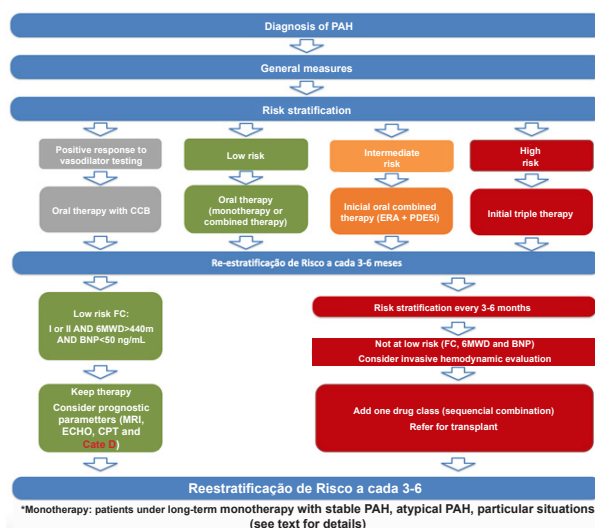


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A Thriving New Field

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It has been approximately 15 years since the term “cardio-oncology” was coined. I remember the beginnings: last session of the last day in local and international cardiology scientific meetings, with the attendance of mostly close friends. The field of cardio-oncology has advanced considerably since that time, with formation of special interest groups and councils in our societies, and development of scientific statements guiding us as to how to evaluate and treat these very complex patients.^{1,2} It is then with great interest that we receive the Brazilian Position Statement on the Use of Multimodality Imaging in Cardio-Oncology -2021, a comprehensive, very well written and practical document that will serve as an invaluable resource to imagers in Brazil and all over the world.

I feel very proud of what we have accomplished but can't help thinking of what needs to be done in the next fifteen years in the field of Imaging in Cardio-Oncology.

Echocardiography is and will continue to be the working horse in the field. Nevertheless, there are still disagreements between oncologists and cardio-oncologists on the value of advanced techniques like 3D echocardiography and strain Imaging. What is the problem? In the field of imaging, we are not used to putting our imaging modalities to the test looking for an impact on hard endpoints. In contrast, oncologists are used to high-quality large randomized clinical trials to test their interventions. They hold us to the same standards. A step

in that direction was taken by the SUCCOUR investigators, randomizing patients to strain vs 3D echocardiography for adjudication of stage B heart failure. Although the primary outcome of change in left ventricular ejection fraction (LVEF) was not significantly different between the two arms, there were fewer patients meeting the cancer therapeutics-related cardiac dysfunction (CTRCD) criteria during follow-up in the global longitudinal strain (GLS)-guided group. Also, the 1-year LVEF was higher in the GLS-guided group when compared with the LVEF-guided arm.³

As far as other modalities are concerned, I see a great future for parametric imaging in cardiac magnetic resonance imaging. When cardiac dysfunction is detected, it is unclear what is the pathophysiologic mechanism driving it; the presence of edema or fibrosis may guide treatment duration in these patients.

Cardiac computed tomography will continue to be very helpful in the assessment of structural heart disease especially in the setting of radiation induced heart disease.

Perhaps the imaging modality that appears the least promising is nuclear cardiology, due to the high doses of radiation administered and the fact that they don't bring to the table anything unique that their non-radiation counterparts can do.

Possibly, the main question is what outcomes oncologists and heart failure doctors expect from imaging modalities to incorporate them in their day-to-day operations – is it mortality or heart failure admissions? A long-term follow-up of a large number of patients will be required. Will they be satisfied with the impact of these techniques on VO₂ max or quality of life questionnaires? What about biomarkers?

I anticipate that the next 15 years will be devoted to the generation of outcome data for our modalities. We will work closely with our oncologists and heart failure doctors to provide them with the level of evidence that they are looking for, taking the field of Cardio-Oncology to the next level.

Keywords

Echocardiography; Heart Failure; Oncologists.

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References

1. 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. doi: 10.1016/j.echo.2014.07.012.
2. 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*. 2017;35(8):893-911. doi: 10.1200/JCO.2016.70.5400.
3. Thavendiranathan P, Negishi T, Somerset E, Negishi K, Penicka M, Lemieux J, et al. Strain-Guided Management of Potentially Cardiotoxic Cancer Therapy. *J Am Coll Cardiol*. 2021;77(4):392-401. doi: 10.1016/j.jacc.2020.11.020.



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A Simple Clinical Risk Score to Predict Post-Discharge Mortality in Chinese Patients Hospitalized with Heart Failure

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Abstract

Background: Cardiovascular diseases are the leading causes of death in China. However, present efforts to identify the risk factors for death in patients hospitalized with heart failure (HF) are primarily focused on in-hospital mortality and 30-day mortality in the United States. Thus, a model similar to the model used for predicting the risk in patients considered for cardiovascular surgical procedures is needed to evaluate the risk of the patients admitted with a diagnosis of HF.

Objective: To identify variables that can predict post-discharge one-year HF mortality and develop a risk score to assess the risk of dying within one year.

Methods: In the present study, 1,742 Chinese patients with HF were randomly divided into two groups: a derivation sample group and a test sample group. A Markov Chain Monte Carlo simulation method was used to identify variables that can predict the one-year post-discharge mortality. Variables with a frequency of >1% in the bivariate analysis and that were considered clinically meaningful were eligible for further modeling analyses. The posterior probability that a variable was statistically and significantly associated with the outcome was calculated as the total number of times that the variable's 95% CI did not overlap with 1 (i.e., the reference point) divided by the total number of iterations. A variable with a probability of 0.9 or higher was considered a robust risk factor for predicting the outcome, and this was included in the final variable list. The level of statistical significance adopted was 5%.

Results: Five variables that could robustly predict the one-year post-discharge mortality were identified: age, female gender, New York Heart Association functional classification score >3, left atrial diameter, and body mass index. Both derivation and test models had a receiver operating curve area of 0.79. These selected variables were used to assess the one-year HF mortality risk score, and these were divided into three groups (low, moderate, and high). The high-risk group corresponds to nearly 86% of the deaths, while the moderate group corresponds to 12% of the deaths.

Conclusion: A simple 5-variable risk score can be used to assess the one-year post-discharge mortality of hospitalized Chinese patients with HF.

Keywords: Heart Failure; Propensity Score; Mortality; Patient Discharge; Epidemiology.

Introduction

Cardiovascular diseases are the leading causes of death in China, accounting for approximately 22.5% of all deaths.¹ Heart failure (HF) is the twelfth leading cause of hospitalization in China, and four million Chinese suffer from this condition.¹ Overall, HF in China has an especially poor prognosis, with up to 40% of patients with HF dying within one year.¹ The financial burden of HF is also substantial.²

However, present efforts to identify the risk factors for death in patients hospitalized with HF, such as the

Framingham risk score, are primarily focused on in-hospital mortality^{3,4} and 30-day mortality in the United States.^{5,6} Since HF is a chronic condition, identifying risk factors for the long-term mortality of patients with HF could bring more benefits to patients. A model similar to the model used for predicting the risk in patients considered for cardiovascular surgical procedures can be used to evaluate the risk of the patients admitted with a diagnosis of HF.⁷ Given the increasing burden of HF in China, it is important to find means to stratify patients based on risk, upon initial diagnosis, and upon discharge. Furthermore, with the Asian population encompassing nearly 5% of the population of the United States and the Chinese population representing 20% of the world's population, the risk scores developed based on Western populations often incorrectly estimate the risk for Asian populations.⁸ Thus, it is important to develop clinically relevant tools for Chinese and other Asian groups. A tool that could specifically provide the likelihood of one-year mortality in Chinese patients with HF would be of

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great clinical utility because this would have the potential to guide clinical decision-making and identify patients who are more likely to require intensive post-discharge monitoring. Furthermore, given that race, ethnicity, and country of origin have a large impact on clinical outcomes, it is important to develop a risk assessment specific to the group of interest, that is, Chinese patients with HF.

The present study aimed to identify risk factors that are most strongly correlated with one-year mortality among Chinese patients with HF and develop a simple risk score to assess the risk of one-year post-discharge mortality for these patients.

Methods

Subjects

The present study has been approved by the Ethics Committee of our hospital, and all patients provided signed written informed consent.

The study cohort was drawn from the Beijing Monitoring Heart Failure Patients and the Building Heart Failure Management Network Study, which included all patients who were ≥ 20 years of age and hospitalized for HF in one of the 14 designated hospitals in Beijing, China, from October 10, 2015, to October 9, 2017. These patients were randomly assigned into two groups, using a random table method: a derivation sample group and a test sample group. The one-year mortality information was obtained from post-discharge phone interviews.

Candidate risk variables and outcome variables

The candidate risk variables included the demographic characteristics (age, gender, and body mass index [BMI]), medical history and comorbidities, lifestyle factors, previous cardiac surgeries, clinical findings, and laboratory test results. Age and BMI were measured as continuous variables, while gender was coded as female (yes/no). The medical history included the history of acute myocardial infarction (AMI), history of HF, and history of coronary heart disease (CHD), Type I or Type II diabetes, and hypertension. The previous cardiac surgeries included previous valve surgery. The clinical findings included the New York Heart Association (NYHA) functional classification score (class >3) and left ventricular ejection fraction ($<40\%$). The lifestyle factors included a history of tobacco use, present use of tobacco, and alcohol consumption. The laboratory test data included heart rate, blood pressure, and left atrial diameter (in millimeters), which was measured as a continuous variable.

The outcome variable was the one-year post-discharge HF mortality, which was defined as all-cause deaths that occurred after an index HF hospitalization. The mortality information was obtained by phone interviews with these patients. The last interview date was February 19, 2019. If a patient died within one year after discharge, the date of death was obtained from family members. Patients were excluded from the study sample when neither themselves nor their family members could be reached.

Statistical analysis

The data of the derivation sample group and test sample group were compared by Chi-square tests for categorical variables and unpaired *t*-tests for continuous variables. Then, clinical judgment and Spearman bivariate correlation analysis were used to identify candidate variables that may be associated with one-year post-discharge mortality. Variables with a frequency of $>1\%$ in the bivariate analysis and which were considered clinically meaningful were eligible for further modeling analyses. For observations with missing data, a dummy variable was created to assign a value of 0 when the value of a variable was present, and a value of 1 when the variable was missing. The missing values were then replaced by the median of non-missing values from that continuous variable, and both the dummy and continuous variables were included in the model. This method of modeling the missing data assumed that these data were missing at random, and permitted the inclusion of all available cases, although this was not as efficient as multiple imputation procedures.

The Markov Chain Monte Carlo (MCMC) simulation method was used in conjunction with the logistic regression technique to identify a set of final risk factors for predicting the one-year post-discharge HF mortality. The simulations were carried out with 10,000 iterations for the derivation sample, and a logistic model was fitted for each iteration, yielding a set of variables that are "statistically significant," or associated with the outcome. Thus, 10,000 iterations of the simulation yielded 10,000 sets of odds ratios (ORs) and 95% confidence intervals (CI), indicating the significance level for each variable's association with the outcome. The posterior probability that a variable was statistically and significantly associated with the outcome was calculated as the total number of times that the variable's 95% CI did not overlap with 1 (i.e., the reference point) divided by the total number of iterations. A variable with a probability of 0.9 or higher was considered a robust risk factor for predicting the outcome, and this was included in the final variable list. This method has been used elsewhere.⁹ The area under the receiver operating characteristic (ROC) curve was calculated for each fitted model per iteration to evaluate its discriminating power.¹⁰

Development of risk score

Based on the simulation results, a simple risk score was constructed based on the variables selected to assess the one-year mortality. Each variable was weighted using the variable-specific standardized coefficient (SC) obtained from a logistic model based on the original derivation sample, with one-year mortality as the outcome and the selected variables as independent variables. The SC, which measured the change in coefficient for one standard deviation (SD) change in the independent variable, was designed to represent the relative importance of the independent variable in a regression model. This allows for the comparison among independent variables using common units. The risk score for each observation in both derivation and validation samples was calculated as: $\text{Score} = \sum \text{Weight}_i \cdot \text{Variable}_i$, where $\text{weight}_i = \text{SC}_i / \sum |\text{SC}_i|$, and $i = 1, 2, 3, \dots$, total number of the final selected variables. Each weight was then rescaled by 100 to allow the score to be user-friendly in practice, except for the weight for age, which only

scales to 10. Each weight was further rounded up or down to its close integer by 5-interval (for example, 32.5 to 30.0, 18.0 to 20.0). Age was rounded down to its close floor with one decimal point. Finally, a base of 100 was added to the score to ensure that there were no negative values in the scores. To validate and test the risk score, two logistic models were fitted. One model used individual variables that were selected from the MCMC simulation as independent variables, while the other model used the risk score as an independent variable. These two models were fitted with both derivation and test samples, and the r-squared and ROC values were calculated from both models to assess the performance of the risk score. All statistical tests were two-sided and had a significance level of 5%, and all analyses were performed using SAS version 9.3 64-bit version (SAS Institute Inc., Cary, North Carolina, USA). All continuous variables were normally distributed as tested by Shapiro–Wilk tests. Continuous variables with normal distribution are described using mean and standard deviation.

Results

Patient characteristics

The final study cohort included a total of 1,742 patients with HF. Among these patients, the derivation and test samples included 882 patients and 860 patients, respectively. The mean (SD) age of the cohort was 57.0 (12.5) years, and 9.5% of these patients were 40 or younger, while 30.9% of these patients were 65 or older. Furthermore, 19.9% of these patients were women. The characteristics of patients in the derivation and validation samples were comparable (Table 1). There were no significant differences between these two groups in terms of age, gender, left atrial diameter, heart rate, LVEF <40 (%), AMI (%), NYHA >3 (%), CHD (%), DM (%), HTN (%), valve surgery (%), smoking history (%), alcohol consumption (%), and one-year mortality (%). However, there were significant differences between these two groups in terms of heart rate >100 (%) and HF (%). There was no significant difference in drugs and medical appointments during the follow-up and no significant difference in lab test results among all patients.

Risk variables for predicting the one-year HF mortality

The observed one-year mortality rates for the derivation and validation samples were 7.3% and 5.8%, respectively ($P = 0.2236$). Figure 1 presents the probability that each variable was associated with one-year HF mortality. Five variables, including age, female gender, BMI, left atrial diameter, and NYHA class >3, had a probability of 0.9 or above for significantly being associated with one-year mortality. These were identified as the final variables (Figures 1a and 1b). Table 2 illustrates the OR, SC, and 95% CI for each of the five selected variables in the derivation dataset. The area under the ROC curve of this 5-variable-based model was 0.789, with an r-squared of 0.1761 and a goodness-of-fit of 0.9013. The predictive ability ranged from 0.04 in the lowest decile to 0.43 in the highest decile, indicating that the model had good discrimination (Figure 1c). This model also performed similarly to the test dataset (Figure 1d and Table 3).

Risk score

The risk score was constructed using the SC estimates in Table 2. The calculation equation is also listed in Table 2. The mean (SD) of the derivation sample-based risk score was 492.5 (177.1), with a range of 89.9–1195.63, and the mean (SD) of the test sample-based score was 493.0, with a range of 89.9–1,073.9. The difference in mean scores between the derivation and test samples was not statistically significant ($p = 0.7324$). The risk score was used as the independent variable to fit a logistic model, which yielded an area under the ROC curve of 0.75 and 0.77 for the derivation and test samples, respectively (Table 3). Figure 2 shows the distribution of the risk score (Figures 2a and 2b) and the exponential relationship between the score and the probability of one-year post-discharge HF mortality (Figure 2c).

The risk score has a good predictive ability. With the derivation sample, the mean predicted probabilities of one-year death were 0.15 and 0.07 for those who died within the one-year window and those who survived after the one-year window, respectively. This pattern was similar for the test sample, in which the mean predicted probabilities of one-year death were 0.14 for those who died and 0.07 for those who survived. The risk score was divided into three ranges based on its distribution: (1) low risk if the score was <300; (2) moderate risk if the score was ≥ 300 and ≤ 800 ; (3) high risk if the score was >800. The proportions of patients in each of these three risk groups were as follows: 11.7% for low-risk groups, 73.8% for moderate-risk groups, and 14.5% for high-risk groups. Figure 2d shows the one-year mortality rates by risk group, and by the derivation and test samples. Figure 3 shows the distribution of risk score by died and survived groups.

Discussion

Developing a Chinese-population-specific risk model for HF is important, given that the present risk scores, such as the widely used Framingham risk score, are developed predominantly in the United States, which cannot correctly estimate the risk in Asian populations.^{8–12} The present study developed and validated a simple 5-variable risk score for assessing the risk of one-year mortality for Chinese patients with HF. This simple score can be added in the present assessment of patients prior to hospital discharge in order to provide a basis for physicians to better allocate resources and identify patients who may need post-discharge care. The final variables identified from the present study were consistent with the risk factors identified in Western cohorts. In addition to age and the NYHA classification, which are well-known risk factors for HF mortality, it was found that female gender and BMI are protective factors within the Chinese cohort, consistent with findings based on the Western population.^{13–14} Similarly, it was found that the left atrial diameter was associated with HF hospitalization and death.¹⁵

The number of patients within the present cohort was similar to risk scores developed for other HF populations.¹⁶ Furthermore, compared to the previous studies, the present study has several strengths. First, unlike previous studies that evaluated the short-term risk of mortality in HF patients, the present study focused on long-term outcomes. Second, these present results are specific to Chinese patients because these

Table 1 – Baseline characteristics of the study population

Patient characteristics	Overall (n=1742)	Derivation sample (n=882)	Test sample (n=860)	P-value
Demographics				
Age, mean (SD) years	57.1 (12.4)	57.0 (12.4)	57.1 (12.5)	0.9295
Age missing, n=4 (%)	0.2	0.2	0.2	0.9798
Female (%)	19.9	19.8	19.9	0.9823
BMI, mean (SD)	25.1 (3.4)	25.1 (3.4)	25.0 (3.4)	0.3455
BMI missing, n=0 (%)	0	0	0	
Clinical findings, and laboratory test				
Left atrial diameter (mm), mean (SD)	39.9 (7.9)	40.0 (8.1)	39.9 (7.7)	0.823
Left atrial size missing, n=66 (%)	3.8	4.2	3.1	0.1611
Heart rate, mean (SD)	73.0 (14.0)	73.3 (14.8)	72.7 (13.2)	0.8762
Heart rate missing, n=12 (%)	0.7	0.5	0.9	0.2291
Heart rate >100 (%)	4.5	5.6	3.4	0.0276
LVEF <40 (%)	35.5	35.8	35.1	0.7564
LVEF missing, n=0(%)	0	0	0	
Medical history				
HF (%)	18.1	20.2	15.8	0.0177
AMI (%)	22.6	23.4	21.9	0.4557
NYHA >3(%)	42.7	42.6	42.8	0.9461
CHD (%)	71.2	70.4	72.0	0.4699
DM (%)	27.8	27.2	28.4	0.5885
HTN (%)	63.6	62.7	64.5	0.4258
Valve surgery (%)	6.1	6.8	5.4	0.2044
Lifestyle				
Smoke (%)	57.8	57.6	57.9	0.8956
Alcohol consumption (%)	35.1	34.5	35.8	0.5561
One-year mortality (%)	6.5	7.3	5.8	0.2236

NYHA: New York Heart Association functional classification score, BMI: Body mass index, CHD: Coronary heart disease, HF: Heart failure, AMI: Acute myocardial infarction, DM: Type I or Type II diabetes, HTN: Hypertension. Continuous data were analyzed by the t-test. Categorical data were analyzed by the chi-squared test. $P<0.05$ is significant.

are not derived from data obtained from other racial or ethnic groups. Therefore, this is more applicable to Chinese patients, when compared to risk scores based largely on Western cohorts. For example, the effect size between the BMI and HF mortality could differ between the Western and Chinese population, because the Chinese population has a different pattern of body fat when compared to the Western population groups. As a result, the universal BMI criteria developed by the World Health Organization (WHO) is not suitable for Chinese and other Asian populations.^{17,18} Similarly, the effect size between the left atrial diameter and HF mortality between the Chinese population and the Western population could differ, showing that Caucasians usually have a large left atrial diameter.¹⁹ Nevertheless, further studies and explorations are required to quantify such differences. The present score was developed using a robust statistical method and was validated using additional data. There was also a high agreement with the derivation results. These five variables appear to meet the

criteria for an ideal variable. These are unaffected by clinical interpretation, widely accepted, available on admission, and easily collected.²⁰ Last, by identifying the modifiable components of the present risk score, public health services can be developed to resolve these specific issues. Given the extraordinarily large population of China, this would allow for the focused use of medical and public health resources that are unavoidably limited.

The present study has several limitations commonly observed in the development of clinic-based risk scores. This does not take into account such factors as the quality of physician and hospital care, socioeconomic influences, or access to care. The thresholds for low-, intermediate-, and high-risk were based on what the investigators considered was an acceptable risk within each category. In addition, important treatment information, such as pharmacological and interventional treatments, including angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-

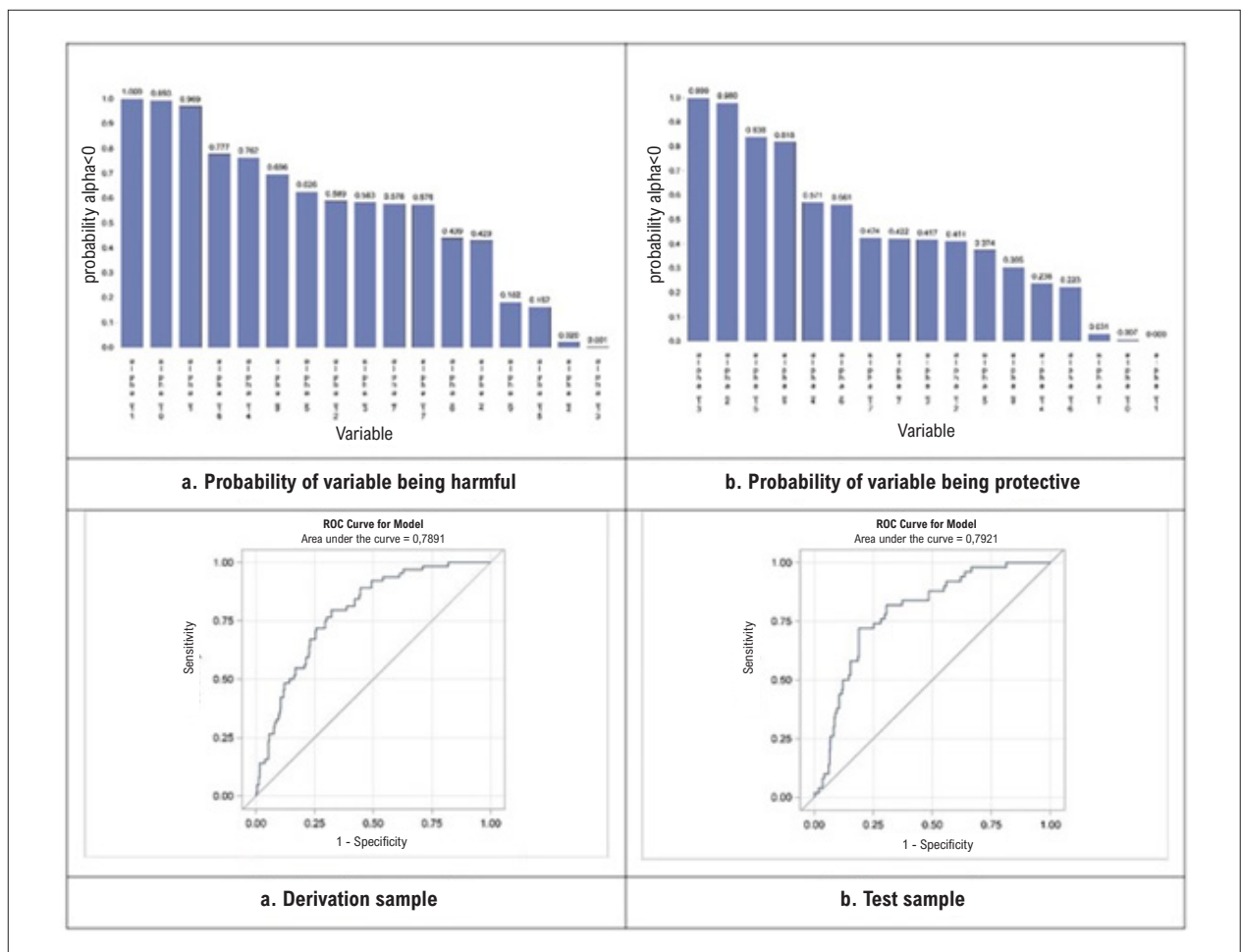


Figure 1 – Variable selection and model development for risk score

Table 2 – Risk factors and corresponding weights in the clinical risk score

Patient characteristics	Posterior probability*	Odds ratio (95% CI)	Standardized coefficient	Initial weight	Direction	Rescaled weight
Age, years	0.969	1.03 (1.01-1.05)	0.1864	0.155891946		1.5
Female	0.02	0.44 (0.20-0.97)	-0.1796	0.150204901	(-)	-15
left atrial diameter (mm)	0.993	1.05 (1.02-1.09)	0.2157	0.180396421		20
BMI	0.001	0.89 (0.82-0.96)	-0.2254	0.188508823	(-)	-20
NYHA ≥ 3	1.000	4.2 (2.07-8.34)	0.3886	0.324997909		30

*Posterior probability that the characteristic increases the probability of one-year HF death. Use of the score:

Score = $100 + 1.5age - 15female + 20 \text{ leftatrium} - 20 \text{ BMI} + 30 \text{ NYHA\_3}$ where NYHA_3 denotes the New York Heart Association functional classification score ≥ 3 . Giving a particular 45-year-old female HF patient with BMI of 23 and left atrial diameter of 30, and NYHA classification=2, the risk score of one-year post HF discharge mortality for this patient can be calculated as Score= $100 + 1.5 \times 45 - 15 \times 1 + 20 \times 30 - 20 \times 23 + 30 \times 0 = 322.5$. The risk score is between the low and moderate range.

blockers, and diuretics, biventricular pacemakers, and automatic implantable cardioverter-defibrillator devices, were not included in the model. Laboratory evaluations, such as hemoglobin and sodium levels, were also not included in the model. Finally, the patients sampled were from 14 hospitals in Beijing, a major city in China. There may be differences between the characteristics

and care of these patients with HF and those residing in more rural or remote areas that are not accounted for, which is a finding that has been observed when assessing cardiovascular risk in China.²¹ In addition, 42% of patients are NYHA ≥ 3 , and mortality is only 6.5%, which should be further evaluated in future studies. Nevertheless, although a number of clinical factors were

Table 3 – Model performance of the different risk scores.

