky B, Tan TC, *et al*. Assessment of echocardiography and biomarkers for the extended prediction of cardiotoxicity in patients treated with anthracyclines, taxanes and traztuzumab. Circ Cardiovasc Imaging. 2012;5(5):596-603.
32. Negishi K, Negishi T, Hare JL, Haluska BA, Plana JC, Marwick TH. Independent and Incremental Value of Deformation Indices for Prediction of Trastuzumab-Induced Cardiotoxicity. J Am Soc Echocardiogr. 2013;26:493-8.

33. Fallah-Rad N, Walker JR, Wassef A, Lytwyn M, Bohonis S, Fang T, *et al*. The utility of cardiac biomarkers, tissue velocity and strain imaging, and cardiac magnetic resonance imaging in predicting early left ventricular dysfunction in patients with human epidermal growth factor receptor ii–positive breast cancer treated with adjuvant trastuzumab therapy. J Am Coll Cardiol. 2011;57:2263-70.

34. Aiken MJ, Suhag V, Garcia CA, Acio E, Moreau S, Priebat DA, *et al*. Doxorubicin-induced cardiac toxicity and cardiac rest gated blood poll imaging. Clin Nucl Med. 2009;34(11):762-7.

35. Schwartz RG, Jain D, Storozynsky E. Traditional and novel methods to assess and prevent chemotherapy-related cardiac dysfunction noninvasively. J Nucl Cardiol. 2013;20(3):443-64.

36. Corbett JR, Akinboboye OO, Bacharach SL, Borer JS, Botvinick EH, DePuey EG, *et al*. Equilibrium radionuclide angiocardiography. J Nucl Cardiol.2006;13(6):e56-e79.

37. Strashun AM, Goldsmith SJ, Horowitz SF. Gated blood pool scintigraphic monitoring of doxorubicin cardiomyopathy: comparison of camera and computerized probe results in 101 patients. J Am Coll Cardiol.1986;8(5):1082-7.

38. Armenian SH, Lacchetti C, Barac A, Carver J, Constine LS, Denduluri N, *et al*. Prevention and Monitoring of Cardiac Dysfunction in Survivors of Adult Cancers: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol. 2016;35:893-911.

39. Fatima N, Zaman UM, Hashmi A, Kamal S, Hameed A. Assessing adriamycin-induced early cardiotoxicity by estimating left ventricular ejection fraction using technetium-99m multiple-gated acquisition scan and echocardiography. Nucl Med Commum.2011;32(5):381-5.

40. Tantawy AA, Elmasry AO, Shaaban M, Toaima DN, Shahat AM. Radionuclide ventriculography detects early anthracycline cardiotoxity in children with Hodgkin Lymphoma. J Pediatr Hematol Oncol.2011;33:e132-e137.

41. Pepe A, Pizzino F, Gargiulo P, Perrone-Filardi P, Cadeddu C, Mele D, *et al*. Cardiovascular imaging in the diagnosis and monitoring of cardiotoxicity: cardiovascular magnetic resonance and nuclear cardiology J Cardiovasc Med 2016, 17 (suppl 1):e45–e54

42. Debatin JF, Nadel SN, Paolini JF, Sostman HD, Coleman RE, Evans AJ, *et al*. Cardiac ejection fraction: phantom study comparing cine MR imaging, radionuclide blood pool imaging, and ventriculography. J Magn Reson Imaging.1992;2(2):135-42.

43. Moon JC, Lorenz CH, Francis JMm, Smith JC, Pennell DJ. Breath-hold FLASH and FISP cardiovascular MR imaging: left ventricular volume differences and reproducibility. Radiology.2002;223(3):789-97.

44. Drafts BC, Twomley KM, D'Agostino R Jr, Lawrence J, Avis N, Ellis LR, *et al*. Low to moderate dose anthracycline-based chemoterapy is associated with early noninvasive imaging evidence of subclinical cardiovascular disease. JACC Cardiovasc Imag. 2013;6(8):877-85.

45. Armstrong GT, Plana JC, Zhang N, Srivastava D, Green DM, Ness KK, *et al*. Screening adult survivors of childhood cancer for cardiomyopathy: comparison of echocardiography and cardiac magnetic ressonance imaging. J Clin Oncol. 2012;30:2876-84.

46. Hundley WG. MRI in detecting heart damage in patients with cancer receiving chemotherapy. http://clinicaltrials.gov/show/NCT01719562. Accessed june 27, 2017.

47. Bollache E, Redheuil A, Clément-Guinaudeau S, Defrance C, Perdrix L, Ladouceur M *et al*. Automated left ventricular diastolic function evaluation from phase-contrast cardiovascular magnetic resonance and comparison with Doppler echocardiography. J Cardiovasc Magn Reson. 2010;12(1):63.

48. Paelinck BP, de Roos A, Bax JJ, Bosmans JM, van Der Geest RJ, Dhondt D, et al. Feasibility of tissue magnetic resonance imaging a pilot study in comparison with tissue Doppler imaging and invasive measurement. J Am Coll Cardiol.2005;45(7);1109-16.

49. Friedman MA, Bozdech MJ, Billingham ME, Rider AK. Doxorubicin cardiotoxicity: Serial endomyocardilal biopsies and systolic time intervals. J Am Med Assoc. 1978;240(15):1603-6.

50. Unverferth DV, Fetters JK, Unverferth BJ, Leier CV, Magorien RD, Arn Ar, *et al*. Human myocardial histologic characteristics in congestive heart failure. Circulation.1983;68(6):1194-200.

51. Souto ALM, Souto RM, Teixeira ICR, Nacif MS. Myocardial viability on cardiac magnetic ressonance. Arq Bras Cardiol.2017;108(5):458-69.

52. Nathan M, Liu CY, Pierre C, David B, Lima JAC. Assessment of myocardial fibrosis with cardiac magnetic resonance. J Am Coll Cardiol.2011;57(8):891-903.

53. Sibley CT, Noureldin RA, Gai N, Nacif MS, Liu S, Turkbey EB, *et al*. T1 Mapping in cardiomyopathy at cardiac MR: comparison with endomyocardial biopsy. Radiology.2012;265(3):724-32.

54. Jordan JH, Vasu S, Morgan TM, D'Agostino Jr RB, Meléndez GC, Hamilton CA, *et al*. Anthracycline-Associated T1 mapping characteristics are elevated independent of the presence of cardiovascular comorbidities in cancer survivors. Circ Cardiovasc Imaging.2016;9:e004325.

55. Lota AS, Gatehouse PD, Mohiaddin RH. T2 mapping and T2* imaging in heart failure. Heart Fail Rev.2017;22:431-40.

56. Thavendiranathan P, Amir E, Bedard P, Crean A, Paul N, Nguyen ET, *et al*. Regional myocardial edema detected by T2 mapping is a feature of cardiotoxicity in breast cancer patients receiving sequential therapy with anthracyclines and trastuzumab. J Cardiovasc Magnet Res.2014;16(Suppl 1):P273.

57. Halliburton SS, Abbara S, Chen MY, Gentry R, Mahesh M. SCCT guidelines on radiation dose and dose-optimization strategies in cardiovascular CT. J Cardiovasc Comput Tomogr.2011;5:198-224.

58. Man SR, Man SB, Lal MJ. Role of cardiac CTA in estimating left ventricular volumes and ejection fraction. World J Radiol.2014;6(9):669-76.

59. Nacif MS, Kawel N, Lee JJ, Chen X, Yao J, Zavodni A, *et al*. Interstitial myocardial fibrosis assessed as extracellular volume fraction with low-radiation-dose cardiac CT. Radiology.2012;264(3):876-83.

Medical Societies and Public Universities

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Medical societies are important and strong institutions in our country. We can take as an example the Brazilian Society of Cardiology (*Sociedade Brasileira de Cardiologia*, SBC), of which most of those reading this text are members. I have never done corporate politics, but I follow it with interest. I am impressed by the determination observed in the fierce disputes between competitors at election time.

These groups, which always include members of university faculties, spend a lot of energy to achieve command positions. Such is the game, which often drifts into tortuous paths. Therefore, the human resources of societies and universities have much in common, since they promote scientific and didactic activities, educating professionals all over the country, using both the face-to-face and the media modalities.

The quality of the received information is directly proportional to that of the universities and their members. Thus, societies must have great interest in the intellectual evolution of our universities. Therefore, some questions should be asked: Are there constructive undertakings for the improvement of public universities by societies? Are these energies, after the elections are finished, used in their benefit? If they are not, what are the plans for greater interaction between these two universes? Would these projects be helpful in alleviating the steady decline in the quality of academies?

The reasons for this decline are well known and financial bankruptcy is undoubtedly the primary cause of this decline. There are other, perhaps more serious causes for this crisis in academies, of which approach is hampered by powerful corporations. These are turning education and health into big businesses; *Their* power has an enormous influence in the absence of the political will to fight them. Could we, as members of a society, have well-defined and constructive positions, when trying to collaborate with the authorities regarding the referral of alleged solutions? How do societies associate with the public power? Is there any interest in this relationship?

In the university scenario, this situation has a deep impact on human resources, leading to disbelief and hopelessness of employees at all levels, even though there are highly qualified and productive professionals who are often undervalued because they are not accepted by the members of the current power systems. This hopelessness is the most destructive feeling, the greatest poison for the productivity of our institutions. The escape of brains, both to the private sector and to other countries, makes this evil equation an even worse one. No wonder our young people have so little interest in academic life.

To make things even more complicated, career plans are attacked by corporatism, physiologism, and nepotism. Important political facts collaborate very much to keep high-level teachers away from our teaching centers. It is sad to see individuals who have dedicated decades of their lives, with exemplary university careers, being neglected, greatly diminishing their dedication to teaching, research, and extended education.

This political side is an important cause of the intellectual decline of human resources. Many brilliant careers have been interrupted by this malignant association of factors. We, therefore, have the perfect recipe for decadence.

Is there a solution or solutions? I believe there are, with the political will that creates changes in the current cultural pattern. Many opinions should be voiced and challenged through serious and healthy dialogues. These are my thoughts:

On the academic side, teachers must and should be involved, humanly and professionally, with their institutions. Being a teacher is different from simply working as one. Being a teacher must and should be the primary mission in their professional life. They must fully meet the needs of their institutions, thus creating no conflicts of interest.

Teachers must and should be appraised periodically on their merits, which should be the key factor for reaching the top of their careers. There should be more Full Professors, who would be impartially chosen among active, institutional teachers with heterogeneous profiles, thus reducing the risk of the formation of dominant oligarchies. They should take the university to the civil society, removing it from its crystal dome, while bringing a productive society to the university, as healthy associations for both. As an idea, medical societies could play an important role in this matter.

Teachers should distance themselves from the utilitarian thinking. One should keep in mind the balance between personal and institutional achievements. Unfortunately, personal conveniences predominate, to the detriment of the entity advancement. This manner of thinking has become a cultural issue that has deep roots. If my institution prospers, I prosper. Cicero said: "Each one must, in all matters, have only one objective, that is to conform his own interest with the general interest".

Genevan Rousseau offered the same lesson, just like many other thinkers. These ideas have been with the human being for a long time. Medical societies would benefit. There would be

Keywords

Societies,Medical/trends; Universities/trends; Education, Medical; Public Health Policy.

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an increase in the quality indexes of didactic and dissemination activities. The question remains, which I believe would be difficult to answer today: is it possible for medical societies to contribute to public universities? If so, which would these contributions be? What could be the participation of societies in future university reformations?[1]

It is an effort that requires a dialogue between all who participate in these two universes. There are highly qualified human resources to carry out this task. There will be much disagreement, but this is the way to build something solid. This text does not intend to propose ideas, only to propose the dialogue. When the latter is present, the results appear. All sectors of this country are in need of healthy reformations, as are our societies and universities. I believe this approach could leave a magnificent legacy for the future, for our successors.

Reference

1. Mady C. O futuro das universidades públicas. [Internet]. [Citado em 2018 jul 19]. Disponível em: https://jornal.usp.br/artigos/o-futuro-das-universidades-publicas/

Author contributions

Conception and design of the research, writing of the manuscript and critical revision of the manuscript for intellectual contente: Mady C.

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Case 2 / 2019 – Complete Atrioventricular Septal Defect, with Down Syndrome, without Pulmonary Hypertension and Natural History at 33 Years of Age

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Clinical data

The patient has developed no symptoms since birth, when heart disease was diagnosed by the presence of heart murmur in the presence of physical elements of Down syndrome. The patient is currently able to walk approximately 30 minutes daily without showing signs of fatigue and accompanies other individuals normally. The patient uses enalapril and levothyroxine for hypothyroidism.

Physical examination: good overall status, eupneic, acyanotic, normal pulses in the 4 limbs. Weight: 41 kg, Height: 131 cm, MBP in the right upper limb: 110 x 60 mmHg, HR: 93 bpm, Sat O_2: 97%.

Precordium: non-palpable ictus cordis, without systolic impulses. Accentuated and constant split second heart sound. Moderate intensity holosystolic murmur at the left lower sternal border and ejection murmur at the high border. Non-palpable liver and lungs clear to auscultation.

Complementary examinations

Electrocardiogram: Sinus rhythm, with no signs of cavitary overload and/or conduction disturbances, with a narrow QRS of 0.87 ms (AQRS = -10º), positive T-wave at V1 (AT = 0º), and normal P-wave (AP = 30º) (Figure 1).

Chest X-ray: Slightly enlarged cardiac silhouette due to double atrium arch and left ventricular arch (CTI = 0.50). Normal pulmonary vascular network (Figure 1).

Echocardiogram: Atrioventricular and ventriculoarterial connections concordant with ostium primum-type atrial septal defect measuring 10 mm in diameter and inflow tract ventricular septal defect measuring 15 mm, with an effective 7-mm orifice by interposition of valve tissue, with interventricular pressure gradient of 78 mmHg. Single atrioventricular valve with two orifices, of which the right one measured 23 mm and the left, 30 mm. There was left valve regurgitation caused by cleft, resulting in left atrial increase. Regurgitation on the right was discreet. The right ventricular systolic pressure was 39 mmHg. The cavities had the following dimensions: RV = 16, LV = 54, LA = 45, Ao = 25, PAs = 17 mm (Figure 2).

Clinical diagnosis: Complete atrioventricular septal defect, with discrete repercussion caused by left atrioventricular valve regurgitation and small manifestation due to left-to-right blood shunting in atrioventricular position with Down's syndrome, in the presence of the natural history of the disease up to adulthood.

Clinical reasoning: There were clinical elements that offered a diagnostic indication of acyanogenic congenital heart disease with a slight clinical repercussion, such as atrial septal defect (ASD) and ventricular septal defect (VSD), in the presence of characteristic auscultation. The electrocardiogram did not show any cavitary overload and the chest X-ray showed a slight preponderant enlargement of the left cavities. The echocardiogram highlighted the diagnostic elements of the defect.

Differential diagnosis: Other acyanogenic cardiopathies such as ASD and / or VSD should be remembered in this context. Regurgitation of the valve on the left could also raise doubts regarding the diagnosis of the partial atrioventricular septal defect.

Clinical conduct: Considering the pulmonary and systemic flow balance over time, with no signs of hypoxemia and / or heart failure and in the presence of good physical tolerance, an expectant conduct was considered.

Comments: It is known that the complete atrioventricular septal defect has an unfavorable evolution, with signs of heart failure after the reduction of the pulmonary vascular resistance at a few days of life, in addition to progressive pulmonary vascular disease from a few months until the end of the first year of life. Thus, the need for early surgical intervention, in the first months of life, when there is a good long-term postoperative evolution.[1]

It can be affirmed that cases with an atrioventricular septal defect with discrete repercussion, of which evolution remains asymptomatic until adult life, are rarely seen. In this condition, the patients do not require early surgical intervention. Therefore, it is important to emphasize that these patients need a stringent and thorough evaluation, aiming to determine the best conduct for the infant, whether expectant or a surgical intervention. However, it is a difficult decision to make, since we have not found in the literature similar reports to the case described herein.

Keywords

Heart Defects, Congenital; Complete atrioventricular defect Clinical/surgery. Down syndrome; Radiography, Thoracic/methods; Echocardiography/methods.

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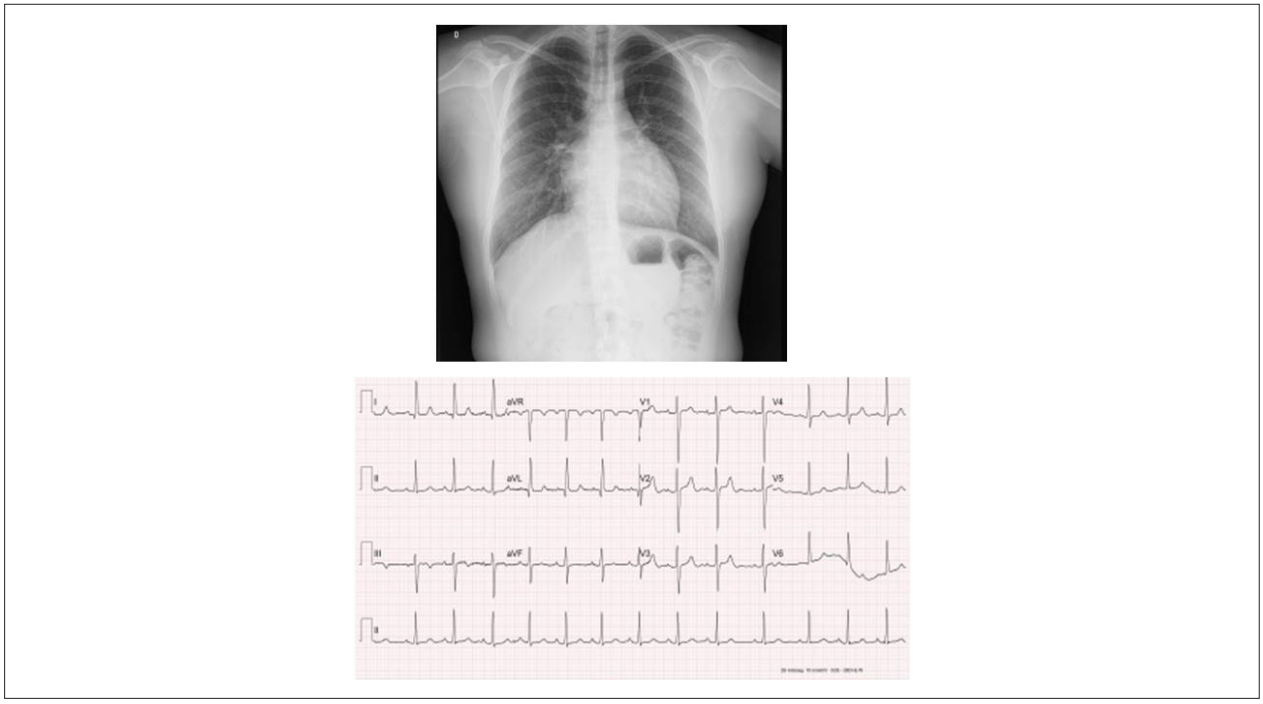

Figure 1 – *Chest radiography showing the slightly enlarged cardiac silhouette with normal pulmonary vascular network, pulmonary and systemic flow balance. Electrocardiogram shows normal without overload or conduction disturbances.*

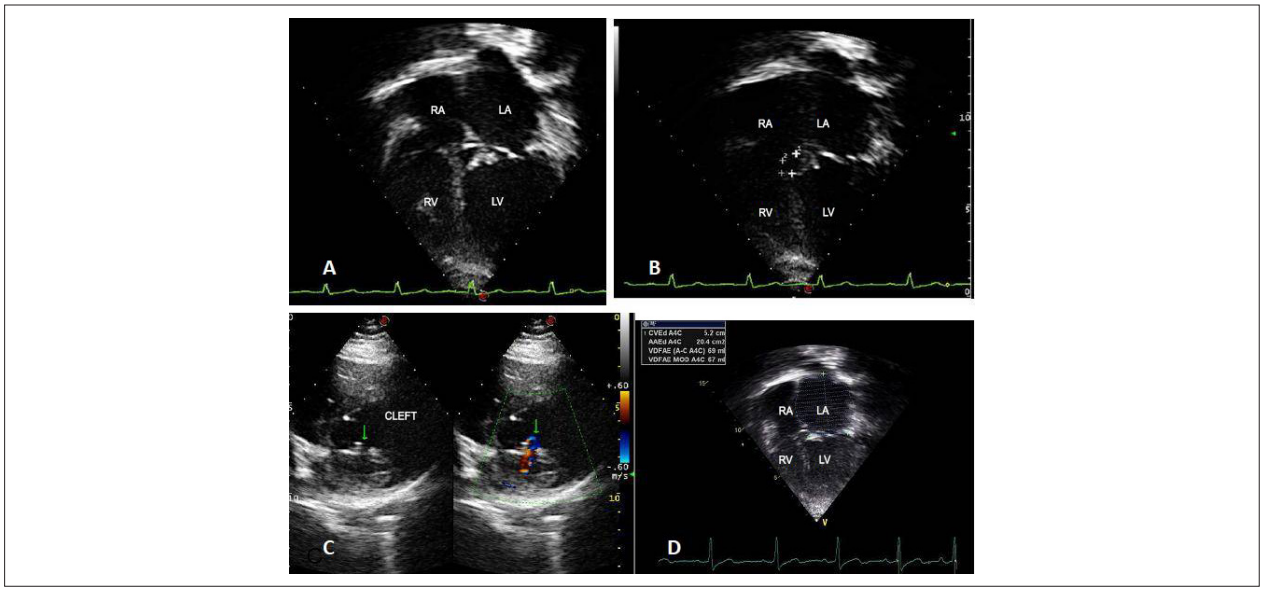

Figure 2 – *Echocardiogram showing in the 4-chamber apical plane, the increase in the left atrium due to the discrete regurgitation of the left atrioventricular valve caused by a cleft in C. The other cavities are normal due to closure of the inflow tract interventricular septal defect and the interatrial septal defect by valvular tissues, in A, B and D.*

Reference

1. Ginde S, Lam J, Hill GD, Cohen S, Woods RK, Mitchell ME, et al. Long-term outcomes after surgical repair of complete atrioventricular septal defect. J Thorac Cardiovasc Surg. 2015;150(2):369-74.

Chronic Aortic Dissection and Pregnancy: Clinical Case Report

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Introduction

Aortic complications during pregnancy can occur in women without risk factors, but they are more often associated with collagen diseases (Marfan and Ehlers-Danlos syndromes) and structural cardiac malformations (aortic coarctation and bivalve aortic valve).[1,2] Approximately half of these events occur during pregnancy in women under 40 years of age, particularly in the third trimester, or in the postpartum period.[3] It is an extremely rare event, accounting for 0.1% to 0.4% of all aortic dissections, affecting 5.5 (95% CI: 4.0 - 7.8) women per 1 million during pregnancy and puerperium.[1,4,5] It is believed that the physiological hemodynamic changes during pregnancy, structural changes determined by compression of the gravid uterus and the hormonal action can aggravate this aortic pathology.[1,6]

The most commonly used classifications are based on the affected anatomical portion. The Stanford group considers: type A (dissection involving ascending aorta) and type B (descending aorta only).[7] Depending on the duration of symptoms until the clinical presentation, aortic dissection can be classified as chronic, if it occurs two weeks or more after symptom onset.[6]

We present herein a case of Stanford type B chronic aortic dissection in a patient at the 36th week of pregnancy and discuss the particularities of the diagnosis and management of the potentially severe maternal and fetal complications.

Case Report

A 35-year-old single pregnant woman, of mixed-race, who had six prior pregnancies with five normal deliveries, at the 36th week of pregnancy, originally from the municipality of Damião, state of Paraíba, Brazil, was referred from Campina Grande, Paraíba, to the intensive care unit (ICU) of IMIP after undergoing an obstetric ultrasonography (USG) that disclosed significant abdominal aorta dilatation. She reported a history of suggestive lancinating abdominal pain approximately one year ago (three months before the diagnosis of pregnancy). She arrived at the Service asymptomatic, receiving α-Methyldopa 750 mg/day, propranolol 40 mg/day, furosemide 40 mg/day and ASA 100 mg/day.

At the physical examination she was conscious, eupneic, acyanotic, afebrile, with normal skin color, blood pressure (BP) of 100x68 mmHg and heart rate (HR) of 84 beats per minute (bpm). Respiratory auscultation showed no alterations and cardiac auscultation showed regular rhythm, normal heart sounds and no murmurs. She had depressible ++ / ++++ edema in the lower limbs; (below the 2.5th percentile for gestational age), physiological tonus, with fetal movements, fetal heart rate of 132 bpm and absence of visceromegaly.

Computed tomography (CT) of the chest and abdomen performed on the first day of hospitalization identified aortic dissection from the aortic arch to the abdominal aorta at the level of the renal arteries (Figures 1 and 2). She underwent an obstetric USG showing a single, live fetus, with estimated weight of 2.316 g, amniotic fluid index of 6 cm, normal umbilical artery Doppler, and gestational age of 35 weeks and 5 days.

She remained asymptomatic until the third day of hospitalization, when she developed lower abdominal pain and uterine dynamics (three contractions in ten minutes), BP of 160x100 mmHg during contractions, and thus, a cesarean section was indicated. The procedure was performed under spinal anesthesia, with the cardiology and vascular surgical teams on alert, without complications, when bilateral tubal ligation was also performed. The newborn was a female, weighing 2.475 g, with an APGAR score of 8/9.

At the postpartum, she was initially followed in the obstetric ICU and remained stable on propranolol 40 mg/day and amlodipine 5 mg/day, with adequate blood pressure control. She underwent an echocardiogram (2nd postoperative day) that showed a 52% ejection fraction, dissection of the aorta with false-lumen flow, and discrete aortic, mitral and tricuspid regurgitation. The heart chambers showed normal dimensions. On the 5th postoperative day after the cesarean section, she was submitted to a thoracic endoprosthesis implantation without complications. On the 3rd postoperative day after the implantation the patient developed a fever, of which origin was not determined and ceased after the use of vancomycin, piperacillin and tazobactam for 7 days, enoxaparin and prednisone. She was discharged from the 35th postoperative day after the cesarean section and 28th postoperative day after the aortic endoprosthesis implantation, on propranolol 120 mg/day, amlodipine 10 mg/day, losartan 100 mg/day and digoxin 0.125 mg/day and referred to cardiology outpatient follow-up.

Discussion

Aortic dissection during pregnancy is considered a potentially devastating clinical calamity for mother and conceptus.[2] Maternal mortality for acute Stanford type A and B dissection corresponds to 21% and 23%, with fetal death rates of 10.3% and 35%, respectively.[2] High rates are related

Keywords

Collagen Diseases/complications; Marfan Syndrome Ehlers-Danlos Syndrome; Aortic Coarction; Pregnancy; Postpartum Period; Aneurysm, Dissecting/surgery.

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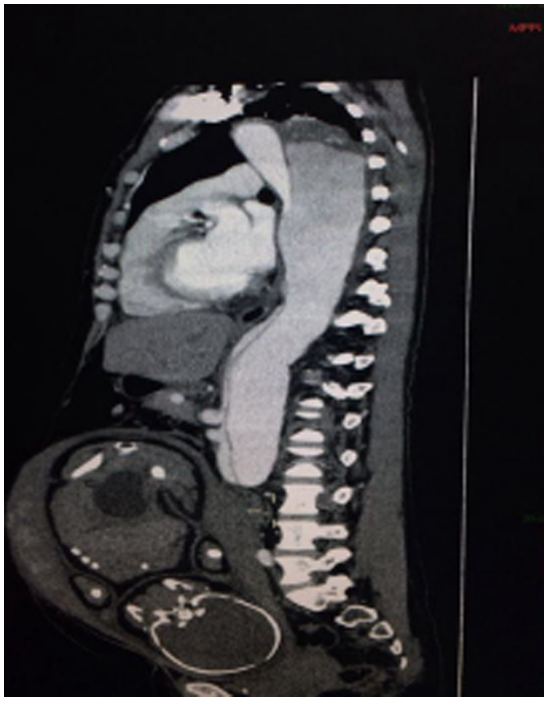

Figure 1 – *Computed tomography illustrating type B dissection.*

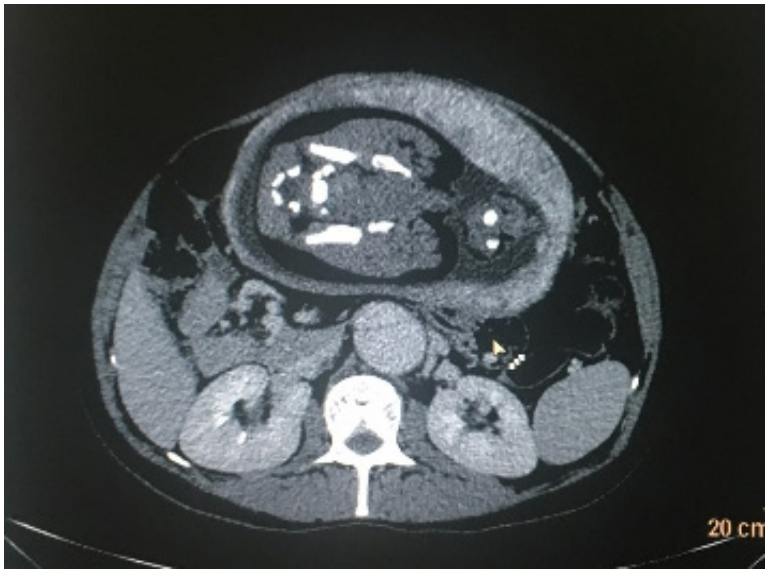

Figure 2 – *Computed tomography in axial view showing the dissection extending to the origin of the renal arteries.*

to vessel rupture, pericardial tamponade, heart failure, and ischemia of vital organs such as the brain, kidneys, and spinal cord.[3]

When the presentation is acute, the dissection symptoms are typical: sudden onset of thoracic, abdominal, or back pain, of the lancinating type.[3] The oligosymptomatic picture, such as that presented by the patient, which is typical of chronic dissections, is frequently underestimated and attributed to the physiological changes that occur during pregnancy, causing a delay in the diagnosis.[6]

Despite the known risk of ionizing radiation for the conceptus, it is known that this is small, and in these cases the benefit of performing a CT overcomes the risk. The USG was important initially for the identification of the aortic dilatation.