Sample	5-risk factor-based model			Risk score-based model		
	ROC	Max-rescaled R-Square	Hosmer and Lemeshow Test	ROC	Max-rescaled R-Square	Hosmer and Lemeshow Test
Derivation	0.789	0.1761	0.9013	0.75	0.1159	0.0243
Test	0.792	0.1514	0.3725	0.771	0.097	0.005
Overall	0.7858	0.1589	0.5945	0.759	0.1069	0.003

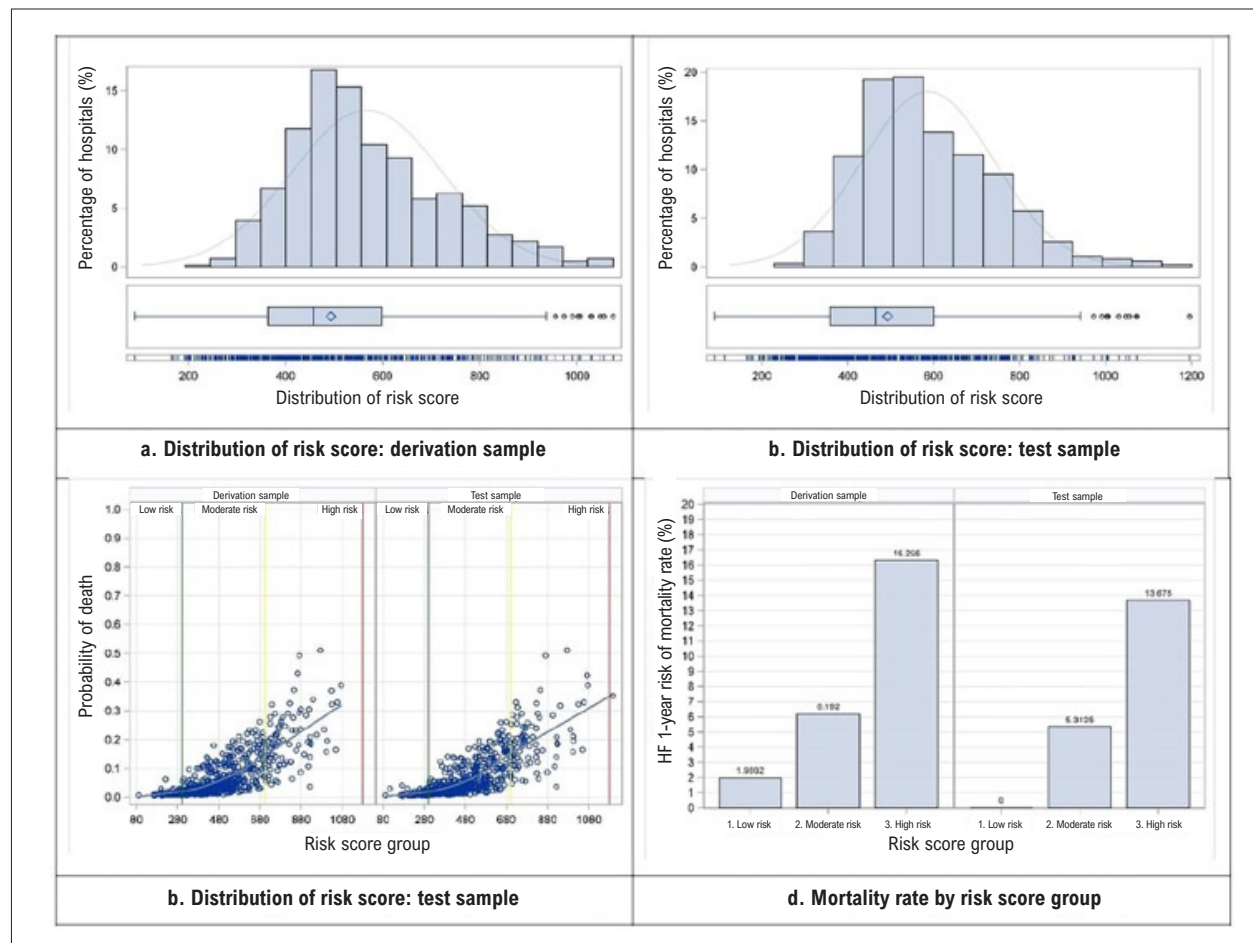


Figure 2 – Distribution of risk score.

not incorporated into the analysis, the purpose of the study was to develop a simple tool with easy-to-define variables to assist physicians.

The present score can be used to identify high-risk patients to provide better post-discharge care. As such, this could be employed as a guide for physicians to plan for the care of patients with HF, derived from evidence-based results of relevant and reliable research. Thus, the results of the present study provide an approach to healthcare, which promotes the collection, interpretation, and integration of valid, important, and applicable patient-reported, clinician-observed, and research-derived evidence, and the use of this evidence for better decision-making.

Conclusion and future directions

The present study showed a model for developing a risk score that is directly applicable to Chinese patients with HF. This model could better ensure that group-specific genetic and environmental factors are taken into account and can be used as a framework for developing risk scores in other racial and ethnic groups.

Author Contributions

Conception and design of the research and Writing of the manuscript: Wang L, Yun-Feng X; Acquisition of data: Li-Qin

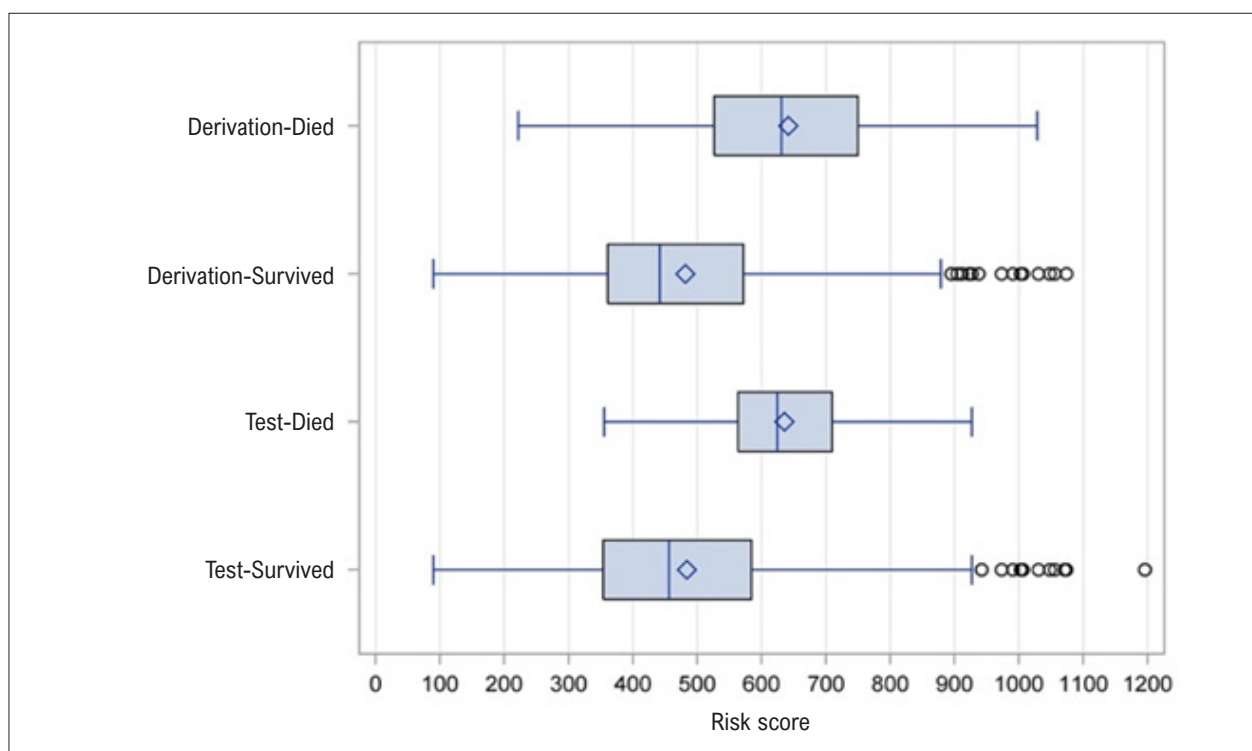


Figure 3 – Distribution of risk score by groups of patients who died and who survived.

W, Mo-Li G; Analysis and interpretation of the data: Li Liang; Statistical analysis: Li-Qin W, Li Liang, Wang C; Obtaining financing: Mo-Li G, Wang C; Critical revision of the manuscript for intellectual content: Wang L, Mo-Li G, Li Liang, Yun-Feng X.

Potential Conflict of Interest

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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 Fourth Medical Center of PLA General Hospital under the protocol number 2020KY002-KS001. 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. Jiang H, Ge J. Epidemiology and clinical management of cardiomyopathies and heart failure in China. *Heart*. 2009;95(21):1727-31.
2. Kaul P, McAlister FA, Ezekowitz JA, Grover VK, Quan H. Ethnic differences in 1-year mortality among patients hospitalised with heart failure. *Heart*. 2011;97:1048-53.
3. Vaughan-Sarrazin MS, Hannan EL, Gormley CJ, Rosenthal GE. Mortality in Medicare beneficiaries following coronary artery bypass graft surgery in states with and without certificate of need regulation. *Jama*. 2002;288(15):1859-66.
4. Hannan EL, Stone CC, Biddle TL, DeBuono BA. Public release of cardiac surgery outcomes data in New York: what do New York state cardiologists think of it? *Am Heart J*. 1997;134(1):1120-8.
5. Murphy GJ, Ascione R, Caputo M, Angelini GD. Operative factors that contribute to post-operative atrial fibrillation: insights from a prospective randomized trial. *Card Electrophysiol Rev*. 2003;7(2):136-9.
6. Mathew JP, Fontes ML, Tudor IC, et al. A multicenter risk index for atrial fibrillation after cardiac surgery. *JAMA*. 2004;291(14):1720-9.
7. Davila-Roman VG, Kouchoukos NT, Schechtman KB, Barzilai B. Atherosclerosis of the ascending aorta is a predictor of renal dysfunction after cardiac operations. *J Thorac Cardiovasc Surg*. 1999;117(1):111-6.
8. Barzi F, Patel A, Gu D, Sretara P, Lam T, Asia Pacific Community et al. Cardiovascular risk prediction tools for populations in Asia. *J Epidemiol Comm Health*. 2007;61(2):115-21.

9. Wang Y. A Multinomial Logistic Regression Modeling Approach for Anomaly Intrusion Detection. *Computers and Security* 2005;24:662-74.
10. Hosmer D, Lemeshow, S. *Applied logistic regression*, 2nd ed Philadelphia: Wiley & Sons, Inc.; 2000.
11. Palaniappan LP, Wong EC, Shin JJ, Fortmann SP, Lauderdale DS. Asian Americans have greater prevalence of metabolic syndrome despite lower body mass index. *Int J Obes (Lond)* 2011;35(3):393-400.
12. Palaniappan LP, Araneta MR, Assimes TL, Barrett-Connor EI, Carnethon E, Criqui M, et al. Call to action: cardiovascular disease in Asian Americans: a science advisory from the American Heart Association. *Circulation* 2010;122(12):1242-52.
13. Adams KF, Jr., Sueta CA, Gheorghiade M, O'Connor CM, Schwartz TA, Koch AA, et al. Gender differences in survival in advanced heart failure. Insights from the FIRST study. *Circulation* 1999;99(14):1816-21.
14. Oreopoulos A, Padwal R, Kalantar-Zadeh K, Fonarow GC, Norris CM, McAlister FA. Body mass index and mortality in heart failure: a meta-analysis. *Am Heart J*. 2008;156(1):13-22.
15. Rossi A, Temporelli PL, Quintana MF, Ghio S, Hillis G, Dini F, et al. Independent relationship of left atrial size and mortality in patients with heart failure: an individual patient meta-analysis of longitudinal data (MeRGE Heart Failure). *Eur J Heart Fail*. 2009;11(10):929-36.
16. O'Connor CM, Whellan DJ, Wojdyla D, Leifer E, Clark RM, Fini RJ, et al. Factors related to morbidity and mortality in patients with chronic heart failure with systolic dysfunction: the HF-ACTION predictive risk score model. *Circ Heart Fail*. 2012;5(1):63-71.
17. World Health Organization. (WHO). Obesity: preventing and managing the global epidemic: WHO technical report series n.o 894. Geneva;2000.
18. Shiwaku K, Anuurad E, Enkhmaa B, Kitajima K, Yamane Y. Appropriate BMI for Asian populations. *Lancet* -.2004; 363(9414):1077. DOI: 10.1016/S0140-6736(04)15856-X
19. Gottdiener JS, Reda DJ, Williams DW, Materson BJ. Left atrial size in hypertensive men: influence of obesity, race and age. *J Am Coll Cardiol*. 1997;29(3):651-8.
20. Radford MJ, Heidenreich PA, Bailey SR, et al. ACC/AHA 2007 Methodology for the Development of Clinical Data Standards: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Data Standards. *J Am Coll Cardiol*. 2007;49(7):830-7.
21. Gu D, Gupta A, Muntner P, Hu S, Suan X, Chen J, et al. Prevalence of cardiovascular disease risk factor clustering among the adult population of China: results from the International Collaborative Study of Cardiovascular Disease in Asia (InterAsia). *Circulation* 2005;112(5):658-65.



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Predictive Models to Enhance our Knowledge: Is It Necessary?

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Short Editorial related to the article: A Simple Clinical Risk Score to Predict Post-Discharge Mortality in Chinese Patients Hospitalized with Heart Failure

Heart Failure (HF) is a condition with an adverse prognosis; 1-year mortality rates in population-based studies have been reported to be 35% to 40%.¹⁻⁵ In Brazil, BREATHE registry, large sample of hospitalized patients with decompensated heart failure from different regions, demonstrated high intrahospital mortality (12.6%).⁶ Although HF admission decreased from 2008 to 2017, it was observed increased rate of length of stay for heart failure in hospitalized patients.⁷ Accurate prognostic information may enhance our ability to predict outcomes, thus informing decisions for patients. Numerous demographics, clinical and biochemical variables have been reported to provide important prognostic value in patients with heart failure, and several predictive models have been developed.⁸ Therefore, knowledge of mortality predictors can be used to generate predictive models that can aid clinicians' decision making by identifying patients who are at high or low risk of death.

Although most previous models are comprehensive and well-validated, there are still some limitations. First, some models were constructed in the period before the recent guideline-directed pharmacological treatment. Second, most previous models aimed to predict the short-term mortality rate. In addition, most were built using population in Western countries. As we have already known, factors that predict mortality in the community setting may differ.⁹

In this issue of the Journal, Wan et al.¹⁰ present the result of 1 742 heart failure patients included in the Beijing Monitoring Heart Failure Patients and Building Heart Failure Management Network Study from October 2015 to October 2017. These patients were randomly assigned into two groups: derivation (882 patients) and validation sample groups (860 patients). The aim was to identify risk factors correlated with one-year mortality among Chinese patients and develop a simple risk score. The outcome variable was one-year heart failure mortality, defined as all-cause death after an index HF hospitalization. The mortality information was obtained by phone interview. One-year mortality rates for the derivation and validation samples were 7.3% and 5.8%, respectively

($p=0.22$). Wan et al.¹⁰ identified five variables associated with one-year mortality: age, female gender, BMI, left atrial diameter and NYHA class > 3 . The area under the ROC curve of these five variables was 0.789, with good discrimination. The final variables identified were consistent with the risk factors previously identified in Western cohorts. It was found that female gender and BMI are protective factors, and NYHA classification, age and left atrial diameter are factors related to HF mortality, as we knew based on the Western population's previous finding.

There are several validated prognostic models, each of which combining different variables, which suggests how difficult it is to estimate risks in patients with HF. Nevertheless, the efforts to develop and improve such probabilistic models are justified because the risk of in-hospital mortality, mortality after discharge, and readmission are still elevated despite the evolution of specific treatment.

The use of such a probability model improves accuracy and offers a range of continuous probabilities, approximating medical thinking to the best form of dealing with uncertainty. However, the limitations of the present study should be recognized. First, the a low incidence of one-year mortality in HF patients even though 42% of patients are NYHA class > 3 . Second, some variables, which could contribute to the outcome, were not included in the model, such as pharmacological treatment. Third, heterogeneity in the quality of care among hospitals was not measured. The association between hospital-level quality of care and mortality has been reported in previous studies outside and inside China.¹¹ Another possible limitation is misclassification of comorbid conditions based on underreporting in the medical record because coexisting but undiagnosed conditions may not be recognized or have variability in abstraction. Finally, the medical history of the disease, especially non-circulatory illnesses, might be incompletely reported and documented. However, this would result in actual effects that are larger because it would tend to bias results toward the null. In addition, there are limitations to causal inference about the relationship between quality and outcomes because of the observational nature of data. However, the results are congruent with other published studies. This scoring system development aimed to identify independent parameters associated with mortality risk rather than determining the causal relationship with mortality. In this scoring system, most of the significant parameters are not modifiable. Therefore, this scoring system aims to help clinicians pay more attention to patients at high risk of mortality during and after hospitalization.

Physicians commonly assess the probability of disease by an unstructured clinical judgment which

Keywords

Cardiovascular Diseases; Risk Assessment; Heart Failure; Hospitalization; China/epidemiology.

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may underestimate or overestimate prognosis in heart failure patients based on passed clinical experiences. Although medical doctors usually put confidence into this type of judgment, it tends to be inaccurate. Several reports have alluded to the need for tools to estimate prognosis quantitatively. In contrast to anecdotal experience, the heart

failure predictive model is an accurate stratification of mortality risk. This simple score, easily obtained and not dependent on a specialized test, could be used as a framework to discuss prognosis and provide evidence to support rational decision-making in heart failure patients at the highest risk in China.

References

1. Ho KK, Anderson KM, Kannel WB, Grossman W, Levy D. Survival after the onset of congestive heart failure in Framingham Heart Study subjects. *Circulation*. 1993;88(1):107-15.
2. Zannad F, Braincon S, Juilliere Y, Mertes PM, Villemo JP, Alia F, et al. Incidence, clinical and etiologic features, and outcomes of advanced chronic heart failure: the EPICAL study. *J Am Coll Cardiol*. 1999;33(3):734-42.
3. Senni M, Tribouilloy CM, Rodeheffer RJ, Jacobsen SJ. Congestive heart failure in the community. *Circulation*. 1998;98(21):2282-9.
4. MacIntyre K, Capewell S, Stewart S, Chalmers JWT, Boyd J, Finlayson A, et al. Evidence of improving prognosis in heart failure. *Circulation*. 2000;102(10): 1126-31.
5. Tu JV, Zhang H. Congestive heart failure outcomes in Ontario. In: Naylor CD, Slaughter PM, eds. *Cardiovascular Health and Services in Ontario: An ICES Atlas*. Toronto, Ontario: Institute for Clinical Evaluative Sciences; 1999: 111-122.
6. Albuquerque DC, Souza Neto JD, Bacal F, Rohde LEP, Bernardes-Pereira S, Berwanger O, Rodrigues D, et al. *Arq Bras Cardiol*; 2015; 104(6): 433-441.
7. Fernandes AD, Fernandes G, Mazza MR, Knijnik LM, Fernandes GS, Vilela AT, Badiye A, Chaparro SV. *Arq Bras Cardiol*; 2020; 114(2): 222-231.
8. MacIntyre K, Capewell S, Stewart S, Chalmers JW, Boyd J, Finlayson A, et al. Evidence of improving prognosis in heart failure: trends in case fatality in 66 547 patients hospitalized between 1986 and 1995. *Circulation*. 2000 Sep 5. 102 (10):1126-31.
9. Sharpe N. Heart failure in the community. *Prog Cardiovasc Dis*. 1998;41(1 suppl 1):73-6.
10. Wan L, Wang L-Q, Gu M, Li L, Wang C, Xia Y. A simple risk score to predict post-discharge mortality in Chinese patients hospitalized with heart failure. *Arq Bras Cardiol*. 2021; 117(4):615-623.
11. He L, Dong Z-J, Du X, Jiang C, Chen N et al. Healthcare quality and mortality 11 mong patients hospitalized for heart failure by hospital level in Beijing, China. *ESC Heart Fail*. 2021. Published online 2021 Jan 5. doi: 10.1002/ehf2.13178



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Association between Helicobacter Pylori Infection and Systemic Arterial Hypertension: A Meta-Analysis

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Abstract

Background: Recent epidemiological studies have shown that alterations in microbiota and its metabolites are associated with systemic arterial hypertension. *Helicobacter pylori* (*H. pylori*) is one of the most common bacterial pathogens, and the potential association between *H. pylori* infection and hypertension are controversial.

Objective: This study aimed to clarify their association and provide a new theoretical basis for uncovering the pathogenesis of hypertension.

Methods: Case-control and cross-sectional studies on the association between *H. pylori* and hypertension published from 1996 to 2019 indexed in PubMed, Google Scholar, Chinese Wan Fang Data, and Chinese National Knowledge Infrastructure (CNKI). The pooled odds ratios (OR) and 95% confidence interval (CI) were estimated. I² was performed to evaluate the statistical heterogeneity. Publication bias was evaluated using Begg's and Egger's test. The extracted data was analyzed in Stata 12.0. Statistical significance was defined as *p*-value < 0.05.

Results: A total of 17 studies involving 6,376 cases of hypertension and 10,850 controls were enrolled. *H. pylori* infection rate in hypertension patients and controls were 64.9% and 56.3%, respectively. A significantly positive association was shown between *H. pylori* infection and hypertension with an overall OR of 2.07 (95% CI: 1.46–2.94; *p* < 0.05). Subgroup analysis revealed that the prevalence of *H. pylori* infection was associated with hypertension in the region of Asia and the case-control group, ORs (95% CI) were 2.26 (1.51–3.38) and 2.53 (1.72–3.72), respectively. After stratifying by detection methods, differences still existed in subgroups (all *p* < 0.05).

Conclusion: This meta-analysis indicated that *H. pylori* infection is positively associated with hypertension.

Keywords: Hypertension; Blood Pressure; Microbiota; Infection; Epidemiology; *Helicobacter Pylori*; Risk Factors; Endothelium Vascular; Cardiovascular Diseases; Meta-Analysis.

Introduction

Systemic arterial hypertension, also known as high or raised blood pressure, is a condition in which the blood vessels have a persistently high pressure. According to the World Health Organization (WHO), an estimated 1.13 billion people worldwide have hypertension, with two-thirds living in low- and middle-income countries.¹ In China, about 270 million people have hypertension, and its prevalence is highest in the North and lowest in the South.² As a global public health problem, hypertension contributes to the burden of heart disease, stroke, and kidney failure, among other diseases.³ It is considered a complex causal disorder, which be influenced by the interaction among many factors, such as unhealthy diet, harmful use of alcohol, physical inactivity, tobacco use, and genetic factors.⁴ Recently, studies in humans and animals

have shown that alterations in microbiota and its metabolites are associated with hypertension.^{5,6}

H. pylori is one of the most common bacterial pathogens and exists in the pylorus of the human stomach.⁷ The prevalence of *H. pylori* in individual countries varies from 18.9% in Switzerland to 87.7% in Nigeria⁸ and has infected more than half of the global population.⁹ *H. pylori* infection causes active chronic inflammation with a continuous recruitment of neutrophils to the inflamed gastric mucosa.¹⁰ Moreover, another study showed that abnormal gut microbiota facilitate AngII-induced vascular dysfunction and hypertension by driving vascular immune cell infiltration and inflammation.¹¹ A recent study has reported that *H. pylori* seropositivity is closely related to arteriosclerosis, and *H. pylori* infection may contribute to the development of cardiovascular disease.¹² Animal research has revealed that co-infection with *Chlamydia pneumoniae* and *H. pylori* result in vascular endothelial dysfunction and enhanced VCAM-1 expression in mice.¹³ These findings highlight the important role of *H. pylori* in regulating endothelial dysfunction and the AngII system, and *H. pylori* infection may be involved in the development of hypertension.

A cross-sectional study involving 5,246 participants found a positive association between *H. pylori* infection and

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hypertension after adjusting for potential confounders.¹⁴ By contrast, *H. pylori* status was not significantly different in patients with different grades of hypertension.¹⁵ Given the above introduction and the diversity of the results about *H. pylori* infection and hypertension, the need to conduct a study to determine *H. pylori* infection with hypertension is quite clear. Thus, to further investigate the potential role of *H. pylori* infection in hypertension, a meta-analysis was conducted to provide a basis for intervention in hypertension.