The CT allowed the diagnostic confirmation, as well as a better detailing of the dissection extent and involvement of the aortic vascular branches, fundamental data for the dissection classification and therapeutic planning.[3]

The decision about clinical management only or the need for surgical intervention before or after the pregnancy interruption should consider the risk of rupture, type of dissection and fetal viability.[3,8]

Delamination in the descending aorta characterized the dissection as type B and clinical treatment was chosen during the pregnancy, followed by the implantation of a thoracic endoprosthesis in the immediate postpartum.[3,8,9] The maternal hemodynamic stability and the strict monitoring of the aortic pathology and fetal vitality allowed this conduct in our service.

Beta-blockers are the first-line drug therapy, as they reduce both HR and BP and, consequently, the shear forces in the aorta, thus limiting the extent of the dissection and reducing the risk of rupture or damage to target-organs.[9] They can be used with relative safety during pregnancy (Propranolol is a Class C drug by the Food and Drug Administration - FDA).[3,8,9]

The pregnancy interruption prior to the dissection repair offered a greater chance of survival to this conceptus, since the reported rates of morbidity and mortality may reach 30% and 9%, respectively, during the repair procedures.[3,8]

The type of delivery in patients with heart disease is controversial. A normal delivery results in less bleeding, faster recovery, and decreases the risk of postoperative complications. In the absence of acute dissection, normal delivery can be performed with an aortic diameter < 40 mm in cases of Marfan Syndrome, with a cesarean section being indicated above this reference value.[3,8] The carrying out of the delivery should include interventions to reduce aortic wall stress, strict blood pressure control, adequate analgesia, and instrumental delivery when indicated.[3,8] The patient's aorta had a maximum diameter of approximately five centimeters, which supported the choice of delivery route by the team. Bilateral tubal ligation was appropriately indicated as a definitive contraceptive method and was based on the high risk of maternal death in the event of a new pregnancy.[8]

The great diversity of cases and the small number of cases reported in the literature do not allow establishing guidelines for the management of aortic dissection during pregnancy. Multidisciplinary management and individualized treatment aim to provide survival opportunities for the mother and fetus, considering maternal hemodynamic stability, fetal viability and the best opportunity for surgical intervention, when indicated.

Author contributions

Conception and design of the research: Taglialegna GM, Katz L, Albuquerque LMA, Freitas MM, Lucena AJG; Acquisition of data: Taglialegna GM, Albuquerque LMA, Freitas MM, Lucena AJG; Analysis and interpretation of the data: Taglialegna GM, Albuquerque LMA, Freitas MM; Writing of the manuscript: Taglialegna GM, Albuquerque LMA, Freitas MM; Critical revision of the manuscript for intellectual content: Katz L, Lucena AJG, Amorim MMR.

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Study Association

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References

1. Kamel H, Roman MJ, Pitcher A, Devereux RB. et al. Pregnancy and the risk of aortic dissection or rupture: a Cohort-Crossover Analysis. Circulation. 2016; 134(7):527-33.
2. Sawlani N, Shroff A, Vidovich MI. Aortic dissection and mortality associated with pregnancy in the United States. J Am Coll Cardiol. 2015; 65(15):1600-1.
3. Zhu JM, Ma WG, Peters S, Wang LF, Chiao ZY, Ziganashin BA, et al. Dissection in pregnancy: management strategy and outcomes. Ann Thorac Surg. 2017;103(4):1199-206.
4. Kamalakannan D, Rosman HS, Eagle KA. Acute aortic dissection. Crit Care Clin. 2007;23(4):779-800.
5. Braverman AC, Harris K, Pyeritz R. Aortic dissection during pregnancy: results from the International Registry of Acute Aortic Dissection (IRAD). J Am Coll Cardiol. 2012; 59:E1903.
6. Thrumurthy Sri G, Karthikesalingam Alan, Patterson Benjamin O, Holt Peter J E, Thompson Matt M. The diagnosis and management of aortic dissection BMJ. 2012 Jan 11;344:D8290.
7. Meszaros I, Morocz J, Szlavi J, Schmidt J, Tornoci L, Nagy L, et al. Epidemiology and clinicopathology of aortic dissection. Chest. 2000;117(5):1271-8.
8. Patel PA, Fernando RJ, Augoustides JG, Yoon J, Gutsche JT, Feinman JW, et al. Acute type-B aortic dissection in pregnancy: therapeutic challenges in a multidisciplinary setting. J Cardiothorac Vasc Anesth. 2017;31(6):2268-76.
9. Kaji S. Update on the therapeutic strategy of Type B aortic dissection. J Artherioscler Tromb. 2017;25(3):203-12.

Do Not Treat Children with Statins

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In their meta-analysis Radaelli et al. conclude that statin treatment is efficient in lowering lipids in children with familial hypercholesterolemia (FH) and suggest that long-term trials should be performed to establish long-term safety.[1] We would warn against their recommendation for several reasons.

Keywords

Statins; Hydroxymethylglutaryl CoA Reductase; Inhibitors; Hypercholesterolemia Type II/genetics; Children; Meta-analysis.

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As we have shown in a recent paper,[2] there is much evidence that high LDL-cholesterol (LDL-C) is not the cause of premature coronary heart disease in FH; it is most likely inborn abnormal coagulation factors, and only a small minority among those with FH inherits these factors. On average, people with FH live just as long as other people because high LDL-C protects against cancer and infectious diseases.[2] Furthermore, to treat children with statins may ultimately cause them harm because cholesterol is necessary for the developing brain and is an essential precursor for metabolic co-factors and hormones, including vitamin D and all sex steroids.

Finally, it is becoming well-known that the number of adverse effects from statin treatment is much larger and much more serious than reported in the trial reports.[3,4] Hence, there is justifiable concern that long-term treatment of children with FH will cause them more harm than benefit.

References

1. Radaelli G, Sausen G, Cesa CC, Santos FS, Portal VL Neyeloff JL, Pellanda LC. Statin treatments and dosages in children with familial hypercholesterolemia: Meta-analysis. Arq Bras Cardiol. 2018;111(6):810-21.
2. Ravnskov U, de Lorgeril M, Kendrick M, Diamond DM. Inborn coagulation factors are more important cardiovascular risk factors than high LDL-cholesterol in familial hypercholesterolemia. Med Hypotheses. 2018;121:60-3.
3. Diamond DM, Ravnskov U. How statistical deception created the appearance that statins are safe and effective in primary and secondary prevention of cardiovascular disease. Expert Rev Clin Pharmacol. 2015;8(2):201–10.
4. Ravnskov U, de Lorgeril M, Diamond DM, Hama R, Hamazaki T, Hammarskjöld B et al. LDL-C does not cause cardiovascular disease: a comprehensive review of current literature. Expert Rev Clin Pharmacol. 2018;11(10):959-70.

Reply

We thank Ravnskov et al.[1] for the letter, which enables the discussion of a relevant issue and concern in clinical practice for the treatment of children and adolescents with dyslipidemia, especially in long term. The reason for the development of our meta-analysis was based on the use of statins to treat children with secondary dyslipidemia which, to our understanding, is not based on solid evidence. This was the main objective of our meta-analysis, *i.e.*, to identify supporting evidence for this practice, rather than to conduct a review of studies on children with familial hypercholesterolemia.

We searched for evidence for treatment of children with statins on PubMed, EMBASE, Bireme, Web of Science, Cochrane Library, SciELO and LILACS databases from inception to February 2016. Of a total of 16,793 potentially relevant citations retrieved from the electronic databases, no randomized clinical trial met the inclusion criteria.[1]

Although we cited studies on familial hypercholesterolemia in the discussion section, we neither reviewed these studies, nor produced any clinical recommendations for this condition. Our only comment to the letter is the fact, the discussion section of our meta-analysis may have been misinterpreted, as it does not support a recommendation for clinical practice and was not written with such intention. We are thankful for the opportunity to make this clear.[2]

Letter to the Editor

We can affirm that there is not sufficient evidence to treat children with dyslipidemia with statins, even those with familial hypercholesterolemia, particularly regarding the long-term safety of this practice. In our opinion, this is a matter of great concern, since we did not find any long-term study, or any study describing potential long-term side-effects of early intervention on cholesterol reduction or delay in the appearance of cardiovascular events. In the article, we reported that "children with serious lipid abnormalities due to genetic disorders may meet the criteria for drug therapy with the statins commonly used in adults" (my emphasis). This is not a recommendation and does not exhaust the subject.

We reiterate our conclusion that, before prescribing statins to children with secondary dyslipidemia, studies should be performed to determine whether these drugs can reduce overall and long-term morbidity and mortality, which, again, was the main objective of our study. We believe that Ravnskov et al. make important contributions to this issue, by adding recent data about causal mechanisms of familial hypercholesterolemia, and concerns about the risk of long-term use of statins in this condition. This is corroborated by the studies published in 2018 cited by the authors. Thus, we agree with the authors in suggesting caution in the long-term use of drugs in pediatric patients with chronic conditions.

Graciane Radaelli

References

1. Radaelli, G., Sausen, G., Cesa, C. C., Portal, V. L., & Pellanda, L. C. (2018). Secondary Dyslipidemia In Obese Children-Is There Evidence For Pharmacological Treatment?. Arq Bras Cardiol. 218;111(3):356-61.
2. Ravnskov U, de Lorgeril M, Kendrick M, Diamond DM. Inborn coagulation factors are more important cardiovascular risk factors than high LDL-cholesterol in familial hypercholesterolemia. Med Hypotheses. 2018;121:60-3.

The Brazilian Society of Cardiology and Brazilian Society of Exercise and Sports Medicine Updated Guidelines for Sports and Exercise Cardiology – 2019

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Note: These Guidelines are for information purposes and are not to replace the clinical judgment of a physician, who must ultimately determine the appropriate treatment for each patient.

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	If the last three years the author/developer of the Guidelines:						
Names Members of the Policy	**Participated in clinical studies and/or experimental trials supported by pharmaceutical or equipment related to the guideline in question**	**Has spoken at events or activities sponsored by industry related to the guideline in question**	**It was (is) advisory board member or director of a pharmaceutical or equipment**	**Committees participated in completion of research sponsored by industry**	**Personal or institutional aid received from industry**	**Produced scientific papers in journals sponsored by industry**	**It shares the industry**
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Thiago Ghorayeb Garcia	No	No	No	No	No	No	No

Updated

Content

1. Presentation and Introduction

Movement is a part of daily life for humans, who must get from one place to another, pick up and carry things, relate to others or simply move for the pleasure of moving. Caspersen et al.'s,[1] classic definition (1985) will be used in this Update, in which all body movement produced by the skeletal muscles that results in energy expenditure is considered physical activity. Physical exercise can be conceptualized as a special type of physical activity that is planned, structured and repetitive, whose ultimate or intermediate goal is to maintain or improve health, physical conditioning, body aesthetics or performance in competition.[1]

Although sports are often associated with leisure, they can also be a person's main activity: individuals can characterize themselves as professional athletes when it becomes their means of livelihood or an important source of income. Recently, the concept of athlete was formally defined as someone who simultaneously meets the following four criteria: (a) trains to improve sports performance or results; (b) actively participates in sports competitions; (c) is formally recognized at a local, regional or national level; (d) regards competition as a main activity (way of life) or as a focus of personal interest, devoting several hours to training every day or most days, exceeding the time allocated to other professional or leisure activities.[2] Those who exercise regularly and but only compete occasionally, such as in marathons or other mass sports events, should be called amateur athletes.[2] Thus, although primarily directed to professional athletes, many aspects covered in this Update also apply to amateurs and some apply to non-athletes who exercise regularly.

These updated guidelines for sports and exercise cardiology will address the following topics: pre-participation screening, structural and non-structural heart diseases, genetic aspects of these pathologies, valvular disease, the hearts of female athletes, as well as basic life support for athletes. Some topics in the 2013 Guidelines[3] will be covered in future publications or can be consulted in other specific Guidelines.

In summary, this document serves as a de facto update for this field of knowledge and can be applied in clinical practice.

2. Pre-Participation Screening

2.1. Introduction

Clinical pre-participation screening (PPS) for sports activities should be understood as a standardized systematic medical evaluation that can cover a broad population of professional and amateur athletes before participating in regular moderate-to-intense exercise. Its purpose is to identify cardiovascular diseases that are incompatible with certain types of exercise. The main objective of this screening, which is conducted prior to initiating training and periodically afterwards, is the prevention of cardiovascular diseases and the early detection of diseases that cause sudden cardiac death (SD). This can be achieved by temporarily or permanently suspending the exercise or by treating the potentially fatal conditions that it could trigger. The American Heart Association,[4] the European Society of Cardiology[5] and the Brazilian Society of Exercise and Sports Medicine[3] recommend PPS for all professional athletes. PPS can also be recommended for correctly prescribing moderate-to-high intensity exercise for non-professionals.

Corrado et al.[6] demonstrated the importance of PPS for preventing SD. Over a 26-year period during which PPS was introduced as a federal law in Italy (1979-2004), the incidence of SD in screened athletes was reduced by 89%: from 3.6 per 100,000 person-years in 1979-1980 to 0.4 per 100,000 person-years in 2003-2004. At present, one of the main issues in PPS is cost-effectiveness. Some societies, such as the American Heart Association, advocate screening with only a questionnaire and a physical examination, believing that the financial and psychological costs associated with false positive results in complementary examinations, such as electrocardiograms (ECG), do not justify the potential benefits.[4] However, the European Society of Cardiology and numerous sporting associations (e.g., FIFA, the NBA), support the use of resting ECG, since it has been shown to affect the incidence of SD among athletes.[7,8]

Although we do not have randomized studies comparing the two models of evaluation, we suggest that PPS for professional athletes should include 12-lead resting ECG, since, first, it helps guarantee their safety and, second, the investments involved in their training.[9-11] These issues will be addressed in this document, which aims to establish norms for PPS in our country.

For didactic purposes, as well as due to clinical, physiological, and epidemiological differences, we have chosen to divide PPS candidates into two groups: amateur athletes and professional athletes. When considering various aspects of exercise, such as intensity, training frequency and volume, a zone of intersection will always exist between these groups. Nevertheless, the medical evaluator's good judgment and individual experience will be fundamental in choosing a way forward in these cases. In light of such divisions, it is of fundamental importance to understand the distinction this Guideline determines between amateur and professional athletes:

Amateurs: adults who participate in regular, moderate-to-high intensity sports activities who occasionally compete, although without professional ties to the sport.

Professionals:[2]

- Individuals who train to improve their sports performance
- Individuals who actively participate in competitions
- Individuals who train and compete as their main activity or as a focus of personal interest. They devote a number of hours on most days to training, exceeding the time spent in other professional or leisure activities.

However, professional athletes can also be classified according to age:

- Young athletes – 12 to 17 years.
- Adult athletes – 18 to 35 years.
- Master athletes – 35 years or older.

2.2. Anamnesis and Physical Examination

Ideally, all candidates for moderate-to-high intensity exercise should undergo PPS, which can identify risk factors and signs and symptoms suggestive of cardiovascular, pulmonary, metabolic or locomotor disorders.[12-14] In anamnesis, issues related to exercise, including family history of disease or sports-related cardiovascular events, should be prioritized. However, a detailed investigation of family history with respect to heart disease or other SD-related diseases must be performed. To do this, adequate knowledge of these medical conditions and a cardiological approach are important.[10,15,16]

In PPS it should be considered that cardiac adaptations to physical exercise are frequency, intensity, and duration dependent and vary among different sports and training systems, as well as among individuals.[17] Due to the latter aspect, different adaptations can be found in individuals involved in similar physical activities. It should be pointed out that the modifications involved in what is referred to as "athlete's heart syndrome" should initially be considered as normal physiological adaptations to exercise, of a transient nature and without negative repercussions on an individual's health.[18]

The Physical Activity Readiness Questionnaire can be applied systematically during anamnesis. This questionnaire, developed in Canada, should be combined with basic questions asked by a physician (Table 1) about cases of SD or inherited heart diseases, family history of sickle cell disease or other hemoglobinopathies, as well as the patient's origin. Determining the patient's origin is important, since certain regions have endemic diseases, such Chagas' disease, or have a higher prevalence of congenital diseases, such as the Veneto region of Italy, where there is a higher prevalence of arrhythmogenic right ventricular dysplasia (ARVD).[19,20] Particular care should be taken when obtaining information about licit or illicit drug use that could be considered as doping or that could be harmful to health (i.e., which could cause SD or other undesirable events).[21,22] Important symptoms include: palpitations, syncope, chest pain or discomfort, exertional dyspnea, dizziness/asthenia, or any other symptom triggered by exercise. Accurate sensitivity is needed to determine whether mentioned symptoms indicate a disease state or are merely the consequence of more intense training or competition. For both amateur and professional athletes, if syncope occurs during exercise rather than post-effort, a detailed investigation should be conducted to discard a primary arrhythmic event.[23]

The physical examination should include inspection for certain clinical conditions, such as anemia, posture changes, infectious foci (e.g., dental), severe systemic or infectious diseases, bronchial asthma, obesity, diabetes mellitus, systemic arterial hypertension, and changes in pulmonary or cardiovascular auscultation. A search for signs related to possible cardiovascular disease should be prioritized, such as: heart murmur, third and fourth heart sounds, valve clicks, pulse changes in the upper and lower limbs, signs of Marfan syndrome or other aortic diseases (e.g., Loeys-Dietz syndrome), as well as adequate blood pressure (BP) in both arms at the first evaluation.[14,24,25]

Recommendation for anamnesis and physical examination	Recommendation grade	Evidence level
Amateur athletes	I	C
Professional athletes	I	A

2.3. Complementary Exams

Laboratory tests, in principle, are unnecessary: requests for them should be based on clinical data, especially cardiocirculatory issues. Routine laboratory tests include: complete blood count, fasting glucose, urea, creatinine, sodium

Table 1 – Details to be included in a personal and family history assessment for athletes

Has any doctor ever told you that you have a heart problem?	Have there been cases of sudden death or heart disease in your family?
Precordial pain or discomfort on exertion or at rest	Do you feel chest pain when exercise?
Pre-syncope or syncope, especially if related to exertion	Do you lose your balance due to dizziness and/or loss of consciousness? Are there cases of heart disease, sudden death before age 50 or cardiac arrhythmias In your family?
Arrhythmias	Observe palpitations (skipped beats or heart racing)
Previously diagnosed pathologies	Previous history of heart murmur Previous history of hypertension Previous history of metabolic disease Use of performance enhancing substances/ use of any medication Live/lived in an area with endemic Chagas disease
Do you have any bone or joint problems that could be made worse by physical activity?	Do you currently take some type of medication? Question directly about anti-hypertensive, NSAID, anabolics, illicit drugs, and alcohol consumption
Is there any other reason why you should not perform physical activity?	Family members with genetic diseases; hypertrophic cardiomyopathy, dilated cardiomyopathy, channelopathies, arrhythmias, Marfan syndrome

NSAID: nonsteroidal anti-inflammatory drug.

and potassium, complete lipid profile, uric acid, glutamic-oxalacetic transaminase, glutamic-pyruvic transaminase, gamma-glutamyl transpeptidase, bilirubin, prothrombin time/international normalized ratio, and common urine testing.

Recommendation grade: I.

Evidence level: B.

For individuals who exercise or compete at altitudes over 2,000 meters, it is important to perform hemoglobin electrophoresis to rule out the possibility of hemoglobinopathies (e.g., sickle cell anemia). In our country, especially in regions of higher incidence, serology for Chagas' disease may also be recommended.[3] Chest radiography may also be requested in many cases.

2.3.1. Resting 12-Lead Electrocardiogram

2.3.1.1. Introduction

Use of this examination in groups of younger athletes is controversial. Although the American Heart Association (American College of Cardiology/American College of Sports Medicine) does not include ECG in PPS, the European Society of Cardiology, in addition to numerous sports organizations, recommend it.[4,5] For master athletes, resting ECG is mandatory, since older adults have a higher prevalence of cardiovascular diseases, especially coronary artery disease (CAD).[26,27]

2.3.1.2. Method

Conventional 12-lead ECG should be performed with the individual in the supine position, recorded at a velocity of 25 mm/s and ideally obtained 24 hours after the last sporting activity. At least 5 minutes of rest is recommended before the examination.[3,28]

2.3.1.3. Analysis

Since there are peculiarities among the resting ECG results of athletes, examinations should be interpreted by physicians with experience in the area. This recommendation is important, because it will prevent common alterations of the athlete's heart from being confused with heart disease. However, in most countries medical knowledge regarding the interpretation of athletes' ECG is still limited, which prohibits broader application of this method.[29]

2.3.1.4. Changes

Regular intense exercise can cause physiological changes to the heart at structural, functional and electrical levels. The ECG findings of more than 80% of high-performance athletes reflect exercise-induced cardiac adaptations as a result of intrinsic changes in automaticity and atrioventricular conduction,[30] as well as of increased vagal tone and cardiac remodeling.

Due to the establishment of criteria that allow a distinction between heart diseases and athlete's heart syndrome, interpretations of athletes' ECG are becoming more uniform.[28,31] It is understood that the false positives associated with athletes' ECG depend on the criteria used in their interpretation, as well as our current understanding of variations of normality. Thus, new criteria represent a major effort to refine the analysis and interpretation of ECG, making it more specific without losing sensitivity. Variations in the prevalence of these criteria are related to gender (higher in males), age (genetic/congenital diseases in young athletes and CAD in master athletes), ethnicity (black athletes have more left ventricular overload and repolarization changes than athletes of other races), training level (variation is more frequent in professional athletes than amateurs) and type of sport (predominantly regarding the dynamic component).[28] It can be especially difficult to differentiate between physiological and pathological adaptations in black athletes, since they have a tendency to develop more hypertrophy in response to exercise than whites. We should also point out that more than 10% of black athletes may have a wall thickness > 12 mm in the echocardiogram.[32]

Failure to distinguish between the physiological and the pathological can have harmful consequences. Athletes can be unnecessarily disqualified from competition due to ECG changes that could be considered normal. Likewise, they may undergo unnecessary examinations, which greatly increase their costs. On the other hand, signs of life-threatening cardiovascular disease may be erroneously interpreted as normal variants of an athlete's ECG, which could put the individual at risk of SD.

Changes in the athlete's ECG can be divided into two groups: common and/or related to training; or uncommon and/or suggestive of heart disease (Table 2). ECG is most useful when performed as part of PPS, when it can identify unexpected changes, such as previous myocardial infarction (in older age groups), arrhythmias, conduction disorders, etc. An ECG may also help diagnose less prevalent diseases, such as hypertrophic cardiomyopathy (HCM), long QT syndrome, short QT syndrome, Brugada syndrome, Wolff-Parkinson-White syndrome (or other pre-excitation syndrome), in addition to arrythmogenic right ventricular dysplasia (ARVD). A 12-lead ECG may also facilitate assessment of significant atrioventricular and intraventricular conduction and rhythm disturbances. It can also detect ST-segment changes, such as early repolarization, T-wave inversion in precordial and/or peripheral leads, and voltage criteria suggestive of left ventricular hypertrophy (LVH).[28,31]

There may be variations in the prevalence of EGC changes, which are more frequent in men than women. In relation to age, we found a higher frequency of inverted T-waves in precordial and/or peripheral leads in master athletes and older adults, as well as criteria for LVH, in addition to conduction disturbances (Table 3). There are also significant variations in 12-lead ECG results in different types of sports.

Recommendation grade: I.

Evidence level: A.

2.3.2. Electrocardiogram: Physiological Changes vs. Changes Suggestive of Heart Disease

Athletes frequently show ECG changes (up to 80% in some series), including: bradycardia/sinus arrhythmia (13% to 69%), first degree atrioventricular block (35%), and early

Table 2 – Electrocardiogram: changes due to exercise vs. changes suggestive of heart disease

Physiological ECG findings in athletes	Abnormal ECG findings in athletes
Sinus Bradycardia (HR > 30bpm)	T-wave inversion > 1 mm in 2 or more leads (except DIII, aVR and V1)
Sinus arrhythmia	ST-segment depression> 0.5 mm in 2 or more leads
Ectopic atrial rhythm	Pathological Q waves > 3 mm or > 40 ms in 2 or more leads (except DIII and aVR)
Junctional escape rhythm	Complete left bundle branch block
1st degree BAV (PR interval > 200 ms)	Nonspecific conduction delay with QRS > 140 ms
2nd degree AVB Mobitz I (Wenckebach)	Deviation of the electrical axis from – 30° to 90°
Incomplete right bundle branch block	Left atrial overload
Isolated QRS voltage criterion for LVH	Right ventricular hypertrophy pattern with RV1 + SV5 > 10.5 mm and axis deviation > 120°
	Ventricular pre-excitation
Early repolarization	QT interval > 470 ms in men and > 480 ms in women
	QT interval < 320 ms
ST-segment elevation accompanied by T-wave inversion in leads V1 to V4 in Black athletes	Brugada pattern
	Sinus bradycardia < 30 bpm or sinus pauses > 3 s
	Atrial tachyarrhythmia
	Ventricular extrasystoles with 2 or more 10-second ECG episodes
	Paired ventricular extrasystoles and NSVT

AVB: atrioventricular block; BPM: beats per minute; ECG: electrocardiogram; HR: heart rate; LVH: left ventricular hypertrophy; NSVT: nonsustained ventricular tachycardia.

Table 3 – Different types of electrocardiographic abnormalities in relation to age found in an unselected European population of 32,652 subjects who underwent sports pre-participation screening

	< 20 years (n = 2.430) %	20-29 years (n = 2.430) %	> 30 years (n = 2.430) %
Incomplete RBBB, increased PR interval, early repolarization pattern	73.1	37.9	30.1
Inverted T-waves	9.5	38.6	37.9
R/S wave voltage increase	3.1	4.6	7.2
RBBB	10.9	12.1	10.9
LAHB, LBBB	2.1	5.7	13.3
Pre-excitation pattern	1.3	1.1	0.6

LAHB: left anterior hemiblock; RBBD: right bundle branch block; LBBB: left bundle branch block. Adapted from Pelliccia et al.[73]

repolarization (50% to 80%). Such findings are usually due to physiological adaptations related to athlete's heart syndrome.[33] Athletes may also present voltage criteria for LVH, which reflects remodeling of this cavity, although without pathological Q-waves, electrical axis deviation, atrial overload or repolarization changes.[31,32] These physiological changes in ECG should be clearly separated from patterns suggestive of heart disease, which can be recognized by repolarization changes, pathological Q waves, marked intraventricular conduction defects, pre-excitation, short or long QT intervals, and Brugada syndrome. These findings are rare (less than 5%) but may express some cardiomyopathy or channelopathy that could predispose the athlete to SD.[33] Another important point concerns atrial dilation (resulting from regular training) to meet increased cardiac demand during exercise, although this is not fully understood. Nevertheless, despite this dilation, atrial function seems to be preserved in athletes, but not in patients with structural heart disease.[34]

Other less common findings that can be identified in athletes are sinus pauses < 3 s (mainly during sleep) and second-degree bicuspid aortic valve (BAV) type I (Wenckebach). Such findings generally disappear during effort and with the administration of substances. Changes that can be considered cardiac adaptations to physical exertion should not cause alarm, and participation in competitive sports should not be prohibited without further evaluation. On the other hand, findings suggestive of heart disease, even if asymptomatic, should be investigated, especially in the absence of a positive

family history or the presence of abnormal findings during physical examination.[35,36]

Recommendation grade: I.

Evidence level: A.

2.3.3. Exercise Stress Testing

As part of a strategy for early cardiovascular disease identification, an exercise stress testing can be recommended for the initial evaluation of amateur or professional athletes of any age group. This test can contribute to the prognosis of asymptomatic patients or when there are symptoms potentially indicative of some pathological condition.[37,38] Its may also be used to evaluate cardiorespiratory fitness during training for certain sports, especially those with a predominantly aerobic component.[39,40]

Asymptomatic individuals with no cardiovascular risk factors can be cleared without this examination. However, an exercise stress testing may be recommended in other conditions.[41] After 35 years of age, CAD is the main cause of mortality. An exercise stress testing is recommended for individuals in this age range, mainly to identify myocardial ischemia, since the results can indicate the probable presence of the disease. In asymptomatic individuals, and even in those with known CAD, exercise stress testing is used for prescribing an adequate level of physical activity.

Changes in resting ECG, often due to physiological LVH, reduce the method's accuracy for diagnosing myocardial ischemia. Simultaneous analysis of other examination variables contributes to a more global assessment.[42] When a patient mentions having palpitations during physical activity, this should be investigated with an exercise stress testing to reproduce the conditions of the complaint in a controlled environment.

2.3.3.1. Variables to be Evaluated in an Exercise Stress Testing

2.3.3.1.1. Functional Capacity

Low functional capacity indicates a poor prognosis. A number of observational studies have demonstrated an inverse association between the metabolic equivalents reached in the exercise stress testing and mortality.[43-45] When an individual's functional capacity is low compared to predicted values for his or her gender and age group, additional investigation may be necessary.[46]

2.3.3.1.2. Chest Pain

An exercise stress testing can reproduce the conditions of chest pain or discomfort during exercise and allows a probable diagnosis of myocardial ischemia due to CAD, which should lead to further investigation and suspension of training. When an exercise stress testing leads to non-ischemic pain similar to that which motivated the test, but there are no changes in any of the test variables, the probability of CAD is low and the athlete can return to competition.[47] On the other hand, chest pain characteristic of angina, even if unaccompanied by ST-segment changes, is usually associated with a poor prognosis. Proper interpretation of an exercise stress testing requires prior knowledge of normal findings for young athletes. Determining whether ST-segment depression in master athletes is related to CAD can be challenging. The possibility of a false positive result related to LVH cannot be ruled out, but ischemia of atherosclerotic origin should always be discarded. Additional investigation may be required before returning to practice and competition.[48]

2.3.3.1.3. ST-T Segment

ST-segment depression > 1 mm is suggestive of CAD, especially when in a horizontal or descending pattern. Such alterations have higher values when occurring concomitantly with chest pain or other manifestations that contribute to a diagnosis of myocardial ischemia.[49] ST-segment elevation ≥ 1 mm at 60 ms after J-point, when not observed in a Q-wave area (inactive zone), is very suggestive of subepicardial (or transmural) injury,[50] indicates ischemia and must be managed as such.

In asymptomatic athletes, when ST alterations occur during an exercise stress testing, even if unaccompanied by chest pain, or when they occur with high double product values and high exercise capacity, especially if associated with frequent cardiac arrhythmias, training should be suspended (temporarily or not). In such cases, it is of fundamental importance to continue investigation into cardiovascular disease. Such an approach is based on the increased cardiovascular demand and increased risk of events during exercise, especially in individuals over 35 years of age or when one or more CAD risk factors are present.