Methods

Literature retrieval

All papers on the relationship between *H. pylori* and hypertension, published from 1996 to 2019, were selected in this meta-analysis. The articles were searched by titles and/or abstracts that contained the terms “*H. pylori*” or “*helicobacter pylori*” and “hypertension” or “high blood pressure”, and which were published in Chinese on the Chinese Wanfang Data Knowledge Service Platform and in the Chinese National Knowledge Infrastructure (CNKI), and in English in the PubMed and Google Scholar Databases. Finally, the references were again filtered to avoid omission, in the screening process of reading the papers.

Inclusion criteria and exclusion criteria

All studies that were identified by the literature search were selected according to the following essentials: patients (individuals who were diagnosed according to systemic arterial hypertension diagnosis standard); exposure (*H. pylori* infection); comparator (normotension); outcome (association between *H. pylori* infection and hypertension); and study design (cross-sectional or case-control study). Studies were excluded if they were ecological and cohort studies, if they were not grouped by hypertension and normotension, if the number of *H. pylori* patients in each group cannot be determined, or if there were possible errors. If the same studies duplicated in different databases or the study population overlapped, only the largest one was selected.

Data extraction and quality assessment in the process

According to the purpose of this study, two independent researchers selected titles and/or abstracts to be included in the articles, and finally reached a consensus through a third expert's evaluation. The required studies were read through the full articles, and the following information and characteristics were recorded: the first author's name, year of publication, country, type of study, average age, number of participants, and testing for *H. pylori* infection.

Statistical analysis

All statistical analyses were performed using Stata 12.0. Pooled odds ratios (ORs) with corresponding 95% confidence interval (CI) were considered as the effect size for all the eligible studies. Two methods (Cochran Q test and the I^2 statistic) were used to assess the statistical heterogeneity among the summary data: if $p < 0.05$ was considered to be

statistically significant for heterogeneity, and the I^2 statistic suggested a significant heterogeneity with a value of $> 50\%$.¹⁶ A random-effects model was used to calculate the overall effect size estimate in this meta-analysis. To examine the sources of heterogeneity among the eligible studies, subgroup analyses were conducted according to different characteristics, such as study design (cross-sectional and case-control studies), study country (Asian and Western) and testing for *H. pylori* infection (urea breath test, serological test, among others). The urea breath test (UBT) included 13C-UBT and 14C-UBT; the serological test included the Colloidal gold method and ELISA; others included Giemsa staining and not available (N/A). Sensitivity analysis was performed to evaluate the effects of individual study on the summarized effects estimate and the stability of results. Begg's and Egger's regression tests were used to assess the publication bias. The meta-regression method was conducted for measurement data, such as sample size, average age, and gender ratio, and a two-tailed p -value < 0.05 was defined as statistically significant.

Results

Basic characteristics of included articles¹⁷⁻³³

A flow diagram of studies for systematic review was shown in Figure 1. Of these, 80 duplicate studies were excluded, and, based on the titles and abstracts of the remaining articles, 57 studies were also excluded. Ultimately, 17 publications were selected after examining the full text of these 22 publications, as specified in the flow diagram.

In total, six cross-sectional studies and eleven case-control studies were selected in the meta-analysis from 1996 to 2019. Among the 17,226 participants, the prevalence of *H. pylori* in 6,376 hypertensive patients was 64.9% and in 10,850 normotensives was 56.3%. The main characteristics of the studies included in this review were presented in Table 1.¹⁷⁻³³

Results of meta-analysis

Based on the random effects model in Figure 2, the general estimate of the pooled OR (95% CI) of *H. pylori* and hypertension was 2.07 (1.46–2.94), which was statistically significant ($p < 0.001$).

Subgroup analysis according to region, study design, and test method

For the subgroup analysis by region (Asian in 5,372 hypertensives and 10,250 normotensives, Western in 1,004 hypertensives and 600 normotensives), the *H. pylori* infection was associated with the risk of hypertension in Asian countries (OR 2.26, 95%CI 1.51–3.38; $I^2 = 95.1\%$, $p < 0.05$), while no significant difference was found in Western nations.

In the subgroup analysis grouped by study design, the pooled OR for *H. pylori* infection for hypertension was 2.53 (95% CI 1.72–3.72; $I^2 = 72.7\%$, $p < 0.05$) in the case-control studies. No statistical difference was observed in the cross-sectional studies (Figure 3 and 4).

In the subgroup analysis of studies that used UBT to test *H. pylori* infection, *H. pylori* infection was associated with an

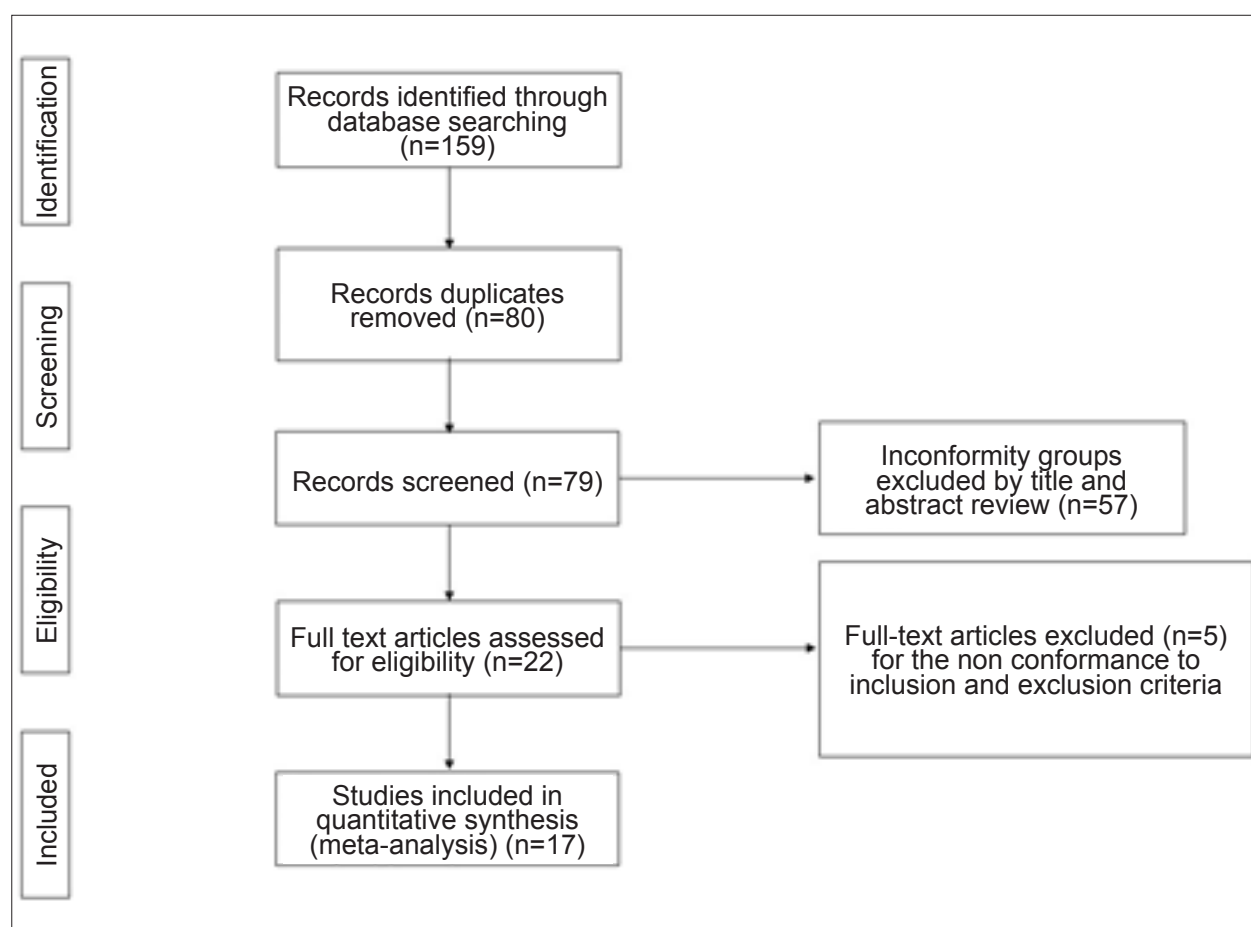


Figure 1 – Flow diagram of studies included in the meta-analysis.

increased risk for hypertension (OR 4.13, 95% CI 2.60-6.54; $I^2 = 76.7\%$, $p < 0.05$). H. pylori infection was also associated with a high risk for hypertension in a subgroup analysis of studies in a serological test (OR 1.33, 95% CI 1.04-1.68; $I^2 = 77.1\%$, $p < 0.05$) (Figure 5).

Publication bias

Begg's test was used to evaluate publication bias, using the funnel plot (Figure 6). This was an asymmetry in the funnel plot for eligible studies. The significant publication bias was also identified in the Egger's regression test ($p = 0.047$).

Sensitivity analysis

A sensitivity analysis was performed to test the sources of heterogeneity and assess the stability of results. The sensitivity analysis results showed that no individual study had extreme influence on the pooled odds ratio (Figure 7).

Meta regression

Individual studies without an average age ($n = 2$) or without the number of men and women ($n = 2$) were excluded. Results of univariable meta-regressions show the lack of significant effects of sample size ($p = 0.181$), average age ($p = 0.542$),

as well as gender ratio ($p = 0.367$) on the association between H. pylori infection and risk of hypertension in the studies (Supplementary Material: Supplementary Figures 1-3).

Discussion

To the best of our knowledge, this is the first systematic review study to demonstrate that the relationship between H. pylori infection and hypertension. The finding showed that the prevalence of H. pylori infection was positively associated with hypertension, and this result was consistent in the case-control group in the subgroup analysis. Mendel et al.³⁴ first put forward the hypothesis of the relationship between H. pylori infection and coronary heart disease. Subsequently, some scholars have carried out research on H. pylori infection in cardiovascular disease.³⁵

A previous cohort study demonstrated that H. pylori-infected, chronic active gastritis positive individuals showed a 29% higher risk for hypertension development during the follow-up period.³⁶ One Chinese study indicated that H. pylori infection was independently associated with higher DBP but not SBP after adjusting for covariates.¹⁴ However, several studies showed that H. pylori infection did not influence blood pressure.^{37,38} Of course, we cannot conclude that H. pylori infection facilitates

Table 1 – Basic characteristic of the seventeen articles included herein

Studies	Year	Country	H. pylori ascertainment	Hypertension (H. pylori + / -)	Normotensive (H. pylori + / -)	Average age	Study design	Gender ratio*	p threshold
Yang ¹⁷	2016	China [#]	14C-UBT	78(66/12)	78(37/41)	N/A	Case-control study	0.79	0.05
Liu ¹⁸	2015	China [#]	14C-UBT	150(125/25)	150(71/79)	63.60	Case-control study	1.04	0.05
Huai ¹⁹	2014	China [#]	13C-UBT	535(338/197)	1051(232/819)	68.30	Cross-sectional study	2.68	0.05
Ma ²⁰	2015	China [#]	Giemsa staining	112(42/70)	170(53/117)	N/A	Case-control study	N/A	0.05
Chu ²¹	2014	China [#]	IgG Colloidal gold	150(67/83)	50(14/36)	60.85	Case-control study	1.41	0.05
Hu ²²	2017	China [#]	N/A	176(82/94)	568(224/344)	52.53	Cross-sectional study	1.23	0.05
Lip ²³	1996	UK ^{\$}	ELISA≥8 units/ml).	124(106/18)	38(25/13)	53.06	Case-control study	1.03	0.05
Liu ²⁴	2007	China [#]	ELISA	488(189/299)	942(317/625)	46.56	Cross-sectional study	0.71	0.05
Sun ²⁵	2018	China [#]	14C-UBT	90(76/14)	65(34/31)	44.74	Case-control study	1.12	0.05
Li ²⁶	1999	China [#]	IgG ELISA	42(16/26)	60(18/42)	55.41	Case-control study	1.62	0.05
Zhao ²⁷	2019	China [#]	14C-UBT	102(43/59)	102(18/84)	47.85	Case-control study	0.94	0.05
Migneco ²⁸	2003	Italy ^{\$}	13C-UBT	72(40/32)	70(35/35)	52.51	Case-control study	0.95	0.05
Vahdat ²⁹	2013	Iran [#]	ELISA >30 RU/ml	459(316/143)	1295(764/531)	40.79	Cross-sectional study	0.97	0.05
Zheng ³⁰	2014	China [#]	Giemsa staining	112(42/70)	170(53/117)	52.19	Case-control study	1.29	0.05
Sung ³¹	2003	Korea [#]	ELISA≥6 U/mL	2838(1964/874)	5509(3818/1691)	48.06	Cross-sectional study	1.36	0.05
Sotuneh ³²	2014	Italy ^{\$}	ELISA>20 ur/ml	808(606/202)	492(385/107)	69.23	Cross-sectional study	N/A	0.05
S.VSM ³³	2012	India [#]	IgG ELISA>40 ur/ml	40(18/22)	40(9/31)	44.09	Case-control study	1.05	0.05

UBT: urea breath test; ELISA: enzyme linked immunosorbent assay; N/A: not available; * Gender ratio: male /female; #Asian countries; \$ Occident countries.

hypertension; however, our meta-analysis now supports the association between H. pylori infection and hypertension.

The prevalence of H. pylori infection varies markedly in different countries and regions. H. pylori infections in Asian nations were common and extensively distributed, and the average infection rate of H. pylori infection in China was 58.07%, with 50% in the age group of 10 to 20 years.³⁹ Epidemiological investigation showed that the cytotoxin-associated gene A (CagA) positive strain from different geographic areas exhibits clear phylogeographic differentiation. More than 90% of H. pylori isolates from East Asian countries, such as China and Japan, contain CagA protein, while only 60% - 70% of H. pylori isolates from Western countries, such as the United States, contain the CagA protein.⁴⁰ Moreover, Migneco A et al.²⁸ found that only among the high CagA positive patients did the DBP decrease, most visibly after the H. pylori had been eradicated, and may be related to the molecular relationship between the CagA antigen of H. pylori and some peptides expressed by endothelial cells and smooth muscle cells. It is notable that the OR of hypertension in Asian populations with H. pylori infection was 2.26-fold more than that of the normotensive subjects in our study. These results suggest that ethnic origin may have a potential impact on the relationship between H. pylori infection and hypertension.

Another issue in determining the relationship between H. pylori infection and hypertension is the method used to test for H. pylori infection. Although serological testing is a popular screen for H. pylori infection, it does not guarantee current H. pylori infection.⁴¹ Diagnostic accuracy of using UBT to detect H. pylori infection in the Asian population, especially 13C-UBT, which had outstanding diagnostic accuracy with a sensitivity of 97% and a specificity of 96%.⁴² In our subgroup analysis, the risk for hypertension was higher when H. pylori infection was determined using UBT compared with other tests.

The mechanisms that link H. pylori infection to hypertension remain unclear. There are several hypotheses supporting the relationship, and one of the most plausible is the levels of inflammatory cytokines. Epstein et al.⁴³ indicated that the chronic inflammation caused by H. pylori infection may consequently result in advanced atherosclerosis. In addition, a prospective study has demonstrated that H. pylori had a positive association with high LDL and low HDL.⁴⁴ Lipids, as an integral part of the cell membrane, play an important role in the development of hypertension.⁴⁵ It is speculated that H. pylori infection leads to the abnormal metabolism of LDL-C, HDL-C, and TC, which in turn results in hypertension. H. pylori infection destroys immune tolerance and causes autoimmune reaction, which may participate in the pathogenesis of hypertension.^{46,47}

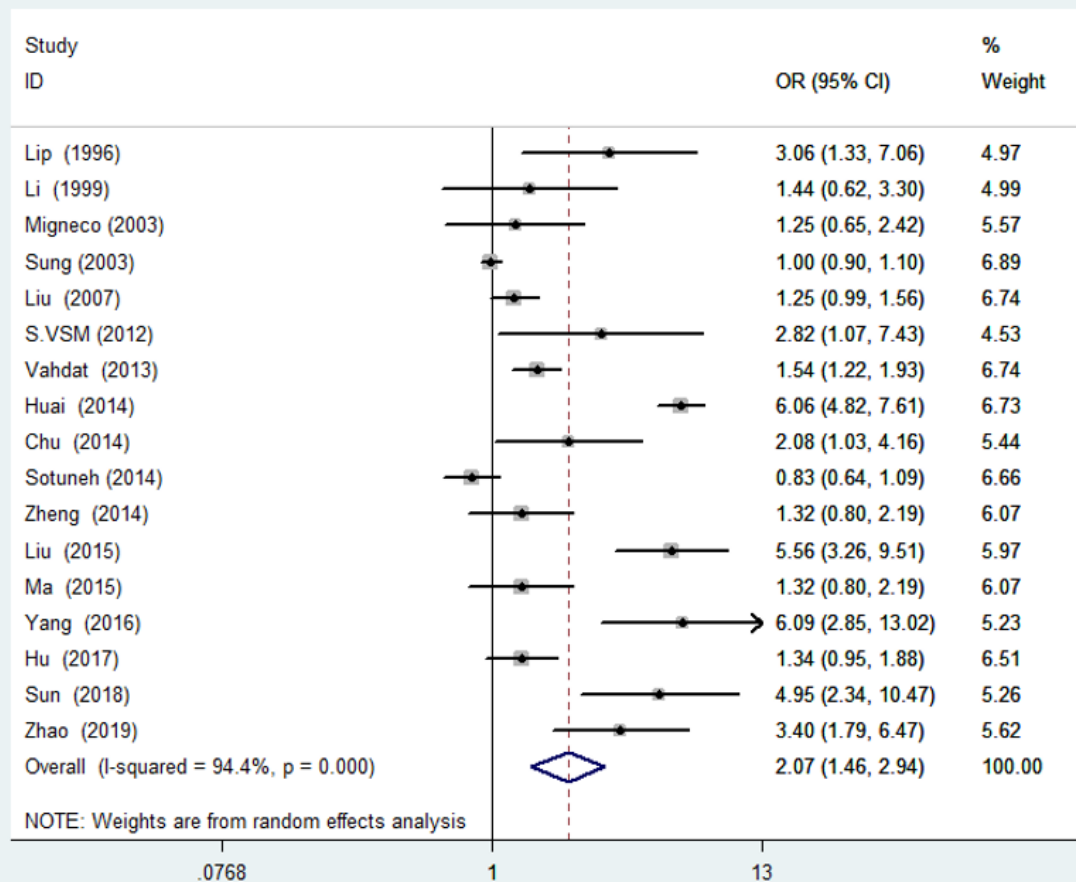


Figure 2 – A forest plot of the association between *H. pylori* infection and hypertension.

Age were found to be independent predictors of *H. pylori* infection, and an increasing trend of prevalence with age, while no difference in prevalence was found between both sexes.⁴⁸ Furthermore, men were more than twice as likely to develop cardiovascular disease as women at least under the age of 60.⁴⁹ However, our study indicates a lack of significant effects of age and gender on the association between *H. pylori* infection and the risk of hypertension. It is possible that different ethnicity, assessment of *H. pylori* infection, sample sizes, and potential confounders may contribute to the discrepancies.

Limitations

There are several limitations in our study. First, all included studies were observational, which made it difficult to estimate a causal association. Second, significant heterogeneity was identified in the meta-analyses, and it was not possible to adjust for potentially confounding variables by other inaccessible information. Third, most original studies were performed in the Asian population, and a publication bias was found in the meta-analysis.

Conclusions

In conclusion, our results indicated that *H. pylori* infection is positively associated with hypertension. The strategies of preventing *H. pylori* infection and eradicating *H. pylori* may have a significant impact on the prevention and treatment of hypertension, and warrants further evaluation.

Author Contributions

Conception and design of the research: Huang M, Zhu L. Acquisition of data: Jin Y, Fang Z. Analysis and interpretation of the data: Fang Z. Statistical analysis: Jin Y. Obtaining financing: Yao Y, Chen Y. Writing of the manuscript: Huang M, Zhu L. Critical revision of the manuscript for intellectual content: Yao Y, Chen Y.

Potential Conflict of Interest

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

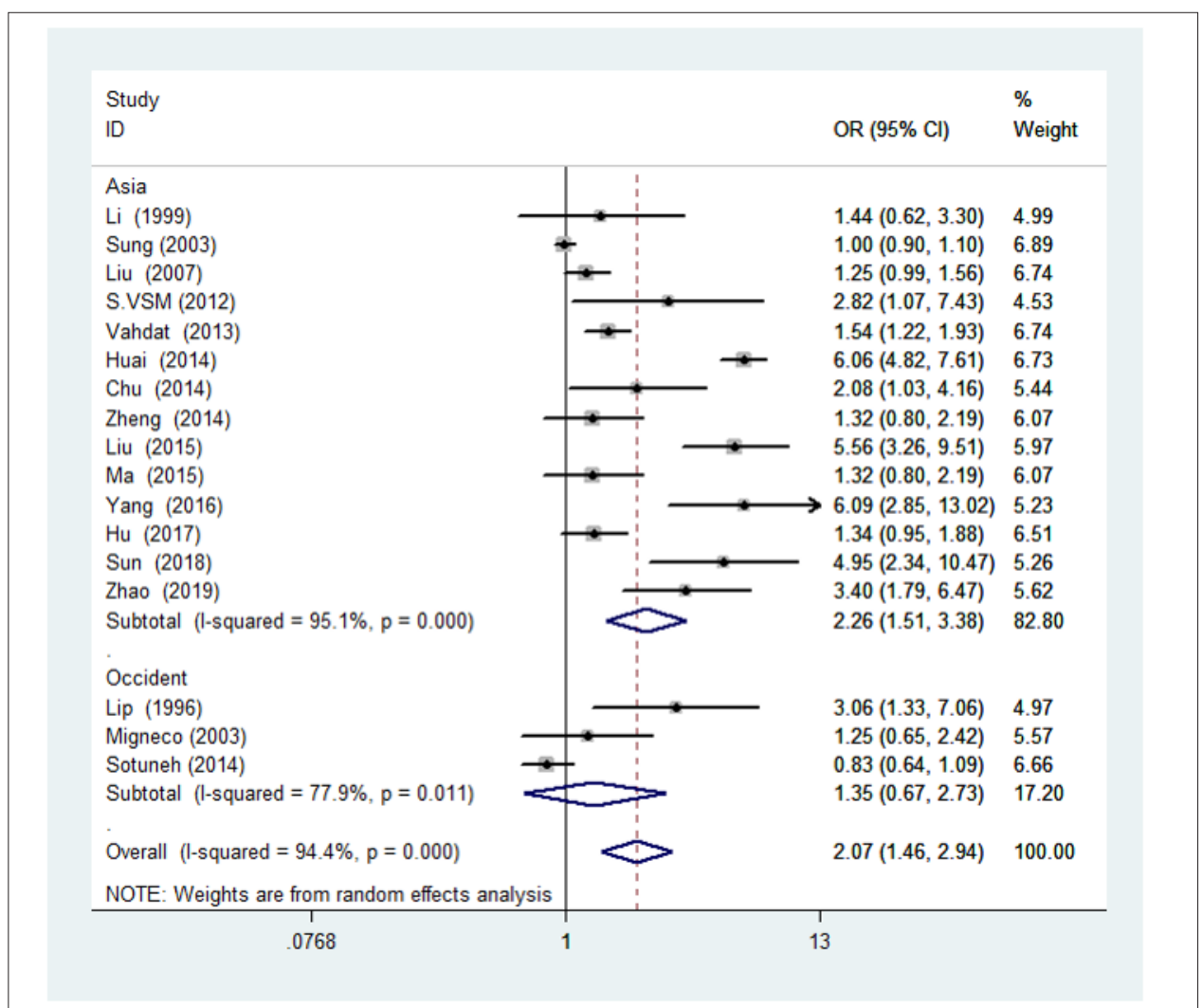


Figure 3 – Forest plot of subgroup analyses comparing Asia with the West.

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Study Association

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

Ethics Approval and Consent to Participate

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

Original Article

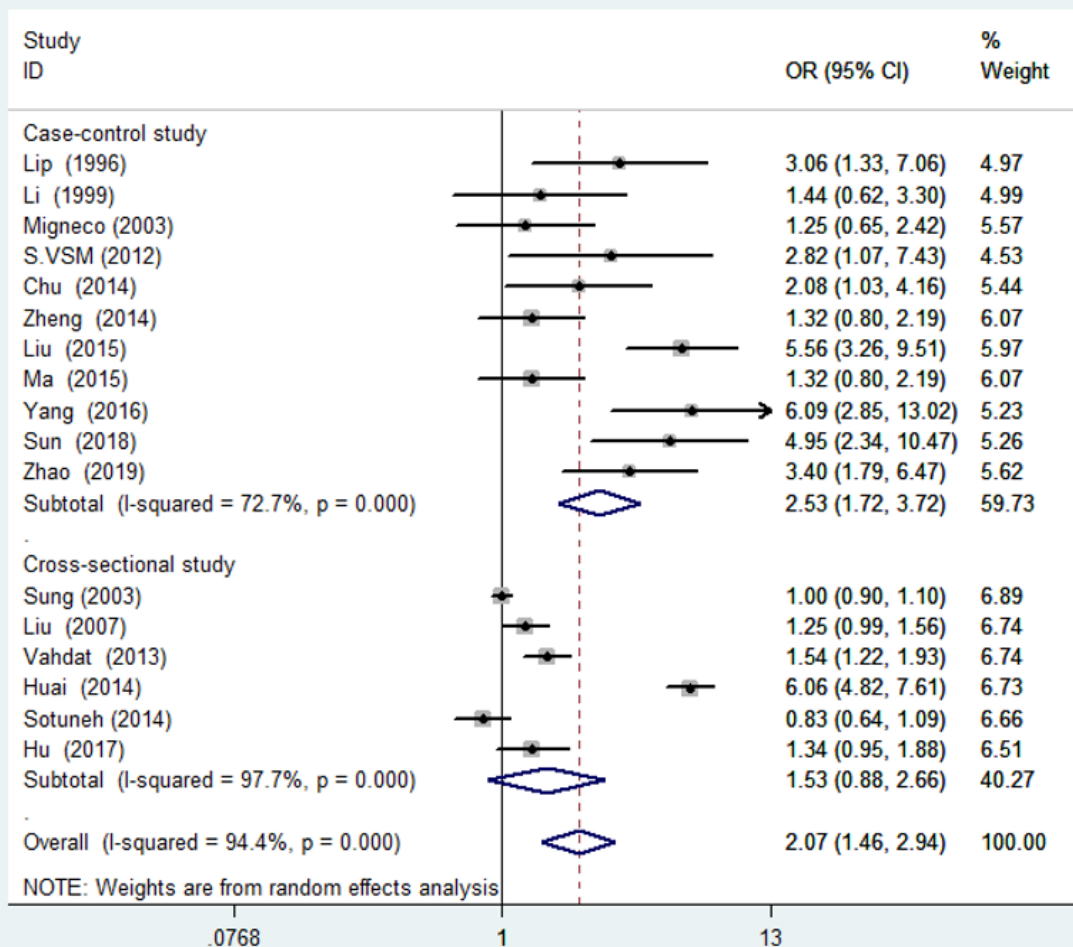


Figure 4 – Forest plot of subgroup analyses comparing case-control study with cross-sectional study.