ST-segment analysis should consider:

- Morphological characteristics, i.e., descending is more serious than horizontal, which is more serious than slow ascending.[51]
- Early onset during exercise and persistent changes late in the recovery phase indicate greater risk and severity.[52]
- ST-segment depression greater than 10% in relation to the immediately preceding R-wave amplitude. This adjustment in ST-segment evaluation should be considered due to recurring high-amplitude R-waves, which can express physiological LVH.[53]

Furthermore, regarding the ventricular repolarization phase, it is important to point out that when starting from an altered ECG, normalization during exercise can indicate a good prognosis (if not accompanied by symptoms).[54,55]

2.3.3.2. Blood Pressure

Excessively high BP during an exercise stress testing in patients who have not been diagnosed with hypertension and who have normal resting levels could be a warning sign, because there is a significantly greater risk of developing hypertension in subsequent years. In patients with newly diagnosed hypertension, laboratory investigation and treatment should begin immediately. However, if there is a progressive decrease in systolic BP during an exercise stress testing, especially when it falls below the pre-effort value, subsequent investigation for heart disease should be carried out, especially in cases of stress-induced systolic dysfunction.

2.3.3.3. Heart Rate

Chronotropic incompetence indicates a poor prognosis and has been associated with endothelial dysfunction, altered autonomic modulation, elevated inflammatory markers and CAD. An inadequate HR response can be considered as the inability to achieve 85% of the estimated maximum HR. The following equation can be used to predict maximum HR: 208 - (age × 0.70). A chronotropic index < 80% is another way to identify chronotropic incompetence, which has prognostic value. It is obtained by the following ratio: (HR reserve obtained/estimated HR reserve) × 100.[56]

Vagal modulation of HR can be inferred from HR reduction in the first minute of recovery in relation to HR at peak exertion. This observation was initially identified when comparing athletes with heart failure (HF) patients.[57,58] Reductions ≤ 12 beats per minute have been associated with higher mortality rates.[59]

2.3.3.4. Cardiac Arrhythmias

Less complex cardiac arrhythmias, such as occasional ventricular extrasystoles during an exercise stress testing, often express an increase in sympathetic autonomic modulation due to graduated exercise. Such conditions alone, without other alterations, do not justify limiting the activity of asymptomatic individuals, nor do they require further investigation. Symptomatic or asymptomatic patients who develop complex ventricular arrhythmias, such as ventricular tachycardia (whether sustained or not), must be investigated before they return to training.

For mild-to-moderate intensity leisure activities in asymptomatic individuals with a cardiovascular risk factor: perform an exercise stress testing at the beginning of participation.

Recommendation grade: III.

Evidence level: C.

For amateur athletes participating in high-intensity sports and competition: perform exercise stress testing at the beginning of training.

Recommendation grade: IIa.

Evidence level: A.

For professional athletes participating in high-intensity athletic activity and competition: perform an exercise stress testing at the beginning of the season.

Recommendation grade: I.

Evidence level: C.

Any time:

When a patient refers to chest pain or discomfort, fatigue or dyspnea of unknown cause, palpitations, or when previously non-existent arrhythmias, exercise-related pre-syncope or syncope or elevated resting BP (with or without compromise a target organ) are identified: perform an exercise stress testing.

Recommendation grade: I.

Evidence level: A.

2.3.4. Cardiopulmonary Exercise Testing

For a long time (including in Brazil), athletes and individuals participating in high-performance activities have undergone cardiopulmonary exercise testing (CPET) to evaluate performance and prescribe aerobic training.[60] As described in Table 4, CPET differs from an exercise stress testing by adding measures and analyses of expired gases.[61] Unlike in exercise tests for clinical diagnosis, when CPET is performed in apparently healthy athletes BP is often not measured and even ECG is often not performed, and HR is obtained by frequency meter. With so much equipment available (e.g., in laboratories, clinics, hospitals, clubs and sports centers) to perform these measures, there is little sense in evaluating an athlete's aerobic condition through a exercise stress testing, which has an error rate of approximately 20% when estimates based on formulas developed for clinical protocols involving treadmills or cycle ergometers are used.

In certain clinical settings and for certain groups of athletes, including a CPET in PPS may be recommended (or even critical for) individual risk stratification, especially due to the data collected from expired gas measurement and analysis. This could be relevant in master athletes, in individuals with cardiovascular and/or pulmonary diseases who are involved in recreational competition (e.g. half-marathons, marathons, mountain climbing, cycling, water sports, etc.), as well as in professional athletes. In these circumstances and whenever possible, it is best to use an exercise stress testing that closely approximates the patient's sport.

Among the additional clinical information that CPET can reveal about athletes or active, healthy individuals, two types stand out: (a) more precise and objective identification of limiting factor(s) for maximum effort (cardiovascular, respiratory and muscular or metabolic) and (b) evaluation of systolic volume behavior, which is obtained by analysis of the curves and maximal values of oxygen pulse (VO_2/HR)

Table 4 – Main differences between exercise stress testing and cardiopulmonary exercise testing

	Exercise testing	
Variable	**Exercise stress testing**	**Cardiopulmonary exercise testing**
Functional capacity	Measured	Measured
Maximum aerobic power	Estimated	Measured
Anaerobic threshold	Undetermined	Determined
V/Q Ratio	Not evaluated	Evaluated
Inotropic response	Limited evaluation	Excellent evaluation
Mechanical Efficiency	Presumed	Measured
Protocol	More dependent	Less dependent
True maximum cardiorespiratory capacity	Presumed	Probable/identified
Etiology of dyspnea	Unidentified	Probable/identified

V/Q ratio: ventilation/perfusion ratio.

and ventilatory equivalents (VE/VO_2 and VE/VCO_2).[62] CPET is already included in cardiological evaluation of HF patients,[63] in identifying the etiology of effort dyspnea[64], and has more recently been considered capable of identifying myocardial ischemia[65,66] or abnormal responses after cardiac surgery.[67] In patients with chest pain, changes in the oxygen pulse during CPET make its diagnostic and predictive accuracy greater than an exercise stress testing for detecting or excluding myocardial ischemia.[68] It is the procedure of choice when a valid and precise measurement of an athlete's aerobic condition is required and HR thresholds must be determined for exercise prescription.

Recommendation	Recommendation grade	Evidence level
Amateur athletes	IIa	C
Professional athletes	I	B
For more precise stratification of exercise-limiting factors	IIa	A

CPET should be used when there is a change in resting ECG that may interfere in its interpretation or when there are suspicious hemodynamic responses.

Recommendation grade: IIa.

Evidence level: B.

The routine use of CPET to stratify risk of sudden death in apparently healthy children and adolescents does not seem especially useful.

Recommendation grade: III.

Evidence level: B.

2.3.5. Echocardiogram

An echocardiogram may play a relevant role in PPS since it can diagnose the main diseases involved in SD in athletes (Table 5). It can also help distinguish between physiological alterations in the athlete's heart and HCM painlessly, quickly and at a relatively low cost. However, it should be reserved for cases where there is a clinical/family history of heart disease or when a physical examination gives suspicious results, as well as when changes in resting ECG indicate cardiomyopathy.[69] Furthermore, in known cases of congenital heart disease, especially those of low complexity, when physical activity and even high-performance sports are not contraindicated, a periodic ECG helps evaluate the evolution of the condition in question and its correct management. Doppler echocardiogram associated with physical effort is important when verifying cardiac function during exercise, and it can aid in diagnosis and determining the course of treatment, especially for HCM patients.[28]

2.3.6. Recommendations

The European Society of Cardiology, in light of the findings of Corrado et al.[6] (the previously mentioned 25-year Italian follow up of athletes), has established a screening program

Table 5 – Main causes of sudden death in athletes

Age < 35	Age > 35
Hypertrophic cardiomyopathy	Coronary artery disease
Arrhythmogenic right ventricular dysplasia	
Anomalous origin of coronary arteries	
Myocarditis	
Valve disease	
Pre-excitation syndrome	
Conduction system disease	

for individuals between 12 and 35 years of age that includes an initial examination consisting of family history, a physical examination, and 12-lead ECG. Additional tests will only be performed after positive findings in initial evaluation.[70] Using ECG in programs for young asymptomatic athletes (12 to 35 years of age) has proven to be a high-cost strategy, and no population studies with adequate follow-up have proven its efficacy. Although this test is considered the most practical method for detecting cardiac structural changes, its use as a screening tool is generally reserved for elite athletes, especially in clubs or teams with the necessary financial resources. ECG may indicate the presence of congenital abnormalities in athletes, even when the results are normal. However, since most of these changes are not implicated in the genesis of SD, its use has not been routinely recommended, especially given that its diagnostic power in asymptomatic athletes with normal physical examination results is very low.[71]

When CAD is suspected in the initial evaluation, further investigation should be carried out with more accurate examinations: ECG with physical or pharmacological stress, myocardial scintigraphy with physical or pharmacological stress or dynamic cardiac MRI. Studies have suggested introducing a limited echocardiogram that is restricted to the two-dimensional mode, which can be performed in 5 minutes. The results showed good sensitivity and specificity for diagnosing various SD-related conditions in athletes, especially HCM,[72] which is implicated in more than 30% of SD cases in young athletes. At the present time, ECG is considered a confirmatory diagnostic modality to be performed after suspicious results are found in PPS.

Recommendation grade: I.

Evidence level: A.

There is no evidence to support the use of routine ECG in population screening programs for asymptomatic individuals.

Recommendation grade: III.

2.3.7. Other Complementary Tests

The use of other diagnostic tools, whether laboratory, graphic, imaging, invasive or non-invasive, should comply with clinical criteria and scientific evidence already established in the literature, depending on the PPS findings.

2.3.8. Final Recommendations

The recommendations in Table 6 can be used as a population screening research strategy. Associations and governing councils of professional athletes currently have their own protocols, given the legal and economic issues involved. PPS based on initial clinical consultation and 12-lead ECG can help identify athletes at greater risk of SD.

3. Genetic Evaluation and Exercise

According to consensus and expert opinion, genetic assessment is not routinely recommended for athletes. If the question of whether a 12-lead resting ECG should be included in routine PPS is still being discussed, it follows that there must be a pressing reason for genetic investigation of an athlete.

There are two occasions when genetic evaluation is especially well indicated when:[74]

a) there is a family history of hereditary heart disease (cardiomyopathy, channelopathies, aortic diseases) or suspicion thereof (episodes of syncope, arrhythmias, cardiac arrest/SD). In such cases, it is important to point out that genetic study must first be performed on the individual or an effected family member. When a causal mutation has been detected, then the other family members should be studied (including the athlete if not initially tested);

b) the athlete has a phenotype that strongly indicates an inherited disease (signs, symptoms and/or test results suggestive or compatible with a specific disease).[75,76]

Clinical genetic assessment should always be the first step before genetic testing is conducted. This assessment should include a thorough anamnesis of family history as well as a complete physical examination. Family history should include aspects such as the age of symptom onset, the activities that triggered the symptoms, diagnosed diseases, and the number of affected relatives and degree of kinship. Thus, a thorough understanding the family tree or "family pedigree" will guide the investigation toward the affected side of the family. When there are no suspect first-degree relatives, the study should be extended to another generation if there is a great suspicion of inherited heart disease.

More recent studies have highlighted the role of genetic study in the "molecular autopsy" of individuals without anatomical changes who died suddenly.[77-79] A comprehensive analysis of genes related to SD in subjects who died suddenly during exercise has identified potential causative variants. However, the effects of many genetic variants are still undetermined and further study is needed to understand their clinical significance. However, comprehensive genetic analysis of individuals who died during exercise could determine potential causative variants and help identify relatives at risk.[77] Specific recommendations about genetic analysis are addressed in the sections on inherited diseases in this Guideline.

3.1. Positive Genotype and Negative Phenotype

Individuals can be considered to have positive genotype/negative phenotype when:

- They have a potentially pathogenic mutation.
- Complementary exams indicate no clinical manifestations or structural/electrical changes in the heart.

The question is whether these subjects are at increased risk of SD, even without the signs of structural heart disease. This is of paramount importance because in certain cases the adrenergic stress of intense or competitive exercise can trigger complications and SD. Reviewing the family history of inherited heart disease can be a great challenge, which is mainly due to variable expressivity (i.e., severity frequently varies, even within the same family), as well as to reduced penetrance (i.e., some patients may never develop the disease).[80] Many investigated diseases are autosomal dominant, although some are due to *de novo* mutations. The age of onset may also vary, with patients remaining asymptomatic over a long period of the disease, which makes initial clinical diagnosis difficult.[76]

When faced with this diagnostic challenge, we must determine that the phenotype is truly negative. A thorough cardiologic investigation with ECG, echocardiogram, cardiac magnetic resonance, Holter monitoring, and provocative tests (exercise or drugs) should be performed when genetic disease is suspected.[81] The current European PPS recommendations state that after a detailed questionnaire (including symptoms and family history) and clinical examination, priority should be given to 12-lead ECG. Athletes with two or more "borderline ECG findings" or any "abnormal ECG findings" require further investigation.[76]

Table 6 – Recommendations by age group and competitive level

	Leisure	Amateurs	Professionals
Children/adolescents	Initial evaluation + 12-lead ECG	Initial evaluation + 12-lead ECG	Initial evaluation + 12-lead ECG
18-35 years	Initial evaluation + 12-lead ECG	Initial evaluation + 12-lead ECG	Initial evaluation + 12-lead ECG
35-59 years	Initial evaluation + CAD risk evaluation + 12-lead ECG + (consider functional test)	Initial evaluation + CAD risk evaluation + 12-lead ECG + (consider functional test)	Initial evaluation + CAD risk evaluation + 12-lead ECG + (consider functional test)
> 60 years	Initial evaluation + 12-lead ECG + functional test	Initial evaluation + 12-lead ECG + functional test	Initial evaluation + 12-lead ECG + functional test

12-lead ECG: resting 12-lead electrocardiogram; CAD: coronary artery disease.

The European Society of Cardiology reported that SD occurs three times more in athletes (2.3 per 100,000 individuals) than non-athletes (0.9 per 100,000 individuals).[76] There have been a limited number of SD cases in asymptomatic HCM patients. Five cases of premature SD have been reported in which the autopsy revealed no macroscopic HCM or mutation of the TNNT2 gene.[82] Two patients were found with ventricular fibrillation and normal hearts who subsequently developed HCM and MYH7 gene mutation.[83] In one ARVD case, a 13-year-old mutation carrier in the non-clinically affected DSP (desmo- toquine) gene suffered SD two years after the genetic study.[84] In an Italian study of 12,500 athletes, only one case of SD due to ARVD was not clinically detected.[85] In the context of dilated cardiomyopathies, a case of SD was also described in a 35-year-old female with LMNA gene (c908-909delCT) mutation in whom no structural disease or conduction disorder was detected.[86]

In assessing positive genotype/negative phenotype in the early development of cardiomyopathy, it is important to remember that intense sports activity can worsen the prognosis for mutation carriers, as in ARVD and HCM.[87,88]

The current recommendations are controversial, being based on expert consensus and the available few longitudinal studies. Table 7 shows general differences between U.S. and European recommendations. For example, the American Heart Association and American College of Cardiology state that patients with HCM-positive genotypes may participate in competitive sports, as long as two-dimensional echocardiogram indicates they are asymptomatic and without evidence of LVH and they have no family history of HCM-related SD (Class IIa; Evidence level C). However, athletes with clinically expressed and diagnosed HCM should not participate in most competitive sports.[89] It is our opinion that future studies should evaluate the pathogenic potential and negative effects of intense exercise on individuals with positive genotypes. Finally, we believe that disqualification should only be used as a final intervention and that adequate information and decision-making (by the family, athlete, coach, sponsor, etc.) should be sought.

4. Individuals with Cardiomyopathies and Myocarditis

4.1. Hypertrophic Cardiomyopathy

HCM is one of the major causes of sports-related SD in individuals under 35 years of age.[90,91] The U.S. National Registry of Sudden Death in Athletes evaluated the causes of SD in competitive athletes between 1980 and 2011. Of 2,406 total deaths identified in young athletes (mean age: 19 years), 842 had some cardiovascular diagnosis. HCM was the most common cause of SD, occurring in 36% of the cases.[92] However, its contribution to SD in athletes has been systematically overestimated. Recent evidence from a meta-analysis[92] indicates that HCM caused 10.3% of athlete deaths, while 27.5% had structurally normal hearts.

HCM is an autosomal dominant genetic disease characterized by myofibrillar disarray in myocytes, accompanied by hypercontractility and asymmetrical hypertrophy (with or without obstruction of the outflow tract), which are unexplained by pressure, volume overload, or another underlying systemic condition. Ventricular hypertrophy (determined by an imaging method) > 15 mm in any segment with no other apparent cause is highly suggestive of HCM.[93] For hypertrophy between 13 and 14 mm, other factors, such as family history, specific ECG changes, symptoms, another imaging method and even genetic evaluation should be considered in the differential diagnosis.[94] In first-degree relatives of a HCM patient, hypertrophy greater than 13 mm is also highly indicative of this disease.[91] Hypertrophy related to pressure overload, physical training and basal septal hypertrophy in the elderly should be considered in the differential diagnosis.

HCM patients may be totally asymptomatic or present symptoms such as lipothymia, syncope, dyspnea, palpitations or angina, especially when related to increased myocardial demand or obstruction of the outflow tract, as occurs during exercise. SD in these patients occurs primarily due to ventricular arrhythmias, although other complications such as supraventricular arrhythmias (with or without pre-excitation),

Table 7 – U.S. vs. European recommendations for athletes with positive genotypes

Heart Disease	American Heart Association/American College of Cardiology	European Society of Cardiology
Cardiomyopathies (HCM, DCM, ARVD)	No restrictions (e.g., asymptomatic and without left ventricular hypertrophy)	Competitive sports prohibited: only non-competitive sports and leisure activities permitted
Long QT	No restrictions (except QTL1 and swimming)	Competitive sports prohibited: only non-competitive sports and leisure activities permitted
Catecholaminergic tachycardia	Competitive sports prohibited	Competitive sports prohibited
Brugada syndrome	No restrictions	No restrictions
Marfan Syndrome	Mild-to-moderate activity only (no family history of aortic dissection or SD)	Competitive sports prohibited

HCM: hypertrophic cardiomyopathy; DCM: dilated cardiomyopathy; ARVD: arrhythmogenic right ventricular dysplasia.

advanced atrioventricular block, asystole, and myocardial infarction may also be the cause of this undesired event.

4.1.1. Genetics and Hypertrophic Cardiomyopathy

At present, at least 20 genes have been implicated in the genesis of this disease,[95] and more than 1,700 mutations related to contractile myocardial protein have been discovered. Mutations in at least 11 different genes that code for sarcomeric proteins have been identified in up to 70% of family cases.[96,97] Mutations of genes in the beta-myosin heavy chain (MYH7) and myosin-binding protein C (MYBPC3) are the most frequent. Together, MYBPC3 and MYH7 account for up to half of all clinically recognized cases of HCM, and make up at least 75% of the index cases in which a mutation is identified.[98] Other less frequent mutations are related to the troponin I and troponin T genes (TNNI3, TNNT2) and alpha-tropomyosin-1 (TPM1), whose frequency is often less than 5%. Still less common (less than 1%) are mutations of muscle LIM protein (CSRP3), troponin C (TNNC1) and titin (TTN). Genetic phenotypes such as Fabry disease, amyloidosis, Danon disease and Friedreich ataxia should also be considered.[95] Mutations in troponin genes, although less common (15% to 30%), have been most closely associated with SD,[99] including, in some reports, individuals with no phenotypic manifestations of the disease.

Genetic counseling by a multidisciplinary team experienced in genetically determined heart disease is recommended for individuals with HCM.

Recommendation grade: I.

Evidence level: C.

Genetic sequencing study for patients with clinically diagnosed HCM (index cases).

Recommendation grade: I.

Evidence level: B.

Assessment for specific mutations in direct relatives of patients diagnosed with genetically determined HCM.

Recommendation grade: I.

Evidence level: B.

4.1.2. Complementary Exams in Hypertrophic Cardiomyopathy

4.1.2.1. Electrocardiogram

ECG should be performed in all patients with suspected HCM.

Recommendation grade: I.

Evidence level: B.

About 90% of patients with HCM have ECG changes, with ST-segment and T-wave being the most common. Athletes with HCM have a higher prevalence of T-wave changes (especially deep T-wave inversion in the lateral leads) and ST-segment changes than non-athletes with the disease. In addition to these changes, there is left atrial enlargement, which is identified by a prolonged P-wave duration (> 120 ms) in leads I or II with a negative P-wave portion ≥ 1 mm in depth and ≥ 40 ms in duration in the V1 lead. Complete left bundle branch block may also be suggestive of HCM. In the past, some ECG changes in athletes were considered potentially pathological, such as: left atrial enlargement and left axis deviation, T-wave inversion confined to V1-V4 preceded by J-point elevation (especially in blacks), Q-waves ≥ 3 to 4 mm (with an amplitude less than one-quarter of the R-wave and a duration < 0.04 s). However, such changes are now considered physiological responses in the athlete's heart, and do not require additional clinical evaluation.[100,101]

4.1.2.2. Echocardiogram

This exam play a fundamental role in HCM assessment. In addition to the degree of hypertrophy, they can determine the gradient between the left ventricle (LV) and the aorta, as well as the presence of mitral valve abnormalities: systolic anterior motion and altered patterns of diastolic function.[93,102] Echocardiograms also have an important role in differentiating between hypertrophy due to HCM and that due to physical training (ventricular hypertrophy in the athlete's heart). A variety information, such as the pattern and distribution of hypertrophy, parietal thickening, cavity size, assessment of diastolic function by tissue Doppler imaging, and family history are required.[103] When not clinically differentiated, ECG, echocardiograph, functional or other imaging methods, such as serial ECG, may be useful when evaluating athletes with suspected HCM before and after a detraining period (Table 8).[104] Regarding prognosis, LV wall thickness > 30 mm is a major risk factor for SD, especially in adolescents and young adults.[105] A gradient above 50 mmHg between the LV and the aorta is also associated with worse prognosis.[106]

When comparing athletes and non-athletes with HCM from an echocardiographic point of view, athletes present the following characteristics: lower LV wall thickness, higher left ventricular end-final diastolic diameter and higher ejection fraction.

4.1.2.2.1. Transthoracic Doppler Echocardiogram

Confirm clinical suspicions of HCM by determining parietal thickening and whether there is a dynamic gradient.

Recommendation grade: I.

Evidence level: B.

Investigate the presence of HCM in first-degree relatives.

Reassessment of clinical evolution, as well as therapeutic interventions.

Recommendation grade: IIa.

Evidence level: C.

Annual reassessment of family members of HCM patients aged 12 to 18 years.

Table 8 - Factors indicative of athlete's heart syndrome (vs. HCM) in athletes with left ventricular hypertrophy in the "gray zone" (i.e., wall thickness: 13-15 mm)

Clinical
No family history
Absence of diffuse T-wave inversion in ECG
Nuclear magnetic resonance
Homogeneous distribution of left ventricular hypertrophy
No late gadolinium enhancement (fibrosis)
Echocardiogram
Increased left ventricular diameter (LVDD > 55 mm)
Symmetrical hypertrophy (septum, posterior wall, apex and base)
Normal diastolic function (E/A ratio > 1, peak velocity to E' > 11.5 cm/s)
Hypertrophy regression after detraining
No HCM-causing mutations found in genetic analysis

LVDD: left ventricular diastolic diameter; ECG: electrocardiogram; HCM: hypertrophic cardiomyopathy.

In individuals over 21 years of age, reevaluation should be done every 5 years.

Tissue Doppler imaging should be performed to differentiate HCM from physiological or pathological cardiac hypertrophy (e.g. hypertension).

An exercise echo stress test should be used in asymptomatic patients who do not show significant gradients at rest or with the Valsalva maneuver.

Recommendation grade: IIa.

Evidence level: C.

4.1.2.2.2. Transesophageal Doppler Echocardiogram

Patients with an inadequate transthoracic window.

Transesophageal Doppler echocardiogram is used to assess valve damage and the mechanism and magnitude of mitral regurgitation when this is unclear after transthoracic ECG.

Intraoperative evaluation for myomectomy and alcohol septal ablation.

Recommendation grade: I.

Evidence level: B.

To clarify the mechanism of atypical mitral regurgitation.

Recommendation grade: IIa.

Evidence level: B.

4.1.2.3. Cardiac Magnetic Resonance Imaging

Cardiac magnetic resonance imaging (CMRI) is used to evaluate patients with suspected HCM when an ECG is inconclusive. Although ECG is the first imaging choice for patients with suspected HCM, this method may be limited by poor acoustic windows, particularly for areas such as the cardiac apex.[107] CMRI can also be used in highly suspicious cases that are not confirmed by ECG. Its excellent spatial resolution provides exclusive information about cardiac muscle and tissue, helping in the differential diagnosis of secondary causes of hypertrophy, such as amyloidosis and sarcoidosis. This examination allows the visualization of subtle changes in the thickness and contractility of the LV over time, as well as the detection of fibrotic areas, and recent studies have reported the presence and amount of fibrosis with prognosis.[107,108]

CMRI is used to evaluate athletes with ECG abnormalities that are suspicious of HCM and inconclusive ECG findings.

Recommendation grade: I.

Evidence level: B.

CMRI should be used for myocardial fibrosis screening in every athlete with suspected HCM.

Recommendation grade: IIa.

Evidence level: B.

4.1.2.4. Exercise Tests and Hypertrophic Cardiomyopathy

The exercise stress testing is an independent means of identifying patients at increased risk of SD. Since the presence of marked ST-segment changes in HCM patients may indicate ischemia but not necessarily heart disease, the exercise stress testing has little diagnostic value. However, it could be a prognostic marker to be taken into consideration, especially when associated with expired gas measurements (CPET).[109,110]

For these patients, a ramp protocol should be used first. This test avoids sudden changes in the recruitment of neuromuscular motor units and the metabolic changes associated with incremental protocols due to the constant and continuous increase of external work. The slope of the ramp should be individualized to last, preferably, from 8 to 12 minutes.[109]

4.1.2.4.1. Exercise Testing Recommendations for Patients with Hypertrophic Cardiomyopathy

The exercise stress testing is recommended for asymptomatic HCM patients who do not present high risk criteria as an associated element in prognostic stratification.

Exercise stress testing is recommended for asymptomatic patients without high risk criteria, but who wish to participate in recreational physical activity.

It is an additional element in differential diagnosis between athlete's heart syndrome and HCM.

Recommendation grade: I.

Evidence level: B.

The exercise stress testing can be used for patients with doubtful symptoms that are not associated with other high-risk criteria (preferably CPET).

It can be used to assess functional capacity and heart rate response to exercise in patients with an implanted defibrillator who wish to participate in low-intensity physical activity.

Recommendation grade: IIa.

Evidence level: C.

In athletes with high risk criteria (symptomatic), it can facilitate differential diagnosis between HCM and physiological hypertrophy.

Recommendation grade: III.

4.1.2.4.2. The Role of Maximal Cardiopulmonary Exercise Testing in Hypertrophic Cardiomyopathy

A maximal CPET can stratify HCM patients regarding cardiovascular morbidity and mortality, helping guide treatment. In athletes who are in the "gray zone" between physiological hypertrophy and the pathological hypertrophy of HCM, measuring oxygen consumption and peak oxygen pulse with a CPET can be of great assistance. In general, highly trained athletes have values between 55 and 70 $mL.kg^{-1}.min^{-1}$. Sharma et al.[111] demonstrated that healthy athletes can actually achieve significantly higher peak oxygen consumption than athletes with HCM (66.2 $mL.kg^{-1}.min^{-1}$ vs. 34.3 $mL.kg^{-1}.min^{-1}$). Since there was no overlap between groups, the researchers postulated a cutoff of 50 $mL.kg^{-1}.min^{-1}$ to discriminate between the pathological hypertrophy of HCM from the dynamic component of the athlete's heart.

Finally, since there are conflicting data regarding CPET and specific predictions of SD in patients with HCM based on VE/VCO_2 slope, neither VE/VCO_2 slope nor peak VO_2 are currently used in risk stratification.[112]

Recommendation grade: IIa.

Evidence level: B.

4.1.3. Sports and Hypertrophic Cardiomyopathy

Why is there a low prevalence of HCM among high-level athletes? The response seems to be related to a natural selection process that excludes individuals with HCM-related functional and structural alterations from the high-intensity training required to become a professional. So, is being a competitive athlete with HCM synonymous with SD? The answer is no. We all know cases of athletes who were diagnosed with this disease well into their professional careers or after they had already retired. The problem is that intense exercise can trigger severe arrhythmias, increased left ventricular outflow obstruction and/or ischemic compression in small blood vessels (possible fibrosis due to repetitive ischemia) during training and competition.

Based on the premise that strenuous exercise can be an important trigger for SD, athletes with a probable or unequivocal diagnosis of HCM should be excluded from most competitive sports. However, it should be pointed out that only a minority of HCM patients have SD or cardiac arrest during exercise.[113] This recommendation is independent of age, sex, phenotype, symptoms, LV outflow tract obstruction, drug treatment, septal ablation, or pacemaker or implanted defibrillator.[89] Although criteria have been suggested[114,115] for establishing SD risk factors in HCM patients (Table 9), it should be pointed out that such criteria should be used with caution, since they do not take important HCM-related aspects into account, such as genetics and CMRI results.

Individuals classified as low risk (especially those without a gradient at rest or during effort)[116] may participate in sports such as golf, billiards, bowling and shooting (group IA). Recreational sports that require high intensity or abrupt changes of intensity are not recommended. Individuals with positive genotype/negative phenotype (without clinical evidence of disease) may participate in sports, provided they are assessed periodically, since the chance of SD is directly related to the presence of hypertrophy and fibrosis. A recent study evaluated vigorous exercise in HCM patients and individuals with positive genotype/negative phenotype. Exercise was associated with higher cardiac volumes and better diastolic function, but not with a higher incidence of ventricular arrhythmias.[117]

Participation in competitive sports for clinically diagnosed HCM patients.

Recommendation grade: III.

Evidence level: B.