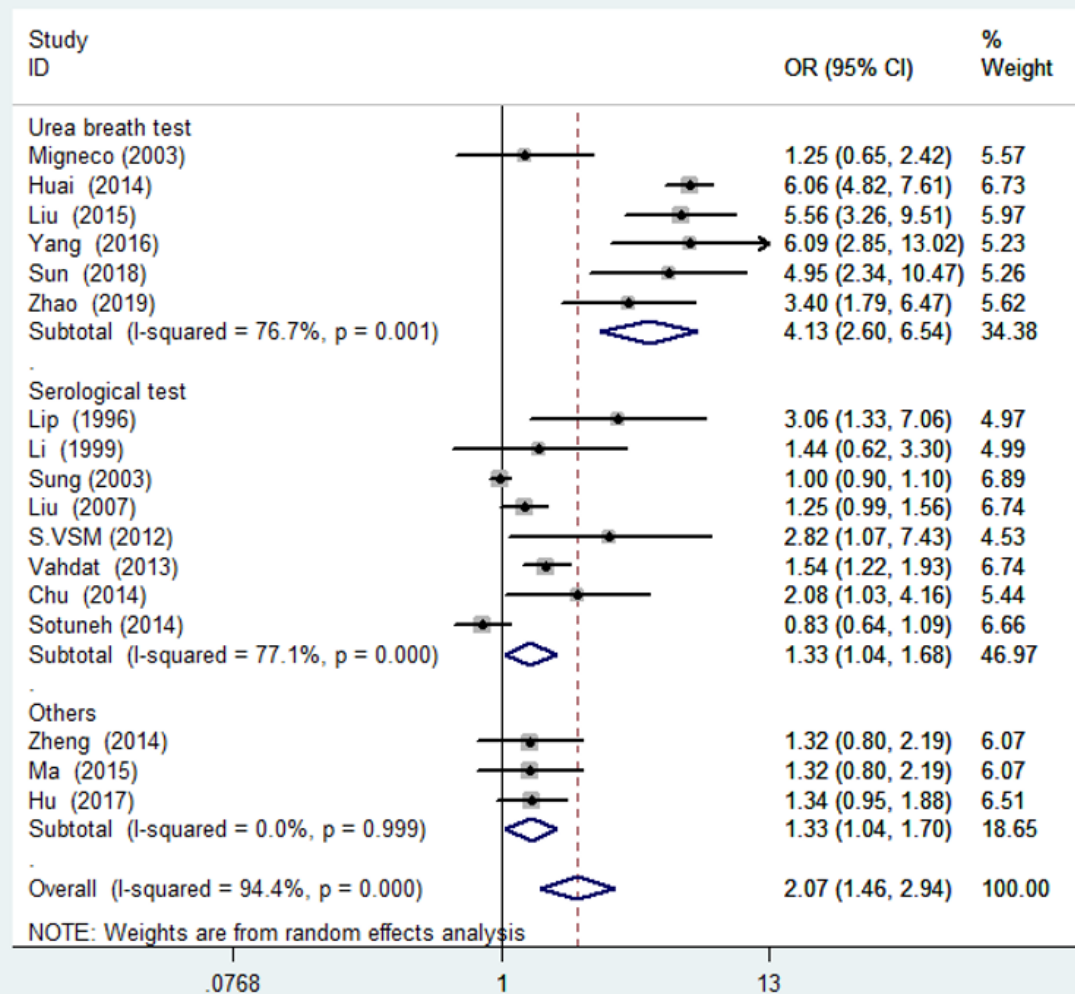


Figure 5 – Forest plot of subgroup analyses comparing in different diagnostic methods.

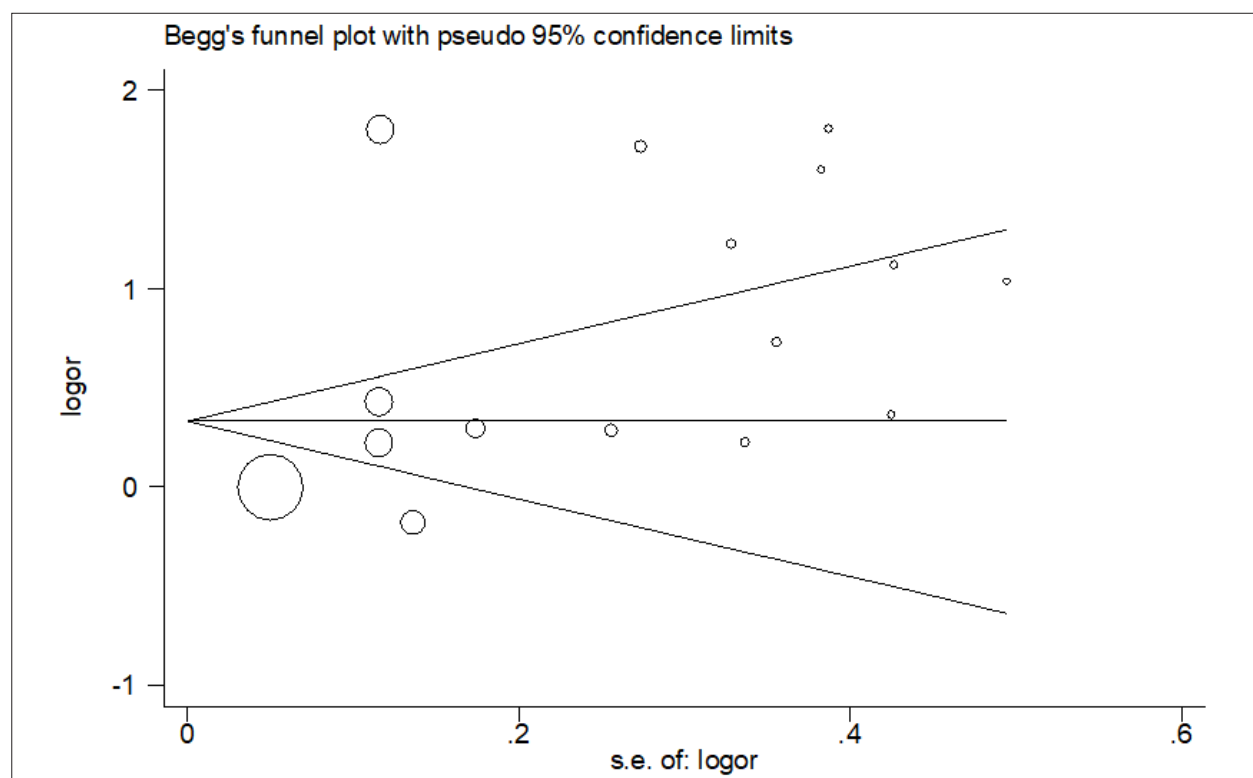


Figure 6 – Begg's Funnel plot with pseudo 95% confidence interval.

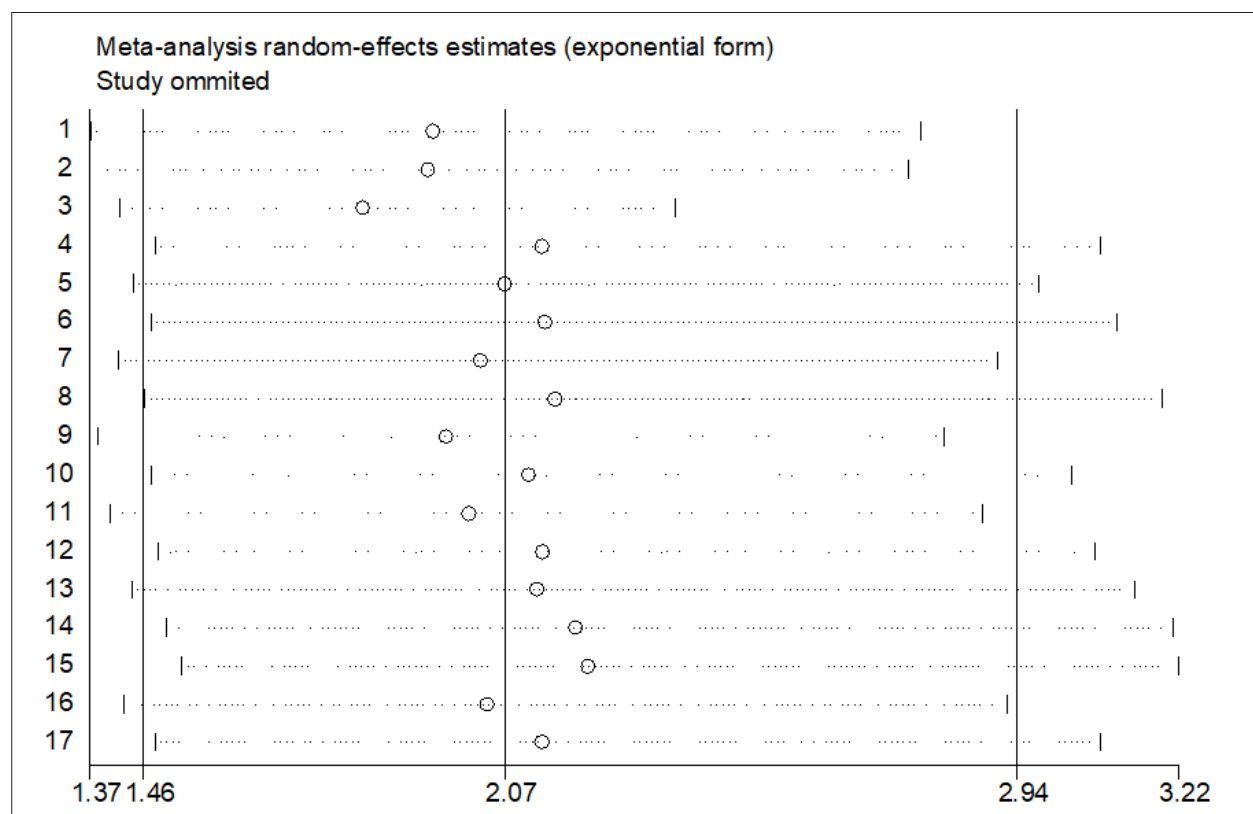


Figure 7 – Sensitivity analyses for association between *H. pylori* and hypertension.

References

- Subasinghe AK, Arabshahi S, Busingye D, Evans RC, Walker KZ, Riddell MA, et al. Association between salt and hypertension in rural and urban populations of low to middle income countries: A systematic review and meta-analysis of population based studies. *Asia Pacific Clin Nutr*. 2016;25(2):402-13.
- Li Y, Wang L, Feng X, Zhang M, Huang Z, Deng Q, et al. Geographical variations in hypertension prevalence, awareness, treatment and control in china: Findings from a nationwide and provincially representative survey. *J Hypertens*. 2018;36(1):178-87.
- Messerli FH, Williams B, Ritz E. Essential hypertension. *Lancet*. 2007;370(9587):591-603.
- Forman JP, Stampfer MJ, Curhan GC. Diet and lifestyle risk factors associated with incident hypertension in women. *Jama*. 2009;302(4):401-11.
- Pevsner-Fischer M, Blacher E, Tatirovsky E, Ben-Dov IZ, Elinav E. The gut microbiome and hypertension. *Curr Opin Nephrol Hypertens*. 2017;26(1):1-8.
- Yang T, Santisteban MM, Rodriguez V, Li E, Ahmari N, Carvajal JM, et al. Gut dysbiosis is linked to hypertension. *Hypertension*. 2015;65(6):1331-40.
- Brown LM. *Helicobacter pylori*: Epidemiology and routes of transmission. *Epidemiol Rev*. 2000;22(2):283-97.
- Hooi JKY, Lai WY, Ng WK, Suen MMY, Underwood FE, Tanyingoh D, et al. Global prevalence of helicobacter pylori infection: Systematic review and meta-analysis. *Gastroenterology*. 2017;153(2):420-9.
- Leja M, Axon A, Brenner H. Epidemiology of helicobacter pylori infection. *Helicobacter*. 2016;21 (Suppl 1):3-7.
- Innocenti M, Thoreson AC, Ferrero RL, Stromberg E, Bolin I, Eriksson L, et al. *Helicobacter pylori*-induced activation of human endothelial cells. *Infect Immun*. 2002;70(8):4581-90.
- Ma J, Li H. The role of gut microbiota in atherosclerosis and hypertension. *Front Pharmacol*. 2018;9:1082.
- Choi JM, Lim SH, Han YM, Lee H, Seo JY, Park HE, et al. Association between helicobacter pylori infection and arterial stiffness: Results from a large cross-sectional study. *PLoS One*. 2019;14:e0221643.
- Liuba P, Pesonen E, Paakkari I, Batra S, Andersen L, Forslid A, et al. Co-infection with chlamydia pneumoniae and helicobacter pylori results in vascular endothelial dysfunction and enhanced vcam-1 expression in apoe-knockout mice. *J Vasc Res*. 2003;40(2):115-22.
- Wan Z, Hu L, Hu M, Lei X, Huang Y, Lv Y. *Helicobacter pylori* infection and prevalence of high blood pressure among chinese adults. *J Hum Hypertens*. 2018;32(2):158-64.
- Lu C, Jia H, Xu A, Tang J, Xu G, Yue W, et al. *Helicobacter pylori* infection and pepsinogen levels have clinical significance in hypertension patients. *Int J Clin Exp Med*. 2014;7(12):5675-80.
- Higgins JP, Thompson SC, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327(7414):557-60.
- Guang Y, Qian-sheng W, Yun-xia L, Xin-rong H, Dong-liang L. Research of helicobacter pylori infection and change of c-reactive protein in patients with essential hypertension. *Chin J Nosocomiol*. 2016;26:2735-7.
- Fei-fei L, Jun S, Hai-yan G. *Helicobacter pylori* infection and its correlation in 150 patients with hypertension. *Prev Treat Cardiovasc Dis*. 2015:42-3.
- Yong-jun H, Gui-chi Z, Hui-ling L. Relationship between helicobacter pylori infection and primary hypertension and hypertensive heart disease. *Clin J Med Offic*. 2014;42:1113-1114+1121.
- Yun-ma S, Xue-mei W, Mei-yue C. Clinical analysis of hypertension with peptic ulcer. *Health Vocational Education*. 2015;33:144-5.
- Hong-jiu C, Wen-dong Y. Correlation between carotid artery atherosclerosis and helicobacter pylori infection in patients with essential hypertension. *Pract J Card Cerebr Pneumol Vasc Dis*. 2014;22:22-4.
- Ming-xi H, Li Y, Yuan-yuan W, Jin-ying G, Lan L. Assess of blood vessel condition on different levels of blood pressure and analysis of the relevant risk factors. *Chin J Laborat Diagn*. 2017;21:1221-5.
- Lip GH, Wise R, Beevers G. Association of helicobacter pylori infection with coronary heart disease. Study shows association between h pylori infection and hypertension. *BMJ*. 1996;312:250-1.
- Liu L, Liu Y, Tong W, Ye H, Zhang X, Cao W, et al. Pathogen burden in essential hypertension. *Circulation*. 2007;71:1761-4.
- Ping S, Jia-he S, Qing-xia X, Li-li Z, Xi-tian H. Serum levels of tnf- α , il-6 and il-8 in hypertensive patients with different types of helicobacter pylori infection. *Infect Dis Info*. 2018;31:165-7.
- Dai-yu L, Hua Z, Liang-hai C, Qing W. A preliminary study on the relationship between serum helicobacter pylori antibody detection and coronary heart disease. *J South Med Univ*. 1999:200-1.
- Wei-hua Z. Correlation analysis between helicobacter pylori infection and lipid metabolism in patients with essential hypertension. *Mod Diagn Treat*. 2019;30:2292-3.
- Migneco A, Ojetti V, Specchia L, Franceschi F, Candelli M, Mettimano M, et al. Eradication of helicobacter pylori infection improves blood pressure values in patients affected by hypertension. *Helicobacter*. 2003;8:585-9.
- Vahdat K, Pourbehi MR, Ostovar A, Hadavand F, Bolkheir A, Assadi M, et al. Association of pathogen burden and hypertension: The persian gulf healthy heart study. *Am J Hypertens*. 2013;26:1140-7.
- Zheng-fa Z. Clinical analysis of peptic ulcer in patients with hypertension. *China Health Care Nutrition*. 2014:72-3.
- Sung KC, Suh JY, Kim BS, Kang JH, Kim H, Lee MH, et al. High sensitivity c-reactive protein as an independent risk factor for essential hypertension. *Am J Hypertens*. 2003;16:429-33.
- Sotuneh N, Hosseini SR, Shokri-Shirvani J, Bijani A, Ghadimi R. *Helicobacter pylori* infection and metabolic parameters: Is there an association in elderly population? *Int J Prev Med*. 2014;5:1537-42.
- S. VSM, Kutty AVM, Annamalai N. *Helicobacter pylori* infection and hypertension: Is there an association? *Biomed Res*. 2012 (0970-938X)
- Mendall MA, Goggin PM, Molineaux N, Levy J, Toosy T, Strachan D, et al. Relation of helicobacter pylori infection and coronary heart disease. *Br Heart J*. 1994;71:437-9.
- Kim YI, Kim YA, Lee JW, Kim HJ, Kim SH, Kim SG, et al. Effect of *Helicobacter pylori* treatment on long-term mortality in patients with hypertension. *Gut Liver*. 2020;14:47-56.
- Barnes RJ, Uff JS, Dent JC, Gear MW, Wilkinson SP. Long-term follow up of patients with gastritis associated with helicobacter pylori infection. *Brit J Gen Pract*. 1991;41:286-8.
- Kopacova M, Koupil I, Seifert B, Fendrichova MS, Spirkova J, Vorisek V, et al. Blood pressure and stature in helicobacter pylori positive and negative persons. *World J Gastroenterol*. 2014;20:5625-31.
- Gunji T, Matsuhashi N, Sato H, Fujibayashi K, Okumura M, Sasabe N, et al. *Helicobacter pylori* infection is significantly associated with metabolic syndrome in the japanese population. *Am J Gastroenterol*. 2008;103:3005-10.
- Wang KJ, Wang RT. Meta-analysis on the epidemiology of helicobacter pylori infection in china. *Zhonghua liu xing bing xue za zhi = Zhonghua liuxingbingxue zazhi*. 2003;24:443-6.
- Yamaoka Y. *Helicobacter pylori* typing as a tool for tracking human migration. *Clin Microbiol Infect*. 2009;15:829-34.
- Sabbagh P, Mohammadnia-Afrouzi M, Javanian M, Babazadeh A, Koppolu V, Vasigala VR, et al. Diagnostic methods for helicobacter pylori infection: Ideals, options, and limitations. *Eur J Clin Microbiol Infect Dis*. 2019;38:55-66.

42. Abd Rahim MA, Johani FH, Shah SA, Hassan MR, Abdul Manaf MR. ¹³C-urea breath test accuracy for *helicobacter pylori* infection in the asian population: A meta-analysis. *Ann Glob Health*. 2019;85.
43. Epstein SE. The multiple mechanisms by which infection may contribute to atherosclerosis development and course. *Circ Res*. 2002;90:2-4.
44. Nam SY, Ryu KH, Park BJ, Park S. Effects of helicobacter pylori infection and its eradication on lipid profiles and cardiovascular diseases. *Helicobacter*. 2015;20:125-32.
45. Zicha J, Kunes J, Devynck MA. Abnormalities of membrane function and lipid metabolism in hypertension: A review. *Am J Hypertens*. 1999;12:315-31.
46. Algood HM, Cover TL. *Helicobacter pylori* persistence: An overview of interactions between h. Pylori and host immune defenses. *Clin Microbiol Rev*. 2006;19:597-613.
47. Rodriguez-Iturbe B, Pons H, Johnson RJ. Role of the immune system in hypertension. *Physiol Rev*. 2017;97:1127-64.
48. Wang W, Jiang W, Zhu S, Sun X, Li P, Liu K, et al. Assessment of prevalence and risk factors of helicobacter pylori infection in an oilfield community in hebei, china. *BMC Gastroenterol*. 2019;19:186.
49. Kannel WB, Hjortland MC, McNamara PM, Gordon T. Menopause and risk of cardiovascular disease: The framingham study. *Ann Intern Med*. 1976;85:447-52.



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Helicobacter Pylori and High Blood Pressure

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Short Editorial related to the article: Association between Helicobacter Pylori Infection and Systemic Arterial Hypertension: A Meta-Analysis

Raised blood pressure (BP) remains the leading cause of death globally, accounting for 10.4 million deaths per year.¹ In addition, data from the World Health Organization highlighted the significant global impact of systemic arterial hypertension (SAH): an estimated 1.13 billion people worldwide have hypertension, most (two-thirds) living in low- and middle-income countries; and is a major cause of premature death worldwide.

BP is determined by several parameters of the cardiovascular system, including blood volume and cardiac output (the amount of blood pumped by the heart per minute) and the balance of arterial tone that is affected by intravascular volume and neurohumoral systems.²

SAH is a chronic elevation of blood pressure that, in the long-term, causes end-organ damage and results in increased morbidity and mortality. Increased systemic vascular resistance, vascular stiffness, and vascular responsiveness to stimuli are central to the pathophysiology of hypertension.³ Furthermore, SAH is a multifactorial condition that depends on genetic (epigenetic), environmental and social factors associated with metabolic risk factors for cardiocirculatory and renal systems diseases, such as dyslipidemia, abdominal obesity, glucose intolerance, and diabetes mellitus.⁴

Among the various possibilities of associations already raised as related to SAH, Huang et al.⁵ bring a hypothesis present in mainly Asian literature that would be the association between Helicobacter pylori and the prevalence of SAH. In this meta-analysis, they included 17 observational studies (11 case-control and 6 cross-sectional) from 1996 to 2019 with

a total of 17226 participants. Detection of H. pylori was 64.9% vs. 56.3% between hypertensive and normotensive individuals. They also detected a statistically significant relationship between H. pylori and SAH (odds ratio 2.07; 95% confidence interval (CI), 1.46, 2.94), which only remained in the Asian population. Recently, Xiong et al.⁶ published a Chinese cross-sectional study with 17,100 participants and found that individuals with H. pylori infection had a higher prevalence of hypertension (57.5% vs. 55.1%, $p = 0.002$). The infection rate of H. pylori in patients with hypertension is higher than that in non-hypertensive individuals (48.8% vs. 46.4%, $p = 0.002$). After adjustment for potential confounders, H. pylori infection increased the prevalence of hypertension (odds ratio, 1.117, 95% CI, 1.029-1.213, $p = 0.008$). This paper adds value to the authors' hypothesis. However, we can see that we have information based on observational studies, which makes it impossible to establish a cause-effect relationship.

The search for factors that might be causally related to disease begins with the idea that people who have the exposure should have a different frequency of the disease from those who do not have the exposure. Confounding is the bias resulting from the presence of common causes of exposures and outcomes. Confounding occurs when a variable is associated with both the exposure and the disease that we are studying.⁷⁻⁹ Determining whether a variable is a confounder requires making untestable assumptions. The only real progress that can be made with empirical testing for confounders is by making other untestable assumptions that logically imply a test for assumptions we care about.¹⁰

The authors have the merit of systematically collecting all available information and performing a meta-analysis on an unexpected association. Furthermore, the challenge of seeking more information about SAH is extremely relevant due to the well-known impact of this condition on significant outcomes at the cardiovascular, renal and neurological levels since SAH has a high worldwide prevalence. However, care and caution are necessary when using data from observational studies that provide more hypothesis-generating information than conclusive data. Therefore, it is necessary to carry out prospective studies, preferably randomized, to elucidate this hypothesis.

Keywords

Hypertension; Helicobacter pylori.

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References

1. GBD 2017 Risk Factor Collaborators. Global, Regional, and National Comparative Risk Assessment of 84 Behavioural, Environmental and Occupational, and Metabolic Risks or Clusters of Risks for 195 Countries and Territories, 1990-2017: A Systematic Analysis for the Global Burden of Disease Study 2017. *Lancet*. 2018;392(10159):1923-94. doi: 10.1016/S0140-6736(18)32225-6.
2. Oparil S, Acelajado MC, Bakris GL, Berlowitz DR, Cifková R, Dominiczak AF, et al. Hypertension. *Nat Rev Dis Primers*. 2018;4:18014. doi: 10.1038/nrdp.2018.14.
3. Foëx P, Sear JW. Hypertension: Pathophysiology and Treatment. *Continuing Education in Anaesthesia Critical Care & Pain*. 2004;4(3):71-5. doi: 10.1093/bjaceaccp/mkh020.
4. Barroso WKS, Rodrigues CIS, Bortolotto LA, Mota-Gomes MA, Brandão AA, Feitosa ADM, et al. Brazilian Guidelines of Hypertension - 2020. *Arq Bras Cardiol*. 2021;116(3):516-658. doi: 10.36660/abc.20201238.
5. Mengyun H, Lijun Z, Yuelong J, Zhengmei F, Yan C, Yingshui Y. Association between Helicobacter Pylori Infection and Systemic Arterial Hypertension: A Meta-Analysis. *Arq Bras Cardiol*. 2021; 117(4):626-636.
6. Xiong X, Chen J, He M, Wu T, Yang H. Helicobacter pylori Infection and the Prevalence of Hypertension in Chinese Adults: The Dongfeng-Tongji Cohort. *J Clin Hypertens*. 2020;22(8):1389-95. doi: 10.1111/jch.13928.
7. Rothman K, Greenland S, Lash T. *Modern Epidemiology*. 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2008.
8. Hernán MA, Hernández-Díaz S, Werler MM, Mitchell AA. Causal Knowledge as a Prerequisite for Confounding Evaluation: An Application to Birth Defects Epidemiology. *Am J Epidemiol*. 2002;155(2):176-84. doi: 10.1093/aje/155.2.176.
9. Hernán MA, Robins JM. Estimating Causal Effects from Epidemiological Data. *J Epidemiol Community Health*. 2006;60(7):578-86. doi: 10.1136/jech.2004.029496.
10. VanderWeele TJ, Shpitser I. On the Definition of a Confounder. *Ann Stat*. 2013;41(1):196-220. doi: 10.1214/12-aos1058.



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Increased, Decreased, or Stable Left Ventricle Ejection Fraction over Time in a Series of 626 Heart Failure Patients Receiving Medical Treatment

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Abstract

Background: Ejection fraction (EF) has been used in phenotype analyses and to make treatment decisions regarding heart failure (HF). Thus, EF has become a fundamental part of daily clinical practice.

Objective: This study aims to investigate the characteristics, predictors, and outcomes associated with EF changes in patients with different types of severe HF.

Methods: A total of 626 severe HF patients with New York Heart Association (NYHA) class III–IV were enrolled in this study. The patients were classified into three groups according to EF changes, namely, increased EF (EF-I), defined as an EF increase $\geq 10\%$, decreased EF (EF-D), defined as an EF decrease $\geq 10\%$, and stable EF (EF-S), defined as an EF change $< 10\%$. A p-value lower than 0.05 was considered significant.

Results: Out of 377 severe HF patients, 23.3% presented EF-I, 59.5% presented EF-S, and 17.2% presented EF-D. The results further showed 68.2% of heart failure with reduced ejection fraction (HFrEF) in the EF-I group and 64.6% of heart failure with preserved ejection fraction (HFpEF) in the EF-D group. The predictors of EF-I included younger age, absence of diabetes, and lower left ventricular ejection fraction (LVEF). The predictors of EF-D were absence of atrial fibrillation, lower uric acid level, and higher LVEF. Within a median follow-up of 40 months, 44.8% of patients suffered from all-cause death.

Conclusion: In severe HF, HFrEF presented the highest percentage in the EF-I group, and HFpEF was most common in the EF-D group.

Keywords: Heart Failure/mortality; Stroke Volume; Ventricular Dysfunction, Left; Prognosis; Drug Utilization.

Introduction

Ejection fraction (EF) has been used in phenotype analyses and to make treatment decisions regarding heart failure (HF).¹ Thus, EF has become a fundamental part of daily clinical practice. HF is currently classified according to EF — heart failure with reduced ejection fraction (HFrEF; EF $< 40\%$), heart failure with mid-range ejection fraction (HFmrEF; EF 40–49%), or heart failure with preserved ejection fraction (HFpEF; EF $\geq 50\%$).² Assessing the baseline EF in all HF patients is essential for diagnosis, treatment, and prognosis. The degree of neurohumoral activation and the response to medical therapy differ among the HF types.^{3–5}

Indications for HF treatment may arise with deteriorating EF.^{6,7} Moreover, EF is not a static measurement, and changes over time are common in all HF groups.^{8–10}

Most of the recent HF studies have included patients with New York Heart Association functional classification (NYHA class) II–IV. However, a few investigations have focused on critically ill patients with NYHA class III–IV. Furthermore, these studies evaluated the whole spectrum of EF changes for all HF groups but did not detail determinants of change and the associated prognosis in patients with severe HF. Thus, we examined patterns of longitudinal EF change in a cohort of severe HF patients and investigated whether EF changes had prognostic implications in HFrEF, HFmrEF, and HFpEF.

Methods

Study population

Patients affected by severe HF were enrolled in this study from January 2011 to December 2016. The attending

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cardiologists made the diagnosis of HF based on the Framingham study criteria.¹¹ HF severity was defined as NYHA class III–IV, N-terminal prohormone of brain natriuretic peptide (NT-proBNP) > 1000 pg/mL, and 6-minute walk test < 150 m. Patients with different types of HF were classified following the new European Society of Cardiology (ESC) Guidelines for the diagnosis and treatment of chronic and acute HF: HFrEF, HFmrEF, and HFpEF. This study was approved by the Ethics Committee of the Beijing Chaoyang Hospital, Capital Medical University, and complied with the declaration of Helsinki. Written informed consent was obtained from all participants.

Inclusion and exclusion criteria

Inclusion criteria: (1) patients with severe HF and NYHA class III–IV; (2) patients with complete clinical and medical history data; (3) patients aged 18 years and older. Exclusion criteria: (1) patients with non-cardiac dyspnea; (2) patients with cardiogenic shock; (3) patients with acute myocardial infarction; (4) patients with terminal diseases and predicted survival time < 1 year (e.g., terminal cancer); (5) pregnant or lactating patients (Figure 1).

Data collection

All patient information, including demographic characteristics, medical history, laboratory tests, echocardiography results, and medication use, was collected from electronic medical records by a single investigator as baseline data.

Patients with at least two EF assessments were enrolled in this study. When the same patient presented more than two EF assessments, the first and last results were considered to calculate the EF change. The time elapsed between the two examinations was shown through a scatter plot (Figure 2). A cardiac sonographer performed all echocardiographic studies using a VV5 ultrasound machine. Standard techniques were adopted to obtain M-mode, 2-dimensional, and Doppler measurements in accordance with the American Society of Echocardiography guidelines.¹² Patients were divided into three groups based on EF change: increased EF (EF-I), defined as an EF increase $\geq 10\%$, decreased EF (EF-D), defined as an EF decrease $\geq 10\%$, and stable EF (EF-S), defined as EF change < 10%. The method used to calculate the estimated glomerular filtration rate (eGFR) was the Modification of Diet in Renal Disease (MDRD) and to measure NT-proBNP was electroluminescence.

All patients were followed up by telephone or in outpatient clinics, and the primary endpoints were recorded. The primary endpoints included all-cause death.

Statistical analysis

We used the SPSS 22.0 software to conduct the statistical analysis. Continuous variables were tested for normal distribution using the Kolmogorov-Smirnov method. Continuous variables were expressed as mean $\pm$ standard deviation (SD) or median with interquartile range (IQR) according to the normality test. Categorical variables were

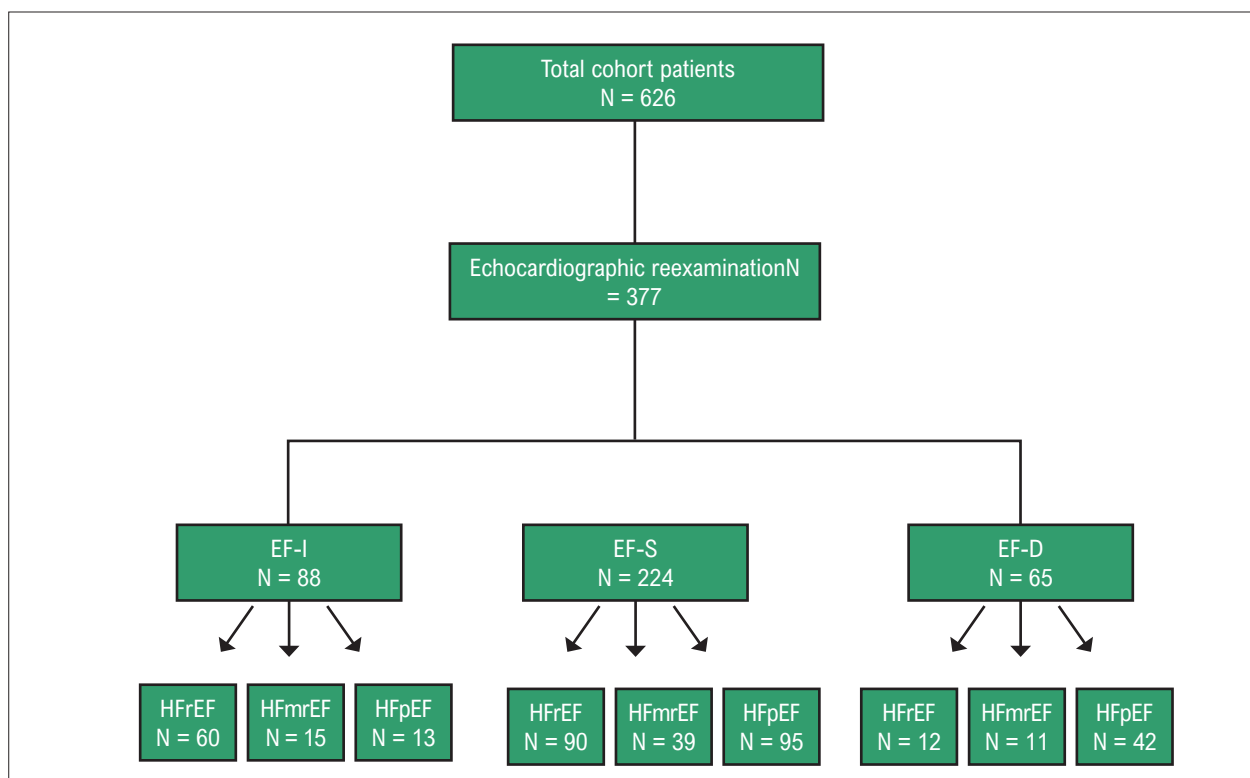


Figure 1 – Flowchart of patients included in the study. EF-I: increased ejection fraction; EF-S: stable ejection fraction; EF-D: decreased ejection fraction; HFrEF: heart failure with reduced ejection fraction; HFmrEF: heart failure with mid-range ejection fraction; HFpEF: heart failure with preserved ejection fraction.

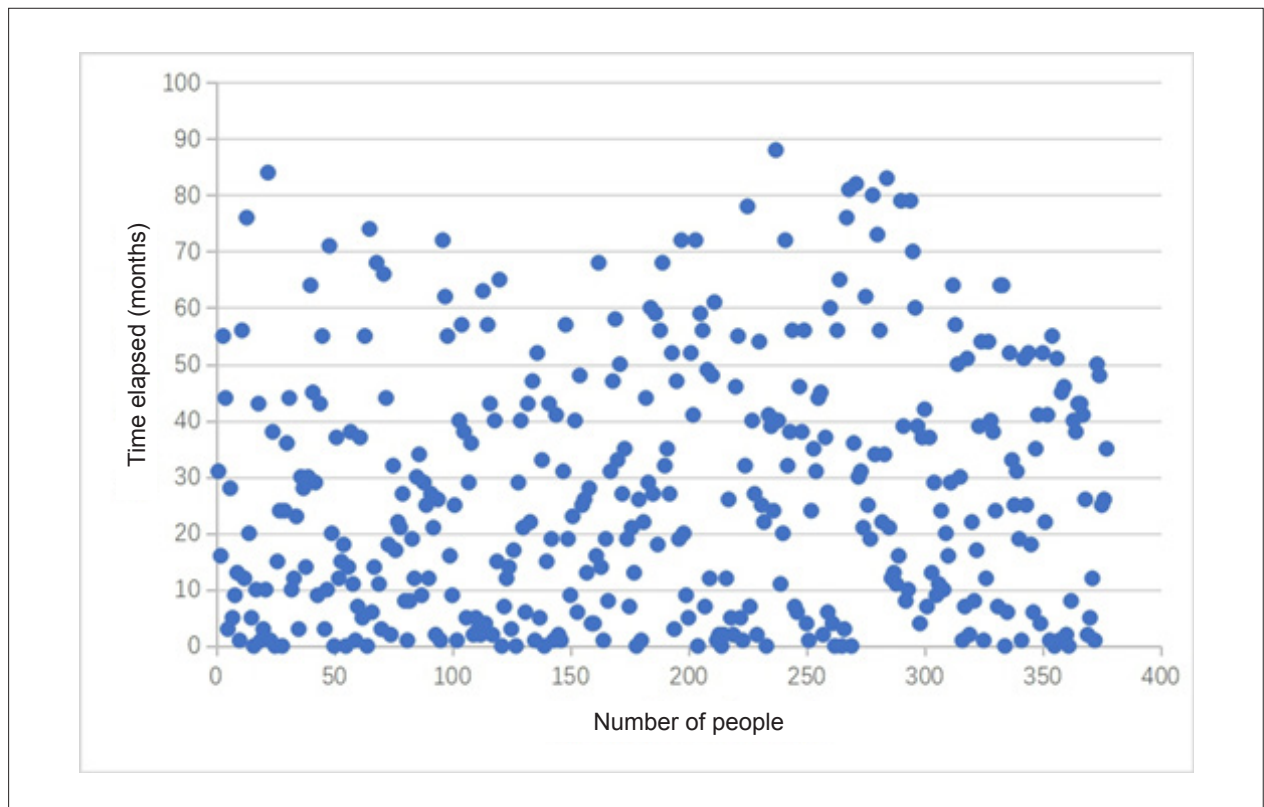


Figure 2 – Scatter plot of the distribution of time elapsed between the ultrasound examinations.

expressed as a percentage (%). For multiple comparisons, every value was compared by one-way analysis of variance (ANOVA) following the Dunnett test when each datum conformed to a normal distribution, while non-normally distributed continuous data were compared by non-parametric tests (Kruskal-Wallis H test). Categorical variables were tested by the chi-square test. Multivariate logistic regression models were applied to assess independent predictors of EF increase or decrease. Since the predictors of EF change were mostly unknown, multivariate models included all clinically relevant variables that could potentially affect EF over time. Kaplan-Meier curves were used to evaluate the association between EF changes and all-cause death and were compared by a log-rank test. A p -value < 0.05 was considered statistically significant.

Results

General data

A total of 626 severe HF patients with NYHA class III–IV were enrolled in this study from January 2011 to December 2016. After a median of 27 months, 377 patients with at least 2 echocardiographic examinations were included in our analysis. Patient information is shown in Figure 1. The overall population profile was: mean age of 67 ± 13 years, 60.2% of males, 43.0% with HFrEF, 17.2% with HFmrEF, and 39.8% with HFpEF. According to the first Doppler measurement, 88 patients (23.3%) presented EF-I — 68.2% HFrEF, 17.0%

HFmrEF, and 14.8% HFpEF; 224 patients (59.5%) presented EF-S — 40.2% HFrEF, 17.4% HFmrEF, and 42.4% HFpEF; and 65 patients (17.2%) presented EF-D — 18.5% HFrEF, 16.9% HFmrEF, and 64.6% HFpEF (Figure 3).

Baseline patient characteristics

Patients with EF-I were younger and mostly male, whereas patients with EF-D had a higher percentage of ischemic heart disease and HFpEF. Also, patients with EF-I had a higher heart rate and lower systolic blood pressure. The mean systolic blood pressure was 129 mmHg, diastolic blood pressure was 80 mmHg, and heart rate was 78 bpm among patients with HFrEF within the EF-I group. However, patients with EF-D had lower hemoglobin and uric acid levels. No difference was found in NT-proBNP and eGFR among the three EF change groups. In addition, patients with EF-I showed lower LVEF levels and larger left ventricular end-diastolic diameter (LVEDD) or left ventricular end-systolic diameter (LVESD). The use of digoxin and mineralocorticoid receptor antagonists (MRA) was higher among patients with EF-I, while the use of β -blockers, angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker (ACEI/ARB), and loop diuretics did not differ among the three groups (Table 1). A total of 106 patients with HFrEF were on β -blockers, 107 were on ACEI/ARBs, and 133 were on MRAs. However, the dose of these medications was hard to collect as the patients took different kinds of β -blockers and ACEI/ARBs.

Table 1 – Baseline characteristics according to ejection fraction changes

	EF-I (n=88)	EF-S (n=224)	EF-D (n=65)	p-value
Age, years	61.2±13.0	68.8±12.8	70.0±11.8	0.001
Male, n (%)	65 (73.9%)	129 (57.6%)	33 (50.8%)	0.007
Etiology, n (%)				0.014
Ischemic	43 (48.9%)	139 (62.1%)	45 (69.2%)	
Valvular	8 (9.1%)	33 (14.7%)	9 (13.8%)	
Cardiopathy	21 (23.9%)	25 (11.2%)	4 (6.2%)	
Hypertension	9 (10.2%)	18 (8.0%)	6 (9.2%)	
Other	7 (8.0%)	9 (4.0%)	1 (1.5%)	
Clinical history, n (%)				
Hypertension	58 (65.9%)	161 (71.9%)	50 (76.9%)	0.318
Diabetes mellitus	32 (36.4%)	112 (50.0%)	29 (44.6%)	0.092
Atrial fibrillation	34 (38.6%)	93 (41.5%)	18 (27.7%)	0.131
Previous heart failure	20 (22.7%)	80 (35.7%)	13 (20.0%)	0.012
Type of HF, n (%)				0.001
HFrEF	60 (68.2%)	90 (41.2%)	12 (18.5%)	
HFmrEF	15 (17.0%)	39 (17.4%)	11 (16.9%)	
HFpEF	13 (14.8%)	95 (42.4%)	42 (64.6%)	
BMI, kg/m ²	25.2±3.9	24.9±4.5	24.1±4.4	0.371
HR, bpm	89.5±23.6	81.4±19.9	80.9±16.2	0.004
SBP, mmHg	133.3±27.6	134.7±24.1	142.4±23.4	0.052
DBP, mmHg	81.5±16.7	77.3±14.7	80.1±13.4	0.060
Hemoglobin, g/L	131.4±23.6	119.8±21.0	118.8±22.1	0.001
Albumin, g/L	33.8±5.4	34.3±4.9	33.1±4.7	0.211
LDL-C, mmol/L	2.2±0.7	2.1±0.8	2.2±0.8	0.568
hs-CRP, mg/L	8.1±6.4	6.7±5.0	7.0±5.0	0.149
cTnI, ng/mL	0.03 (0.00–0.08)	0.03 (0.00–0.08)	0.04 (0.01–0.14)	0.909
CK-MB, ng/mL	0.8 (0.4–1.8)	0.9 (0.4–1.4)	1.0 (0.7–1.7)	0.488
NT-proBNP, pg/mL	3140 (1420–8345)	3071 (1499–6961)	3866 (1541–10163)	0.439
BUN, mmol/L	8.5±5.0	9.2±5.3	8.3±4.6	0.310
eGFR, mL/min/1.73m ³	65.9±29.8	57.3±36.6	56.1±33.0	0.111
URIC, umol/L	432.4±126.1	426.1±139.7	371.5±119.9	0.008
Sodium, mmol/L	139.2±3.3	143.6±6.6	138.7±3.5	0.695
Potassium, mmol/L	4.0±0.6	4.0±0.6	4.0±0.6	0.722
Blood glucose, mmol/L	5.9±2.8	6.2±2.6	6.5±2.8	0.387
HbA1c, % Echocardiography	6.6±1.3	6.7±1.3	6.8±1.3	0.749
LVEF, %	36.8±11.6	47.4±15.7	55.3±14.4	0.001
LVEDD, mm	59.6±8.5	56.5±9.1	53.8±9.3	0.001
LVESD, mm	48.9±9.7	42.8±11.4	38.3±10.9	0.001
Medication, n (%)				
Digoxin	60 (68.2%)	125 (55.8%)	25 (38.5%)	0.001
β-blockers	56 (63.6%)	126 (56.3%)	41 (63.1%)	0.381
ACEI/ARB	57 (64.8%)	117 (52.2%)	34 (52.3%)	0.118
Loop diuretics	76 (86.4%)	188 (83.9%)	50 (76.9%)	0.279
MRA	70 (79.5%)	160 (71.4%)	39 (60.0%)	0.030

BMI: body mass index; HR: heart rate; SBP: systolic blood pressure; DBP: diastolic blood pressure; LDL-C: low-density lipoprotein cholesterol; hs-CRP: high-sensitivity C-reactive protein; cTnI: cardiac troponin I; CK-MB: creatine-kinase MB isoenzyme; NT-proBNP: N-terminal prohormone brain natriuretic peptide; BUN: blood urea nitrogen; eGFR: estimated glomerular filtration rate; URIC: uric acid; HbA1c: glycated hemoglobin; LVEF: left ventricular ejection fraction; LVEDD: left ventricular end-diastolic diameter; LVESD: left ventricular end-systolic diameter; ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blocker; MRA: mineralocorticoid receptor antagonists.

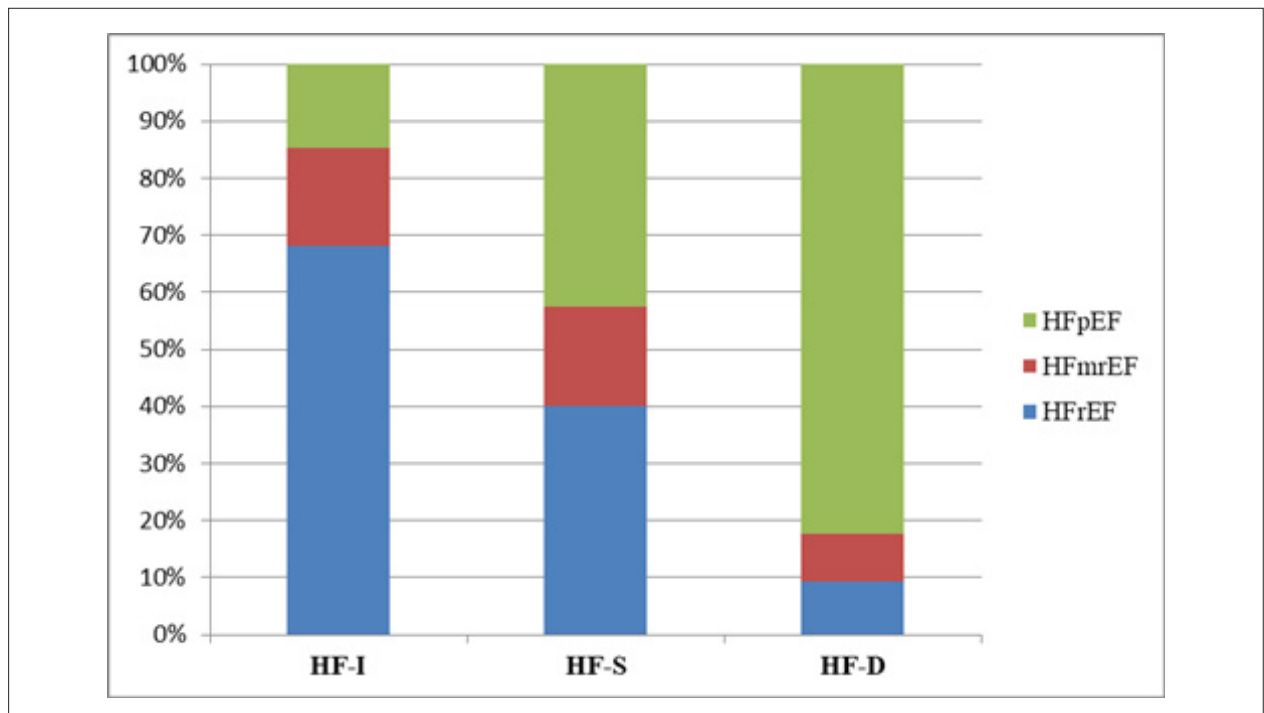


Figure 3 – Different types of heart failure according to changes in ejection fraction. EF-I: increased ejection fraction; EF-S: stable ejection fraction; EF-D: decreased ejection fraction; HFrEF: heart failure with reduced ejection fraction; HFmrEF: heart failure with mid-range ejection fraction; HFpEF: heart failure with preserved ejection fraction.

Predictors of ejection fraction increase and decrease

Table 2 presents the adjusted odds ratio (OR) for EF-I and EF-D after the multivariate logistic regression analysis. Younger age, absence of diabetes, and lower LVEF were independently associated with EF-I. On the other hand, variables predicting EF-D included absence of atrial fibrillation, lower uric acid level, and higher LVEF. No medications were associated with EF change after being adjusted for multivariate factors (Table 2).

Clinical outcomes

All-cause mortality according to EF changes in overall HF, HFrEF, HFmrEF, and HFpEF was as follows: within a median follow-up of 40 months, 44.8% of all study patients suffered from all-cause death. The EF-I group had a higher survival rate than the EF-S and EF-D groups, although this increase was not statistically significant ($p=0.064$) (Table 3).

In HFrEF, patients with EF-I presented significantly lower mortality compared to those with EF-S and EF-D. At the same time, we found no difference in all-cause mortality related to EF changes in HFmrEF and HFpEF. Kaplan-Meier curves estimated mortality for different types of HF, as shown in Figure 4.