4.2. Arrhythmogenic Right Ventricular Dysplasia

ARVD is a cardiac muscle disease of genetic origin characterized by changes during the formation of desmosomes. It is clinically manifested by the replacement of myocardial tissue with fatty and/or fibrous tissue, generally affecting the right ventricle and with more pronounced clinical manifestations when the apical septum of the LV is affected. Mutations in non-desmosomal genes have also been identified, such as filamin C, TMEM43 and phospholambam, especially in cases involving the LV.[118,119] Among athletes from the Veneto region of Italy, ARVD is a major cause of SD: one study found a five-fold increase in SD risk for young athletes who participated in competitive sports.[120] Based on recent data, ARVD is ranked as the third most frequent cause of SD the United Kingdom.[88] ARVD is a rare condition in the

Table 9 – Risk factors for sudden death in HCM patients

Greater risk factors
Cardiorespiratory arrest survivor
Spontaneous sustained ventricular tachycardia
Family history of SD in patients < 40 years
Unexplained syncope or pre-syncope
Interventricular septum > 30 mm
Minor risk factors
Abnormal blood pressure response to exercise
Patients under 30 years of age
Nonsustained ventricular tachycardia

HCM: hypertrophic cardiomyopathy; SD: sudden death.

general population, with an estimated prevalence of 1 in 5,000, although in some European countries, such as Italy and Germany, the prevalence is 1 in 2,000.[121] Diagnosis can be challenging given the need to exclude other disorders that may present with similar signs and symptoms.[122] The main clinical manifestations are palpitations, syncope, chest pain, complex ventricular arrhythmias and SD. Since highly trained athletes may have right ventricular (RV) hypertrophy, in addition to a variety of changes in depolarization, repolarization, and nerve conduction, a differential diagnosis between "athlete's heart syndrome" and ARVD should always be performed. Since an echocardiogram may have technical limitations with respect to RV images, its structural and functional analysis may be impaired. However, akinesia, dyskinesia or RV aneurysms associated with the dilation of this chamber are among the most important criteria in the revised classification. CMRI is a noninvasive imaging technique that has become the main tool for diagnosing ARVD. Segmental or global dysfunction of the RV or a substantial increase in this cardiac chamber, associated with myocardial thinning and presence of late enhancement (fibrosis and/or edema), supports a diagnosis of ARVD.[121,123] A 12-lead resting ECG and Holter monitoring can help with diagnosis, principally by detecting arrhythmias such as branch block pattern ventricular tachycardia, inverted T-waves in the right precordial leads (V1 to V3) and epsilon waves (present in 30% of ARVD patients). Family history should always be investigated, and a confirmed case in a first degree relative is a major criterion. Thus, suspected first-degree cases or confirmed second-degree cases are minor criteria. In especially difficult cases, a biopsy of the RV can be performed. The final clinical diagnosis may not be simple. The presence of two major criteria, one major and two minor criteria (different categories) or four minor criteria (different categories) confirm the diagnosis.

New evidence suggests that ECG adaptations, such as isolated right ventricular overload or T-wave inversion from V2 to V4 (associated with right axis right deviation in black athletes) are related to benign structural adaptations of the heart in competitive athletes. In these individuals careful investigation for the other criteria is necessary, and research on family history is of fundamental importance.[124]

4.2.1. Diagnosis and Management of Athletes with Suspected Arrhythmogenic Right Ventricular Dysplasia

4.2.1.1. Echocardiography

In athletes with a family history of ARVD or with ECG changes suggestive of ARVD.

Recommendation grade: I.

Evidence level: C.

4.2.1.2. Cardiac Magnetic Resonance Imaging

CRMI should be used when there is a strong suspicion, despite a non-diagnostic ECG or in cases where an echocardiogram could not adequately assess the RV.

Recommendation grade: I.

Evidence level: C.

Competitive physical activity in patients with a definite or probable diagnosis of ARVD.

Recommendation grade: III.

Evidence level: B.

There is sufficient evidence that exercise can trigger SD in individuals with ARVD. Probable causes include: increased sympathetic tone and even greater dilation of the ventricular chambers during exercise, which, associated with myocardial fibrosis, leads to the appearance of complex arrhythmias.[125,126] Adhesion between the cells could be compromised by genetic factors, and in the meantime, mechanical stress from exercise can lead to cardiomyocyte apoptosis and worsening of the disease.[127,128] Group 1A sports can be allowed on an individual basis. More recent studies have confirmed the deleterious role of sustained vigorous physical activity (> 6 metabolic equivalents) in the occurrence of ventricular arrhythmias in ARVD patients, and reducing exercise after diagnosis is associated with a lower occurrence of severe arrhythmias.[129,130]

4.3. Myocarditis

Myocarditis has a heterogeneous clinical profile and, although not very prevalent, it is the probable cause of 5 to 22% of SD cases in athletes, depending on age and region.[88,131] This disease is characterized by an inflammatory process with consequent non-ischemic degeneration and necrosis of the myocardium. Generally, myocarditis is the result of an infection (viruses, bacteria, fungi, protozoa), but it may be associated with substance use or autoimmune diseases.[132] SD may occur in the acute phase (when a myocarditis patient does not abstain from sports for 6 months), or even in the chronic phase, when there is already scar tissue in the myocardium, which is a consequence of complex arrhythmias triggered by an unstable electrical substrate. In this phase, exercise may be the arrhythmogenic trigger due to increased venous return and muscle fiber stretching from physical activity.[133,134]

In athletes, the main symptoms are palpitations, precordialgia, dyspnea, fatigue and syncope. ECG changes include ventricular arrhythmias, ST-T segment changes, and rhythm and conduction disorders. It may evolve with left ventricular enlargement due to the disease, hypertrophy due to physical training or a combination of both.[135,136] CMRI and myocardial biopsy (although less common in our country) may facilitate diagnosis. Due to their prevalence in Brazil, we point out that myocarditis may also be caused by the dengue and HIV viruses, as well as by Chagas' disease.

4.3.1. Recommendations for Athletes with Myocarditis

Competitive physical activity for patients with active myocarditis.

Recommendation grade: III.

Evidence level: B.

Athletes diagnosed with myocarditis should be advised against practicing any competitive sports and should undergo a period of convalescence. Although there is no consensus,

many experts recommend that this period be at least six months after the onset of clinical manifestations. However, some experts have been more "liberal", recommending shorter periods of convalescence.

These athletes may resume training and competition after:

- Left ventricular function, ventricular wall motion, and cardiac dimensions return to normal values (based on stress and resting echocardiography and radionuclide imaging).
- Complex or frequent forms of ventricular and supraventricular arrhythmias and clinically relevant arrhythmias are absent.
- Inflammatory and heart failure markers are normalized.
- Resting ECG is normalized, although the persistence of ST-segment changes alone should not impede the athlete's return to training and competition.

4.4. Dilated Cardiomyopathy

Dilated cardiomyopathy (DCM) has an estimated prevalence of 40 cases per 100,000 individuals. It is defined as a myocardial disease, characterized by LV dilation and global systolic dysfunction, and there may be overlapping segmental abnormalities with increased myocardial mass. DCM includes disorders of genetic origin, disorders due to infection, inflammation, exposure to toxic substances or metabolic diseases, and disorders of idiopathic origin (although at least 40% of disorders classified as idiopathic are, in fact, of genetic origin). Up to 40 genes have been identified, with proteins from several cellular structures being affected (sarcomere, sarcolemma and intercellular junction).[137] DCM patients vary widely in clinical presentation and hemodynamics.[138]

Long-term aerobic training may lead to changes in cardiac morphology, including increased LV cavity size and mass. Increased cavity size may produce a greater systolic volume and thus, the resting ejection fraction may be at the lower limit of normal or slightly reduced. In this context, it is important to differentiate between LV increase due to systematic training and that due to DCM.[138]

4.4.1. Complementary Examinations for Dilated Cardiomyopathy

4.4.1.1. Exercise Stress Testing and Cardiopulmonary Exercise Testing

Although exercise performance may only be slightly reduced in young DCM patients, arrhythmias are usually present at a very early stage of the disease (including supraventricular and ventricular tachyarrhythmia, as well as conduction delays).

Recommendations for exercise stress testing and CPET[38]	Recommendation grade	Evidence level
Exercise stress testing or CPET to assess individuals with known or suspected ventricular arrhythmias during exercise, regardless of age	I	C
Exercise stress testing to assess DCM severity	IIb	B
CPET to assess DCM severity	Ia	B
Exercise stress testing to identify pathophysiological mechanisms and clarify symptoms	IIb	B
CPET to identify pathophysiological mechanisms and clarify symptoms	I	B

CPET: cardiopulmonary exercise testing.

4.4.1.2. Echocardiogram

An echocardiogram is more sensitive than ECG for diagnosing LVH and accurately quantifies LV mass. Thus, cardiac abnormalities detected by an echocardiogram have additional predictive value.[138,139]

Recommendations for performing ECHO	Recommendation grade	Evidence level
Assessment of patients with suspected DCM or heart failure	I	B
Assessment for differential diagnosis between DCM and "athlete's heart syndrome"	I	B

Echo: echocardiogram.

4.4.1.3. Cardiac Magnetic Resonance Imaging

CMRI can clearly and effectively demonstrate and quantify anatomical and functional changes in DCM. This examination has been found useful for evaluating HF patients by accurately calculating the function of both ventricles. It also helps distinguish idiopathic DCM from other forms of ventricular dysfunction, such as ventricular dysfunction caused by coronary artery disease.[140] In addition, the method makes an important contribution to prognostic evaluation. Determining the presence and extent of fibrosis by myocardial late enhancement has good prognostic value, since it represents a substrate for arrhythmia and SD. Further research is needed to confirm the role of CMRI in the prognostic stratification of DCM, especially when defining the arrhythmic risk of these patients.[141]

4.4.2. Sports and Dilated Cardiomyopathy

DCM is an uncommon myocardial disease that deserves consideration because it is a potential cause of SD in athletes.[142-144] In reality, there is little information on the risk of SD during physical activity or the relative risk of physical training for athletes with DCM. Thus, it is not clear whether asymptomatic DCM patients are at risk of SD during physical activity or competitive sports, since tachyarrhythmias are much more common in patients with more advanced disease, i.e., with explicit cardiac symptoms and reduced ejection fraction.

4.4.2.1. Recommendations for Athletes Diagnosed with Dilated Cardiomyopathy

Until further information is available, symptomatic DCM athletes should not participate in competitive sports except for those in class IA and selected cases.

Recommendation grade: III.

Evidence level: B.

Athletes with a definite DCM diagnosis but a low risk profile (asymptomatic, no family history of SD, slightly reduced ejection fraction, normal pressure response to exercise and no complex ventricular arrhythmias) could participate in low-to-moderate intensity dynamic exercise and low-intensity static exercise (recommendations IA and IB).

These recommendations apply to competitive exercise. Physical activity of a therapeutic nature (cardiac rehabilitation) is indicated for all DCM and heart failure patients.[145]

4.5. Non-Compacted Cardiomyopathy

Non-compacted cardiomyopathy is a rare cardiac disease that has been recently recognized. It is due to embryonic interruption of myocardial compaction and is characterized by segmental thickening of the LV walls that consists of two layers: a compacted epicardial layer and an endocardial layer with marked trabeculations and deep intratrabecular recesses that are filled by blood flow. In non-compacted cardiomyopathy, left ventricular capacity is usually increased and the ejection fraction is reduced.[146,147]

Although considered a rare condition by some researchers, the incidence and prevalence of non-compacted cardiomyopathy are uncertain. Using echocardiography, a study at a large institution found a prevalence of 0.05%. Among HF patients, the prevalence of non-compacted cardiomyopathy is 4%.[148] Diagnosis is quite difficult due to the lack of clear criteria, as well as the condition's heterogeneous clinical spectrum and the usual need for MRI for a reliable diagnosis.

This disease may be asymptomatic or present with HF, ventricular and/or atrial arrhythmias, pre-excitation, thromboembolic events or SD. However, the risk of adverse consequences, including SD, seems to be associated with the degree of LV systolic dysfunction and/or ventricular tachycardia.[149] There are no universally accepted criteria or precise guidelines for morphological diagnosis. However, a non-compacted/compacted myocardium ratio of > 2.1:1 at the end of systole in an echocardiogram or of 2.3:1 at the end of systole in CMRI is currently the most widely accepted criterion.[150]

Non-compacted cardiomyopathy can be found alone or combined with congenital heart defects, neuromuscular disorders or as part of genetic syndromes.[149] It is a genetically heterogeneous disease, with familial or sporadic cases, and with pathogenic mutations involving the cytoskeleton, mitochondria, sarcomeres and z-line proteins. Therefore, different forms have been described: autosomal dominant, autosomal recessive, X-linked, and with mitochondrial patterns of inheritance, although the most common form has an autosomal dominant trait.[146]

4.5.1. Sports and Non-Compacted Cardiomyopathy

Neither the extent to which physical training can alter non-compacted cardiomyopathy nor the prevalence of non-compacted LV morphology among healthy athletes have been determined.[151,152] Since forensic reports of SD in young athletes do not include non-compacted cardiomyopathy as a possible cause, it is not possible to apply risk stratification strategies for new patients with this disease.

Recent studies have found a higher prevalence of increased LV trabeculation among athletes than controls (18.3% vs. 7%). It is believed that these abnormalities represent a non-specific epiphenomenon that increases with higher image resolution in echocardiography. In addition, increased LV trabeculation or isolated echocardiographic criteria for cardiomyopathies are likely to be of little significance and may be a part of the athlete's heart.[153,154] Thus, not all athletes with isolated ventricular non-compaction should be diagnosed with non-compacted cardiomyopathy. Therefore, functional parameters such as ejection fraction must be considered in patient management.[154]

4.5.1.1. Recommendations for Athletes Diagnosed with Non-Compacted Cardiomyopathy

Athletes with an unequivocal diagnosis of non-compacted cardiomyopathy and compromised systolic function, major ventricular tachyarrhythmias in Holter monitoring or at an exercise testing or a history of syncope should not participate in competitive sports, with the possible exception of low-intensity sports (class IA), at least until more clinical information becomes available.

Recommendation grade: III.

Evidence level: C.

4.6. Chagas Disease

Chagas disease continues to be one of the most important causes of non-ischemic cardiomyopathy in Latin America. Approximately 8-10 million people are estimated to be infected with *Trypanosoma cruzi*,[155] and this protozoa is responsible for approximately 12,000 deaths per year.[156] The disease usually manifests itself in 30% to 40% of those infected, and clinical findings usually appear 10 to 30 years after initial infection.[157] Cardiac arrhythmias and SD are common and may occur at any stage of progression, even in individuals without significant structural disease.[158,159] Sustained ventricular tachycardia is the main cause of SD, and is associated with LV dysfunction, syncope and non-sustained ventricular tachycardia in Holter monitoring or the exercise testing.[160,161] In addition, sinus node dysfunction, atrioventricular and intraventricular conduction disorders are common findings in patients with Chagas disease and may progress to complete atrioventricular block. Few studies have evaluated the risk of SD in Chagas patients during intense exercise, and a lack of symptoms does not exclude the presence of cardiomyopathy, even in high-level athletes.[162] Diagnosis involves epidemiological and serological evaluation (immunofluorescence). ECG and echocardiogram facilitate diagnosis of cardiomyopathy and conduction disorders. An exercise stress testing or a CPET, MRI, Holter monitoring and even electrophysiological study can more accurately assess the risk of SD. The exercise recommendations are similar to those for individuals with DCM.

5. Channelopathies

5.1. Introduction

Channelopathies are inherited arrhythmogenic heart diseases that do not involve structural impairment and are caused by genetic changes that result in dysfunction of the cardiac ion channels, which leads to risk of SD.[163] The most commonly known channelopathies are long QT syndrome, short QT syndrome, Brugada syndrome, and catecholaminergic polymorphic ventricular tachycardia (CPTV)[75] Sinus node disease and Lenegre disease or conduction system disease are also examples of channelopathies.

Ion channels, the ion currents moving through these channels, proteins that attach to the membrane structure of myocardial cells, and the junctions between these structures are involved in electrical impulse formation and the synchronous transmission of these impulses throughout the heart, which generates cardiac action potential.[164,165] The performance of each of these functions is determined by different genes. Mutations in related genes cause specific dysfunctions and cause channelopathies.[166,167] The ion channels in the cell membrane allow ions to enter and exit following a voltage gradient. Genetic mutation in these channels can lead to gain or loss of function. With the recent increases in knowledge about these entities, defibrillator use and easier access to genetic evaluation, decisions shared between the medical team and the family have allowed a more permissive stance toward exercise in individuals with channelopathies.[168] Detailed recommendations on the most prevalent syndromes are described below.

5.2. Long QT Syndrome

Long QT syndrome (LQTS) is the prototype channelopathy. First described more than 50 years ago as an autosomal recessive disease, Jervell and Lange-Nielsen syndrome[169,170] includes congenital deafness, increased QTc intervals, and syncope or SD. Subsequently, an autosomal dominant form called Roman-Ward syndrome (prolonged QTc without deafness) was discovered. Several types of LQTS are currently known, which are determined by gene mutations that cause distinct changes in ventricular depolarization and repolarization.

The typical clinical features of LQTS include syncope or SD associated with increased QTc intervals and ventricular tachyarrhythmias such as torsade de pointes.[171] Typically, certain factors trigger syncope in LQTS, which are related by subtype and genotype. The most common triggers are: adrenergic activity in SQTL1, sudden awakening and an acute auditory stimulus in SQTL2 and sleeping/resting in SQTL3. However, phenotypic presentations vary widely. Carriers can be asymptomatic, have no increase in QTc interval or have syncope or SD in the first days of life. Thus, diagnostic criteria were developed to score alterations, which are divided into three main groups: clinical history, family history and ECG.[163]

5.2.1. Genetic Alterations in Long QT Syndrome

Genetic alterations are known in approximately 60% of the clinical cases of LQTS, and at least 17 genes have been associated with this clinical entity. Generally, patients have mutations in three specific genes: KCNQ1, KCNH2 or SCN5A.[172] Hundreds of mutations have already been described, with the most prevalent type being cardiac.[173] The most common mutation occurs in the KCNQ1 gene, which is responsible for more than 30% of the genetic variants and pathological mutations identified in LQTS and causes SQTL1.[173] This type of mutation causes a loss of function in the IKs potassium current,[166] which plays an important role in cell repolarization and QT interval adaptation to heart rate. SQTL5, a mutation caused by the KCNE1 gene, is much less frequent (considered rare) and is responsible for IKs loss-of-function.[166] The KCNH2 (HERG) gene, which encodes the alpha subunit of the fast potassium channels, and KCNE2, which encodes the beta subunit, are responsible for the rapid entry of potassium during phase 3 of the action potential.[174] Loss of alpha subunit function accounts for 40% of genotyped LQTS and is responsible for SQTL2.[175] SQTL3 accounts for approximately 10% of all mutations diagnosed in LQTS, due to changes in the SCN5A gene, whose functional gain produces a continuous sodium input during the plateau phase, which facilitates early depolarization in cardiac cells. Although hundreds of other mutations have been described, treatment and follow-up of LQTS patients and families are restricted to the most known forms.[176]

5.2.2. Risk Stratification in Long QT Syndrome

Genetic analysis has been widely used for risk stratification and determining specific therapeutic interventions in LQTS patients and their relatives. Since LQTS is an uncommon clinical condition and data have only been obtained through cohort studies, the evidence level for recommendations about risk stratification and treatment strategies has been limited to B. The most robust risk marker of LQTS is a previous episode of aborted SD, and its most common cause is polymorphic ventricular tachycardia, degenerating or not into ventricular fibrillation. Patients who have experienced such a condition have a 13-fold increased risk of new SD episodes. Previous syncope is also an extremely unfavorable risk marker, which could double the risk.[177]

However, the risk of having an arrhythmic event is not the same for all patients. Evidence shows that individuals with SQTL2 and SQTL3 have a higher risk of events than those with the mutations that cause SQTL1. In addition, individuals with a QTc duration > 500 ms are at higher risk than those with shorter QTc durations.[172] Mutations involving the gene segment that encodes the channel pore are also related to poorer prognosis. Therefore, once again, the value of genotyping in patients with this syndrome is clear. A family history of SD did not prove to be a higher risk marker for events.[178]

5.2.3. Recommendations for Athletes with Long QT Syndrome

A few years ago, LQTS patients were advised not to participate in competitive sports based on the understanding that they were exposed to an increased risk of SD. In 2015, Aziz et al.[179] studied more than 100 patients with a positive LQTS genotype, all engaged in some type of sports program.

Of these, 25% practiced competitive sports. Interestingly, the authors found no disease-related symptoms during sports, confirming that no event or SD had been described in those undergoing proper treatment.[179] This and other evidence led to a revision of the recommendation to universally restrict LQTS patients from competitive sports. Thus, the American Heart Association/American College of Cardiology published new eligibility recommendations for athletes with channelopathies.[180] Participation in competitive sports was reconsidered for athletes with LQTS due to a lack of evidence that asymptomatic athletes with positive genotype/negative phenotype may be at increased risk of malignant arrhythmias during sports. However, athletes must be under treatment and asymptomatic for 3 months before returning to training. Furthermore, precautionary measures, such as an automatic external defibrillator (Table 10), are advisable. However, it is important to stress that water sports are contraindicated for athletes with SQTL1.

Recommendation grade: IIb.

Evidence level: C.

Regarding water sports, Ackerman et al.[180] described the follow up of swimmers diagnosed with SQTL1 and treated with beta-blockers, many with an implantable cardioverter-defibrillator (ICD), who chose to continue competing. The incidence of events was low, with only two events (both in the same individual) among 74 patients diagnosed with LQTS. It should be noted that this individual had a history of aborted SD and was not using beta-blockers.

Beta-blockers are the basis for managing LQTS, and are indicated for all symptomatic or asymptomatic individuals with a QTc interval ≥ 470 ms. Therefore, all patients with a prolonged QT interval should receive beta-blockers, although protection is incomplete for patients with LQTS2 and 3 (class I intervention). For patients with a mutation (positive genotype) but a normal QT interval, prophylactic use of beta-blockers is also recommended, given their good tolerability and the fact that at least 10% of asymptomatic individuals will develop symptoms over time.[181,182]

Recommendation grade: IIa.

Evidence level: B.

An ICD is recommended for all cardiac arrest survivors with good functional status and life expectancy > 1 year.

Table 10 – Precautionary measures for patients with channelopathies

Avoid substances that prolong the QT interval (www.crediblemeds.org)
Avoid substances that exacerbate Brugada syndrome (www.brugadadrugs.org)
Hydration and replacement of electrolytes: avoid dehydration (trigger)
Avoid hyperthermia, whether due to fever or excessive heat in athletes with long QT and Brugada syndrome
An external automatic defibrillator should be part of the athlete's equipment
Establish an emergency action plan

Recommendation grade: I.

Evidence level: B.

Patients who develop syncope despite the use of beta-blockers may also benefit from ICD.

Recommendation grade: IIa.

Evidence level: B.

An ICD can be considered in patients at high risk of SD, such as those with SQTL3, even if asymptomatic. Individuals with a QTc interval > 500 ms present a very high risk.[183]

Recommendation grade: IIb.

Evidence level: B.

Sympathetic denervation may be considered for patients with syncope or CPTV who are already using beta-blockers.[181,184]

Recommendation grade: IIb.

Evidence level: B.

5.3. Short QT Syndrome

Short QT syndrome is a very rare condition that has been known for less than 20 years.[185] In this disease, shortening of repolarization occurs, which favors the development of ventricular arrhythmias by reentry. It is characterized by a short QT interval (QTc < 320 ms) with peaked T-waves (that could have increased amplitude) with a normal ascending phase and a rapid descending phase.[186,187] A QTc interval ≤ 340 ms is a risk marker. Short QT syndrome should also be considered when the patient has a QTc interval ≤ 360 ms in association with a confirmed genetic mutation, a family history of short QT syndrome, a family history of SD in individuals under 40 years of age and/or in survivors of cardiorespiratory arrest.[188] Since the clinical parameters are still unclear, genetic analysis is useful to confirm the diagnosis in suspected cases. Mutations in three genes that encode potassium channels have been described: KCNH2, KCNQ1 and KCNJ2, all resulting in function gains in the IKr, IKs and IK1 channels, respectively, and determining short QT syndrome types 1, 2 and 3.[187] Three other genes that encode calcium channels, CACNA1C (short QT syndrome type 4), CACNB2 (short QT syndrome type 5) and CACNA2D1 (short QT syndrome type 6) were also identified.[188] Given that the number of patients with a confirmed diagnosis is very small, it has not yet been determined whether any specific type of mutation determines a worse prognosis. Moreover, new generation sequencing does not identify any genetic cause in up to 40% of individuals with a clear phenotype.[188] Risk factors for arrhythmias are also not known. Treatment for this condition is still controversial: in patients with a KCNH2 gene mutation, quinidine has been shown to prolong refractoriness and suppress the induction of arrhythmias during an electrophysiological study,[189] although for other mutations its usefulness has not been established. The disease appears to be highly lethal, but there may be a diagnostic bias toward severe cases. Although the use of ICD may be considered,

inappropriate shocks may occur due to the double-counting phenomenon (QRS complexes and T-waves).[190,191]

Regarding exercise recommendations, participation in competitive sports may be considered for short QT patients as long as they are asymptomatic, have been under treatment for 3 months and precautionary measures are taken (automatic external defibrillator).

Recommendation grade: IIa.

Evidence level: C.

5.4. Brugada Syndrome

This syndrome is characterized by the occurrence of syncope or SD caused by polymorphic ventricular tachycardia in structurally normal hearts. Its diagnosis may be based on a specific EGC pattern, defined as an ST-segment elevation ≥ 2mm (0.2 mV) in the right precordial leads. However, this diagnosis may be unstable.[192] Its most peculiar aspect is J-spot elevation in the right precordial leads (V1 to V3), although this phenomenon has also been described in lower leads.[193-195] However, the ECG results may be unimpressive, requiring the use of sodium channel blockers to unmask the condition. The tracking and proper identification of these patients are essential, since SD is rarely the first symptom.[192]

This syndrome is highly influenced by gender, since 90% of cases occur in men. To date, only functional loss mutations in SCN5A, present in about 20% of those affected, have been identified. Currently, a total of 23 genes have been implicated in Brugada syndrome (BrS1-BrS23), and the vast majority of them are very rare.[196] Clinically, the disease manifests with syncope or SD, predominantly in the third or fourth decade of life, with fever as a trigger for arrhythmias.

In risk stratification, individuals with spontaneous J-point elevation have a worse prognosis than those in whom the typical pattern was observed only after infusion of flecainide, procainamide or ajmaline. The occurrence of syncope, associated with spontaneous J-point elevation, increases the risk of SD by up to 6 times. Neither a family history of SD nor detecting a mutation in the SCN5A gene proved useful for risk stratification.[197,198]

Sports have not been described as a SD risk factor in Brugada syndrome. However, since there is a greater risk of events related to parasympathetic activity in this syndrome, arrhythmias can occur after exercise/training, a point in which there is vagal recovery and sympathetic withdrawal. In addition, significant elevations in body temperature due to intense physical activity in unfavorable environments may also trigger SD.

Defibrillators are recommended for:

Aborted SD patients.

Recommendation grade: I.

Evidence level: B.

Patients with spontaneous J-point elevation and syncope, or with previously documented ventricular tachycardia.

Recommendation grade: IIa.

Evidence level: B.

Exercise and competitive sports may be considered for Brugada patients, provided they are asymptomatic and have been undergoing treatment for 3 months.

Recommendation grade: IIa.

Evidence level: C.

5.5. Catecholaminergic Polymorphic Ventricular Tachycardia

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is triggered by physical exertion or emotional stress in children and young adults with structurally normal hearts.[199,200] The patient's resting ECG will appear normal, except for relative bradycardia for age and frequent U-waves. The disease manifests clinically as syncope.[199]

At least four mutations have been described in several genes (RyR2, CASQ2, TRDN, CALM1) that potentially cause CPVT. The most common cause is functional gain mutation in RyR2 (about 60% to 75% of cases), the gene that encodes type 2 ryanodine receptor, which is the protein responsible for releasing calcium from the sarcoplasmic reticulum. Anomalies in the CASQ2, the gene that encodes cardiac calsequestrin, which is a calcium-binding protein in the sarcoplasmic reticulum, account for up to 5% of CPVT cases. The CALM1 gene encodes calmodulin, a protein that binds to calcium and stabilizes the RyR2 channel, and accounts for less than 1% of the cases. Finally, there is also the TRDN gene (identified in two families with CPVT), which encodes triadin, a protein that binds RyR2 and calsequestrin to the sarcoplasmic reticulum.[201-203] Genetic analysis does not contribute to risk stratification, but it is important for identifying mutation carriers that have not yet manifested symptoms. The initial presentation of about 30% of patients is SD, and up to half of the patients suffer cardiac arrest between the ages of 20 and 30 years.[204] CPVT is a penetrating disease, and the prevalence of "silent" cases could be up to 20%.[205] However, cardiac events may occur even in this subgroup of individuals, who should be treated according to current guidelines. In these cases, genetic analysis plays a central role.[206,207]

Arrhythmias during exercise are the typical manifestation, frequently 120 to 130 beats per minute, beginning with isolated ventricular extrasystoles and progressing to episodes of unsustained and sustained ventricular tachycardia if effort is continued, usually with 180° rotation in the front plane (bidirectional). Atrial arrhythmias, atrial fibrillation and supraventricular tachycardia are also common in the syndrome. Beta-blockers, the main therapeutic pillar for CPVT,[208,209] are very effective and are recommended for:

Patients with clinical manifestations.

Recommendation grade: I.

Evidence level: B.

Asymptomatic mutation carriers.

Recommendation grade: IIa.

Evidence level: B.

An ICD is recommended for individuals with aborted SD.

Recommendation grade: I.

Evidence level: B.

Individuals with sustained syncope or ventricular tachycardia despite the use of beta-blockers.

Recommendation grade: IIa.

Evidence level: B.

Recommendations about competitive sports in this disease are quite restrictive: athletes with symptomatic or asymptomatic CPVT should not participate in competitive sports (except class IA).

Recommendation grade: III.

Evidence level: C.

6. Athletes with Valvular Heart Disease

6.1. Introduction

The assessment and follow-up of physically active individuals with valve disease are important pillars of sports cardiology. For athletes with valvular heart disease, eligibility criteria are based on cohort studies and expert consensus. However, randomized clinical trials with prospective data are scarce.

Athletes with intermediate degrees of valve disease are the most challenging group. Serial evaluation and stratification of disease severity are fundamental. As new symptoms develop, they should be treated promptly.