Discussion

The outcomes of this study revealed that, among 377 severe HF patients, 23.3% presented EF-I, 59.5% presented EF-S, and 17.2% presented EF-D. Moreover, 68.2% of patients with HFrEF were in the EF-I group, and 64.6% of those with HFpEF were in the EF-D group. Predictors of EF-I included younger

age, absence of diabetes, and lower LVEF. The predictors of EF-D were absence of atrial fibrillation, lower uric acid level, and higher LVEF. Within a median follow-up of 40 months, 44.8% of patients suffered from all-cause death. Mortality in the EF-I group was lower than in the EF-D group among HFrEF patients. However, we found no difference in all-cause mortality related to EF change in HFmrEF and HFpEF patients.

Ejection fraction change in severe heart failure patients

Severe HF has worrying symptoms and results regarding cardiac function, leading to extremely high mortality rates and poor prognoses. Some previous studies have investigated EF improvement in patients with HFrEF.^{6,7,13-15} Still, the extent of the EF change in severe HF patients has been poorly reviewed. Zhang et al.¹⁶ revealed that metoprolol combined with irbesartan, hydrochlorothiazide, and non-invasive ventilation helped recover normal cardiac function, increasing cardiac output and normalizing the EF of severe HF patients. Our study showed that 23.3% of severe HF patients had EF-I, 17.2% had EF-D, and 59.5% had EF-S. Dunlay et al.⁹ reported that a significant proportion of patients with HFpEF had a decline in EF of $<50\%$, and a similar proportion of patients with HFrEF experienced an increase in EF of $\geq 50\%$. The present research also identified that the natural history of HF was similar in patients with severe HF.

Clinical characteristics and predictors of ejection fraction change

Understanding the clinical characteristics and predictors of EF change is essential, as they provide important information

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Table 2 – Association between clinical backgrounds and ejection fraction changes

Variables	EF-I		EF-D	
	OR (95%CI)	p	OR (95%CI)	p
Age (per 10-year increase)	0.677 (0.509–0.902)	0.008		
Diabetes	0.509 (0.285–0.909)	0.022		
Atrial fibrillation			0.430 (0.230–0.805)	0.008
URIC (per 100 umol/L increase)			0.743 (0.575–0.960)	0.023
LVEF	0.947 (0.926–0.968)	0.001	1.048 (1.028–1.067)	0.001

EF-I: increased ejection fraction; EF-D: decreased ejection fraction; LVEF: left ventricular ejection fraction.

Table 3 – All-cause mortality for ejection fraction changes in different types of heart failure

	EF-I	EF-S	EF-D	p
HF	31 (35.2%)	104 (46.4%)	34 (52.3%)	0.064
HFrEF	18 (30.0%)	42 (46.7%)	6 (50.0%)	0.048
HFmrEF	6 (40.0%)	17 (43.6%)	5 (45.5%)	0.981
HFpEF	7 (53.8%)	45 (47.4%)	23 (54.8%)	0.976

EF-I: increased ejection fraction; EF-S: stable ejection fraction; EF-D: decreased ejection fraction; HFrEF: heart failure with reduced ejection fraction; HFmrEF: heart failure with mid-range ejection fraction; HFpEF: heart failure with preserved ejection fraction.

and can be used for risk stratification and for guiding the therapy for patients with severe HF. In the present study, multivariate logistic regression showed that younger age, absence of diabetes, and the lower LVEF were associated with EF-I. In turn, the variables predicting EF-D were the absence of atrial fibrillation, lower uric acid level, and higher LVEF.

Previous studies have reported patients with EF improvement to be younger.⁹ However, our analysis identified the absence of diabetes as a predictor of EF-I, which could be explained by previous studies that detected an inverse association of diabetes mellitus, ischemic heart disease, and MRA prescription at discharge with HF and improved EF.^{17–19}

The predictor absence of atrial fibrillation was related to EF-D, in accordance with a report indicating that atrial fibrillation was a positive predictor for improving EF. Surprisingly, lower uric acid level was a predictor for EF-D, which is difficult to explain.

Our study found that lower LVEF was associated with EF-I, while higher LVEF was associated with EF-D. Dunlay et al.⁹ also identified this result in their analysis, since EF decreased by 5.8% in HFpEF patients. Conversely, EF increased by 6.9% in HFrEF patients over 5 years.

Ejection fraction change and outcomes in the different types of heart failure

Little is known from published studies about the prognostic implication of EF change in different types of severe HF. This study showed that the EF-I group had a higher survival rate than the EF-S and EF-D groups, although this increase was not statistically significant.

In the HFrEF group, EF change was inversely associated with all-cause mortality, which is consistent with the findings of

previous studies indicating that recovery from reduced LVEF is connected with better outcomes.^{8,10} Lupon et al.⁶ found that by using the HF-recovered group as a reference, the hazard ratio (HR) of cardiovascular death or HF hospitalization was 2.33 for HFpEF and 1.99 for HFrEF. These lines of evidence strongly suggest that recovery from HFrEF was associated with a better prognosis in HF patients. Thus, we underline the importance of management aiming at increasing EF in HFrEF patients.

The present research identified that the prognostic implications of EF change among HFmrEF and HFpEF patients were less evident. The lack of risk associations with EF change in HFmrEF and HFpEF might result from the lack of a linear relationship between EF and HF outcomes when EF is higher.

Highlights of this study

Previous HF studies assessed patients with NYHA class II–IV, whereas our study focused on critically ill patients with NYHA class III–IV. Furthermore, other investigations report that the prognosis improves with the increase in the EF value. In addition, the present study found that in patients with severe HF and HFrEF, EF increased after treatment, thus suggesting that the prognosis can be improved. The other two types of HF patients were not associated with EF change and prognosis after receiving treatment. The above-mentioned contents were the highlights of this article.

Limitations

This study has several limitations. First, the sample, especially in the EF-D group, was relatively small, which may reduce the statistically significant differences among these patients. Second, this study is a single-center and retrospective analysis; the findings might not be generalizable to other

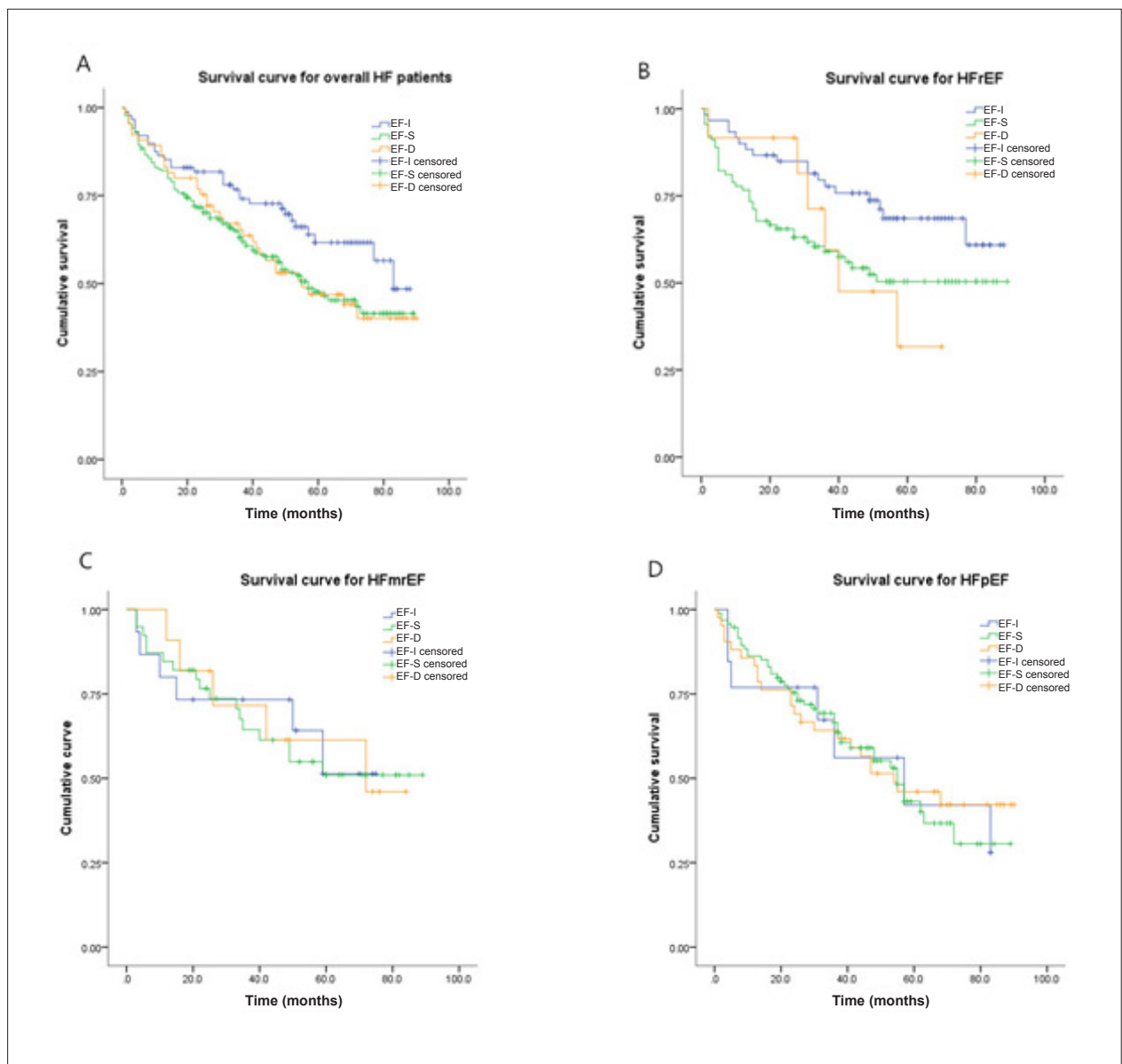


Figure 4 – A) Kaplan-Meier curve of all-cause mortality for ejection fraction change in overall heart failure. B) Kaplan-Meier curve of all-cause mortality for ejection fraction change in heart failure with reduced ejection fraction. C) Kaplan-Meier curve of all-cause mortality for ejection fraction change in heart failure with mid-range ejection fraction. D) Kaplan-Meier curve of all-cause mortality for ejection fraction change in heart failure with preserved ejection fraction.

cohorts. Third, the patients had at least two echocardiograms for the initial and final EF measurement, with a median of 27 months. However, we did not record the echocardiogram at the 1-year follow-up, which could have provided further results. Finally, no consensus has been reached on the appropriate definition of EF change. We recognize that small improvements in LVEF that still qualify as EF-I have probable and different prognostic implications than larger improvements. Therefore, in order to quantify this effect, we defined EF-I as an EF increase $\geq 10\%$, EF-D as an EF decrease $\geq 10\%$, and EF-S as an EF change $< 10\%$, other than the transition to the other HF phenotypes.

Conclusions

In severe HF, HFrEF presented the highest percentage in the EF-I group, and HFpEF was more common in the EF-D group. EF change was associated with a series of clinical characteristics, predictors, and outcomes, especially in HFrEF patients.

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Author Contributions

Conception and design of the research: Meng-Meng H, Wen-Shu Z, Kui-Bao L, Cai-Jing D, Zhang J, Jia-Mei L, Mu-Lei C, Xin-Chun Y, Wang H, Xu L; Acquisition of data: Meng-Meng H, Wen-Shu Z, Xiao-Rong X, Wang X, Kui-Bao L, Zhang J, Jia-Mei L, Xin-Chun Y, Wang H; Analysis and interpretation of the data: Kui-Bao L, Cai-Jing D, Mu-Lei C, Xin-Chun Y, Wang H, Xu L; Statistical analysis: Xiao-Rong X, Wang X, Cai-Jing D, Zhang J; Obtaining financing: Wang X, Cai-Jing D; Writing of the manuscript: Meng-Meng H, Wen-Shu Z, Xiao-Rong X, Wang H, Xu L; Critical revision of the manuscript for intellectual content: Meng-Meng H, Wen-Shu Z, Jia-Mei L, Mu-Lei C, Wang H, Xu L.

Potential Conflict of Interest

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

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Study Association

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

References

1. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur Heart J*. 2012;33(14):1787-847.
2. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J*. 2016;37(27):2129-2200.
3. Kapoor JR, Kapoor R, Ju C, Heidenreich PA, Eapen ZJ, Hernandez AF, et al. Precipitating clinical factors, heart failure characterization, and outcomes in patients hospitalized with heart failure with reduced, borderline, and preserved ejection fraction. *JACC Heart Fail*. 2016;4(6):464-72.
4. Chioncel O, Lainscak M, Seferovic PM, Anker SD, Crespo-Leiro MG, Harjola VP, et al. Epidemiology and one-year outcomes in patients with chronic heart failure and preserved, mid-range and reduced ejection fraction: an analysis of the ESC Heart Failure Long-Term Registry. *Eur J Heart Fail*. 2017;19(12):1574-85.
5. Vedin O, Lam CSP, Koh AS, Benson L, Teng THK, Tay WT, et al. Significance of ischemic heart disease in patients with heart failure and preserved, midrange, and reduced ejection fraction: a Nationwide Cohort Study. *Circ Heart Fail*. 2017;10(6):e003875.
6. Lupón J, Díez-López C, Antonio M, Domingo M, Zamora E, Moliner P, et al. Recovered heart failure with reduced ejection fraction and outcomes: a prospective study. *Eur J Heart Fail*. 2017;19(12):1615-23.
7. Park CS, Park JJ, Mebazaa A, Oh IY, Park HA, Cho HJ, et al. Characteristics, outcomes, and treatment of heart failure with improved ejection fraction. *J Am Heart Assoc*. 2019;8(6):e011077.
8. Savarese G, Vedin O, D'Amario D, Uijl A, Dahlström U, Rosano G, et al. Prevalence and prognostic implications of longitudinal ejection fraction change in heart failure. *JACC Heart Fail*. 2019;7(4):306-17.
9. Dunlay SM, Roger VL, Weston SA, Jiang R, Redfield MM. Longitudinal changes in ejection fraction in heart failure patients with preserved and reduced ejection fraction. *Circ Heart Fail*. 2012;5(6):720-6.
10. Tsuji K, Sakata Y, Nochioka K, Miura M, Yamauchi T, Onose T, et al. Characterization of heart failure patients with mid-range left ventricular ejection fraction—a report from the CHART-2 Study. *Eur J Heart Fail*. 2017;19(10):1258-69.
11. Nieminen MS, Harjola VP. Definition and epidemiology of acute heart failure syndromes. *Am J Cardiol*. 2005;96(6A):5G-10G.
12. 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.
13. Kalogeropoulos AP, Fonarow GC, Georgiopoulos V, Burkman G, Siwamogsatham S, Patel A, et al. Characteristics and outcomes of adult outpatients with heart failure and improved or recovered ejection fraction. *JAMA Cardiol*. 2016;1(5):510-8.
14. Florea VG, Rector TS, Anand IS, Cohn JN. Heart failure with improved ejection fraction: clinical characteristics, correlates of recovery, and survival: results from the Valsartan Heart Failure Trial. *Circ Heart Fail*. 2016;9(7):e003123.
15. Basuray A, French B, Ky B, Vorovich E, Olt C, Sweitzer NK, et al. Heart failure with recovered ejection fraction: clinical description, biomarkers, and outcomes. *Circulation*. 2014;129(23):2380-7.
16. Zhang F, Zhou G, Guo L, Lu F, Zhou G. Comparison of clinical efficacy of metoprolol combined with irbesartan and hydrochlorothiazide and non-invasive ventilator in the emergency treatment of patients with severe heart failure. *Exp Ther Med*. 2018;16(6):5059-66.
17. Kotecha D, Flather MD, Altman DG, Holmes J, Rosano G, Wikstrand J, et al. Heart rate and rhythm and the benefit of beta-blockers in patients with heart failure. *J Am Coll Cardiol*. 2017;69(24):2885-96.
18. Kotecha D, Manzano L, Krum H, Rosano G, Holmes J, Altman DG, et al. Effect of age and sex on efficacy and tolerability of β blockers in patients with heart failure with reduced ejection fraction: individual patient data meta-analysis. *BMJ*. 2016;353:i1855.
19. Garg R, Yusuf S. Overview of randomized trials of angiotensin-converting enzyme inhibitors on mortality and morbidity in patients with heart failure. Collaborative Group on ACE Inhibitor Trials. *JAMA*. 1995;273(18):1450-6.



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Cardiac Autonomic Modulation is a Key Factor for High Blood Pressure in Adolescents

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Abstract

Background: The interest regarding hypertension among children and adolescents has increased since the blood pressure rating system was updated to be compared with the adult rating system, changing the terminology from “normal high” to “prehypertension”.

Objective: This study aimed to analyze the association between cardiac autonomic modulation and pressure levels of adolescents.

Methods: 203 adolescents were grouped according to systolic blood pressure (SBP) and diastolic blood pressure (DBP). One group was characterized as prehypertension, and the other as normotensive. Anthropometric, cardiovascular and sleep quality characteristics were collected. Initially, the data were submitted to the Kolmogorov-Smirnov normality test. Continuous quantitative variables were analyzed using the unpaired Student t-test. For the analysis of categorical variables, a chi-square test was used. A logistic regression model was performed. The level of significance was set at $p < 0.05$. The data were expressed as mean $\pm$ standard deviation and confidence interval. The R software was used for data analysis. The effect size was calculated using the Cohen's formula.

Results: The prehypertension group showed an increase in Shannon entropy and a decrease in total variance. Also, in the logistic regression model, adolescents in this group were 1.03 times more likely to have Shannon entropy's affected when SBP was adjusted for gender, sexual maturation, school time, age, waist circumference, and sleep quality.

Conclusion: Our data show that autonomic modulation may play an important role in the development of elevated blood pressure in adolescents, when controlling for other factors, such as school time and sleep quality.

Keywords: Cardiovascular Diseases; Blood Pressure; Hypertension; Pre-Hypertension; Obesity; Adolescent.

Introduction

In the most recent report on the global cause of deaths, cardiovascular diseases once again led the all-cause mortality for non-communicable diseases,¹ and hypertension was one of the leading causes in this category. Due to the rise of deaths related to cardiovascular diseases, the screening for the development of these diseases has grown and is being addressed to the younger part of the population.²

The interest in childhood hypertension has increased since the publication, in 2004, of the National High Blood Pressure Education Program Working Group, which updated the blood pressure classification system in children

and adolescents to match the classification system of adults, changing the terminology from “normal high” to “prehypertension”.³

The “prehypertension” classification was created to warn physicians and justify the introduction of lifestyle changes in those who may be at risk for the development of hypertension at a young age. Currently, it is known that children with high blood pressure are more likely to develop hypertension in adulthood.⁴ Also, recent evidence suggests that prehypertensive children may develop hypertension even before they reach adulthood.⁵

Recognizing the ongoing evidence gaps and the need for an updated and relevant literature review, a 2020 study highlighted that the diagnosis of hypertension in children and adolescents – in contrast with adulthood – is based on their age percentile curves and height.⁶ Therefore, it is worth mentioning that in 2017 the American Academy of Pediatrics (AAP) and its Council on Quality Improvement and Patient Safety developed practical guidelines to provide updated information on topics that are relevant for the diagnosis, assessment, and treatment of hypertension in children and

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adolescents. Now, for children aged ≥ 13 years, high blood pressure is characterized as 120/80 to 129/80 mmHg; stage 1 hypertension is 130/80 to 139/89 mmHg; and stage 2 hypertension is $\geq 140/90$ mmHg.⁷

The autonomic nervous system plays an important role in the rapid regulation of blood pressure, and has been long investigated regarding its function in the development of hypertension.⁸ One of the most important factors correlated with hypertension is autonomic imbalance, which is also correlated to cardiovascular risk.^{8,9}

One of the most used tools for the assessment of autonomic modulation is the Heart Rate Variability (HRV), mainly due to its noninvasive approach and great reliability.^{4,9} Among all HRV indexes, the nonlinear ones measure the complexity of the ECG signal, standing out from more common HRV methods, such as the Frequency domain, that can be affected by noise. Shannon entropy is an indicator of the complexity of the signal, being widely correlated with autonomic modulation. However, adolescents are also affected by other cardiovascular risk factors, such as obesity⁵⁻¹⁰ and poor sleep quality due to school routine.^{11,12} Therefore, it is important to determine the real contribution of autonomic imbalance for the development of high blood pressure levels. This study aimed to evaluate the association of cardiac autonomic modulation with blood pressure levels in adolescents.

Methods

Sample

The sample size of this study was established based on statistical calculations using the G*power software, taking into account the two-tailed t-test, with an effect size of 0.30, confidence interval of 95% and probability of error of 5%. For these characteristics, a sample size of 134 participants and power of 0.95 were found.

Thus, the present study was conducted with 203 adolescents (70 boys and 133 girls), aged between 11 and 18 years, grouped according to SBP and DBP. One group was characterized as pre-hypertension (44 adolescents; SBP $> 120/80$ mmHg), and the other was characterized as normotensive (159 adolescents; SBP $< 120/80$ mmHg). All subjects were selected from a state public school (Centro Anil Rio Anil - CINTRA) in São Luís, Maranhão, Brazil. All methods used in this study were approved by the institutional ethics committee and followed the guidelines from the Declaration of Helsinki.

Anthropometric measurements

At first, measurements of weight, height, and waist circumference were taken according to the National Heart, Lung and Blood Institute, as previously described.¹³ We chose the Slaughter (1988) method, which uses only the tricipital and subscapular skinfolds for body fat estimation in adolescents.¹⁴

Sexual maturation

To determine the biological age of the sample, we used the self-applied Tanner's Sexual Maturation Scale, as described elsewhere.^{15,16}

Sleep Quality

Sleep quality and the presence of sleep disturbances were evaluated using the Pittsburgh Sleep Quality Index, as originally described by de Buysse.¹⁷ The score of each component was added to provide an overall score, ranging from 0 to 21 points. The higher the value obtained, the worse the sleep quality (global score is between six and 21).

Blood Pressure

Blood pressure (BP) was verified using an automatic blood pressure monitor (OMRON, HEM-7200, São Paulo, Brazil), validated for blood pressure measurements in adolescents.¹⁸ The protocols used for the analysis of BP were based on the 7th Brazilian Guideline of Arterial Hypertension¹⁹ and the Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents,¹⁹ including an age-appropriate cuff according to height percentiles.¹⁹

The adolescents were grouped according to their level of SBP, following the recommendations from the Clinical Practice Guideline for Screening and Management of High Blood Pressure in Children and Adolescents⁷ and the Brazilian Guideline of Arterial Hypertension.¹⁹ Thus, the adolescents were divided into two groups according to SBP and DBP values:

Normotensive (n=159): healthy adolescents with SBP 100-119 mm Hg and DBP 60-79 mm Hg.

Prehypertension (n=44): healthy adolescents with SBP 120-139 mm Hg and DBP 80-89 mm Hg.

Heart Rate Variability

The HRV was analyzed using a 12-lead electrocardiogram developed for HRV data collection (Micromed Biotechnology, Wincardio). The data were collected with the subjects in the supine position during a 10-minute period. After data collection, the RR intervals were analyzed with the Kubios software (Kuopio, Finland), using the Fast Fourier Transform, as described earlier.²⁰ We used time (Heart rate (bpm); mean RR (ms); SDNN (ms); RMSSD (ms); pNN50 (%)) and total variance (ms²) and nonlinear domains (SD1 (ms); SD2 (ms) and the Shannon entropy).

Statistical analysis

Initially, the data were submitted to the Kolmogorov-Smirnov test to assess the normality of its distribution. Then, a descriptive analysis was conducted and the data were expressed as mean, standard deviation and confidence interval for baseline characteristics and continuous variables, and as absolute frequencies and percentage rates for categorical variables. The unpaired Student t-test was chosen to analyze continuous quantitative variables with normal distribution. Categorical variables were analyzed using the chi-square test. Logistic regression was performed to understand which

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variable would be best associated with blood pressure in the sample. Point estimates for the associations were expressed as odds ratios (OR) and respective 95% confidence intervals (95%CI). The R software was used for data analysis. The effect size was calculated according to the Cohen's formula.²¹ The significance level established for this study was $p < 0.05$.

Results

The study was carried out with 203 adolescents grouped according to their SBP and DBP levels. One group was characterized as prehypertension (44 adolescents; SBP from 120/80 to 129/80 mmHg), and the other as normotensive (159 adolescents; SBP $< 120/80$ mmHg).

Table 1 shows the analysis of the baseline anthropometric, cardiovascular and sleeps quality characteristics of adolescents. No statistical differences were found between groups regarding age, height, weight, sleep quality index, waist circumference, fat percentage, and the Tanner scale. However, there was a statistical difference and a strong effect size for SBP ($ES = 0.83$) and DBP ($ES = 3.05$) in the prehypertensive group when compared to the normotensive group (Table 1).

Regarding the analyses of qualitative variables in the study, we observed that only the sex of the adolescents presented statistical difference, considering the higher prevalence of prehypertensive boys, as shown in Table 2.

The data on cardiac autonomic modulation of the adolescents are shown in Table 3. In the time domain, it was possible to notice that only the total variance (ms^2) showed statistical difference and a strong effect size. Adolescents with prehypertension had lower total variance ($ES = 0.87$) when compared to normotensive adolescents. In the non-linear domain, only Shannon entropy showed a statistical difference and a strong effect size ($ES = 1.88$).

Also, through the logistic regression model, prehypertensive adolescents presented 1.03 more chances of having an impact on Shannon entropy when SBP was adjusted for gender, sexual maturation, school time, age, waist circumference, and sleep quality. However, the other variables showed no association, as shown in Table 4.

Discussion

This study aimed to analyze the association between cardiac autonomic modulation and blood pressure levels in adolescents. The main findings of the present study show that adolescents in the prehypertension group showed increased Shannon entropy and decreased total variance. Also, in the logistic regression model, Shannon entropy was the variable that was mostly associated with changes in blood pressure pattern, showing that adolescents in the prehypertension group had 1.03 more chances of having Shannon entropy affected when the SBP was adjusted by gender, sexual maturation, school time, age, waist circumference and sleep quality.

Our data corroborate the findings of other studies,^{22,23} providing more evidence to show that an increase in BP levels among adolescents is associated with the autonomic imbalance observed by the lower total variance and higher Shannon entropy. These findings are highly clinically relevant for understanding the pathophysiology of hypertension, since changes in HRV patterns provide a sensitive and early indicator of health impairment. As described by McCraty et al., high HRV is a sign of good cardiovascular adaptation, characterizing a healthy individual with efficient autonomic mechanisms. On the other hand, low HRV is generally an indicator of abnormal and insufficient adaptation of the baroreflex, which may indicate the presence of autonomic dysfunction.²⁴

In addition, the study by Farah et al.²⁵ showed that HRV can be affected by factors including sex, age, waist circumference and sleep quality, which corroborates other pre-existing findings in the literature.^{26,27} However, according to our study, the prehypertension group did not show any significant differences in the analysis of the following variables: age, height, weight, waist circumference, fat percentage and sleep quality, which excluded the possibility of these isolated factors influencing HRV. However, in the logistic regression model, these associated factors were related to increased chances of affecting Shannon entropy.

In the study by Amara et al.,²⁸ they published more evidence supporting that family history of hypertension is

Table 1 – Baseline analysis of anthropometric, cardiovascular characteristics and sleep quality in groups of normotensive and prehypertensive adolescents

	Normotensive (n= 159)	Prenhypertensive (n= 44)	Δ (CI)	p value	ES
Age (years)	16.00 $\pm$ 2.08	16.00 $\pm$ 1.71	0.00 (-0.67/0.67)	1.00	0.00
Height (cm)	161.38 $\pm$ 12.19	162.32 $\pm$ 9.90	0.94 (-3.00/4.88)	0.63	0.08
Weight (kg)	58.09 $\pm$ 10.94	56.74 $\pm$ 12.07	-1.35 (-5.10/2.40)	0.47	0.11
Waist circumference (cm)	68.60 $\pm$ 7.05	71.00 $\pm$ 9.46	2.40 (-0.16/4.96)	0.06	0.28
Body fat (%)	25.12 $\pm$ 8.35	25.10 $\pm$ 9.70	-0.02 (-2.92/2.88)	0.98	-0.002
Systolic Blood Pressure (mmHg)	107.00 $\pm$ 7.10	129.50 $\pm$ 7.60	20.08 (20.08/24.92)	0.0001*	3.05
Diastolic Blood Pressure (mmHg)	64.00 $\pm$ 7.02	73.00 $\pm$ 7.33	9.00 (6.62/11.38)	0.0001*	1.25
Pittsburgh Sleep Quality Index	1.86 $\pm$ 1.19	2.04 $\pm$ 1.76	0.18 (-0.26/0.62)	0.42	0.11

BP: blood pressure; * $p < 0.05$ vs normotensive; CI: confidence interval; ES: effect size.

Table 2 – Analysis of factors associated with blood pressure

	Normotensive n=159 (%)	Prehypertensive n=44 (%)	χ^2
Sex			
Male	44 (27.68)	26 (59.10)	[15.0575] p= 0.0001
Female	115 (72.32)	18 (40.90)	
Family history of hypertension			
Hypertensive parents	39 (24.57)	17 (38.65)	[3.4338] p= 0.6387
Normotensive parents	120 (75.43)	27 (61.35)	
School time			
In the morning	72 (45.29)	20 (45.46)	[0.0004] p= 0.9838
In the afternoon	87 (54.71)	24 (54.54)	
Tanner's sexual maturation index			
1	0 (0.00)	0 (0.00)	[5.1891] p=0.1584
2	17 (8.09)	6 (2.67)	
3	121 (59.32)	29 (14.00)	
4	14 (8.61)	9 (4.15)	

χ^2 Chi square test; [chi square value].

Table 3 – Cardiac autonomic modulation data of adolescents with high blood pressure and normotensive

	Normotensive (n= 159)	Prehypertensive (n= 44)	Δ (CI)	p value	ES
Time domain measures of heart rate variability					
Heart rate (bpm)	77.85 $\pm$ 12.74	79.91 $\pm$ 16.48	2.06 (-2.51/6.37)	0.37	0.14
Mean RR (ms)	801.54 $\pm$ 110.51	806.99 $\pm$ 161.58	5.45 (-35.94/46.84)	0.79	0.03
SDNN (ms)	55.72 $\pm$ 27.26	50.96 $\pm$ 18.84	-4.76 (-13.39/3.78)	0.27	0.20
RMSSD (ms)	53.10 $\pm$ 27.01	48.06 $\pm$ 24.03	-5.04 (-13.90/3.82)	0.26	0.19
pNN50 (%)	32.28 $\pm$ 20.99	28.47 $\pm$ 21.64	-3.81 (-10.90/3.28)	0.29	0.17
Total variance (ms ²)	3104.71 $\pm$ 743.10	2596.92 $\pm$ 354.94	-507.79 (-735.85/-279.83)	0.0001*	0.87
Nonlinear analysis					
SD1 (ms)	35.52 $\pm$ 15.17	39.65 $\pm$ 28.51	4.64 (-26.63/35.91)	0.19	0.18
SD2 (ms)	71.92 $\pm$ 100.62	76.56 $\pm$ 57.72	5.30 (-25.54/36.14)	0.77	0.05
Shannon entropy	1.74 $\pm$ 0.27	2.68 $\pm$ 0.65	0.94 (0.81/1.06)	0.0001*	1.88

SDNN: Standard deviation of all normal RR intervals recorded in a time interval; RMSSD: root mean square of successive differences; pNN50 the proportion of NN50 divided by the total number of NNs; SD1: dispersion of the points perpendicular to the line of identity is an index of instantaneous recording of the variability of beat-to-beat; SD2: dispersion of points along the identity line; represents HRV in long-term records; Values are presented as mean $\pm$ standard error; *p<0.05 vs normotensive; CI: confidence interval; ES: Effect size.

an important factor influencing HRV, up to 30%, and that hypertension is twice as common in individuals who have one or two hypertensive parents. In the present study, the family history of hypertension probably did not show any relationship with changes in HRV due to the absence of factors such as the genetic profile of adolescents and the presence of polymorphisms, which can influence the expression and production of regulatory components that are present in the endocrine system, such as the renin-angiotensin-aldosterone system.

Thus, although the precise mechanisms involved in the development of prehypertension in adolescents have not yet been clearly explained, recent studies, such as the ones by Pal et al. and Wu et al., have demonstrated an association between autonomic imbalance and decreased vagal modulation with prehypertension.^{29,30} Other studies corroborate these findings, reporting that the decrease in vagal modulation and HRV are the main causes of increased cardiovascular risk in adolescents with prehypertension; besides, obesity, psychosocial stress and dyslipidemia have been reported as important risk factors for prehypertension and hypertension.²⁹⁻³¹

Table 4 – Logistic regression model of the association between blood pressure and autonomic modulation

	Shannon entropy	Total variance	GOF p
PAS ^a (OR, 95% CI)	1.03 (1.02 – 1.04)	1.01 (0.98 – 1.03)	1.0000
PAD ^a (OR, 95% CI)	0.98 (0.97 – 1.00)	1.02 (0.99 – 1.02)	1.0000

Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were adjusted (a) for sex, sexual maturation, school time, age, waist circumference, sleep quality and family history of hypertension; GOF: Hosmer and Lemeshow's goodness of fit test; OR: odds ratio; 95% CI: confidence interval.

Currently, according to several studies,²⁻⁸ autonomic imbalance has been widely accepted as being fundamental to the etiology of hypertension. In adolescents, this autonomic imbalance is mainly caused by increased activity of the sympathetic nervous system, which has also been associated with an increased risk of cardiovascular events, obesity and sleep disorders.¹⁷⁻²⁶ However, although sympathetic hyperactivity is linked to other factors, such as obesity and sleep disorders, our data did not show differences in sleep quality between groups.

Regarding the gender of adolescents, some studies have observed that boys have higher prevalence of high BP than girls.^{32,33} In this sense, the studies by Sztajzel et al. and Jackson et al., using ambulatory BP monitoring in children, revealed that with age there is an increase in blood pressure among boys and girls. However, after the onset of puberty, the blood pressure in boys is higher than that of girls at the same age. This is because young women have higher day and night vagal tone than men of similar age.^{34,35}

Our study faced limitations such as the absence of a direct measure of sleep quality (polysomnography) and a limited number of subjects, as it is a preliminary phase of the study. Despite these limitations, we were able to assess the association of cardiac autonomic modulation with the different pressure levels of adolescents.

Conclusion

In conclusion, our data show that autonomic modulation may play a role in the development of elevated blood pressure, when controlling for other factors, such as school time and sleep quality. This finding has an important application considering that autonomic imbalance can be an early sign for the development of high levels of blood pressure in adolescents.

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Author Contributions

Conception and design of the research: Macêdo SRD, Silva-Filho AC, Nivaldo Junior, Dias CJ, Dias Filho CAA, Maciel AW, Rabêlo G, Mostarda CT; Acquisition of data: Silva-Filho AC, Vieira A, Nivaldo Junior, Dias CJ, Dias Filho CAA, Maciel AW, Rodrigues B, Pires FO, Ribeiro RM; Analysis and interpretation of the data: Macêdo SRD, Silva-Filho AC, Nivaldo Junior, Dias CJ, Maciel AW, Rabêlo G, Pires FO, Ribeiro RM; Statistical analysis: Macêdo SRD, Silva-Filho AC, Rabêlo G, Rodrigues B, Mostarda CT; Obtaining financing: Dias Filho CAA, Rodrigues B, Mostarda CT; Writing of the manuscript: Macêdo SRD, Vieira A, Nivaldo Junior, Dias Filho CAA, Rodrigues B, Mostarda CT, Pires FO, Ribeiro RM; Critical revision of the manuscript for intellectual content: Macêdo SRD, Silva-Filho AC, Vieira A, Nivaldo Junior, Dias CJ, Maciel AW, Rodrigues B, Mostarda CT.

Potential Conflict of Interest

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

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

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo under the protocol number 2.795.564. 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

- 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* (London, England). 2015;385:1990–2013.
- Havlicekova Z, Tonhajzerova I, Jurko Jr A, Jesenak M, Durdik P, Nosal S, et al. Cardiac autonomic control in adolescents with primary hypertension. *Eur J Med Res*. 2009;14(4):101.
- National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. *Pediatrics*. 2004;114(4):101.
- Bao W, Threftfoot SA, Srinivasan SR, Berenson GS. Essential hypertension predicted by tracking of elevated blood pressure from childhood to adulthood: The Bogalusa heart study. *Am J Hypertens*. 1995;8(7):657–65.
- Falkner B, Gidding SS, Portman R, Rosner B. Blood Pressure Variability and Classification of Prehypertension and Hypertension in Adolescence. *Pediatrics*. 2008;122(2):238–42.
- Goeder D, Oberhoffer R. Prävention von Herz-Kreislauf-Erkrankungen im Kindes- und Jugendalter. *Herz*. 2020;1–6.
- Flynn JT, Kaelber DC, Baker-Smith CM, Blowey D, Carroll AE, Daniels SR, et al. Clinical Practice Guideline for Screening and Management of High Blood Pressure in Children and Adolescents. *Pediatrics*. 2017;140(3):194.
- Wulsin LR, Horn PS, Perry JL, Massaro JM, D’Agostino RB. Autonomic imbalance as a predictor of metabolic risks, cardiovascular disease, diabetes, and mortality. *J Clin Endocrinol Metab*. 2015;100(6):2443–8.
- Thayer JF, Yamamoto SS, Brosschot JF. The relationship of autonomic imbalance, heart rate variability and cardiovascular disease risk factors. *International Journal of Cardiology*. 2010. p. 122–31.
- Chu Duc H, Nguyen Phan K, Nguyen Viet D. A Review of Heart Rate Variability and its Applications. *APCBEE Procedia*. 2013;7:80–5.
- Hall MH, Lee L, Matthews KA. Sleep duration during the school week is associated with C-reactive protein risk groups in healthy adolescents. *Sleep Med*. 2015;16:73–8.
- Nagai N, Matsumoto T, Kita H, Moritani T. Autonomic nervous system activity and the state and development of obesity in Japanese school children. *Obes Res*. 2003;11:25–32.
- Initiative NOE, Heart N, Lung, Institute B, for the Study of Obesity NAA, on the Identification EP, et al. The practical guide: identification, evaluation, and treatment of overweight and obesity in adults. The Institute; 2000.
- Slaughter MH, Lohman TG, Boileau R a, Horswill C a, Stillman RJ, Van Loan MD, et al. Skinfold equations for estimation of body fatness in children and youth. *Hum Biol an Int Rec Res*. 1988;709–23.
- Marshall WA, Tanner JM. Variations in the pattern of pubertal changes in boys. *Arch Dis Child*. 1970;45:13–23.
- Marshall WA, Tanner JM. Variations in pattern of pubertal changes in girls. *Arch Dis Child*. 1969;44(235):291.
- Buyse DJ, Reynolds CF 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: A New Instrument for Psychiatric Practice and Research. *Psychiatry Res*. 1989. p. 193–213.
- Furusawa EA, Ruiz MF, Saito MI, Koch VH. Evaluation of the Omron 705-CP blood pressure measuring device for use in adolescents and young adults. *Arq Bras Cardiol*. 2005;84(5):367–70.
- Malachias M, Souza W, Plavnik F, Rodrigues C, Brandão A, Neves M, et al. 7a Diretriz Brasileira de Hipertensão Arterial. *Arq Bras Cardiol*. 2016;107(3):1–103.
- Cutrim ALC, Duarte AAM, Silva-Filho AC, Dias CJ, Urtado CB, Ribeiro RM, et al. Inspiratory muscle training improves autonomic modulation and exercise tolerance in chronic obstructive pulmonary disease subjects: A randomized-controlled trial. *Respir Physiol Neurobiol*. 2019;263:31–7.
- Cohen J. Statistical power analysis for the behavioral sciences. Lawrence Erlbaum Associates. 1988.
- Pal GK, Adithan C, Ananthanarayanan PH, Pal P, Nanda N, Durgadevi T, et al. Effects of gender on sympathovagal imbalance, prehypertension status, and cardiovascular risks in first-degree relatives of Type 2 diabetics. *Am J Hypertens*. 2014;27(3):317–24.
- Laranjo S, Tavares C, Oliveira M, Trigo C, Pinto F, Rocha I. An insight into the autonomic and haemodynamic mechanisms underlying reflex syncope in children and adolescents: A multiparametric analysis. *Cardiol Young*. 2015;25(4):647–54.
- McCarty R, Shaffer F. Heart rate Variability: new perspectives on physiological Mechanisms, assessment of self-regulatory Capacity, and Health risk. *Glob Adv Heal Med*. 2015;4(1):46–61.
- Farah BQ, Christofaro DGD, Cavalcante BR, Andrade-Lima A, Germano-Soares AH, Vanderlei LCM, et al. Cutoffs of Short-Term Heart Rate Variability Parameters in Brazilian Adolescents Male. *Pediatric Cardiology*. 2018;1397–403.
- Tessier S, Lambert A, Scherzer P, Jemel B, Godbout R. REM sleep and emotional face memory in typically-developing children and children with autism. *Biol Psychol*. 2015;110:107–14.
- Miranda JM de Q, Dias L da C, Mostarda CT, Angelis K De, Figueira Junior AJ, Wichi RB. Efeito do treinamento de força nas variáveis cardiov asculares em adolescentes com sobrepeso. *Rev Bras Med do Esporte*. 2014;20(2):125–30.
- Amara A, Mrad M, Sayeh A, Lahideb D, Layouni S, Haggui A, et al. The effect of ACE I/D polymorphisms alone and with concomitant risk factors on coronary artery disease. *Clin Appl Thromb*. 2018;24(1):157–63.
- Pal GK, Adithan C, Ananthanarayanan PH, Pal P, Nanda N, Thiagarajan D, et al. Association of sympathovagal imbalance with cardiovascular risks in young prehypertensives. *Am J Cardiol*. 2015;112(11):1757–62.
- Wu S, Huang Z, Yang X, Li S, Zhao H, Ruan C, et al. Cardiovascular events in a prehypertensive Chinese population: four-year follow-up study. *Int J Cardiol*. 2013;167(5):2196–9.
- Pal GK, Pal P, Nanda N, Amudharaj D, Adithan C. Cardiovascular dysfunctions and sympathovagal imbalance in hypertension and prehypertension: physiological perspectives. *Future Cardiol*. 2013;9(1):53–69.
- Hoffmann M, Silva ACP da, Siviero J. Prevalência de hipertensão arterial sistêmica e interrelações com sobrepeso, obesidade, consumo alimentar e atividade física, em estudantes de escolas municipais de Caxias do Sul. *Pediatr (São Paulo)*. 2010;32(3):163–72.
- Barros MVG, Ritti-Dias RM, Barros SSH, Mota J, Andersen LB. Does self-reported physical activity associate with high blood pressure in adolescents when adiposity is adjusted for? *J Sports Sci*. 2013;31(4):387–95.
- Sztajzel J, Jung M, Bayes de Luna A. Reproducibility and gender-related differences of heart rate variability during all-day activity in young men and women. *Ann Noninvasive Electrocardiol*. 2008;13(3):270–7.
- Jackson L V, Thalange NKS, Cole TJ. Blood pressure centiles for Great Britain. *Arch Dis Child*. 2007;92(4):298–303.

Original Article



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Pre-Hypertension in Adolescents: A New Old Issue

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Short Editorial related to the article: Cardiac Autonomic Modulation is a Key Factor for High Blood Pressure in Adolescents

As there is no doubt that the risk of hypertension is proportional to the increase in blood pressure (BP) and has no specific threshold, the higher the pressure, the higher the risk. In this context, the identification of individuals with increased cardiovascular risk in the subclinical asymptomatic stage is of paramount importance¹ in the future to improve patients' quality of life and reduce the costs and burden of health services.

From the first attempt to measure the arterial pulse, performed by Santorio Sanctorius (1561–1636),² to Riva-Rocci,³ who put an end to the search for a simple clinical method for BP assessment, BP control has gained more and more prominence among clinicians and researchers. Consequently, BP values considered to be normal have gradually become lower and lower.

In fact, strong evidence demonstrates that cardiovascular disease (CVD) risk factors can be observed early in life⁴ and, for the most part, can be avoided to reduce the occurrence of hypertension in childhood and/or adolescence. Among these risks are sedentarism and obesity, whose prevention has been a major challenge in recent years.⁵ Currently, it is believed that 57% of children will be obese by the age of 35.⁶ Importantly, most causes of obesity and hypertension in childhood and adolescence are modifiable. Among them, we can highlight physical inactivity and eating disorders due to the access to unhealthy foods.⁷ Therefore, the great concern to monitor BP early and the effort to avoid those factors that could lead to hypertension are justified.

From 2000 to 2015, the increasing prevalence of childhood hypertension fluctuated between 75% and 79%.⁸ Nowadays, the pandemic caused by the SARS-CoV-2 virus has increased sedentary lifestyles due to forced confinement and made the situation even more worrying. A sedentary lifestyle, among other effects, stimulates the remodeling of our intestinal microbiome, leading to a predominance of obesogenic colonization.⁹

Therefore, there is an urgent need to prevent the risk of CVD in young people. It is necessary to improve management of the disease in childhood or adolescence in order to minimize the occurrence of hypertension in adulthood. The BP values that classify an individual as normotensive have been significantly reduced in recent years, drawing attention to the need to monitor the BP of young people and increasingly earlier interventions.

The possibility of using non-invasive, painless and low-cost BP monitoring techniques such as heart rate variability (HRV) measurement significantly facilitates the diagnosis and management of pre-hypertension and hypertension states. In this sense, HRV has been gaining prominence. HRV reflects the efficiency of the sympathetic and parasympathetic nervous systems in controlling the cardiovascular system.¹⁰

In the article by Macêdo et al.,¹¹ the importance of HRV in adolescents with pre-hypertension is made clear. The authors draw attention to the association between increased systolic and diastolic BP and a reduction in HRV in adolescents. Collectively, the reduction in HRV and the increase in Shannon entropy demonstrated an imbalance in sympathovagal control when the systolic BP was above 120mmHg. The techniques that assess HRV, although non-invasive and inexpensive, are hardly utilized in clinical medicine. However, they have shown to be efficient for the monitoring of sympathetic and parasympathetic systems and could also be helpful for monitoring patients, even before symptom onset.

On the other hand, although literature data point to an association between BP and genetic ancestry,¹²⁻¹⁴ the authors did not find this association among the adolescents. Furthermore, literature data indicate that the imbalance in the autonomic modulation probably precedes changes in the vascular endothelium,¹² which is an important component of BP control.

Collectively, these findings demonstrate the complexity of BP control and explain, at least in part, the difficulties of controlling BP in hypertensive patients. Despite great advances in the discoveries regarding BP control, more than 400 years separate us from Riva-Rocci and the management of hypertension remains a major challenge.

It is critical to know the prevalence of hypertension and pre-hypertension in the population. In addition, electronic patient charts should be introduced for all clinicians. The files should be created so that the physician cannot proceed to introduce other medical information without first entering the BP measurement. This simple step would prevent several problems in the future and would facilitate epidemiological records.

Moreover, the autonomic nervous system monitoring, through the observation of HRV, can be a low-cost alternative for the identification and early-onset treatment of the cardiovascular system autonomic modulation. Thus, it will be possible to make an early diagnosis of reflex disorders that contribute to the onset of hypertension and therefore work more rigorously to prevent hypertension from controllable causes. It is necessary to measure BP to prevent the consequences of CVD as soon as possible and not just to treat them when the problem is almost beyond remedy.

Keywords

Adolescents; Hypertension; Prehypertension; Arterial Pressure; Sedentarism; Quality of Life; Risk Factors; Early Medical Intervention/trends.

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References

1. Climie RE, Park C, Avolio A, Mynard JP, Kruger R, Bruno RM. Vascular Ageing in Youth: A Call to Action. *Heart Lung Circ.* 2021;S1443-9506(21)01112-4 doi: 10.1016/j.hlc.2021.065.516
2. Bigotti F, Santorio, Sanctorius. In: *Encyclopedia of Early Modern Philosophy and the Sciences* [Internet]. [Cited in 2020 Dec 12] Available from: http://link.springer.com/10.1007/978-3-319-20791-9_309-2
3. Booth J. A Short History of Blood Pressure Measurement. *Proc R Soc Med.* 1977;70(11):793-9.
4. Urbina EM, Khouiry PR, Bazzano L, Burns TL, Daniels S, Dwyer T, et al. Relation of Blood Pressure in Childhood to Self-Reported Hypertension in Adulthood. *Hypertension.* 2019;73(6):1224-30.
5. Reuter CP, Brand C, da Silva PT, Reuter ÉM, Renner JDP, Franke SIR, et al. Relationship between dyslipidemia, cultural factors, and cardiorespiratory fitness in schoolchildren. *Arq Bras Cardiol.* 2019;112(6):729-36.
6. Ward ZJ, Long MW, Resch SC, Giles CM, Craddock AL, Gortmaker SL. Simulation of Growth Trajectories of Childhood Obesity into Adulthood. *N Engl J Med.* 2017;377(22):2145-53.
7. Healy C, Brannigan R, Dooley N, Coughlan H, Clarke M, Kelleher I, et al. Childhood and adolescent psychotic experiences and risk of mental disorder: A systematic review and meta-analysis. *Psychological Medicine.* Vol 49;2019.
8. Song P, Zhang Y, Yu J, Zha M, Zhu Y, Rahimi K, et al. Global Prevalence of Hypertension in Children: A Systematic Review and Meta-analysis. Vol. 173, *JAMA Pediatrics.* 2019;173(12):1157-63.
9. Wang B, Kong Q, Li X, Zhao J, Zhang H, Chen W, et al. A high-fat diet increases gut microbiota biodiversity and energy expenditure due to nutrient difference. *Nutrients.* 2020;12(10):3197.
10. Milovanovic B, Djajic V, Bajic D, Djokovic A, Krajnovic T, Jovanovic S, et al. Assessment of Autonomic Nervous System Dysfunction in the Early Phase of Infection With SARS-CoV-2 Virus. *Front Neurosci.* June 21; <https://doi.org/10.3389/fnins.2021.640835>.
11. Macêdo SRD, Silva-Filho AC, Vieira ASM, Soares Junior NJ, Dias CJ, Dias Filho CAA, et al. Cardiac Autonomic Modulation is a Key Factor for High Blood Pressure in Adolescents. *Arq Bras Cardiol.* 2021; 117(4):648-654.
12. Vargas W, Rigatto K. Family history of hypertension impairs the autonomic balance, but not the endothelial function, in young soccer players. *Arq Bras Cardiol.* 2020;115(1):52-8.
13. Farrell MC, Giza RJ, Shibao CA. Race and sex differences in cardiovascular autonomic regulation. *Clin Auton Res.* 2020;30(5):371-9.
14. Amara A, Mrad M, Sayeh A, Lahideb D, Layouni S, Haggui A, et al. The effect of ACE I/D polymorphisms alone and with concomitant risk factors on Coronary Artery Disease. *Clin Appl Throm Hemost.* 2018;24(1):157-63.



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Palliative Endovascular Intervention in Infants with Tetralogy of Fallot: A Case Series

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Abstract

Background: Endovascular stent placement in the right ventricular outflow tract (RVOT) has been an alternative to Blalock-Taussig (BT) surgery in the treatment of Tetralogy of Fallot (TOF) in symptomatic infants with low birth weight and complex anatomy.