To qualify for competition, athletes must initially be classified according to symptoms, degree of valvular damage and left ventricular dysfunction.

Stage A: Asymptomatic athletes at risk of developing stenosis or significant valve regurgitation, e.g., mitral valve prolapse or BAV, as well as individuals whose physical examination is consistent with the underlying pathology (mitral, aortic ejection), but not classic valve dysfunction.

Stage B: Asymptomatic athletes with mild-to-moderate valve disease with preserved LV function.

Stage C: Asymptomatic athletes with severe valve disease with preserved LV systolic function (C1) or LV systolic dysfunction (C2).

Stage D: Symptomatic athletes with severe valve disease (with or without LV dysfunction).

6.2. Aortic Valve Disease

Aortic impairment is usually degenerative and is a result of aortic stenosis in middle-aged/elderly athletes and BAV in younger athletes. In Brazil, rheumatic etiology should be considered. Primary aortic diseases are common causes of aortic regurgitation, although there are also rheumatic and congenital causes (e.g., BAV).[210,211]

6.2.1. Aortic Stenosis

Aortic stenosis is considered a progressive disease and survival during the asymptomatic phase has been found similar to that of age-matched controls.[212] In 2010, approximately 40 million people worldwide aged 65 or older had aortic stenosis, and this number is expected to reach 72 million by 2030.[213] Lower exercise tolerance, effort dyspnea, and angina in athletes with systolic murmur are suggestive of clinically important aortic stenosis. Dyspnea is due to increased LV filling pressure or an inability to increase cardiac output with exercise.

Aortic stenosis is also recognized as responsible for SD in young athletes, although the prevalence of less than 4%.[214] It is important to point out that almost 70% of SD episodes in subjects with severe aortic stenosis were not preceded by any of the classic symptoms of the disease.[212]

Echocardiography with Doppler color flow mapping is the method of choice for diagnosis, classification and evaluation of aortic stenosis[215] (Table 11).

Transthoracic echocardiography provides evidence of aortic valve anatomy (e.g., the number of cusps and the extent of calcification), as well as valve hemodynamics (to confirm severity) and their consequences on LV function. Pulmonary hypertension, concomitant valvular disease and aortic root dilation can also be evaluated.[216]

Cardiac MRI is useful for patients with an unfavorable transthoracic window and/or when there is disagreement between two-dimensional echocardiographic parameters.[217] Computed tomography of the heart can be used to quantify valve calcification. A calcium score of less than 700 Agatston units excludes severe aortic stenosis and has a high negative predictive value. On the other hand, scores over 2,000 Agatston units suggest severe aortic stenosis.[213]

Due to potential progressive aortic valve narrowing, athletes with mild or moderate (stage B) aortic stenosis should be assessed annually.

In asymptomatic or oligosymptomatic patients, exercise testing (exercise stress testing or CPET) could reveal those with low functional capacity, intraoperative hypotension and/or electrocardiographic changes during exercise. Such findings will conflict with the recommendations about sports participation. Recently, Saeed et al.[218] analyzed almost 800 exercise tests and found that patients with moderate-to-severe asymptomatic aortic stenosis can perform the test safely and with good tolerability. In addition, event-free survival at 1 year was almost 90% in asymptomatic patients, but less than 70% in those who reported symptoms during exercise.

BAV patients without stenosis (stage A) should have an annual physical examination to detect new heart murmurs. Athletes with mild-to-moderate aortic stenosis (stage B) should

Table 11 – Aortic stenosis severity rating

Impairment (degree)	Jet velocity (m/s)	Medium gradient (mmHg)	Aortic valve area (cm^2)
Mild	< 3	< 25	> 1.5
Moderate	3-4	25-40	1.0-1.5
Severe	> 4	> 40	< 1.0 (< 0.6 cm^2/m^2)

undergo anamnesis, a physical examination, echocardiography (to evaluate disease progression), and exercise testing to ensure that their exercise tolerance is compatible with their physical activity, that no episodes of hypotension occur during exercise, and that there is no electrocardiographic evidence of complex ischemia/arrhythmia.

6.2.1.1. Recommendations and Evidence Level

Athletes with aortic stenosis should be evaluated annually to continue participating in sports.

Recommendation grade: I.

Evidence level: C.

Athletes with discrete aortic stenosis (stage B) and an appropriate physiological response to a maximal exercise testing may participate in any sport.

Recommendation grade: IIa.

Evidence level: C.

Athletes with moderate aortic stenosis (stage B) can participate in competitive sports with low-to-moderate static and dynamic components (classes IA, IB and IIA) if the exercise testing results are sufficient for the activity level required in competition, with clinical, hemodynamic and ECG responses to exercise and without ventricular tachyarrhythmias.

Recommendation grade: IIa.

Evidence level: C.

Asymptomatic athletes with severe aortic stenosis (stage C) should not participate in competitive sports, except for those with low static and dynamic components (class IA).

Symptomatic athletes with aortic stenosis (stage D) should not participate in competitive sports.

Recommendation grade: III.

Evidence level: C.

6.2.2. Aortic Regurgitation

The prevalence of aortic regurgitation increases with age, although it is very low (1%) in individuals less than 70 years of age. After that age, its prevalence increases to over 2%.[219] In the native valve, aortic regurgitation may be the result of abnormalities of the valve leaflets, the aortic root or both. The main causes of aortic regurgitation are diseases that affect the aortic ring or root without directly involving the aortic valve: BAV, connective tissue genetic disorders (Marfan, Ehlers-Danlos and Loeys-Dietz syndromes), inflammatory diseases (in particular syphilitic aortitis, Takayasu arteritis and giant cell arteritis), rheumatic heart disease and hypertensive dilation. In fact, so-called "idiopathic" aneurysms of the ascending aorta have a genetic diagnosis in at least 30% of the cases.[210,219] Aortic regurgitation is invariably well tolerated and asymptomatic for years; however, eccentric hypertrophy progressively develops and LV systolic and diastolic volumes increase, which could lead to LV systolic dysfunction.

Aortic regurgitation is diagnosed in asymptomatic athletes when physical examination reveals wide arterial pulse pressure, a diastolic murmur in the aortic area or Erb's point, or a systolic murmur related to increased systolic volume. An echocardiogram is definitive for diagnostic confirmation and classifying aortic regurgitation. With color Doppler echocardiography, the size of the regurgitant jet and the flow convergence can be determined, allowing the regurgitant orifice area to be calculated.[210,220]

CMRI may be used as a complement to echocardiography when quantifying aortic regurgitation. In fact, it has been reported that quantitative volume and regurgitant fraction can be calculated with better reproducibility through CRMI than echocardiography.[221,222]

Because the pathophysiology of aortic regurgitation leads to LV dilation in elite athletes, it must be differentiated from the physiological alterations in athlete's heart syndrome. Therefore, when evaluating increased LV volume in elite athletes with suspected or diagnosed aortic regurgitation, only LV volumes that exceed normal physiological response to sports training should be considered.

Although up to 45% of male athletes have a LV end-diastolic diameter (LVDD) > 55 mm, only 14% of elite male athletes have a LVDD > 60 mm, and LVDD rarely exceeds 70 mm. A LVDD > 55 mm occurs in < 10% of elite female athletes, while only 1% have a LVDD > 60 mm.[223-225] The same is true for LV end-systolic diameter (LVSD): in elite athletes, the upper limit for LVSD is 49 mm for males and 38 mm for females. Only index data on body surface area and height are available regarding LVDD, which indicate upper limits of 35.3 mm/m^2 and 40.8 mm/m^2 for male female athletes, respectively.[223-226]

A normal LV ejection fraction response to exercise is observed in aortic regurgitation patients until there is significant LV dilation. When evaluating the progressive effects of severe aortic impairment in athletes with normal LV ejection fraction, serial analysis of LVSD is of great value. The American Heart Association/American College of Cardiology define preserved systolic function (stage C1) in patients with significant aortic impairment as a LV ejection fraction ≥ 50% and LVSD ≤ 50 mm or index LVSD ≤ 25 mL/m^2.[210,227] Thus, in athletes with significant aortic impairment and a LVDD that exceeds the above-mentioned reference values. There is a higher probability that severe aortic impairment contributes to LV dilation. Such athletes require a more careful evaluation to verify that no ventricular increase has occurred and whether signs and/or symptoms occur during exercise, such as dyspnea on exertion or reduced functional capacity.

6.2.2.1. Recommendations and Evidence Level

Athletes with aortic regurgitation should be evaluated annually to continue participating in sports.

To confirm that athletes with aortic regurgitation are truly asymptomatic, they should undergo an exercise testing involving at least the activity level achieved during training and competition and have a physiological hemodynamic response.

Athletes with mild-to-moderate aortic impairment (stage B), a physiological response to a maximal exercise testing, normal

or discretely dilated LV and a normal ejection fraction may participate in any sport (with frequent reassessment).

Recommendation grade: I.

Evidence level: C.

Athletes with mild to moderate aortic regurgitation (stage B), a physiological response to a maximal exercise testing, a moderately dilated LV (LVSD < 50 mm [men], < 40 mm [women] or < 25 mm/m² [both sexes]) and a normal ejection fraction may participate in any sport (with frequent reassessment).

Recommendation grade: IIa.

Evidence level: C.

Athletes with severe aortic regurgitation (stage C1), a physiological response to a maximal exercise testing, a moderately dilated LV (LVSD < 50 mm [men], < 40 mm [women] or < 25 mm/m² [both sexes]), a normal ejection fraction and no progression of aortic impairment or LV regurgitation according to echocardiography may participate in any sport (with frequent reassessment).

Athletes with aortic regurgitation whose aortic diameters are 41 to 45 mm may participate in sports in which there is no risk of collision (with frequent reassessment).

Recommendation grade: IIb.

Evidence level: C.

Symptomatic athletes with significant aortic regurgitation (stage D), LV systolic dysfunction with an ejection fraction < 50% (stage C2), LVSD > 50 mm or > 25 mm/m² (stage C2) or a significant increase in LVDD (> 70 mm or ≥ 35.3 mm/m² [men], > 65 mm or ≥ 40.8 mm/m² [women]) should not participate in competitive sports.

Recommendation grade: III.

Evidence level: C.

6.2.3. Bicuspid Aortic Valve

BAV is the most common congenital heart disease, affecting 1.3% of the population.[228] There is already consensus that an association exists between BAV and changes in vascular connective tissue, and that dilation of the aortic root can occur, including a risk of dissection, even in the absence of hemodynamically significant aortic stenosis or aortic regurgitation.[229,230]

6.2.3.1. Recommendations

Athletes with BAV but not aortic root dilation (less than 40 mm, or equivalent in children and adolescents according to body surface area), significant aortic stenosis, or aortic regurgitation may participate in any competitive sport.

Athletes with BAV and aortic root measurements between 40 and 45 mm may participate in competitive sports with a low-to-moderate static component or a low-to-moderate dynamic component (classes IA, IB, IIA and IIB) but should avoid sports that involve a risk of collision or trauma.

Athletes with BAV and aortic root dilation greater than 45 mm may participate only in competitive sports with low static and dynamic components (class IA).

6.3. Mitral Valve Disease

6.3.1. Mitral Stenosis

A mitral valve area of 4 to 6 cm² is considered normal. Mitral stenosis affects women twice as frequently as men.[231] As mitral stenosis progresses, particularly when the area becomes smaller than 2 cm², a diastolic pressure gradient develops between the left atrium (LA) and the LV, causing elevation in LA pressures and decreased flow towards the LV.[232] Frequently of rheumatic origin, mitral stenosis rarely causes SD. However, exercise may lead to a marked increase in pulmonary and pulmonary capillary pressure, sometimes culminating in acute pulmonary edema.[233] Athletes with mitral stenosis are more likely to develop atrial fibrillation as a result of strenuous exercise in an already enlarged atrium. Systemic embolization is the main complication, but there is no evidence that strenuous exercise increases risk. When atrial fibrillation occurs in an athlete with mitral stenosis, anticoagulant therapy should be applied.

As in other valvular heart diseases, the evaluation of athletes with mitral stenosis requires a well-documented anamnesis, as well as an echocardiogram (Table 12).[215] This disease is considered severe when there is a resting mean transmitral gradient of 5 to 10 mmHg, which is dependent on transvalvular flow and the diastolic filling phase, factors that vary widely with increased heart rate during exercise.[210]

Athletes with mitral stenosis, whether asymptomatic or with minimal symptoms, should perform an exercise testing involving at least the activity level achieved during training/competition, especially if the disease severity is uncertain. The intensity of physical activity should depend on the size of the left atrium and the severity of the defect. Pulmonary artery systolic pressure during exercise can be estimated noninvasively with an echocardiogram, which can be of great value in quantitative analysis of the safe training range for mitral stenosis patients.[210]

6.3.1.1. Recommendations and Evidence Level

Athletes with mitral stenosis should undergo an annual evaluation to continue participating in sports.

An exercise testing should be performed involving at least the activity level achieved during training/competition with a hemodynamic response to confirm the symptom status.

Table 12 – Echocardiographic features of severe mitral stenosis

Mitral valve area < 1.5 cm²
Mean left atrial/left ventricular diastolic gradient ≥ 10 mmHg
Pulmonary artery systolic pressure ≥ 50 mmHg at rest
Pulmonary artery systolic pressure ≥ 60 mmHg on effort

Recommendation grade: I.

Evidence level: C.

Athletes with mild mitral stenosis (mitral valve area > 2.0 cm^2, mean gradient < 10 mmHg at rest) in normal sinus rhythm may participate in any competitive sport.

Recommendation grade: IIa.

Evidence level: C.

Athletes with significant mitral stenosis should not participate in competitive sports, with the possible exception of sports with low static and dynamic components (class IA).

Athletes with any degree of mitral stenosis and atrial fibrillation or who have a history of atrial fibrillation on anticoagulant therapy should not participate in competitive sports involving collision/trauma risk.

Recommendation grade: III.

Evidence level: C.

6.3.2. Mitral Regurgitation

The prevalence of mitral regurgitation is age dependent, with a frequency > 6% in adults over 65 years of age.[234] The pathogenesis varies from mitral-valve prolapse (sometimes with myxomatous degeneration) to rheumatic causes, connective tissue diseases (e.g., Marfan syndrome) and infective endocarditis, to secondary causes such as coronary artery disease and dilated cardiomyopathy. Diagnostic suspicion arises from auscultating a systolic murmur at the apex, which is confirmed and quantified by echocardiography.[220] Generally, athletes with mild or moderate mitral regurgitation are asymptomatic (Stage B).

The severity of mitral regurgitation is related to LV regurgitant volume into the left atrium, with increased atrial pressure, increased ventricular diastolic volume and posterior LV dilation.[235] Due to overestimation of the LV ejection fraction, LV systolic dysfunction in athletes with mitral insufficiency is defined as a LV ejection fraction < 60% or LVSD > 40 mm. As in aortic regurgitation, it is difficult to distinguish LV dilation due to exercise from that caused by major mitral regurgitation when LVDD is < 60 mm (or < 40 mm/m^2). However, LVDD > 60 mm strongly suggests significant mitral regurgitation, thus justifying subsequent investigation.[210]

Dynamic exercise generally decreases the regurgitant fraction due to reduced systemic vascular resistance. On the other hand, static exercise with increased systemic BP, HR and systemic vascular resistance increase regurgitant volume, which increases the pressure in pulmonary capillaries. The assessment of athletes with mitral regurgitation, which should occur at least annually, should include complete anamnesis and an echocardiogram. This test can noninvasively estimate pulmonary artery systolic pressure during exercise and is useful for decision making about the intensity of safe physical activity, especially in those with more severe mitral regurgitation.[210]

The recommendations listed below should be considered in patients with secondary causes of mitral regurgitation (e.g., infective endocarditis, rupture of the mitral valve chordae) due to a marked increase in LV systolic pressure, which could further damage valve tissue.

6.3.2.1. Recommendations and Evidence Level

Athletes with mitral regurgitation should be evaluated annually to continue participation in sports.

Athletes with mitral regurgitation should undergo an exercise stress testing or CPET involving at least the activity level achieved in during training and competition, with a hemodynamic response to confirm symptom status.

Athletes with mild-to-moderate mitral regurgitation, normal sinus rhythm, normal LV diameter and function, and normal pulmonary arterial pressures (stage B) may participate in any competitive sport.

Recommendation grade: I.

Evidence level: C.

Athletes with moderate mitral regurgitation (stage B), normal sinus rhythm, normal LV ejection fraction, and moderate LV dilation (compatible with that resulting exclusively from exercise [LVDD < 60 mm or < 35 mm/m^2 in men or < 40 mm/m^2 in women) may participate in any sport.

Recommendation grade: IIa.

Evidence level: C.

Athletes with significant mitral regurgitation, normal sinus rhythm, a normal LV ejection fraction at rest, and mild LV dilation (compatible with that which can only result from exercise [LVDD < 60 mm or < 35.3 mm/m^2 in men or < 40 mm/m^2 in women]) (stage C1) may participate in sports with a low-to-moderate static component and a low dynamic component, as well as in sports with a low static component and a moderate dynamic component (classes IA, IIA and IB).

Recommendation grade: IIb.

Evidence level: C.

Athletes with mitral regurgitation and significant LV dilation (LVDD ≥ 65 mm or ≥ 35.3 mm/m^2 [men] or ≥ 40 mm/m^2 [women]), pulmonary hypertension and LV ejection fraction < 60% or LVSD > 40 mm should not participate in any competitive sport, with the possible exception of low static and dynamic component sports (class IA).

Athletes with mitral regurgitation and a history of atrial fibrillation and long-term anticoagulation therapy should not participate in sports that involve a risk of collision/trauma.

Recommendation grade: III.

Evidence level: C.

6.3.3. Mitral-Valve Prolapse

This pathology, which has an estimated prevalence of 2% to 4% in the general population, appears to be more common in women. Diagnosed with echocardiography, it is defined as systolic displacement of one or both mitral leaflets ≥ 2 mm into the left atrium, as well as by the mitral annular plane in the

parasternal cross-section of the long axis.[235,236] It occurs in two forms: the classical form, with diffusely thickened leaflets (≥ 5 mm) with bileaflet prolapse; or the non-classical form, in which there is limited (< 5 mm) or absent thickening and segmental prolapse. Classical prolapse can be further subdivided into symmetrical (when the leaflets meet at a common ring point) and asymmetrical (when one leaflet is moved further towards the atrium).[237] A mitral valve leaflet thickness > 5 mm in the echocardiogram has been associated with an increased risk of SD, stroke and endocarditis in patients with classic prolapse.[236]

The etiology can be primary (degenerative disease) or secondary (Marfan syndrome, Ehlers-Danlos syndromes, pseudoxanthoma elasticum). These patients can be identified through auscultation by the presence of a meso-telesystolic click and/or a mitral regurgitation murmur, as well as by chest pain, dyspnea, exercise intolerance, syncope and/or dizziness.

The major risks related to mitral-valve prolapse include severe progressive mitral regurgitation requiring valve surgery, infective endocarditis, embolic events, atrial and ventricular tachyarrhythmias and SD (which appears to be associated with structural abnormalities of the mitral valve, as in the classical form), with diffuse thickening, stretching and redundancy, and, in some cases, rupture of chordae tendineae.

The prognosis for mitral-valve prolapse is controversial. For example, the Framingham Heart Study[238] described mitral-valve prolapse as a benign entity, but other studies indicate that a subgroup of patients may be at a greater risk of cardiac arrest, which is the most devastating consequence. Thus, the risk for serious adverse events secondary to mitral-valve prolapse remains uncertain.[239,240]

SD associated with isolated mitral-valve prolapse is rare among young people, particularly with respect to exercise, and is also rare among professional athletes: its frequency in these groups is no greater than that of the general population. It predominantly occurs in patients over 50 years of age with severe mitral regurgitation and/or systolic dysfunction. However, Basso et al.[241] have shown a growing interest in mitral-valve prolapse, highlighting this entity as a neglected cardiac abnormality that could be associated with severe cardiac events, including SD in youth and adults. Caselli et al.[242] evaluated a large cohort of competitive athletes from 2000 to 2010, finding that mitral-valve prolapse was a relatively common finding, although predominantly benign. In addition, they recommend that detecting moderate-to-severe mitral regurgitation, as well as ventricular arrhythmias, may be useful for identifying athletes with mitral-valve prolapse who are at greater risk.

Some individuals with mitral-valve prolapse present a phenotype described as MASS (mitral valve, aorta, skeleton, and skin), which involves connective tissue changes, long limbs, deformity of the thoracic cage, and joint hypermobility). In such patients the risk of progression to aortic dilation/dissection or SD is greater. The MASS phenotype only applies if the aortic diameter z-score is < 2, the systemic score is ≥ 5 and the patient is at least 20 years old.[243-246]

6.3.3.1. Recommendations

Athletes with mitral-valve prolapse but no prior syncope (especially if of arrhythmogenic origin), sustained supraventricular or unsustained tachycardia or complex ventricular tachycardia according to 24 h Holter monitoring, severe mitral regurgitation according to an echocardiogram, LV systolic dysfunction (LV ejection fraction < 50%), previous embolic event or family history of SD related to mitral-valve prolapse may participate in any competitive sport.

Athletes with mitral-valve prolapse who exhibit any of the above characteristics may participate in competitive sports with low static and dynamic components (class IA).

Recommendations for athletes with mitral-valve prolapse and hemodynamic overload secondary to moderate-to-severe mitral regurgitation should be guided by the mitral regurgitation.

6.3.4. Tricuspid Stenosis

In isolation, tricuspid stenosis is rare. It is mainly caused by rheumatic disease and is usually associated with mitral stenosis. Although less common, tricuspid stenosis may result from congenital/genetic abnormalities, such as Ebstein's anomaly, Fabry disease, Whipple disease, or active infective endocarditis.[247] In summary, tricuspid stenosis patients should be considered according to degree of severity (Table 13).[215]

6.3.4.1. Recommendations

Asymptomatic athletes may participate in any competitive sport. An exercise testing involving at least the activity level achieved during training and competition should be performed.

6.3.5. Tricuspid Regurgitation

Tricuspid regurgitation is reported as the most common heart valve disease, affecting up to 85% of the population.[248] It is divided into two categories: primary (or organic) and secondary tricuspid regurgitation, which is the most common form. Namely, only 8% to 10% of tricuspid regurgitation cases are primary,[246] being associated with rheumatic heart disease, pacemaker electrode and defibrillator leads (iatrogenic complications) myxomatous degeneration, myocardial degeneration, tricuspid valve prolapse, infectious diseases (e.g., endocarditis) and congenital heart diseases (e.g., Ebstein's anomaly). It may also be related to postoperative complications. Physical examination and chest X-ray may help estimate tricuspid regurgitation, but echocardiogram is the gold standard for assessing the mechanism and severity of the condition. Three-dimensional echocardiography is even more sensitive, allowing a simultaneous view of all the leaflets.[249] If RV function cannot be adequately evaluated with this method, CMRI, due to its capacity to quantify RV volumes and ejection fraction, is an important introductory step.[248] If these measures

Table 13 – Echocardiographic features of severe tricuspid stenosis

Tricuspid valve area ≤ 1.0 cm^2
Mean diastolic gradient right atrium/right ventricle ≥ 5 mmHg
Isolated right atrial enlargement
Tricuspid pressure half-time ≥ 190 ms

cannot be estimated/determined non-invasively, right cardiac catheterization is used for such evaluation.

"Physiological" tricuspid regurgitation can be detected by echocardiography in approximately 80% of healthy athletes and does not imply any structural valve abnormality.[231]

6.3.5.1. Recommendations

Athletes with primary tricuspid regurgitation, regardless of severity, and normal RV function, in the absence of right atrial pressure > 20 mmHg or elevated RV systolic pressure, may participate in any competitive sport.

6.3.6. Multivalvular Heart Disease

Multivalvular heart disease, a combination of stenotic and/or regurgitant lesions of two or more heart valves, is a highly prevalent clinical condition among patients with valvular heart disease. It occurrence is mainly due to rheumatic heart disease, although the incidence of this etiological factor has decreased dramatically in the last five decades.[250] Myxomatous valvulopathy and infective endocarditis are also associated with multivalvular disease. Diagnosis is through physical examination, echocardiogram (the main imaging mode for diagnosis and follow-up), and sometimes cardiac/coronary angiography.

6.3.6.1. Recommendations

The cumulative effects of multiple significant valve lesions on an individual's physiological response to exercise may be difficult to predict, and multiple moderate lesions may also have physiological effects on the somatosensory system. Generally speaking, athletes with moderate-to-severe multivalvular disease should not participate in competitive sports.

6.4. Sports after Valve Surgery

Although much progress has been made in cardiac surgery, mortality after valve replacement is still higher than that of the general population of the same age group.

Mechanical heart valve prosthesis requires anticoagulant therapy and transvalvular gradients of varying degrees, which could be exacerbated by exercise. Thus, for athletes who have had a valve replacement, such factors determine their adequacy for competitive sports.[251]

An exercise stress testing or CPET involving at least at the activity level achieved during training and competition is of great value for analyzing the functional capacity of the athletes who have undergone valve replacement/repair.

6.4.1. Recommendations and Evidence Level

Athletes with an aortic or mitral bioprosthesis who are not on anticoagulant therapy and have normal LV ejection fraction and valvular function may participate in competitive sports (class IA, IB, IC and IIA).

Athletes with an aortic or mitral mechanical heart valve prosthesis who are undergoing anticoagulant therapy and have normal LV ejection fraction and valvar function may participate in competitive sports (class IA, IB and IIA) if there is no risk of collision/trauma.

Athletes who have undergone successful mitral balloon valvuloplasty or surgical commissurotomy may participate in competitive sports based on the severity of their residual mitral regurgitation or aortic stenosis and their pulmonary arterial pressure during rest and exercise.

Athletes who have undergone mitral valve surgery to correct mitral regurgitation or aortic valve repair, having no residual or moderate mitral regurgitation and having normal LV ejection fraction, may participate in sports (class IA, IB and IIA), but only at the discretion of the attending physician and if there is no risk of collision/trauma.

Recommendation grade: IIa.

Evidence level: C.

6.4.2. Transcatheter Aortic Valve Implantation

Transcatheter aortic valve implantation is a minimally invasive percutaneous procedure that was performed for the first time in 2002. It is considered the gold standard for patients with aortic stenosis who are at high surgical risk, especially older adults.[252] Since these patients often have low functional capacity, therapeutic exercise intervention can improve their physical integrity and performance in activities of daily living.

Several recent studies have confirmed the benefits of exercise in patients who have undergone transcatheter aortic valve implantation. They are unanimous in reporting improved functional capacity (as measured by CPET or the 6-minute walk test).[253-256] Altisent et al.,[257] in a 4-year follow-up, found that an increase < 20% in the 6-minute walk test 6 months after the procedure correlates with an all-cause mortality of 65%. Therefore, exercise increases the functional capacity of these individuals, improving prognosis and quality of life. It should be pointed out that we are not aware of any studies on athletes who have undergone transcatheter aortic valve implantation.

7. Athlete's Heart Syndrome in Women

7.1. Introduction

Since the passage of Title IX in 1972, women's participation in sports has increased dramatically. During the 2014-2015 school year, approximately 8 million United State. high school students participated in sports, over 40% of whom were girls.[258] Female athletes have been historically underrepresented in research that has guided exercise and sports cardiology. However, in the last three decades there has been an exponential increase in the number of women participating in competitive sports. Thus, female gender should be considered an important biological variable in this context.

As in men, the body of female athletes also undergoes physiological adaptations to physical training and may present structural and electrical changes compatible with athlete's heart syndrome. Such adaptations can occur in all athletes, but their magnitude depends on several factors, including gender. There are anthropometric, physiological

and biochemical differences between men and women, including smaller stature, lower body mass, smaller LV diameter, less testosterone and a different physical work capacity.[259] In hemodynamic terms, higher resting HR have been observed, although maximum levels during exercise are reached in a manner similar to men. Systolic BP and systolic volume increase less on effort, and maximal O_2 consumption (VO_2max) is lower. Nevertheless, female cardiac output is 5% to 10% higher than that of males at any level of submaximal oxygen consumption.[260] In absolute values, female work capacity is lower, but when assessed at the same intensity percentage, the cardiovascular performance of men and women are similar.

Since physical training can result in a series of cardiovascular system modifications and adaptations, knowing how to differentiate physiological responses due to regular exercise from pathological ones can be a challenge when performing detailed clinical evaluations of athletes.

7.2. Complementary Exams

7.2.1. Twelve-Lead Electrocardiogram

7.2.1.1. Electrocardiogram: Physiological Changes vs. Changes Suggestive of Heart Disease

Both physiological and pathological adaptations may differ between female and male athletes in ECG. However, data on specific ECG differences between genders are limited. Using the criteria of Pelliccia et al. (2000),[261] women had a higher prevalence of normal ECG than men (78% vs. 55%) in a cohort of European Olympic athletes. On the other hand, according to the latest Seattle criteria,[262] no significant differences were observed between genders (96% of males and 97% of females had normal ECG). This contrast could be justified by the fact that the Seattle Criteria are much more rigorous, which increases specificity without sensitivity loss.

Female athletes appear to have a lower prevalence of physiological changes in ECG, especially regarding isolated increases in QRS complex amplitude (in about 10% of women), incomplete RBBB and early repolarization (four times less than men).[263,264] However, female athletes had a higher frequency of QT interval increase, as well as inverted T-wave in the V1-V2 leads (1% vs. 0.2% in male athletes),[265] such findings are considered non-pathological adaptations. Inverted T-waves in the inferior and/or lateral walls are more prevalent in male athletes, being more commonly associated with underlying structural heart disease.[266] On the other hand, anterior precordial T wave inversion is more common in women and, when limited to V1-V3 leads, does not appear to be related to structural heart disease.[267,268] However, ventricular repolarization changes in lateral leads are less common and should always serve as a warning for a possible pathology.[269]

One important point to consider is that the international guidelines for interpreting ECG in athletes do not differ according to gender, but are unanimous in stipulating a higher QTc interval cut-off point for women than men, since women, regardless of cardiac remodeling, have longer QTc intervals than men (≥ 480 ms vs. ≥ 470 ms, respectively).[101,270]

7.3. Echocardiogram

The echocardiogram is one tool available for PPS and determining sports eligibility. In a study of 600 female athletes who participated in different sports, it was found that the LV cavity is rarely greater than 54 mm (a threshold value for normality in women) and never above 66 mm. The thickness of the LV wall rarely measures over 11 mm, reaching a maximum of 13 mm, usually in blacks.[225,271] Finocchiaro et al.[264] confirmed these findings: none of the women in their sample had an LV wall thickness > 12 mm, and only 7% had a LV end-diastolic diameter > 54 mm. In fact, these results are clinically relevant, since a LV cavity < 54 mm can distinguish, for example, an "athlete's heart" from HCM with excellent sensitivity and specificity.[272]

It has long been known that one adaptation to regular physical training is increased LV mass, observed mainly in endurance athletes. However, when LV wall thickness is accompanied by a reduction in cavity size, a pathological process such as HCM should be suspected. LV wall thickness > 12 mm in men or > 10 mm in women is considered abnormal in white athletes, and further investigation is necessary.[273] In black athletes, an LV wall thickness of 11 mm can be observed, which can reach up to 12 or even 13 mm in exceptional situations.[271] Since none of the athletes Finocchiaro et al.'s sample had a LV wall ≥ 13 mm, it would be reasonable to infer that an LV wall thickness of 13 mm probably represents the upper physiological limit of LV hypertrophy in black and asymptomatic athletes where there is no family history of HCM.

Recent experiments have demonstrated that women with "athlete's heart" have eccentric LV hypertrophy. Initially, there is an increase in the cavity which, although smaller (5%) than that of a man, is larger when indexed to body surface. LV wall thickness and LV mass do not increase proportionally, being smaller than those of male athletes (23% and 31%, respectively). It is suggested that a relative LV wall thickness > 0.48 is a marker of pathology.[269]

D'Ascenzi et al.[274] investigated the morphology and function of the left and right atria in competitive volleyball athletes, observing a biatrial increase with normal filling pressures and low complacency. In women, these characteristics are typical of athlete's heart and should be thus interpreted as a physiological adaptation to intense physical training.

7.4. Exercise Testing

Prior to this decade, the exercise stress testing was considered less accurate when diagnosing CAD in women. However, more recent studies have vindicated its effectiveness, especially for variables besides ST-segment. Women are more likely to have baseline ST-segment and T-wave changes, as well as ST-segment depression, during exercise. This is believed to be a consequence of a "digoxin-like" estrogen effect, since the changes seem

to vary according to menstrual cycle and postmenopausal hormone replacement.[275] Unlike men, ST-segment change in asymptomatic women does not correlate with mortality. In many circumstances, due to the relatively higher prevalence of false-positive traits in women, those with ST-segment depression generally receive non-cardiac diagnoses, with no additional exams or subsequent cardiac treatment.[276]

In men and women, a chronotropic index < 0.8 and HR recovery < 12 bpm after the first minute correlate with increased mortality and are valuable measures for prognostic evaluation.

Functional capacity, obtained though the exercise stress testing, is especially useful for athletes, besides being an independent predictor of CAD and mortality. For accurate evaluation of exercise capacity, as well as for training adjustments, an association of exercise ECG and expired gas measurements (CPET) is recommended.[259]

Recommendation	Recommendation grade	Evidence level
Exercise stress testing in initial assessment for competition or a series of tests for training load adjustment	IIb	B
CPET (previous item)	IIa	B

CPET: cardiopulmonary exercise testing.

7.5. Sudden Death

Curiously, the occurrence of SD differs between male and female athletes. Several types of evidence indicate that SD is overwhelmingly more prevalent in male athletes.[277-280] This disproportional occurrence would seem to suggest that women have some "protective factor" against heart disease, in whom SD is less likely than men under similar conditions. However, little is known about other factors that could be decisive in this outcome. Moreover, it has been shown that 92% of young athletes with SD were men, and that only 53% of women had some structural change.[281]

The proportion of women among master athletes (> 40 years of age) has grown. There has been much discussion about whether intense exercise over a period of many years has deleterious effects. Myocardial fibrosis, atherosclerotic plaques, and a higher incidence of atrial fibrillation have been found in some groups of athletes.[282] However, whether the additional risk from very intense exercise applies equally to men and women has also been questioned. A recent meta-analysis involving more than 149,000 women[283] found that moderate exercise reduces the chance of developing atrial fibrillation, especially in comparison to sedentary women, and that women who exercised intensely on a regular basis had a 28% lower risk of atrial fibrillation. In contrast, a prospective study suggested that the risk of atrial fibrillation in women followed the same pattern as in men.[284] According to this study, the risk in more active women was higher than in moderately active women and similar to that of sedentary women. Thus, further investigation is necessary to better understand the relationship between exercise and atrial fibrillation in women.

8. Basic Life Support for Athletes

8.1. Sudden Death among Athletes

Although rare, SD at a sporting event causes a public commotion, especially when involving elite athletes. Statistics show that in the general population the incidence of SD during exercise is approximately 0.46 cases per 100,000 person-years.[285] In young athletes this incidence is also low: (a) 0.5 for every 100,000 person-years among athletes in Minnesota; (b) 2.3 per 100,000 person-years among competitive athletes in northern Italy;[7] (c) 1 to 3 for every 100,000 person-years in professional American football players.[286] However, the true incidence of cardiac SD in athletes still requires further investigation. More recently, Emery and Kovacs[144] pointed out that the studies estimating these events vary methodologically, diverging between the number of athletes who suffered SD (numerator) and the number of athletes at risk (denominator). In addition, some included only events that resulted in death, while others also included those who survived cardiorespiratory arrest.

Several structural and non-structural changes (channelopathies) are responsible for most cases of cardiac arrest among athletes. Studies conducted in the 1990s pointed to HCM as the main cause of SD,[287,288] and data from another experiment conclusively showed that HCM is the main cause of SD in young athletes, accounting for 26% of cases.[289] Nevertheless, a meta-analysis of retrospective cohort studies, registries, and autopsy series by Ullal et al.[290] challenged these conclusions: in more than 4,000 young SD victims, structurally normal hearts were the most common findings (26.7%). Interestingly, the proportion of HCM was much lower among their sample (10.3%). Irrespective of these controversies, however, vigorous exercise, when associated with heart disease, appears to trigger malignant events.

PPS generally consists of a detailed history, a physical examination and resting 12-lead ECG, although whether ECG should be mandatory has been debated in the international scientific community.[5] An important Italian study showed that mandatory ECG use reduced the annual incidence of cardiac SD by 90%.[291] The American Heart Association/American College of Cardiology question the cost-effectiveness of this strategy, the high rate of false-positive results, and the availability of qualified personnel to interpret the results.[292] On the other hand, the European Society of Cardiology recommends ECG for PPS.[35] Regardless of this controversy, PPS cannot eliminate SD among athletes. Thus, a second pillar must be further developed: basic life support.

8.2. Initial Care for Athletes

The basic emergency care strategy can be summarized as a set of actions taken in the first few minutes following a sudden cardiac event: (1) the organization and planning of an emergency response team at the activity site; (2) training first responders in cardiopulmonary resuscitation and AED use. Places where sports activities occur (e.g., training centers, schools, colleges, gymnasiums, etc.) must have a well-organized emergency care plan, including personnel trained in basic life support and fast and effective

communication with emergency services who can perform advanced cardiac life support.

Effective treatment for an athlete who has suffered sudden cardiorespiratory arrest depends on a sequence of interdependent actions that, when linked together, form a chain reaction that increases the victim's chance of survival. The American Heart Association calls this a "chain of survival" that consists of the following links: rapid access, early cardiopulmonary resuscitation, early defibrillation and early advanced cardiac life support .

Most sudden cardiorespiratory arrest in athletes is due to tachyarrhythmia (ventricular fibrillation),[293] and can be treated with immediate defibrillation and cardiopulmonary resuscitation (CPR). Reducing mortality among athletes who have suffered sudden cardiorespiratory arrest requires CPR training programs and AED use, as well as personnel who can recognize emergencies, activate the emergency system, provide quality CPR, and use an AED. Current guidelines for sports facilities require the installation of strategically placed defibrillators in those with more than 2,500 patrons or those that host activities for individuals in certain at-risk groups (e.g., heart disease patients or older adults).[294,295]

It is a well-established fact that for each minute without CPR, the cardiorespiratory arrest victim's chance of survival decreases from 7% to 10%. However, regarding structural diseases, ventricular arrhythmias appear to be more susceptible to minor delays in defibrillation than structurally sound hearts,[296] which might explain why the survival rate of athletes declines more significantly when AED use is delayed. This highlights the extreme importance of early defibrillation, the third link in the chain.

Numerous studies have documented increased survival rates due to programs promoting public access to defibrillation, including locations such as casinos,[297] airports[298] and airplanes.[299] If resuscitation is delayed until the arrival of emergency services, survival rates are very low, around 1 to 2%.[300] The use of AED in public places has led to survival rates of up to 74% for out-of-hospital cardiac arrests.[301] However, due to the rarity of such events among athletes, little is known about this initiative's specific impact on them.

An important risk marker, PPS should be mandatory, since it can detect cardiovascular changes that predispose an athlete to SD. Despite differing international recommendations, there is consensus that the assessment of every athlete should include clinical history, a physical examination and 12-lead ECG, being complemented with other exams according to the degree of suspicion.

Athletes who experience SD require immediate high-quality cardiopulmonary resuscitation to provide vital blood flow to the brain and heart. Defibrillation should be performed, ideally, 3 to 5 minutes after collapse to increase the chance of success. If, as in most cases, the post-shock rhythm cannot achieve effective perfusion, CPR should be restarted immediately.

Finally, periodic medical evaluation, an effective local emergency protocol, and personnel trained in basic life support can ensure high-quality CPR and early defibrillation. This, plus quick access to centers with advanced cardiac life support are fundamental for decreasing the number of SD cases in athletes and increasing their chance of survival.

8.3. Special Aspects in Preventing Exercise/Sports-Related Sudden Death

8.3.1. Doping: Illicit Substances in Sports

Some substances used for doping can have deleterious repercussions especially on the cardiovascular system, including SD. Among the most commonly used substances, we highlight anabolic steroids, ephedrine and amphetamines. Among recreational drugs, we will address the use of cocaine and 3, 4-methylenedioxymethamphetamine, also known as ecstasy.

8.3.1.1. Anabolic Steroids

Anabolic steroids cause a number of side effects, including undesirable cardiovascular effects. Anabolic steroids can induce secondary hypertension and nephrosclerosis. Testosterone may increase the vascular response to norepinephrine and, as a consequence, promote fluid retention and elevated peripheral vascular resistance, leading to increased blood pressure.

Tagarakis et al.[302] were the first to describe another important effect of steroids at the microscopic level: the adaptation of cardiac capillaries and myocytes to concomitant steroid use and physical training, which leads to a disproportionate increase of in myocardial mass in relation to the cardiac capillaries. The results of this study suggest that anabolic steroids could cause an imbalance between oxygen supply and consumption, especially during exercise. Recently, it has been shown that the long-term administration of nandrolone decanoate to rats affects the physiology of the cardiac autonomic system, resulting in a greater predisposition to cardiovascular risk and SD. In addition, discontinued usage did not result in an immediate return to normality.[303] In humans, anabolic steroids may be associated with a shortened QT interval, thus negatively impacting cardiac electrical activity.[304] In addition, indiscriminate use of anabolic steroids seems to be an independent risk factor for morbidity and premature death.[305]

8.3.1.2. Ephedrine

In general, stimulants lead to tachycardia and increased myocardial oxygen consumption, which may lead to arrhythmias and acute myocardial infarction in susceptible individuals. Ephedrine may cause symptomatic ventricular tachycardia, frequent ventricular extrasystoles, atrial fibrillation, and SD. It is important to point out that many products called "natural" or "herbal" contain ephedrine-like substances that go unmentioned in the product description.

8.3.1.3. Amphetamines

Amphetamines are the prototype central nervous system stimulants. They come in a great variety of formulas and presentations, with the most commonly used being dextroamphetamine sulfate. This substance directly stimulates adrenergic receptors at the cortical level and the

ascending reticular activating system, and its indirect action includes displacing endogenous catecholamines from their sites in nerve endings. Its most pronounced general side effects are insomnia, dizziness, profuse sweating, tremors and euphoria; the cardiovascular effects are palpitations, tachycardia and precordial discomfort; cerebral hemorrhage is the neurological effect.

8.3.1.4. Cocaine

Cocaine causes generalized vasoconstriction, with the main consequence being hypertension. Although cocaine use causes more intense vasoconstriction in the central nervous system, it can also affect other organs such as the kidneys, resulting in glomerular, tubular, vascular and interstitial changes that lead to renal damage.[306,307] Cocaine may also cause acute myocardial infarction, cardiac arrhythmias, congestive cardiomyopathy, myocarditis, subarachnoid hemorrhage, aortic rupture, rhabdomyolysis, arterial hypertension, spontaneous or exercise-induced myocardial ischemia, and cardiac SD.

8.3.1.5. Ecstasy

Ecstasy is a hallucinogen similar to amphetamine. Due to its low cost and availability in tablet form, its popularity and consumption have increased significantly. Ecstasy increases the release of serotonin, dopamine and norepinephrine by presynaptic neurons. It also prevents the metabolism of these neurotransmitters by inhibiting monoamine oxidase. Its main cardiovascular effects are hypertension, tachycardia and arrhythmias, which can lead to SD.[308-310]

8.4. Evaluating Athletes and the Organization and Planning of Emergency Care

Sports-related SD is a dramatic event, and some measures can (and should) be taken by doctors to try to prevent this rare but tragic complication of sports/exercise.

8.4.1. Aspects Related to the Athlete

8.4.1.1. Pre-participation Screening

Considering that, in most cases, sports-related SD is caused by known or undiagnosed heart disease, everyone who intends to participate in sports should undergo PPS, regardless of age. This clinical examination should be preceded by a thorough anamnesis with particular attention paid to family history of cardiovascular disease and SD.

PPS, in attempting to detect these pathologies, is the most efficient way to prevent a fatal cardiovascular event.[311] In 2009, the International Olympic Committee published a paper on the importance of periodic medical evaluation in elite athletes.[312,313]

Although isolated clinical examination may fail to detect all forms of heart disease with the potential to cause SD, this procedure, whose emphasis on examining the cardiovascular system is preceded by a thorough anamnesis and previous pathological history (including family history), is nevertheless the first step in proper evaluation of the athlete.

The clinical examination should ideally include a resting 12-lead ECG. Although there is disagreement between U.S. (who recommend only anamnesis and physical examination) and European authorities (who recommend adding 12-lead ECG to anamnesis and clinical examination),[314] the Brazilian Society of Cardiology considers 12-lead ECG as mandatory at the first cardiological examination.[315] Resting ECG can diagnose numerous heart diseases that can lead to SD, including long QT syndrome,[316] Brugada syndrome,[193] Wolf-Parkinson-White syndrome[317] and HCM.[318] The European protocol, which includes anamnesis, physical examination and ECG, is currently used by the International Olympic Committee, the Italian Olympic Committee, FIFA and the Union of European Football Associations.[292,319,320] The clinical examination should include family and personal history and specific screening for Marfan syndrome.[312] A more detailed approach to PPS is available in another section of this Guideline.

8.4.1.2. Regarding the Athlete's Preparation

Follow-up for athletes must be thorough. To prevent clinical and cardiovascular events, basic preventive measures, such as adequate nutrition and hydration are also important, respecting rest periods and avoiding training and competition during the hottest periods of the day. Athletes in training and competition must be monitored and observed by qualified medical staff, preferably who have experience in sports medicine and first aid in case of emergency.

8.4.2. Aspects Related to Training Venues and Competition

8.4.2.1. Emergency Care and Medical Contingency Planning

In addition to procuring the necessary equipment for cases of cardiorespiratory arrest, training and competition venues should develop a medical contingency plan that includes personnel trained in cardiorespiratory resuscitation and optimized transport to a hospital with advanced cardiac life support when applicable.[286,321]

8.4.2.2. Automatic External Defibrillators

The AED is a computerized device that can identify the occurrence of ventricular fibrillation and tachycardia, the cardiac abnormalities that respond to shock. These devices should be available for use in less than 5 minutes at training venues and competitions, clubs, arenas, stadiums, gyms and cardiovascular rehabilitation clinics, which should also have a team trained in cardiopulmonary resuscitation.[145,322]

Among young athletes, CPR arrest usually occurs after intense training sessions or during a competition. Although the occurrence of these events is rare (corresponding to 1% of those occurring in middle-aged or older adults), prompt care and successful resuscitation increase long-term survival.[323,324]

Erratum

In the "The Brazilian Society of Cardiology and Brazilian Society of Exercise and Sports Medicine Updated Guidelines for Sports and Exercise Cardiology - 2019", the following names have been omitted from the publication: Japy Angelini Oliveira Filho, associate editor and fifth name in the authorship, from the Universidade Federal de São Paulo (UNIFESP); Antonio Claudio Lucas da Nobrega, from the Universidade Federal Fluminense; Luiz Gustavo Marin Emed, from the Hospital Cardiológico Costantini; and Roberto Vital, from the Comitê Paralímpico Brasileiro (CPB) and Universidade Federal do Rio Grande Do Norte (UFRN), inserted at the end of the authorship, in this order, and their respective institutions.

References

1. Caspersen CJ, Powell KE, Christenson GM. Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research. Public Health Rep. 1985;100(2):126-31.
2. Araujo CG, Scharhag J. Athlete: a working definition for medical and health sciences research. Scand J Med Sci Sports. 2016;26(1):4-7.
3. Ghorayeb N, Costa RV, Castro I, Daher DJ, Oliveira Filho JA, Oliveira MA; Sociedade Brasileira de Cardiologia. [Guidelines on exercise and sports cardiology from the Brazilian Society of Cardiology and the Brazilian Society of Sports Medicine]. Arq Bras Cardiol. 2013;100(1 Suppl 2):1-41. Erratum in: Arq Bras Cardiol. 2013;100(5):488.
4. Maron BJ, Levine BD, Washington RL, Baggish AL, Kovacs RJ, Maron MS; American Heart Association Electrocardiography and Arrhythmias Committee of Council on Clinical Cardiology, Council on Cardiovascular Disease in Young, Council on Cardiovascular and Stroke Nursing, Council on Functional Genomics and Translational Biology, and American College of Cardiology. Eligibility and Disqualification Recommendations for Competitive Athletes With Cardiovascular Abnormalities: Task Force 2: Preparticipation Screening for Cardiovascular Disease in Competitive Athletes: A Scientific Statement From the American Heart Association and American College of Cardiology. Circulation. 2015;132(22):e267-72.
5. Mosterd A. Pre-participation screening of asymptomatic athletes: "don't do stupid stuff". Neth Heart J. 2018;26(3):123-6.
6. Corrado D, Basso C, Pavei A, Michieli P, Schiavon M, Thiene G. Trends in sudden cardiovascular death in young competitive athletes after implementation of a preparticipation screening program. JAMA. 2006;296(13):1593-601.
7. Corrado D, Zorzi A. Sudden death in athletes. Int J Cardiol. 2017 Jun 15;237:67-70.
8. Schmied C, Borjesson M. Sudden cardiac death in athletes. J Intern Med. 2014;275(2):93-103.
9. De Wolf D, Matthys D. Sports preparticipation cardiac screening: what about children? Eur J Pediatr. 2014;173(6):711-9.
10. Lehman PJ, Carl RL. The preparticipation physical evaluation. Pediatr Ann. 2017;46(3):e85-e92.
11. Ackerman M, Atkins DL, Triedman JK. Sudden cardiac death in the young. Circulation. 2016;133(10):1006-26.
12. Riebe D, Franklin BA, Thompson PD, Garber CE, Whitfield GP, Magal M, et al. Updating ACSM's recommendations for exercise preparticipation health screening. Med Sci Sports Exerc. 2015;47(11):2473-9. Erratum in: Med Sci Sports Exerc. 2016;48(3):579.
13. Whitfield GP, Riebe D, Magal M, Liguori G. Applying the ACSM preparticipation screening algorithm to U.S. adults: National Health and Nutrition Examination Survey 2001-2004. Med Sci Sports Exerc. 2017;49(10):2056-63.
14. Mirabelli MH, Devine MJ, Singh J, Mendoza M. The preparticipation sports evaluation. Am Fam Physician. 2015;92(5):371-6.
15. Oxborough D, Augustine D, Gati S, George K, Harkness A, Mathew T, et al. A guideline update for the practice of echocardiography in the cardiac screening of sports participants: a joint policy statement from the British Society of Echocardiography and Cardiac Risk in the Young. Echo Res Pract. 2018;5(1):G1-G10.
16. Maiorana AJ, Williams AD, Askew CD, Levinger I, Coombes J, Vicenzino B, et al. Exercise professionals with advanced clinical training should be afforded greater responsibility in pre-participation exercise screening: a new collaborative model between exercise professionals and physicians. Sports Med. 2018;48(6):1293-1302.
17. Corrà U, Giannuzzi P. Role of cardiopulmonary exercise testing in today's cardiovascular prevention and rehabilitation. Eur J Cardiovasc Prev Rehabil. 2006;13(4):473-4.
18. Beaumont A, Grace F, Richards J, Hough J, Oxborough D, Sculthorpe N. Left ventricular speckle tracking-derived cardiac strain and cardiac twist mechanics in athletes: a systematic review and meta-analysis of controlled studies. Sports Med. 2017;47(6):1145-70.
19. Agir A, Bozyel S, Celikyurt U, Argan O, Yilmaz I, Karauzum K, et al. Arrhythmogenic right ventricular cardiomyopathy in pregnancy. Int Heart J. 2014;55(4):372-6.
20. Corrado D, Zorzi A, Cerrone M, Rigato I, Mongillo M, Bauce B, et al. Relationship between arrhythmogenic right ventricular cardiomyopathy and Brugada Syndrome: new insights from molecular biology and clinical implications. Circ Arrhythm Electrophysiol. 2016;9(4):e003631.
21. Halabchi F, Seif-Barghi T, Mazaheri R. Sudden cardiac death in young athletes; a literature review and special considerations in asia. Asian J Sports Med. 2011;2(1):1-15.
22. Carbone A, D'Andrea A, Riegler L, Scarafile R, Pezzullo E, Martone F, et al. Cardiac damage in athlete's heart: When the "supernormal" heart fails! World J Cardiol. 2017;9(6):470-80.
23. Bille K, Figueiras D, Schamasch P, Kappenberger L, Brenner JI, Meijboom FJ, et al. Sudden cardiac death in athletes: the Lausanne Recommendations. Eur J Cardiovasc Prev Rehabil. 2006;13(6):859-75.
24. Martin U, Holder R, Hodgkinson J, McManus R. Inter-arm blood pressure differences compared with ambulatory monitoring: a manifestation of the 'white-coat' effect? Br J Gen Pract. 2013;63(607):e97-103. Erratum in: Br J Gen Pract. 2013;63(610):240.
25. Grazioli G, Sanz de la Garza M, Vidal B, Montserrat S, Sarquella-Brugada G, Pi R, et al. Prevention of sudden death in adolescent athletes: Incremental diagnostic value and cost-effectiveness of diagnostic tests. Eur J Prev Cardiol. 2017;24(13):1446-54.
26. Lippi G, Favaloro EJ, Sanchis-Gomar F. Sudden cardiac and noncardiac death in sports: epidemiology, causes, pathogenesis, and prevention. Semin Thromb Hemost. 2018 Jun 4. [Epub ahead of print].
27. Bohm P, Scharhag J, Meyer T. Data from a nationwide registry on sports-related sudden cardiac deaths in Germany. Eur J Prev Cardiol. 2016;23(6):649-56.
28. Riding NR, Sheikh N, Adamuz C, Watt V, Farooq A, Whyte GP, et al. Comparison of three current sets of electrocardiographic interpretation criteria for use in screening athletes. Heart. 2015;101(5):384-90.
29. Sharma S, Drezner JA, Baggish A, Papadakis M, Wilson MG, Prutkin JM, et al. International recommendations for electrocardiographic interpretation in athletes. Eur Heart J. 2018;39(16):1466-80.
30. Scharhag J, Löllgen H, Kindermann W. Competitive sports and the heart: benefit or risk? Dtsch Arztebl Int. 2013;110(1-2):14-23.

31. Panhuyzen-Goedkoop NM, Jørstad HT, Smeets JL. A new consensus document on electrocardiographic interpretation in athletes: does it help to prevent sudden cardiac death in athletes? Neth Heart J. 2018;26(3):127-32.

32. Sharma S, Papadakis M. Interpreting the Athlete's EKG: are all repolarization anomalies created equal? Circulation. 2015;131(2):128-30.

33. Bessem B, De Bruijn MC, Nieuwland W, Zwerver J, Van Den Berg M. The electrocardiographic manifestations of athlete's heart and their association with exercise exposure. Eur J Sport Sci. 2018;18(4):587-93.

34. Guasch E, Mont L, Sitges M. Mechanisms of atrial fibrillation in athletes: what we know and what we do not know. Neth Heart J. 2018;26(3):133-45.

35. Dhutia H, Malhotra A, Gabus V, Merghani A, Finocchiaro G, Millar L, et al. Cost implications of using different ECG criteria for screening young athletes in the United Kingdom. J Am Coll Cardiol. 2016;68(7):702-11.

36. Thiene G, Corrado D, Basso C. Revisiting definition and classification of cardiomyopathies in the era of molecular medicine. Eur Heart J. 2008;29(2):144-6.

37. Löllgen H, Leyk D. Exercise testing in sports medicine. Dtsch Arztebl Int. 2018;115(24):409-416.

38. Meneghelo RS, Araújo CG, Stein R, Mastrocolla LE, Albuquerque PF, Serra SM, et al; Sociedade Brasileira de Cardiologia. [III Guidelines of Sociedade Brasileira de Cardiologia on the exercise test]. Arq Bras Cardiol. 2010;95(5 Suppl 1):1-26.

39. Beltz NM, Gibson AL, Janot JM, Kravitz L, Mermier CM, Dalleck LC. Graded exercise testing protocols for the determination of VO2max: historical perspectives, progress, and future considerations. J Sports Med (Hindawi Publ Corp). 2016;2016:3968393.

40. Jemni M, Prince MS, Baker JS. Assessing cardiorespiratory fitness of soccer players: is test specificity the issue?-A review. Sports Med Open. 2018;4(1):28.

41. Garner KK, Pomeroy W, Arnold JJ. Exercise stress testing: indications and common questions. Am Fam Physician. 2017;96(5):293-9.

42. Myers J, Prakash M, Froelicher V, Do D, Partington S, Atwood JE. Exercise capacity and mortality among men referred for exercise testing. N Engl J Med. 2002;346(11):793-801.

43. Franklin BA, Brinks J, Berra K, Lavie CJ, Gordon NF, Sperling LS. Using metabolic equivalents in clinical practice. Am J Cardiol. 2018;121(3):382-7.

44. Kokkinos P. Physical activity, health benefits, and mortality risk. ISRN Cardiol. 2012;2012:718789.

45. Faselis C, Doumas M, Pittaras A, Narayan P, Myers J, Tsimploulis A, et al. Exercise capacity and all-cause mortality in male veterans with hypertension aged > 70 years. Hypertension. 2014;64(1):30-5.

46. Löffler AI, Perez MV, Nketiah EO, Bourque JM, Keeley EC. Usefulness of achieving ≥ 10 METs with a negative stress electrocardiogram to screen for high-risk obstructive coronary artery disease in patients referred for coronary angiography after exercise stress testing. Am J Cardiol. 2018;121(3):289-93.

47. Sik EC, Batt ME, Heslop LM. Atypical chest pain in athletes. Curr Sports Med Rep. 2009;8(2):52-8.

48. Moran B, Bryan S, Farrar T, Salud C, Visser G, Decuba R, et al. Diagnostic Evaluation of Nontraumatic Chest Pain in Athletes. Curr Sports Med Rep. 2017;16(2):84-94.

49. Puymirat E, Simon T, Cayla G, Cottin Y, Elbaz M, Coste P, et al; USIK, USIC 2000, and FAST-MI investigators. Acute myocardial infarction: changes in patient characteristics, management, and 6-month outcomes over a period of 20 years in the FAST-MI Program (French Registry of Acute ST-Elevation or Non-ST-Elevation Myocardial Infarction) 1995 to 2015. Circulation. 2017;136(20):1908-19.

50. Vaidya GN. Application of exercise ECG stress test in the current high cost modern-era healthcare system. Indian Heart J. 2017;69(4):551-5.

51. Katritsis GD, Katritsis DG. The electrocardiogram in athletes revisited. Arrhythm Electrophysiol Rev. 2013;2(2):99-104.

52. Ibrahim M, Hasan R, Pitonak P. Exercise-induced ST-segment elevation during the recovery phase of an exercise stress test. Exp Clin Cardiol. 2013;18(2):e92-4.

53. Azarbal B, Hayes SW, Lewin HC, Hachamovitch R, Cohen I, Berman DS. The incremental prognostic value of percentage of heart rate reserve achieved over myocardial perfusion single-photon emission computed tomography in the prediction of cardiac death and all-cause mortality: superiority over 85% of maximal age-predicted heart rate. J Am Coll Cardiol. 2004;44(2):423-30.

54. Cole CR, Foody JM, Blackstone EH, Lauer MS. Heart rate recovery after submaximal exercise testing as a predictor of mortality in a cardiovascularly healthy cohort. Ann Intern Med. 2000;132(7):552-5.

55. Frolkis JP, Pothier CE, Blackstone EH, Lauer MS. Frequent ventricular ectopy after exercise as a predictor of death. N Engl J Med. 2003;348(9):781-90. Erratum in: N Engl J Med. 2003;348(15):1508.

56. Dhoble A, Lahr BD, Allison TG, Kopecky SL. Cardiopulmonary fitness and heart rate recovery as predictors of mortality in a referral population. J Am Heart Assoc. 2014;3(2):e000559.

57. Lessa I. Medical care and deaths due to coronary artery disease in Brazil, 1980-1999. Arq Bras Cardiol. 2003;81(4):336-42.

58. Huston TP, Puffer JC, Rodney WM. The athletic heart syndrome. N Engl J Med. 1985;313(1):24-32.

59. Ulucan Ş, Kaya Z, Keser A, Katlandur H, Karanfil M, Ateş İ. Deterioration of heart rate recovery index in patients with erectile dysfunction. Anatol J Cardiol. 2016;16(4):264-9.

60. Herdy AH, Ritt LE, Stein R, Araújo CG, Milani M, Meneghelo RS, et al. Cardiopulmonary exercise test: background, applicability and interpretation. Arq Bras Cardiol. 2016;107(5):467-81.

61. Reeves T, Bates S, Sharp T, Richardson K, Bali S, Plumb J, et al; Perioperative Exercise Testing and Training Society (POETTS). Cardiopulmonary exercise testing (CPET) in the United Kingdom-a national survey of the structure, conduct, interpretation and funding. Perioper Med (Lond). 2018 Jan 26;7:2. Erratum in: Perioper Med (Lond). 2018 May 4;7:8.

62. Nadruz W Jr, West E, Sengeløv M, Santos M, Groarke JD, Forman DE, et al. Prognostic value of cardiopulmonary exercise testing in heart failure with reduced, midrange, and preserved ejection fraction. J Am Heart Assoc. 2017;6(11). pii: e006000.

63. Kleber FX, Köln PJ. Oxygen consumption trajectory flattening-yet another cardiopulmonary exercise testing parameter in chronic heart failure. Eur J Heart Fail. 2018;20(7):1125-7.

64. Morosin M, Farina S, Vignati C, Spadafora E, Sciomer S, Salvioni E, et al. Exercise performance, haemodynamics, and respiratory pattern do not identify heart failure patients who end exercise with dyspnoea from those with fatigue. ESC Heart Fail. 2018;5(1):115-9.

65. Malhotra R, Bakken K, D'Elia E, Lewis GD. Cardiopulmonary exercise testing in heart failure. JACC Heart Fail. 2016;4(8):607-16.

66. Keteyian SJ, Patel M, Kraus WE, Brawner CA, McConnell TR, Piña IL, et al; HF-ACTION Investigators. Variables measured during cardiopulmonary exercise testing as predictors of mortality in chronic systolic heart failure. J Am Coll Cardiol. 2016;67(7):780-9.

67. Bhagwat M, Paramesh K. Cardio-pulmonary exercise testing: an objective approach to pre-operative assessment to define level of perioperative care. Indian J Anaesth. 2010;54(4):286-91.

68. Belardinelli R, Lacalaprice F, Tiano L, Muçai A, Perna GP. Cardiopulmonary exercise testing is more accurate than ECG-stress testing in diagnosing myocardial ischemia in subjects with chest pain. Int J Cardiol. 2014;174(2):337-42.

69. Leischik R, Dworrak B, Foshag P, Strauss M, Spelsberg N, Littwitz H, et al. Pre-participation and follow-up screening of athletes for endurance sport. J Clin Med Res. 2015;7(6):385-92.

70. Corrado D, Pelliccia A, Bjørnstad HH, Vanhees L, Biffi A, Borjesson M, et al; Study Group of Sport Cardiology of the Working Group of Cardiac Rehabilitation and Exercise Physiology and the Working Group of Myocardial and Pericardial Diseases of the European Society of Cardiology. Cardiovascular pre-participation screening of young competitive athletes for prevention of sudden death: proposal for a common European protocol. Consensus Statement of the Study Group of Sport Cardiology of the Working Group of Cardiac Rehabilitation and Exercise Physiology and the Working Group of Myocardial and Pericardial Diseases of the European Society of Cardiology. Eur Heart J. 2005;26(5):516-24.

71. Sharma S, Merghani A, Gati S. Cardiac screening of young athletes prior to participation in sports: difficulties in detecting the fatally flawed among the fabulously fit. JAMA Intern Med. 2015;175(1):125-7.

72. Thompson PD, Franklin BA, Balady GJ, Blair SN, Corrado D, Estes NA 3rd, et al; American Heart Association Council on Nutrition, Physical Activity, and Metabolism; American Heart Association Council on Clinical Cardiology; American College of Sports Medicine. Exercise and acute cardiovascular events placing the risks into perspective: a scientific statement from the American Heart Association Council on Nutrition, Physical Activity, and Metabolism and the Council on Clinical Cardiology. Circulation. 2007;115(17):2358-68.

73. Pelliccia A, Culasso F, Di Paolo FM, Accetura D, Cantore R, Castagna W, et al. Prevalence of abnormal electrocardiograms in a large, unselected population undergoing pre-participation cardiovascular screening. Eur Heart J. 2007;28(16):2006-10.

74. Campuzano O, Sanchez-Molero O, Fernandez A, Mademont-Soler I, Coll M, Perez-Serra A, et al. Sudden arrhythmic death during exercise: a post-mortem genetic analysis. Sports Med. 2017;47(10):2101-15.

75. Priori SG, Blomström-Lundqvist C, Mazzanti A, Blom N, Borggrefe M, Camm J, et al; ESC Scientific Document Group. 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: The Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC). Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC). Eur Heart J. 2015;36(41):2793-867.

76. Mont L, Pelliccia A, Sharma S, Biffi A, Borjesson M, BrugadaTerradellas J, et al. Pre-participation cardiovascular evaluation for athletic participants to prevent sudden death: position paper from the EHRA and the EACPR, branches of the ESC. Endorsed by APHRS, HRS, and SOLAECE. Eur J Prev Cardiol. 2017;24(1):41-69.

77. Stein R, Trujillo JP, Silveira AD, Lamounier Júnior A, Iglesias LM. Genetic evaluation, familial screening and exercise. Arq Bras Cardiol. 2017;108(3):263-70.

78. Marcondes L, Crawford J, Earle N, Smith W, Hayes I, Morrow P, et al; Cardiac Inherited Disease Group New Zealand. Long QT molecular autopsy in sudden unexplained death in the young (1-40 years old): Lessons learnt from an eight year experience in New Zealand. PLoS One. 2018;13(4):e0196078.

79. Rueda M, Wagner JL, Phillips TC, Topol SE, Muse ED, Lucas JR, et al. Molecular autopsy for sudden death in the young: is data aggregation the key? Front Cardiovasc Med. 2017;4:72.

80. Cooper DN, Krawczak M, Polychronakos C, Tyler-Smith C, Kehrer-Sawatzki H. Where genotype is not predictive of phenotype: towards an understanding of the molecular basis of reduced penetrance in human inherited disease. Hum Genet. 2013;132(10):1077-130.

81. Galderisi M, Cardim N, D'Andrea A, Bruder O, Cosyns B, Davin L, et al. The multi-modality cardiac imaging approach to the Athlete's heart: an expert consensus of the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging. 2015;16(4):353.

82. Varnava A, Baboonian C, Davison F, de Cruz L, Elliott PM, Davies MJ, et al. A new mutation of the cardiac troponin T gene causing familial hypertrophic cardiomyopathy without left ventricular hypertrophy. Heart. 1999;82(5):621-4.

83. Christiaans I, Lekanne dit Deprez RH, van Langen IM, Wilde AA. Ventricular fibrillation in MYH7-related hypertrophic cardiomyopathy before onset of ventricular hypertrophy. Heart Rhythm. 2009;6(9):1366-9.

84. Tabib A, Loire R, Chalabreysse L, Meyronnet D, Miras A, Malicier D, et al. Circumstances of death and gross and microscopic observations in a series of 200 cases of sudden death associated with arrhythmogenic right ventricular cardiomyopathy and/or dysplasia. Circulation. 2003;108(24):3000-5.

85. Bauce B, Rampazzo A, Basso C, Mazzotti E, Rigato I, Steriotis A, et al. Clinical phenotype and diagnosis of arrhythmogenic right ventricular cardiomyopathy in pediatric patients carrying desmosomal gene mutations. Heart Rhythm. 2011;8(11):1686-95.

86. Ehlermann P, Lehrke S, Papavassiliu T, Meder B, Borggrefe M, Katus HA, et al. Sudden cardiac death in a patient with lamin A/C mutation in the absence of dilated cardiomyopathy or conduction disease. Clin Res Cardiol. 2011;100(6):547-51.

87. Corrado D, Wichter T, Link MS, Hauer R, Marchlinski F, Anastasakis A, et al. Treatment of arrhythmogenic right ventricular cardiomyopathy/dysplasia: an international task force consensus statement. Eur Heart J. 2015;36(46):3227-37.

88. Finocchiaro G, Papadakis M, Robertus JL, Dhutia H, Steriotis AK, Tome M, et al. Etiology of sudden death in sports: insights from a United Kingdom Regional Registry. J Am Coll Cardiol. 2016;67(18):2108-15.

89. Maron BJ, Udelson JE, Bonow RO, Nishimura RA, Ackerman MJ, Estes NA 3rd, et al; American Heart Association Electrocardiography and Arrhythmias Committee of Council on Clinical Cardiology, Council on Cardiovascular Disease in Young, Council on Cardiovascular and Stroke Nursing, Council on Functional Genomics and Translational Biology, and American College of Cardiology. Eligibility and disqualification recommendations for competitive athletes with cardiovascular abnormalities: Task Force 3: Hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy and other cardiomyopathies, and myocarditis: a Scientific Statement from the American Heart Association and American College of Cardiology. Circulation. 2015;132(22):e273-80.

90. Bagnall RD, Weintraub RG, Ingles J, Duflou J, Yeates L, Lam L, et al. A prospective study of sudden cardiac death among children and young adults. N Engl J Med. 2016;374(25):2441-52.

91. Liew AC, Vassiliou VS, Cooper R, Raphael CE. Hypertrophic cardiomyopathy-past, present and future. J Clin Med. 2017;6(12). pii: E118.

92. Maron BJ, Haas TS, Ahluwalia A, Murphy CJ, Garberich RF. Demographics and epidemiology of sudden deaths in young competitive athletes: from the United States National Registry. Am J Med. 2016;129(11):1170-7.

93. Inciardi RM, Galderisi M, Nistri S, Santoro C, Cicoira M, Rossi A. Echocardiographic advances in hypertrophic cardiomyopathy: three-dimensional and strain imaging echocardiography. Echocardiography. 2018;35(5):716-26.

94. Espinola-Zavaleta N, Vega A, Basto DM, Alcantar-Fernández AC, Guarner Lans V, Soto ME. Survival and clinical behavior of hypertrophic cardiomyopathy in a Latin American cohort in contrast to cohorts from the developed world. J Cardiovasc Ultrasound. 2015;23(1):20-6.

95. Geske JB, Ommen SR, Gersh BJ. Hypertrophic cardiomyopathy: clinical update. JACC Heart Fail. 2018;6(5):364-75.

96. Pasquale F, Syrris P, Kaski JP, Mogensen J, McKenna WJ, Elliott P. Long-term outcomes in hypertrophic cardiomyopathy caused by mutations in the cardiac troponin T gene. Circ Cardiovasc Genet. 2012;5(1):10-7.

97. Zhou N, Qin S, Liu Y, Tang L, Zhao W, Pan C, et al. Whole-exome sequencing identifies rare compound heterozygous mutations in the MYBPC3 gene associated with severe familial hypertrophic cardiomyopathy. Eur J Med Genet. 2018 Mar 8. [Epub ahead of print].

98. Burke MA, Cook SA, Seidman JG, Seidman CE. Clinical and mechanistic insights into the genetics of cardiomyopathy. J Am Coll Cardiol. 2016;68(25):2871-86.

99. Lu QW, Wu XY, Morimoto S. Inherited cardiomyopathies caused by troponin mutations. J Geriatr Cardiol. 2013;10(1):91-101.

100. Zorzi A, Calore C, Vio R, Pelliccia A, Corrado D. Accuracy of the ECG for differential diagnosis between hypertrophic cardiomyopathy and athlete's heart: comparison between the European Society of Cardiology (2010) and International (2017) criteria. Br J Sports Med. 2018;52(10):667-673.

101. Drezner JA, Sharma S, Baggish A, Papadakis M, Wilson MG, Prutkin JM, et al. International criteria for electrocardiographic interpretation in athletes: Consensus statement. Br J Sports Med. 2017;51(9):704-31.

102. Semsarian C; CSANZ Genetics Council Writing Group. Update on the diagnosis and management of hypertrophic cardiomyopathy. Heart Lung Circ. 2018;27(3):276-9.

103. Dominguez F, González-López E, Padron-Barthe L, Cavero MA, Garcia-Pavia P. Role of echocardiography in the diagnosis and management of hypertrophic cardiomyopathy. Heart. 2018;104(3):261-73.

104. Biffi A, Maron BJ, Culasso F, Verdile L, Fernando F, Di Giacinto B, et al. Patterns of ventricular tachyarrhythmias associated with training, deconditioning and retraining in elite athletes without cardiovascular abnormalities. Am J Cardiol. 2011;107(5):697-703.

105. Al-Khatib SM, Stevenson WG, Ackerman MJ, Bryant WJ1, Callans DJ, Curtis AB, et al. 2017 AHA/ACC/HRS Guideline for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death: Executive Summary. Circulation. 2018;138(13):e210-e271. Erratum in: Circulation. 2018;138(13):e415-e418.

106. Kobayashi S, Sakai Y, Taguchi I, Utsunomiya H, Shiota T. Causes of an increased pressure gradient through the left ventricular outflow tract: a West Coast experience. J Echocardiogr. 2018;16(1):34-41.

107. Quarta G, Aquaro GD, Pedrotti P, Pontone G, Dellegrottaglie S, Iacovoni A. Cardiovascular magnetic resonance imaging in hypertrophic cardiomyopathy: the importance of clinical context. Eur Heart J Cardiovasc Imaging. 2018;19(6):601-10.

108. Marchesini M, Uguccioni L, Parisi R, Mattioli G, Terzi F, Olivieri R. The role of cardiac magnetic resonance imaging in hypertrophic cardiomyopathy. Rev Cardiovasc Med. 2016;17(1-2):57-64.

109. Magrì D, Santolamazza C. Cardiopulmonary exercise test in hypertrophic cardiomyopathy. Ann Am Thorac Soc. 2017;14(Supplement_1):S102-S109.

110. Coats CJ, Rantell K, Bartnik A, Patel A, Mist B, McKenna WJ, et al. Cardiopulmonary exercise testing and prognosis in hypertrophic cardiomyopathy. Circ Heart Fail. 2015;8(6):1022-31.

111. Sharma S, Elliott P, Whyte G, Jones S, Mahon N, Whipp B, et al. Utility of cardiopulmonary exercise in the assessment of clinical determinants of functional capacity in hypertrophic cardiomyopathy. Am J Cardiol. 2000;86(2):162-8.

112. Rowin EJ, Maron BJ, Olivotto I, Maron MS. Role of exercise testing in hypertrophic cardiomyopathy. JACC Cardiovasc Imaging. 2017;10(11):1374-86.

113. Hindieh W, Adler A, Weissler-Snir A, Fourey D, Harris S, Rakowski H. Exercise in patients with hypertrophic cardiomyopathy: a review of current evidence, national guideline recommendations and a proposal for a new direction to fitness. J Sci Med Sport. 2017;20(4):333-8.

114. Norrish G, Cantarutti N, Pissaridou E, Ridout DA, Limongelli G, Elliott PM, et al. Risk factors for sudden cardiac death in childhood hypertrophic cardiomyopathy: A systematic review and meta-analysis. Eur J Prev Cardiol. 2017;24(11):1220-30.

115. Weissler-Snir A, Adler A, Williams L, Gruner C, Rakowski H. Prevention of sudden death in hypertrophic cardiomyopathy: bridging the gaps in knowledge. Eur Heart J. 2017;38(22):1728-37.

116. Maron MS, Rowin EJ, Olivotto I, Casey SA, Arretini A, Tomberli B, et al. Contemporary natural history and management of nonobstructive hypertrophic cardiomyopathy. J Am Coll Cardiol. 2016;67(12):1399-409.

117. Dejgaard LA, Haland TF, Lie OH, Ribe M, Bjune T, Leren IS, et al. Vigorous exercise in patients with hypertrophic cardiomyopathy. Int J Cardiol. 2018 Jan 1;250:157-63.

118. Tsatsopoulou A. Arrhythmogenic right ventricular cardiomyopathy and pregnancy. Int J Cardiol. 2018 May 1;258:199-200.

119. Wang W, James CA, Calkins H. Diagnostic and therapeutic strategies for arrhythmogenic right ventricular dysplasia/cardiomyopathy patient. Europace. 2018 Apr 23. [Epub ahead of print].

120. Calkins H, Corrado D, Marcus F. Risk stratification in arrhythmogenic right ventricular cardiomyopathy. Circulation. 2017;136(21):2068-82.

121. Corrado D, Link MS, Calkins H. Arrhythmogenic right ventricular cardiomyopathy. N Engl J Med. 2017;376(1):61-72.

122. Tsatsopoulou A, Bossone E. Common presentation of rare diseases: arrhythmogenic right ventricular cardiomyopathy and its mimics. Int J Cardiol. 2018 Apr 15;257:371-7.

123. Etoom Y, Govindapillai S, Hamilton R, Manlhiot C, Yoo SJ, Farhan M, et al. Importance of CMR within the Task Force Criteria for the diagnosis of ARVC in children and adolescents. J Am Coll Cardiol. 2015;65(10):987-95.

124. Zaidi A, Sheikh N, Jongman JK, Gati S, Panoulas VF, Carr-White G. Clinical differentiation between physiological remodeling and arrhythmogenic right ventricular cardiomyopathy in athletes with marked electrocardiographic repolarization anomalies. J Am Coll Cardiol. 2015;65(25):2702-11.

125. Paul M, Meyborg M, Boknik P, Gergs U, Gerss J, Schmitz W, et al. Autonomic dysfunction in patients with arrhythmogenic right ventricular cardiomyopathy: biochemical evidence of altered signaling pathways. Pacing Clin Electrophysiol. 2014;37(2):173-8.

126. La Gerche A. Defining the interaction between exercise and arrhythmogenic right ventricular cardiomyopathy. Eur J Heart Fail. 2015;17(2):128-31.

127. Haugaa KH, Bundgaard H, Edvardsen T, Eschen O, Gilljam T, Hansen J, et al. Management of patients with Arrhythmogenic Right Ventricular Cardiomyopathy in the Nordic countries. Scand Cardiovasc J. 2015;49(6):299-307.

128. James CA, Bhonsale A, Tichnell C, Murray B, Russell SD, Tandri H, et al. Exercise increases age-related penetrance and arrhythmic risk in arrhythmogenic right ventricular dysplasia/cardiomyopathy-associated desmosomal mutation carriers. J Am Coll Cardiol. 2013;62(14):1290-7.

129. Wang W, Orgeron G, Tichnell C, Murray B, Crosson J, Monfredi O, et al. Impact of exercise restriction on arrhythmic risk among patients with arrhythmogenic right ventricular cardiomyopathy. J Am Heart Assoc. 2018;7(12). pii: e008843.

130. Lie OH, Dejgaard LA, Saberniak J, Rootwelt C, Stokke MK, Edvardsen T, et al. Harmful effects of exercise intensity and exercise duration in patients with arrhythmogenic cardiomyopathy. JACC Clin Electrophysiol. 2018;4(6):744-53.

131. Shah N, Phelan DM. Myocarditis in the athlete. Am Coll Cardiol. 2018 Jan 31. [Epub ahead of print].

132. Trachtenberg BH, Hare JM. Inflammatory cardiomyopathic syndromes. Circ Res. 2017;121(7):803-18.

133. Chandra N, Bastiaenen R, Papadakis M, Sharma S. Sudden cardiac death in young athletes: practical challenges and diagnostic dilemmas. J Am Coll Cardiol. 2013;61(10):1027-40.

134. Caforio AL, Pankuweit S, Arbustini E, Basso C, Gimeno-Blanes J, Felix SB, et al; European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. 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.

135. Sagar S, Liu PP, Cooper LT Jr. Myocarditis. Lancet. 2012;379(9817):738-47.

136. Ukena C, Mahfoud F, Kindermann I, Kandolf R, Kindermann M, Bohm M. Prognostic electrocardiographic parameters in patients with suspected myocarditis. Eur J Heart Fail. 2011;13(4):398-405

137. Zorzi A, Pelliccia A, Corrado D. Inherited cardiomyopathies and sports participation. Neth Heart J. 2018;26(3):154-65.

138. Weintraub RG, Semsarian C, Macdonald P. Dilated cardiomyopathy. Lancet. 2017;390(10092):400-14.

139. McNally EM, Mestroni L. Dilated cardiomyopathy: genetic determinants and mechanisms. Circ Res. 2017;121(7):731-48.

140. Pi SH, Kim SM, Choi JO, Kim EK, Chang SA, Choe YH, et al. Prognostic value of myocardial strain and late gadolinium enhancement on cardiovascular magnetic resonance imaging in patients with idiopathic dilated cardiomyopathy with moderate to severely reduced ejection fraction. J Cardiovasc Magn Reson. 2018;20(1):36.

141. Merlo M, Cannatà A, Gobbo M, Stolfo D, Elliott PM, Sinagra G. Evolving concepts in dilated cardiomyopathy. Eur J Heart Fail. 2018;20(2):228-39.

142. Asif IM, Harmon KG. Incidence and etiology of sudden cardiac death: new updates for athletic departments. Sports Health. 2017;9(3):268-79.

143. Asatryan B, Vital C, Kellerhals C, Medeiros-Domingo A, Gräni C, Trachsel LD, et al. Sports-related sudden cardiac deaths in the young population of Switzerland. PLoS One. 2017;12(3):e0174434.

144. Emery MS, Kovacs RJ. Sudden cardiac death in athletes. JACC Heart Fail. 2018;6(1):30-40.

145. Herdy AH, López-Jimenez F, Terzic CP, Milani M, Stein R, Carvalho T, et al; Sociedade Brasileira de Cardiologia. South American Guidelines for Cardiovascular Disease Prevention and Rehabilitation. Arq Bras Cardiol. 2014;103(2 Supl.1):1-31.

146. Towbin JA, Lorts A, Jefferies JL. Left ventricular non-compaction cardiomyopathy. Lancet. 2015;386(9995):813-25.

147. Sedaghat-Hamedani F, Haas J, Zhu F, Geier C, Kayvanpour E, Liss M, et al. Clinical genetics and outcome of left ventricular non-compaction cardiomyopathy. Eur Heart J. 2017;38(46):3449-60.

148. Hotta VT, Tendolo SC, Rodrigues AC, Fernandes F, Nastari L, Mady C. Limitations in the diagnosis of noncompaction cardiomyopathy by echocardiography. Arq Bras Cardiol. 2017;109(5):483-8.

149. Finsterer J, Stöllberger C, Towbin JA. Left ventricular noncompaction cardiomyopathy: cardiac, neuromuscular, and genetic factors. Nat Rev Cardiol. 2017;14(4):224-37.

150. Thavendiranathan P, Dahiya A, Phelan D, Desai MY, Tang WH. Isolated left ventricular non-compaction controversies in diagnostic criteria, adverse outcomes and management. Heart. 2013;99(10):681-9.

151. Ganga HV, Thompson PD. Sports participation in non-compaction cardiomyopathy: a systematic review. Br J Sports Med. 2014;48(20):1466-71.

152. Coris EE, Moran BK, De Cuba R, Farrar T, Curtis AB. Left ventricular non-compaction in athletes: to play or not to play. Sports Med. 2016;46(9):1249-59.

153. Gati S, Chandra N, Bennett RL, Reed M, Kervio G, Panoulas VF, et al. Increased left ventricular trabeculation in highly trained athletes: do we need more stringent criteria for the diagnosis of left ventricular non-compaction in athletes? Heart. 2013;99(6):401-8. Erratum in: Heart. 2013;99(7):506.

154. Caselli S, Ferreira D, Kanawati E, Di Paolo F, Pisicchio C, Attenhofer Jost C, et al. Prominent left ventricular trabeculations in competitive athletes: a proposal for risk stratification and management. Int J Cardiol. 2016 Nov 15;223:590-5.

155. Monge-Maillo B, López-Vélez R. Challenges in the management of Chagas disease in Latin-American migrants in Europe. Clin Microbiol Infect. 2017;23(5):290-5.

156. Cucunubá ZM, Okuwoga O, Basáñez MG, Nouvellet P. Increased mortality attributed to Chagas disease: a systematic review and meta-analysis. Parasit Vectors. 2016 Jan 27;9:42.

157. Traina MI, Hernandez S, Sanchez DR, Dufani J, Salih M, Abuhamidah AM, et al. Prevalence of Chagas Disease in a U.S. population of Latin American immigrants with conduction abnormalities on electrocardiogram. PLoS Negl Trop Dis. 2017;11(1):e0005244.

158. Merejo Peña CM, Reis MS, Pereira BB, Nascimento EM, Pedrosa RC. Dysautonomy in different death risk groups (Rassi score) in patients with Chagas heart disease. Pacing Clin Electrophysiol. 2018;41(3):238-45.

159. Gadioli LP, Miranda CH, Pintya AO, de Figueiredo AB, Schmidt A, Maciel BC, et al. The severity of ventricular arrhythmia correlates with the extent of myocardial sympathetic denervation, but not with myocardial fibrosis extent in chronic Chagas cardiomyopathy: Chagas disease, denervation and arrhythmia. J Nucl Cardiol. 2018;25(1):75-83.

160. Costa HS, Nunes MC, Souza AC, Lima MM, Carneiro RB, Sousa GR, et al. Exercise-induced ventricular arrhythmias and vagal dysfunction in Chagas disease patients with no apparent cardiac involvement. Rev Soc Bras Med Trop. 2015;48(2):175-80.

161. Tassi EM, Continentino MA, do Nascimento EM, Pereira BB, Pedrosa RC. Relationship between fibrosis and ventricular arrhythmias in Chagas heart disease without ventricular dysfunction. Arq Bras Cardiol. 2014;102(5):456-64.

162. Matos LD, Azevedo LF, Brum PC, Sosa EA, Martinelli M, Negrão CE. Long distance runner with dilated cardiomyopathy and excellent performance. Arq Bras Cardiol. 2011;96(1):e3-6.

163. Panhuyzen-Goedkoop NM, Wilde AA. Athletes with channelopathy may be eligible to play. Neth Heart J. 2018;26(3):146-53.

164. Garg P, Garg V, Shrestha R, Sanguinetti MC, Kamp TJ, Wu JC. Human induced pluripotent stem cell-derived cardiomyocytes as models for cardiac channelopathies: a primer for non-electrophysiologists. Circ Res. 2018;123(2):224-43.

165. Despa S, Vigmond E. From single myocyte to whole heart: the intricate dance of electrophysiology and modeling. Circ Res. 2016;118(2):184-6.

166. Fonseca DJ, Vaz da Silva MJ. Cardiac channelopathies: the role of sodium channel mutations. Rev Port Cardiol. 2018;37(2):179-99.

167. Lazzerini PE, Capecchi PL, Laghi-Pasini F, Boutjdir M. Autoimmune channelopathies as a novel mechanism in cardiac arrhythmias. Nat Rev Cardiol. 2017;14(9):521-35.

168. Etheridge SP, Saarel EV, Martinez MW. Exercise participation and shared decision-making in patients with inherited channelopathies and cardiomyopathies. Heart Rhythm. 2018;15(6):915-20.

169. Jervell A, Lange-Nielsen F. Congenital deaf-mutism, functional heart disease with prolongation of the Q-T interval and sudden death. Am Heart J. 1957;54(1):59-68.

170. Schwartz PJ, Crotti L, Insolia R. Long-QT syndrome: from genetics to management. Circ Arrhythm Electrophysiol. 2012;5(4):868-77. Erratum in: Circ Arrhythm Electrophysiol. 2012;5(6):e119-20.

171. Garcia-Elias A, Benito B. Ion channel disorders and sudden cardiac death. Int J Mol Sci. 2018;19(3). pii: E692.

172. Mazzanti A, Maragna R, Vacanti G, Monteforte N, Bloise R, Marino M, et al. Interplay between genetic substrate, QTc duration, and arrhythmia risk in patients with long QT syndrome. J Am Coll Cardiol. 2018;71(15):1663-71.

173. Moreno C, Oliveras A, Bartolucci C, Muñoz C, de la Cruz A, Peraza DA, et al. D242N, a KV7.1 LQTS mutation uncovers a key residue for IKs voltage dependence. J Mol Cell Cardiol. 2017 Sep;110:61-69.

174. Liu L, Tian J, Lu C, Chen X, Fu Y, Xu B, et al. Electrophysiological Characteristics of the LQT2 Syndrome Mutation KCNH2-G572S and Regulation by Accessory Protein KCNE2. Front Physiol. 2016 Dec 27;7:650.

175. Jackson HA, Accili EA. Evolutionary analyses of KCNQ1 and HERG voltagegated potassium channel sequences reveal location-specific susceptibility and augmented chemical severities of arrhythmogenic mutations. BMC Evol Biol. 2008 Jun 30;8:188.

176. Zimmer T, Surber R. SCN5A channelopathies--an update on mutations and mechanisms. Prog Biophys Mol Biol. 2008;98(2-3):120-36.

177. Wilde AA, 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.

178. Priori SG, Schwartz PJ, Napolitano C, Bloise R, Ronchetti E, Grillo M, et al. Risk stratification in the long-QT syndrome. N Engl J Med. 2003;348(19):1866-74.

179. Aziz PF, Sweeten T, Vogel RL, Bonney WJ, Henderson J, Patel AR, et al. Sports participation in genotype positive children with long QT syndrome. JACC Clin Electrophysiol. 2015;1(1-2):62-70.

180. Ackerman MJ, Zipes DP, Kovacs RJ, Maron BJ. Eligibility and disqualification recommendations for competitive athletes with cardiovascular abnormalities: task force 10: the cardiac channelopathies: a scientific statement from the American Heart Association and American College of Cardiology. J Am Coll Cardiol. 2015;66(21):2424-8.

181. Steinberg C. Diagnosis and clinical management of long-QT syndrome. Curr Opin Cardiol. 2018;33(1):31-41.

182. Ahn J, Kim HJ, Choi JI, Lee KN, Shim J, Ahn HS, et al. Effectiveness of beta-blockers depending on the genotype of congenital long-QT syndrome: a meta-analysis. PLoS One. 2017;12(10):e0185680.

183. Pérez-Riera AR, Barbosa-Barros R, Daminello Raimundo R, da Costa de Rezende Barbosa MP, Esposito Sorpreso IC, de Abreu LC. The congenital long QT syndrome Type 3: an update. Indian Pacing Electrophysiol J. 2018;18(1):25-35.

184. Shah SR, Park K. Long QT syndrome: a comprehensive review of the literature and current evidence. Curr Probl Cardiol. 2018 May 10. pii: S0146-2806(18)30051-3.

185. Bjerregaard P. Diagnosis and management of short QT syndrome. Heart Rhythm. 2018;15(8):1261-7.

186. Sharma S, Drezner JA, Baggish A, Papadakis M, Wilson MG, Prutkin JM, et al. International recommendations for electrocardiographic interpretation in athletes. J Am Coll Cardiol. 2017;69(8):1057-75.

187. Cubeddu LX. Drug-induced inhibition and trafficking disruption of ion channels: pathogenesis of QT abnormalities and drug-induced fatal arrhythmias. Curr Cardiol Rev. 2016;12(2):141-54.

188. El-Battrawy I, Lan H, Cyganek L, Zhao Z, Li X, Buljubasic F, et al. Modeling short QT syndrome using human-induced pluripotent stem cell-derived cardiomyocytes. J Am Heart Assoc. 2018;7(7). pii: e007394.

189. Gaita F, Giustetto C, Bianchi F, Schimpf R, Haissaguerre M, Calò L, et al. Short QT syndrome: pharmacological treatment. J Am Coll Cardiol. 2004;43(8):1494-9.

190. Mondoly P, Cardin C, Rollin A, Duparc A, Maury P. Use of a subcutaneous ICD in a patient with short QT syndrome. Clin Case Rep. 2015;4(1):35-8.

191. Schimpf R, Wolpert C, Bianchi F, Giustetto C, Gaita F, Bauersfeld U, et al. Congenital short QT syndrome and implantable cardioverter defibrillator treatment: inherent risk for inappropriate shock delivery. J Cardiovasc Electrophysiol. 2003;14(12):1273-7.

192. Gourraud JB, Barc J, Thollet A, Le Marec H, Probst V. Brugada syndrome: diagnosis, risk stratification and management. Arch Cardiovasc Dis. 2017;110(3):188-95.

193. Argenziano M, Antzelevitch C. Recent advances in the treatment of Brugada syndrome. Expert Rev Cardiovasc Ther. 2018;16(6):387-404.

194. Antzelevitch C, Yan GX, Ackerman MJ, Borggrefe M, Corrado D, Guo J, et al. J-Wave syndromes expert consensus conference report: emerging concepts and gaps in knowledge. Europace. 2017;19(4):665-694.

195. Ghouse J, Have CT, Skov MW, Andreasen L, Ahlberg G, Nielsen JB, et al. Numerous Brugada syndrome-associated genetic variants have no effect on J-point elevation, syncope susceptibility, malignant cardiac arrhythmia, and all-cause mortality. Genet Med. 2017;19(5):521-8.

196. Gray B, Hasdemir C, Ingles J, Aiba T, Makita N, Probst V, et al. Lack of genotype-phenotype correlation in Brugada syndrome and sudden arrhythmic death syndrome families with reported pathogenic SCN1B variants. Heart Rhythm. 2018;15(7):1051-1057.

197. Wu W, Tian L, Ke J, Sun Y, Wu R, Zhu J, et al. Risk factors for cardiac events in patients with Brugada syndrome: a PRISMA-compliant meta-analysis and systematic review. Medicine (Baltimore). 2016;95(30):e4214.

198. Antzelevitch C, Brugada P, Borggrefe M, Brugada J, Brugada R, Corrado D, et al. Brugada syndrome: report of the second consensus conference. Heart Rhythm. 2005;2(4):429-40.

199. Pérez-Riera AR, Barbosa-Barros R, de Rezende Barbosa MP, Daminello-Raimundo R, de Lucca AA Jr, de Abreu LC. Catecholaminergic polymorphic ventricular tachycardia, an update. Ann Noninvasive Electrocardiol. 2018;23(4):e12512.

200. Kannankeril PJ, Moore JP, Cerrone M, Priori SG, Kertesz NJ, Ro PS, et al. Efficacy of flecainide in the treatment of catecholaminergic polymorphic ventricular tachycardia: a randomized clinical trial. JAMA Cardiol. 2017;2(7):759-66.

201. Li N, Wang Q, Sibrian-Vazquez M, Klipp RC, Reynolds JO, Word TA, et al. Treatment of catecholaminergic polymorphic ventricular tachycardia in mice using novel RyR2-modifying drugs. Int J Cardiol. 2017 Jan 15;227:668-73.

202. Sumitomo N. Current topics in catecholaminergic polymorphic ventricular tachycardia. J Arrhythm. 2016;32(5):344-51.

203. Wall JJ, Iyer RV. Catecholaminergic polymorphic ventricular tachycardia. Pediatr Emerg Care. 2017;33(6):427-431.

204. Roston TM, Vinocur JM, Maginot KR, Mohammed S, Salerno JC, Etheridge SP, et al. Catecholaminergic polymorphic ventricular tachycardia in children: analysis of therapeutic strategies and outcomes from an international multicenter registry. Circ Arrhythm Electrophysiol. 2015;8(3):633-42.

205. Priori SG, Napolitano C, Memmi M, Colombi B, Drago F, Gasparini M, et al. Clinical and molecular characterization of patients with catecholaminergic polymorphic ventricular tachycardia. Circulation. 2002;106(1):69-74.

206. Imberti JF, Underwood K, Mazzanti A, Priori SG. Clinical challenges in catecholaminergic polymorphic ventricular tachycardia. Heart Lung Circ. 2016;25(8):777-83.

207. Liu N, Ruan Y, Priori SG. Catecholaminergic polymorphic ventricular tachycardia. Prog Cardiovasc Dis. 2008;51(1):23-30.

208. Xiong J, Liu X, Gong Y, Zhang P, Qiang S, Zhao Q, et al. Pathogenic mechanism of a catecholaminergic polymorphic ventricular tachycardia causing-mutation in cardiac calcium release channel RyR2. J Mol Cell Cardiol. 2018 Apr;117:26-35.

209. Ackerman MJ, Priori SG, Dubin AM, Kowey P, Linker NJ, Slotwiner D, et al. Beta-blocker therapy for long QT syndrome and catecholaminergic polymorphic ventricular tachycardia: Are all beta-blockers equivalent? Heart Rhythm. 2017;14(1):e41-e44.

210. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP 3rd, Guyton RA, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014;63(22):2438-88. Erratum in: J Am Coll Cardiol. 2014;63(22):2489.

211. Siu SC, Silversides CK. Bicuspid aortic valve disease. J Am Coll Cardiol. 2010;55(25):2789-800.

212. Taniguchi T, Morimoto T, Shiomi H, Ando K, Kanamori N, Murata K, et al; CURRENT AS Registry Investigators. Sudden death in patients with severe aortic stenosis: observations from the CURRENT AS registry. J Am Heart Assoc. 2018;7(11). pii: e008397.

213. Kanwar A, Thaden JJ, Nkomo VT. Management of patients with aortic valve stenosis. Mayo Clin Proc. 2018;93(4):488-508.

214. Maron BJ. Sudden death in young athletes. N Engl J Med. 2003;349(11):1064-75.

215. Tarasoutchi F, Montera MW, Ramos AI, Sampaio RO, Rosa VE, Accorsi TA, et al. Atualização das Diretrizes Brasileiras de Valvopatias: Abordagem das Lesões Anatomicamente Importantes. Arq Bras Cardiol. 2017;109(6 Supl. 2):1-34.

216. Baumgartner H, Otto CM. Aortic stenosis severity: do we need a new concept? J Am Coll Cardiol. 2009;54(11):1012-3.

217. Mantini C, Di Giammarco G, Pizzicannella J, Gallina S, Ricci F, D'Ugo E, et al. Grading of aortic stenosis severity: a head-to-head comparison between cardiac magnetic resonance imaging and echocardiography. Radiol Med. 2018;123(9):643-54.

218. Saeed S, Rajani R, Seifert R, Parkin D, Chambers JB. Exercise testing in patients with asymptomatic moderate or severe aortic stenosis. Heart. 2018 Apr 13. [Epub ahead of print].

219. Nadeau-Routhier C, Marsit O, Beaudoin J. Current management of patients with severe aortic regurgitation. Curr Treat Options Cardiovasc Med. 2017;19(2):9.

220. Zoghbi WA, Enriquez-Sarano M, Foster E, Grayburn PA, Kraft CD, Levine RA, et al; American Society of Echocardiography. Recommendations for evaluation of the severity of native valvular regurgitation with twodimensional and Doppler echocardiography. J Am Soc Echocardiogr. 2003;16(7):777-802.

221. Cawley PJ, Hamilton-Craig C, Owens DS, Krieger EV, Strugnell WE, Mitsumori L, et al. Prospective of valve regurgitation quantitation by cardiac magnetic resonance imaging and transthoracic echocardiography. Circ Cardiovasc Imaging. 2013;6(1):48-57.

222. Gabriel RS, Renapurkar R, Bolen MA, Verhaert D, Leiber M, Flamm SD, et al. Comparison of severity of aortic regurgitation by cardiovascular magnetic resonance versus transthoracic echocardiography. Am J Cardiol. 2011;108(7):1014-20.

223. Pelliccia A, Culasso F, Di Paolo FM, Maron BJ. Physiologic left ventricular cavity dilatation in elite athletes. Ann Intern Med. 1999;130(1):23-31.

224. Pelliccia A, Kinoshita N, Pisicchio C, Quattrini F, Dipaolo FM, Ciardo R, et al. Long-term clinical consequences of intense, uninterrupted endurance training in Olympic athletes. J Am Coll Cardiol. 2010;55(15):1619-25.

225. Pelliccia A, Maron BJ, Culasso F, Spataro A, Caselli G. Athlete's heart in women: echocardiographic characterization of highly trained elite female athletes. JAMA. 1996;276(3):211-5.

226. Dujardin KS, Enriquez-Sarano M, Schaff HV, Bailey KR, Seward JB, Tajik AJ. Mortality and morbidity of aortic regurgitation in clinical practice: a long-term follow-up study. Circulation. 1999;99(14):1851-7.

227. Bonow RO, Lakatos E, Maron BJ, Epstein SE. Serial long-term assessment of the natural history of asymptomatic patients with chronic aortic regurgitation and normal left ventricular systolic function. Circulation. 1991;84(4):1625-35.

228. Yoon SH, Maeno Y, Kawamori H, Miyasaka M, Nomura T, Ochiai T, et al. Diagnosis and outcomes of transcatheter aortic valve implantation in bicuspid aortic valve stenosis. Interv Cardiol. 2018;13(2):62-5.

229. Martín M, Lorca R, Rozado J, Alvarez-Cabo R, Calvo J, Pascual I, et al. Bicuspid aortic valve syndrome: a multidisciplinary approach for a complex entity. J Thorac Dis. 2017;9(Suppl 6):S454-S464.

230. Svensson LG, Kim KH, Lytle BW, Cosgrove DM. Relationship of aortic cross-sectional area to height ratio and the risk of aortic dissection in patients with bicuspid aortic valves. J Thorac Cardiovasc Surg. 2003;126(3):892-3.

231. Parker MW, Thompson PD. Exercise in valvular heart disease: risks and benefits. Prog Cardiovasc Dis. 2011;53(6):437-46.

232. Harb SC, Griffin BP. Mitral valve disease: a comprehensive review. Curr Cardiol Rep. 2017;19(8):73.

233. Rahimtoola SH, Durairaj A, Mehra A, Nuno I. Current evaluation and management of patients with mitral stenosis. Circulation. 2002;106(10):1183-8.

234. Sandoval Y, Sorajja P, Harris KM. Contemporary management of ischemic mitral regurgitation: a review. Am J Med. 2018;131(8):887-95.

235. Bonow RO. Chronic mitral regurgitation and aortic regurgitation: have indications for surgery changed? J Am Coll Cardiol. 2013;61(7):693-701.

236. Parwani P, Avierinos JF, Levine RA, Delling FN. Mitral valve prolapse: multimodality imaging and genetic insights. Prog Cardiovasc Dis. 2017;60(3):361-9.

237. Thacoor A. Mitral valve prolapse and Marfan syndrome. Congenit Heart Dis. 2017;12(4):430-4.

238. Freed LA, Levy D, Levine RA, Larson MG, Evans JC, Fuller DL, et al. Prevalence and clinical outcome of mitral-valve prolapse. N Engl J Med. 1999;341(1):1-7.

239. Narayanan K, Uy-Evanado A, Teodorescu C, Reinier K, Nichols GA, Gunson K, et al. Mitral valve prolapse and sudden cardiac arrest in the community. Heart Rhythm. 2016;13(2):498-503.

240. Delling FN, Rong J, Larson MG, Lehman B, Fuller D, Osypiuk E, et al. Evolution of mitral valve prolapse: insights from the Framingham heart study. Circulation. 2016;133(17):1688-95.

241. Basso C, Perazzolo Marra M, Rizzo S, De Lazzari M, Giorgi B, Cipriani A, et al. Arrhythmic mitral valve prolapse and sudden cardiac death. Circulation. 2015;132(7):556-66.

242. Caselli S, Mango F, Clark J, Pandian NG, Corrado D, Autore C, et al. Prevalence and clinical outcome of athletes with mitral valve prolapse. Circulation. 2018;137(19):2080-2.

243. Corrado D, Basso C, Nava A, Rossi L, Thiene G. Sudden death in young people with apparently isolated mitral valve prolapse. G Ital Cardiol. 1997;27(11):1097-105.

244. Glesby MJ, Pyeritz RE. Association of mitral valve prolapse and systemic abnormalities of connective tissue: a phenotypic continuum. JAMA. 1989;262(4):523-8.

245. Rippe M, De Backer J, Kutsche K, Mosquera LM, Schüler H, Rybczynski M, et al. Mitral valve prolapse syndrome and MASS phenotype: Stability of aortic dilatation but progression of mitral valve prolapse. Int J Cardiol Heart Vasc. 2016 Jan 21;10:39-46.

246. Graffunder FP, Sties SW, Gonzáles AI, de Carvalho T. Differential diagnosis of Marfan syndrome in a teenage volleyball athlete. Int J Cardiovasc Sci. 2017;30(2):181-4.

247. Cevasco M, Shekar PS. Surgical management of tricuspid stenosis. Ann Cardiothorac Surg. 2017;6(3):275-82.

248. Arsalan M, Walther T, Smith RL 2nd, Grayburn PA. Tricuspid regurgitation diagnosis and treatment. Eur Heart J. 2017;38(9):634-8.

249. Badano LP, Agricola E, Perez de Isla L, Gianfagna P, Zamorano JL. Evaluation of the tricuspid valve morphology and function by transthoracic real-time threedimensional echocardiography. Eur J Echocardiogr. 2009;10(4):477-84.

250. Unger P, Clavel MA, Lindman BR, Mathieu P, Pibarot P. Pathophysiology and management of multivalvular disease. Nat Rev Cardiol. 2016;13(7):429-40.

251. Rahimtoola SH. Choice of prosthetic heart valve for adult patients. J Am Coll Cardiol. 2003;41(6):893-904.

252. Cahill TJ, Chen M, Hayashida K, Latib A, Modine T, Piazza N, et al. Transcatheter aortic valve implantation: current status and future perspectives. Eur Heart J. 2018;39(28):2625-34.

253. Pressler A, Christle JW, Lechner B, Grabs V, Haller B, Hettich I, et al. Exercise training improves exercise capacity and quality of life after transcatheter aortic valve implantation: a randomized pilot trial. Am Heart J. 2016 Dec;182:44-53.

254. Völler H, Salzwedel A, Nitardy A, Buhlert H, Treszl A, Wegscheider K. Effect of cardiac rehabilitation on functional and emotional status in patients after transcatheter aortic-valve implantation. Eur J Prev Cardiol. 2015;22(5):568-74.

255. Tarro Genta F, Tidu M, Bouslenko Z, Bertolin F, Salvetti I, Comazzi F, et al. Cardiac rehabilitation after transcatheter aortic valve implantation compared to patients after valve replacement. J Cardiovasc Med (Hagerstown). 2017;18(2):114-20.

256. Russo N, Compostella L, Tarantini G, Setzu T, Napodano M, Bottio T, et al. Cardiac rehabilitation after transcatheter versus surgical prosthetic valve implantation for aortic stenosis in the elderly. Eur J Prev Cardiol. 2014;21(11):1341-8.

257. Abdul-Jawad Altisent O, Puri R, Regueiro A, Chamandi C, Rodriguez-Gabella T, Del Trigo M, et al. Predictors and association with clinical outcomes of the changes in exercise capacity after transcatheter aortic valve replacement. Circulation. 2017;136(7):632-43.

258. Thein-Nissenbaum J, Hammer E. Treatment strategies for the female athlete triad in the adolescent athlete: current perspectives. Open Access J Sports Med. 2017 Apr 4;8:85-95.

259. Sharma S. Athlete's heart - effect of age, sex, ethnicity and sporting discipline. Exp Physiol. 2003;88(5):665-9.

260. Finochiaro G, Sharma S. Do endurance sports affect female hearts differently from male hearts? Future Cardiol. 2016;12(2):105-8.

261. Pelliccia A, Maron BJ, Culasso F, Di Paolo FM, Spataro A, Biffi A, et al. Clinical significance of abnormal electrocardiographic patterns in trained athletes. Circulation. 2000;102(3):278-84.

262. Drezner JA, Ackerman MJ, Anderson J, Ashley E, Asplund CA, Baggish AL, et al. Electrocardiographic interpretation in athletes: the 'Seattle criteria'. Br J Sports Med. 2013;47(3):122-4.

263. Wasfy MM, DeLuca J, Wang F, Berkstresser B, Ackerman KE, Eisman A, et al. ECG findings in competitive rowers: normative data and the prevalence of abnormalities using contemporary screening recommendations. Br J Sports Med. 2015;49(3):200-6.

264. Finocchiaro G, Dhutia H, D'Silva A, Malhotra A, Steriotis A, Millar L, et al. Effect of sex and sporting discipline on LV adaptation to exercise. JACC Cardiovasc Imaging. 2017;10(9):965-72.

265. Serratosa-Fernández L, Pascual-Figal D, Masiá-Mondéjar MD, Sanz-de laGarza M, Madaria-Marijuan Z, Gimeno-Blanes JR, et al; Grupo de Cardiología del Deporte de la Sociedad Española de Cardiología. Comments on the New International Criteria for Electrocardiographic Interpretation in Athletes. Rev Esp Cardiol (Engl Ed). 2017;70(11):983-90.

266. Malhotra A, Dhutia H, Gati S, Yeo TJ, Dores H, Bastiaenen R, et al. Anterior T-wave inversion in young white athletes and nonathletes: prevalence and significance. J Am Coll Cardiol. 2017;69(1):1-9.

267. Petek BJ, Wasfy MM. Cardiac adaption to exercise training: the female athlete. Curr Treat Options Cardiovasc Med. 2018;20(8):68.

268. Sheikh N, Papadakis M, Schnell F, Panoulas V, Malhotra A, Wilson M, et al. Clinical profile of athletes with hypertrophic cardiomyopathy. Circ Cardiovasc Imaging. 2015;8(7):e003454.

269. Malhotra A, Dhutia H, Gati S, Dores H, Meller L, Merghani R, et al. Prevalence and significance of anterior T wave inversion in females. Heart. 2014;100(Suppl 3):A60.

270. Pickham D, Zarafshar S, Sani D, Kumar N, Froelicher V. Comparison of three ECG criteria for athlete pre-participation screening. J Electrocardiol. 2014;47(6):769-74.

271. Rawlins J, Carre F, Kervio G, Papadakis M, Chandra N, Edwards C, et al. Ethnic differences in physiological adaptation to intense physical exercise in highly trained female athletes. Circulation. 2010;121(9):1078-85.

272. Caselli S, Maron MS, Urbano-Moral JA, Pandian NG, Maron BJ, Pelliccia A. Differentiating left ventricular hypertrophy in athletes from that in patients with hypertrophic cardiomyopathy. Am J Cardiol. 2014;114(9):1383-9.

273. Brosnan MJ, Rakhit D. Differentiating athlete's heart from cardiomyopathies: the left side. Heart Lung Circ. 2018;27(9):1052-62.

274. D'Ascenzi F, Pelliccia A, Natali BM, Zacà V, Cameli M, Alvino F, et al. Morphological and functional adaptation of left and right atria induced by training in highly trained female athletes. Circ Cardiovasc Imaging. 2014;7(2):222-9.

275. Gulati M, Pratap P, Kansal P, Calvin JE Jr, Hendel RC. Gender differences in the value of ST-segment depression during adenosine stress testing. Am J Cardiol. 2004;94(8):997-1002.

276. Sharma S, Mehta PK, Arsanjani R, Sedlak T, Hobel Z, Shufelt C, et al. False-positive stress testing: Does endothelial vascular dysfunction contribute to ST-segment depression in women? A pilot study. Clin Cardiol. 2018;41(8):1044-8.

277. Mathews SC, Narotsky DL, Bernholt DL, Vogt M, Hsieh YH, Pronovost PJ, et al. Mortality among marathon runners in the United States, 2000-2009. Am J Sports Med. 2012;40(7):1495-500.

278. Maron BJ, Haas TS, Murphy CJ, Ahluwalia A, Rutten-Ramos S. Incidence and causes of sudden death in U.S. college athletes. J Am Coll Cardiol. 2014;63(16):1636-43.

279. Harmon KG, Asif IM, Maleszewski JJ, Owens DS, Prutkin JM, Salerno JC, et al. Incidence and etiology of sudden cardiac arrest and death in high school athletes in the United States. Mayo Clin Proc. 2016;91(11):1493-502.

280. Harris KM, Creswell LL, Haas TS, Thomas T, Tung M, Isaacson E, et al. Death and cardiac arrest in U.S. triathlon participants, 1985 to 2016: a case series. Ann Intern Med. 2017;167(8):529-35.

281. Finocchiaro G, Papadakis M, Robertus JL, Mellor G, Behr E, Sharma S, et al. Sudden death in sport: insights from a national pathology referral center. Eur Heart J. 2015;36(Suppl 1):332.

282. Estes NA 3rd, Madias C. Atrial fibrillation in athletes: a lesson in the virtue of moderation. JACC Clin Electrophysiol. 2017;3(9):921-8.

283. Mohanty S, Mohanty P, Tamaki M, Natale V, Gianni C, Trivedi C, et al. Differential Association of Exercise Intensity With Risk of Atrial Fibrillation in Men and Women: Evidence from a Meta-Analysis. J Cardiovasc Electrophysiol. 2016;27(9):1021-9.

284. Morseth B, Graff-Iversen S, Jacobsen BK, Jørgensen L, Nyrnes A, Thelle DS, et al. Physical activity, resting heart rate, and atrial fibrillation: the Tromsø Study. Eur Heart J. 2016;37(29):2307-13.

285. Landry CH, Allan KS, Connelly KA, Cunningham K, Morrison LJ, Dorian P. Sudden cardiac arrest during participation in competitive sports. N Engl J Med. 2017;377(20):1943-53.

286. Siebert DM, Drezner JA. Sudden cardiac arrest on the field of play: turning tragedy into a survivable event. Neth Heart J. 2018;26(3):115-9.

287. Burke AP, Farb A, Virmani R, Goodin J, Smialek JE. Sports-related and non-sports-related sudden cardiac death in young adults. Am Heart J. 1991;121(2 Pt 1):568-75.

288. Van Camp SP, Bloor CM, Mueller FO, Cantu RC, Olson HG. Non-traumatic sports death in high school and college athletes. Med Sci Sports Exerc. 1995;27(5):641-7.

289. Saberi S, Day SM. Exercise and hypertrophic cardiomyopathy: time for a change of heart. Circulation. 2018;137(5):419-21.

290. Ullal AJ, Abdelfattah RS, Ashlev EA, Froelicher VF. Hypertrophic cardiomyopathy as a cause of sudden cardiac death in the young: a meta-analysis. Am J Med. 2016;129(5):486-96.

291. Schmehil C, Malhotra D, Patel DR. Cardiac screening to prevent sudden death in young athletes. Transl Pediatr. 2017;6(3):199-206.

292. Fuller C, Scott C, Hug-English C, Yang W, Pasternak A. Five-year experience with screening electrocardiograms in National Collegiate Athletic Association Division I Athletes. Clin J Sport Med. 2016;26(5):369-75.

293. Panhuyzen-Goedkoop NM, Wellens HJ, Piek JJ. Early recognition of sudden cardiac arrest in athletes during sports activity. Neth Heart J. 2018;26(1):21-25.

294. Saberi S, Day SM. Exercise prescription for the athlete with cardiomyopathy. Cardiol Clin. 2016;34(4):591-601.

295. Drezner JA, Asif IM, Harmon KG. Automated external defibrillators in health and fitness facilities. Phys Sportsmed. 2011;39(2):114-8.

296. Gu W, Li CS. What is more important: defibrillation or compression? J Thorac Dis. 2016;8(8):E778-80.

297. Bækgaard JS, Viereck S, Møller TP, Ersbøll AK, Lippert F, Folke F. The effects of public access defibrillation on survival after out-of-hospital cardiac arrest: a systematic review of observational studies. Circulation. 2017;136(10):954-65.

298. Garcia EL, Caffrey-Villari S, Ramirez D, Caron JL, Mannhart P, Reuter PG, et al. [Impact of onsite or dispatched automated external defibrillator use on early survival after sudden cardiac arrest occurring in international airports]. Presse Med. 2017;46(3):e63-e68.

299. Mark DB, Hansen SM, Starks ML, Cummings ML. Drone-based automatic external defibrillators for sudden death? do we need more courage or more serenity? Circulation. 2017;135(25):2466-9.

300. Hung KK, Graham CA, Chan LK, Poon WK, Rainer TH, Cocks RA. Performance of automated external defibrillators under conditions of in-flight turbulence. Resuscitation. 2018 Sep;130:41-3.

301. Hansen SM, Hansen CM, Folke F, Rajan S, Kragholm K, Ejlskov L, et al. Bystander defibrillation for out-of-hospital cardiac arrest in public vs residential locations. JAMA Cardiol. 2017;2(5):507-14.

302. Tagarakis CV, Bloch W, Hartmann G, Hollmann W, Addicks K. Anabolic steroids impair the exercise-induced growth of the cardiac capillary bed. Int J Sports Med. 2000;21(6):412-8.

303. Marocolo M, Silva-Neto JA, Barbosa Neto O. Acute interruption of treatment with nandrolone decanoate is not sufficient to reverse cardiac autonomic dysfunction and ventricular repolarization disturbances in rats. Steroids. 2018 Apr;132:12-7.

304. Angell P, Chester N, Green D, Somauroo J, Whyte G, George K. Anabolic steroids and cardiovascular risk. Sports Med. 2012;42(2):119-34.

305. Thiblin I, Garmo H, Garle M, Holmberg L, Byberg L, Michaëlsson K, et al. Anabolic steroids and cardiovascular risk: A national population-based cohort study. Drug Alcohol Depend. 2015 Jul 1;152:87-92.

306. Novick T, Liu Y, Alvanzo A, Zonderman AB, Evans MK, Crews DC. Lifetime cocaine and opiate use and chronic kidney disease. Am J Nephrol. 2016;44(6):447-53.

307. Goel N, Pullman JM, Coco M. Cocaine and kidney injury: a kaleidoscope of pathology. Clin Kidney J. 2014;7(6):513-7.

308. Vizeli P, Liechti ME. Safety pharmacology of acute MDMA administration in healthy subjects. J Psychopharmacol. 2017;31(5):576-88.

309. Suarez RV, Riemersma R. "Ecstasy" and sudden cardiac death. Am J Forensic Med Pathol. 1988;9(4):339-41.

310. Chandra YG, Shetty AR, Jayanth SH, Hugar BS, Praveen S, Harish S. A death due to ecstasy - a case report. Med Leg J. 2016;84(1):46-8.

311. Mont L, Pelliccia A, Sharma S, Biffi A, Borjesson M, Terradellas JB, et al. Pre-participation cardiovascular evaluation for athletic participants to prevent sudden death: position paper from the EHRA and the EACPR, branches of the ESC. Endorsed by APHRS, HRS, and SOLAECE. Europace. 2017;19(1):139-63.

312. Ljungqvist A, Jenoure PJ, Engebretsen L, Alonso JM, Bahr R, Clough AF, et al. The International Olympic Committee (IOC) consensus statement on periodic health evaluation of elite athletes, March 2009.Clin J Sport Med. 2009;19(5):347-65.

313. Hainline B, Drezner J, Baggish A, Harmon KG, Emery MS, Myerburg RJ, et al. Interassociation Consensus Statement on Cardiovascular Care of College Student-Athletes. J Athl Train. 2016;51(4):344-57.

314. van der Wall EE. ECG screening in athletes: optional or mandatory? Neth Heart J. 2015;23(7-8):353-5.

315. Barbosa ET. Critérios para solicitação de exames complementares do aparelho cardiovascular. Arq Bras Cardiol. 1997;68(3):1-9.

316. Lane CM, Bos JM, Rohatgi RK, Ackerman MJ. Beyond the length and look of repolarization: defining the non-QTc electrocardiographic profiles of patients with congenital long QT syndrome. Heart Rhythm. 2018 Sep;15(9):1413-9.

317. Lyon A, Ariga R, Mincholé A, Mahmod M, Ormondroyd E, Laguna P, et al. Distinct ECG phenotypes identified in hypertrophic cardiomyopathy using machine learning associate with arrhythmic risk markers. Front Physiol. 2018 Mar 13;9:213.

318. Olen MM, Baysa SJ, Rossi A, Kanter RJ, Fishberger SB. Wolff-Parkinson-White syndrome: a stepwise deterioration to sudden death. Circulation. 2016;133(1):105-6.

319. Heron N, Cupples M. The health profile of football/soccer players in Northern Ireland - a review of the uefa pre-participation medical screening procedure. BMC Sports Sci Med Rehabil. 2014;6(1):5.

320. Dvorak J, Kramer EB, Schmied CM, Drezner JA, Zideman D, Patricios J, et al. The FIFA medical emergency bag and FIFA 11 steps to prevent sudden cardiac death: setting a global standard and promoting consistent football field emergency care. Br J Sports Med. 2013;47(18):1199-202.

321. Kramer EB, Botha M, Drezner J, Abdelrahman Y, Dvorak J. Practical management of sudden cardiac arrest on the football field. Br J Sports Med. 2012;46(16):1094-6.

322. Leusveld E, Kleijn S, Umans VA. Usefulness of emergency medical teams in sport stadiums. Am J Cardiol. 2008;101(5):712-4.

323. Moretti MA, Cesar LA, Nusbacher A, Kern KB, Timerman S, Ramires JA. Advanced cardiac life support training improves long-term survival from in-hospital cardiac arrest. Resuscitation. 2007;72(3):458-65.

324. Capucci A, Aschieri D, Guerra F, Pelizzoni V, Nani S, Villani GQ, et al. Community-based automated external defibrillator only resuscitation for out-of-hospital cardiac arrest patients. Am Heart J. 2016 Feb;172:192-200.

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