Objective: To evaluate endovascular stent placement in the RVOT as a primary treatment for infants with TOF who are not candidates for BT surgery, and evaluate medium-term outcomes until the stent is removed during corrective surgery.

Methods: Six infants with TOF were treated with RVOT stenting from October 2015 to April 2018. Hemodynamic parameters were compared between the pre- and post-stenting periods.

Results: At the time of stenting, participants had a median age and weight of 146.5 days and 4.9 kg, respectively. Peak systolic gradient decreased from 63.5 mm Hg to 50.5 mm Hg, while the diameter of the left and right pulmonary arteries increased from 3.5 mm to 4.9 mm and 4.3 mm, respectively. The Nakata index increased from 96.5 mm to 108.3 mm; weight increased from 4.9 kg to 5.5 kg; and oxygen saturation, from 83.5% to 93%. There was one case of stent migration and two deaths, one caused by stent embolization and the other unrelated to study procedures.

Conclusions: RVOT stenting is a promising alternative for the palliative treatment of TOF in infants with low birth weight and complex anatomy.

Keywords: Heart Defects, Congenital; Tetralogy of Fallot; Surgical Procedures Operative; Infant; Blalock-Taussig Procedure.

Introduction

Tetralogy of Fallot (TOF) is the most common cyanotic congenital heart defect, affecting three in every 10,000 live births worldwide, and occurring more frequently in males.^{1,2} It is characterized by four basic anomalies: interventricular communication, obstructed right ventricular outflow tract (RVOT), right ventricular hypertrophy and dextroposition of the aorta.^{1,2} The symptomatology varies depending on the degree of stenosis in the RVOT and the extent of intraventricular communication, but typical manifestations include bluish-purple discoloration of the skin, fatigue during feeding, and episodes of hypoxia relieved by squatting.^{3,4} TOF can be diagnosed during pregnancy through morphological ultrasound and should be confirmed after birth using fetal or transthoracic echocardiography. In inconclusive cases or during preoperative assessment, procedures such as catheterization, magnetic resonance imaging, or computed tomography can also be helpful.^{3,5}

Treatment alternatives include corrective surgery, possibly preceded by palliative procedures such as the placement of a Blalock-Taussig (BT) shunt, and RVOT stenting.

BT shunts have been the treatment of choice for TOF since 1945. The procedure involves the surgical placement of a systemic-pulmonary shunt between the subclavian and pulmonary arteries. In neonates and infants younger than 3 months, this procedure is associated with high rates of shunt occlusion, death, and destruction of the pulmonary valve annulus.³ An alternative treatment for these low-birth-weight infants with complex anatomical defects and moderate to severe symptoms is RVOT stenting,⁶ a less invasive strategy with lower morbidity and mortality rates that can restore neuronal development and improve quality of life until they undergo definitive corrective surgery.⁶⁻⁸

In light of these observations, this study aimed to evaluate the RVOT stenting as a primary treatment for children with TOF who are not candidates for BT surgery, and evaluate echocardiographic characteristics in the pre- and postoperative periods until the stent is removed during corrective surgery.

Method

This study was submitted and approved by a research ethics committee under protocol number CAAE 17443119.3.0000.5580. All procedures were conducted per the guidelines and criteria established in National

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Health Council (Conselho Nacional de Saúde; CNS) Resolution No. 466, issued on December 12, 2012, which stipulates ethical principles for the preservation of data integrity, privacy, and anonymity.

This was an observational, descriptive longitudinal study involving retrospective quantitative data collected at a large pediatric hospital in Curitiba, in the state of Paraná.

Inclusion criteria were having TOF and undergoing palliative endovascular treatment with RVOT stenting. Exclusion criteria were as follows: stenting due to congenital heart disease other than TOF; having a stent in another anatomical region of the heart; having other cardiac malformations.

The present study evaluated a series of 6 consecutive infants with TOF who underwent RVOT stenting between October 2015 and April 2018.

The following data were collected from medical records for subsequent analysis:

- Sociodemographic data: sex, age in days.
- Anthropometric data: weight in kg.
- Clinical data: percent oxygen saturation.
- Echocardiographic data: mean and peak systolic pressure gradients in the RVOT, measured in mm Hg; type and severity of stenosis in the RVOT; and the size of the left and right pulmonary arteries, the pulmonary trunk, and the pulmonary valve annulus, measured in mm; Nakata index of the pulmonary artery, measured in mm.

- Endovascular prosthesis data: brand and size (diameter in mm x length in mm).
- Surgical data: description of the stenting technique.

These outcome variables were collected at 3 different time points: preoperatively, in the immediate postoperative period of RVOT stenting, and in the late postoperative period of stent removal during corrective surgery.

Statistical analysis

The data was entered into a Microsoft Excel spreadsheet and analyzed using descriptive methods. Results were expressed using median, minimum, and maximum values, as well as percentages.

Results

The sample consisted of 6 infants, 3 of whom were female while 3 were male. The median age at the time of RVOT stenting was 146.5 days (range, 68-121). At the time of stent removal, the median age of the sample was 367 days, as shown in Table 1.

The manufacturers and sizes of the stents used in the study are shown in Table 2. The most commonly used brand was Dynamic-Biotronik. In two cases, the manufacturer of the stents used was not indicated.

The stenting technique used in the present study is described below:

Table 1 – Median age of patients at the time of RVOT stenting and stent removal during corrective surgery; length of interval between stent placement and removal

Patient	Age at RVOT stenting (days)	Age at stent removal during corrective surgery (days)	Interval between placement and removal of stent in the RVOT (days)
A	261	1211	950
B	68	1078	1010
C	151	367	216
D	74	184	110
W	142	200	58
F	170	-	-
Median	146.5	367	216

RVOT: Right ventricular outflow tract.

Table 2 – Manufacturer and size of endovascular prosthesis (stent)

Patient	Stent manufacturer	Stent size (diameter mm x length mm)
A	Dynamic - Biotronik	8 x 12
B	Dynamic - Biotronik	8 x 15
C	Woven - NIH	8 x 15
D	Dynamic - Biotronik	7 x 15
E	-	-
F	-	-

RVOT: Right ventricular outflow tract.

Table 3 – Distribution of anthropometric and echocardiographic variables in the late postoperative period after stent removal from the RVOT

Patient	Systolic Gradient	Systolic Gradient	Weight (kg)
	Peak across RVOT (mm Hg)	Mean across RVOT (mm Hg)	
A	24	-	16.5
B	41	19	10.1
C	-	-	6.5
D	17.4	10	11
W	85	51	8
F	-	-	-
Median	50.5	19	11

RVOT: Right ventricular outflow tract.

- I. Patient under general anesthesia;
- II. Placement of 6F and F5 sheaths in the right femoral vein and artery, respectively;
- III. Judkins catheter advanced over a 0.035" hydrophilic guidewire and manometry performed;
- IV. Collection of serial blood samples for gasometry, oximetry, and measurements of flow and resistance;
- V. Cineangiography via pigtail catheters;
- VI. Exchange of the 0.035" for a 0.014" guidewire;
- VII. Placement of the stent in the RVOT followed by balloon inflation;
- VIII. Removal of guidewires and sheaths, application of compression, and referral to the ICU.

Prior to stenting, the median peak systolic gradient across the RVOT was 63.5 (range, 52-97) mm Hg, while the median value for the mean systolic gradient at the RVOT was 46 (range, 38-56) mm Hg. Infundibular stenosis of the right ventricle was present in 4 out of 6 patients, while valve stenosis was less frequently observed. The median Nakata index for the pulmonary artery was 96.5 (range, 68.44-138) mm, while the oxygen saturation ranged from 75 to 90% during the pre-stenting period. The median size of the left and right pulmonary branches, pulmonary trunk, and pulmonary valve annulus were 3.5 (range, 2.1-4.8) mm, 3.5 (range, 2-5) mm, 6.9 (range, 3.5-7.5) mm, and 4.2 (3.5 - 6.5) mm, respectively. The median weight of patients at the time of stenting was 4.9 (range, 4.0-8.2) kg. These variables are described in Table 3, appendix A.

In the immediate post-operative period after stenting, the peak systolic gradient across the RVOT in the sample ranged from 28 to 72 mm Hg, with a median value of 50.5 mm Hg. However, the records of 3 patients revealed the presence of mild, moderate, and significant residual stenosis in the RVOT. The median sizes of the left and right pulmonary branches were 4.9 (range, 2.5-6.0) mm and 4.3 (2.8-5.2) mm, respectively. The median Nakata index for the pulmonary artery was 108.6 (range, 42.44-138) mm, while median oxygen saturation was 93% (range, 68-98%). Lastly, at this time, the median weight in the sample was 5.5 (range, 4.9-8.5) kg, as described in Table 1, supplementary material.

In the late postoperative period after stent removal and corrective surgery, the peak systolic gradient across the RVOT ranged from 17.4 to 85 mm Hg, with a median value of 50.5 mm Hg. The mean systolic pressure gradient had a median value of 19 (range, 10-51) mm Hg. Patients weighed a median of 11 (range, 6.5-16.5) kg, as described in Table 3.

In all cases, the stent was successfully inserted in the RVOT, although 2 cases had an unfavorable clinical course. Patient E experienced stent embolization 28 h after implantation, requiring emergency surgery to reposition the stent. This was eventually followed by hemodynamic instability and death. Patient F died 82 h after stenting for causes unrelated to the procedure. The overall mortality rate in the present study was 33% (2/6). With regard to other complications observed after the procedure, Patient A displayed a right bundle branch block, while Patient C had bradycardia during stent placement, which was reversed with atropine, as well as infundibular stenosis below the graft due to stent migration.

Discussion

In 1969, Dotter developed a technique involving the endovascular implantation of a prosthetic device to support the structure of the venous lumen. The device was referred to as a stent. Since then, studies have evaluated the use of vascular prostheses in a variety of cases, although few focused on patients with intracardiac flow obstruction as seen in TOF, whose manifestations include pulmonary atresia and/or hypoplasia, and distal pulmonary branch stenosis.⁷⁻⁹

A palliative alternative to RVOT stenting for the treatment of congenital heart disorders is the placement of a duct stent, described in a publication by Gibbs in 1991 as a non-surgical alternative to ensure adequate pulmonary flow in neonates and infants.² This technique is indicated for cases of ductus arteriosus-dependent pulmonary flow or infundibular pulmonary stenosis not associated with the pulmonary valve or interventricular communication, as in the case of TOF.^{7,10}

Stenting the ductus arteriosus can exacerbate infundibular stenosis and lead to deformation of the pulmonary artery so that its use in the treatment of patients with TOF would have several negative consequences.^{7,11}

In a study of the immediate results of arterial stent placement, Sandoval et al.¹¹ found the procedure to be successful in over 80% of cases, with early mortality rates of 0-10% and effectiveness in promoting the growth of the pulmonary vascular tree, especially in cases of severe stenosis of the RVOT.¹¹ Rosenthal et al.¹² determined that in the medium- and long-term, arterial stents are associated with a higher likelihood of restenosis relative to BT and systemic-pulmonary fistula (modified BT shunt); arterial stents are associated with a restenosis rate of 43%, in addition to neointimal proliferation in the intrastent segment and the aortic and pulmonary borders.^{11,12} Another known limitation of arterial stents is the risk of luminal obstruction, which can reach 75% in the 6 months after the palliative intervention - a much shorter time than observed in RVOT stenting.¹²

Though some patients had predominantly valvular stenosis, all showed a significant degree of dynamic infundibular obstruction, so that balloon valvuloplasty alone would have unsatisfactory results.^{10,13} We therefore opted for RVOT stenting (Figures 1, 2, and 3).

In the present study, the median age of patients at the time of stent placement was 146.5 days, while at the time of removal and corrective surgery, patients had a median age of 367 days. The time spent with the stent in place was approximately 216 days. This is in line with previous research, which highlights the early age of patients submitted to stenting, and the need to wait for a sufficient time before performing definitive surgery.^{9,13-15} It was also possible to confirm that patients had adequate weight gain for their age, proportional to the time with the stent, allowing for sufficient growth and development to improve survival after the invasive surgical procedure. In addition to improving postoperative survival, RVOT stenting has other advantages such as optimizing the

time interval for definitive surgery; reducing the number of palliative surgeries required; and restoring neuronal development and quality of life until corrective surgery.^{6,7,9}

The anatomy of RVOT stenosis can vary significantly between patients concerning the origin of the obstruction, which can be in the infundibulum, the pulmonary artery, and/or the pulmonary artery branches. In the present study, the first two patients (A and B) had predominantly valvar stenosis, while the other patients had infundibular stenosis. These findings reflect the results of previous studies, such as that of Costa et al., 2016, who found that 43% of a sample of 30 patients with TOF who underwent RVOT stenting had infundibular stenosis.^{9,13-15}

Concerning the different treatment possibilities for patients with TOF, Sandoval et al.,¹¹ compared four groups. One underwent RVOT stenting; two groups with patients younger than 3 months—one group with pulmonary stenosis and the other with pulmonary atresia—underwent early corrective surgery; and the last underwent corrective surgery at 3 to 11 months of age. Infants submitted to RVOT stenting had lower Nakata indices than those in all other groups, with values below 100 mm²/m². This was also observed in the present study, with Patients A and B showing indices of 68.4 mm²/m² and 82 mm²/m² in the pre-stenting period, respectively. In the post-stenting period, these values increased significantly and exceeded 100 mm²/m², confirming that participants were good candidates for total correction of TF.^{5,16}

Regarding the manufacture of the stents used in the present study, 3 of the 4 patients received devices produced by Dynamic-Biotronik, while one patient received an endoprosthesis made by Woven-NIH. The devices varied in length and diameter depending on the degree of stenosis in the RVOT. This information was unavailable for 2 patients.

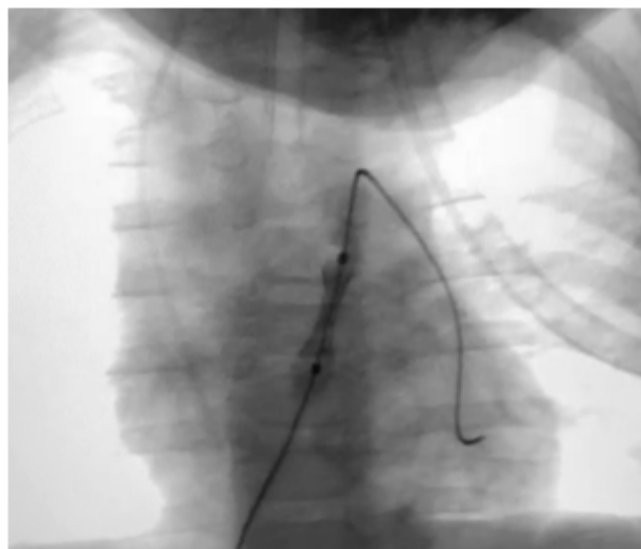


Figure 1 – Stent implantation in the right ventricular outflow tract. Cineangiography of Patient A: start of balloon expansion. Source: Hemodynamics service. Large pediatric hospital (Curitiba - PR).

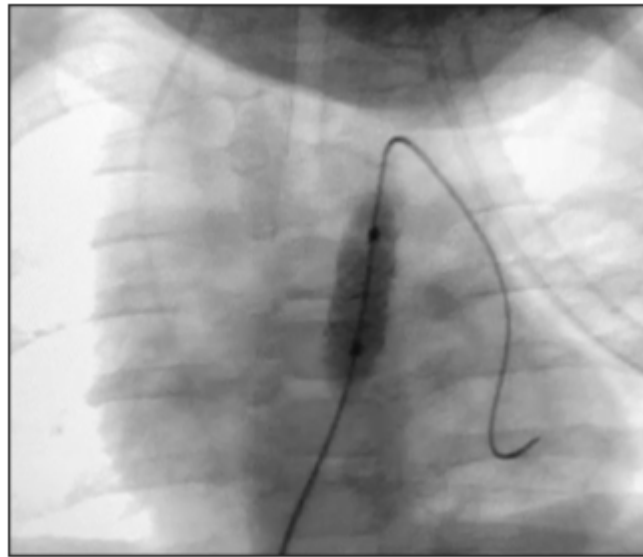


Figure 2 – During stent implantation in the right ventricular outflow tract. Cineangiography of patient A: end of balloon expansion and stent positioning. Source: Hemodynamics service. Large pediatric hospital (Curitiba - PR).

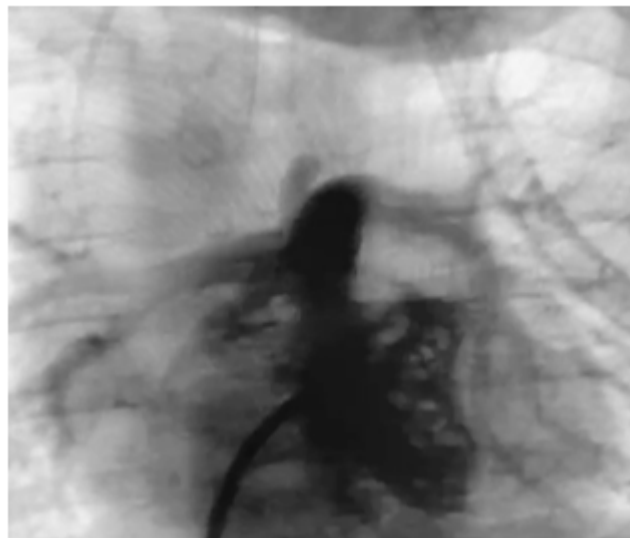


Figure 3 – After stent implantation in the right ventricular outflow tract. Cineangiography of Patient A: final result of the procedure. Source: Hemodynamics service. Large pediatric hospital (Curitiba - PR).

The median peak systolic gradient across the VSOT decreased from 69.4 mm Hg in the pre-implant period to 50.5 mm Hg in the immediate post-implant period, following a similar pattern to that described by Peng et al., 2006, and Ovaert et al.,¹⁷ 1999, who observed a decrease in the peak systolic gradient and right ventricular pressure overload immediately after surgery, confirming that the procedure had fulfilled its main purpose.^{14,17}

Transthoracic echocardiography also showed the growth rate of the left and right pulmonary branches before and immediately after the placement of the stent in the RVOT. The median sizes of the right and left pulmonary arteries prior to stenting were 3.5 mm, but increased to 4.9 mm and 4.3 mm, respectively, after the procedure. These changes were especially evident in Patient C, whose right pulmonary artery increased in size from 3.7 mm to 6 mm, while the

left went from 3.5 mm to 5.2 mm. Patients submitted to RVOT stenting rather than other palliative procedures or early corrective surgery usually exhibit risk factors for poor prognosis, such as low birth weight; lower Nakata index; anatomical malformations small pulmonary artery branches, which have an increased risk of complications such as pulmonary hypoplasia. This was also observed in a case series by Bigdelian et al.,⁵ 2019, who compared 3 groups: 8 patients who underwent RVOT stenting, 7 who underwent BT surgery, and 15 who underwent early corrective surgery. Even though patients with stent placement initially had smaller pulmonary artery branches than the other participant groups, their lung development was similar to that of patients who underwent BT surgery, while their weight gain did not differ from that of the other participants. As described by Bigdelian et al., 2019, the increased size of pulmonary artery branches results in improvements to the oxygen saturation and hemodynamic status of these critical patients.⁵

The information available on patient records showed that 4 participants had oxygen saturation values ranging from 75 and 90% prior to stent placement. However, immediately after stenting, there was a substantial improvement in 4 of the 5 patients for whom this information was available. The 4 participants showed values over 89%, indicating that stenting was successful;¹⁴ one patient, however, experienced complications after stenting and had a saturation of 68%. No information was available on the degree and duration of cyanosis or the presence of hypoxia before and immediately after stenting in previously published studies.^{5,13,14,16}

Complications are rarely described in the literature, but the most concerning include thrombosis and malpositioning of the endoprosthesis, which may require surgical removal and/or replacement of the *stent*.^{14,17} In this study, 2 patients ultimately died. One death was associated with the occurrence of stent embolization 28 hours after stent placement, which was followed by unsuccessful attempts at stent removal and reimplantation. The other patient had undergone a liver transplant and had biliary atresia. The patient experienced complications and died 72 hours after stenting. In the case of Patient C, the stent could not be adequately positioned, resulting in infundibular stenosis below the placement site. However, this had no significant clinical consequences, with the patient showing an increase in the size of the right and left pulmonary artery branches - from 3.7 to 6 mm and 3.5 to 5.2 mm, respectively - and a

reduction in peak systolic gradient across the RVOT, which fell from 69 mm Hg before stenting to 40 mm Hg in the immediate period after stent placement.

Limitations of this study include the sample size and a lack of data on echocardiographic variables, hemodynamic parameters, and clinical outcomes due to incomplete medical records.

Conclusion

Despite the small sample size, the present study demonstrated that an endovascular intervention consisting of the placement of a stent in the RVOT was effective at delaying the need for immediate surgical intervention, extending the survival of patients with TOF, and allowing for the definitive surgical correction of congenital disorders in low-birth-weight neonates with anatomical defects.

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Author Contributions

Conception and design of the research and Critical revision of the manuscript for intellectual content: Souza JM; Acquisition of data, Statistical analysis and Writing of the manuscript: Kupas KD, Oldoni I; Analysis and interpretation of the data: Kupas KD, Oldoni I, Souza JM.

Potential Conflict of Interest

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

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Study Association

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

References

1. Bailliard F, Anderson RH. Tetralogy of Fallot. *Orphanet J Rare Dis*. 2009; 4:2.
2. Silva ARS, Silva FD, Moura MCM, Luna TR, Barbosa FK. et al. Avanços no processo de tratamento da tetralogia de Fallot. (Boletim) Rucp. Ou/Dez 2017; 14(37).
3. Bautista-Hernández V. Tetralogía de Fallot con estenosis pulmonar: aspectos novedosos. *Cir Cardiov*. 2014; 21(2): 127-31.
4. Kouchoukos N. Ventricular septal defect with pulmonary stenosis or atresia. Cardiac surgery: morphology, diagnostic criteria, natural history, techniques, results and indications. *Rev Bras Cir Cardiovasc*. 2003; 18(1): 13-31.
5. Bigdelian H, Ghaderian M, Sedighi M. Surgical repair of tetralogy of Fallot following primary palliation: right ventricular outflow track stenting versus modified Blalock-Taussig shunt. *Indian Heart J*. 2018; 70(3): 394-8.
6. Van Doorn C. The unnatural history of tetralogy of Fallot: surgical repair is not as definitive as previously thought. *Heart*. 2002; 88(5): 447-8.
7. Neves JR, Arrieta R, Cassar RS et al. Implante de stent na via de saída de ventrículo direito: alternativa à palição cirúrgica convencional? *Rev Bras Cardiol Inv*. 2011; 19(2): 212-7.

8. Guerios EE, Bueno RRL, Andrade PMP, Nercolini AL, Pacheco AL. Stents. Uma revisão da literatura. *Arq Bras Cardiol.* 1998; 71(1): 77-87.
9. Costa BO, Marras AB, Furlan MFFM. Evolução clínica de pacientes após correção total de tetralogia de Fallot em unidade de terapia intensiva cardiológica pediátrica. *Arq Cienc Saude.* 2016; 23(1): 42-6.
10. Gibbs J, Rothman M, Rees M, Maya CG, Aristizabal G. Stenting of the arterial duct: a new approach to palliation of pulmonary atresia. *Br Heart J.* 1992; 67(3): 240-5.
11. Sandoval JP, Cerdeira CZ, Montes JAG, Maya LG. Implante de stent ductal em cardiopatias com circulação pulmonar canal-dependente. *Soc Latinoamericana de Cardiologia Intervencionista. (Boletim)* 2019; 110: 1-8.
12. Rosenthal E, Qureshi SA, Tabatabaie AH, Persaud AP, Kakadeksr AP, Baker EJ, et al. Medium-term results of experimental stent implantation into the ductus arteriosus. *Am Heart J.* 1996; 132(3): 657-63.
13. Quandt D, Ramchandani B, Stickley JCM, Mehta C, Bhole V, Barron DJ, et al. Stenting of the right ventricular outflow tract promotes better pulmonary arterial growth compared with modified Blalock-Taussig shunt palliation in tetralogy of Fallot-Type Lesions. *Cardiovasc Interv.* 2017; 10(17): 1785-7.
14. Peng LF, McElhinney DB, Nugent AW, Powell A, Marshall AC. Endovascular stenting of obstructed right ventricle-to-pulmonary artery conduits: a 15-year experience. *Circ Cardiovasc Interv.* 2006; 113(22): 2598-605.
15. Lee CH, Kwak JG, Lee C. Primary repair of symptomatic neonates with tetralogy of Fallot with or without pulmonary atresia. *Korean J Pediatr.* 2014; 57(1): 19-25.
16. Sandoval JP, Chaturvedi RR, Benson L, Morgan G, Van Arsdell G, Honjo O. Right ventricular outflow tract stenting in tetralogy of Fallot infants with risk factors for early primary repair. *Circ Cardiovasc Interv.* 2016; 9(12): 79-89.
17. Ovaert C, Caldarone CA, McCrindle BW, Nykanen D, Freedom RM, Coles JG, et al. Endovascular stent implantation for the management of postoperative right ventricular outflow tract obstruction: clinical efficacy. *J Thorac Cardiovasc Surg.* 1999; 118(5): 886-93.

*Supplemental Materials

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Transcatheter Palliation for Tetralogy of Fallot

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Short Editorial related to the article: Palliative Endovascular Intervention in Infants with Tetralogy of Fallot: A Case Series

The Tetralogy of Fallot (TOF) is the most common cyanotic congenital heart defect. The morphologic key feature of TOF is the malalignment of the infundibular septum. The infundibular septum malalignment makes the aorta override interventricular septum (dextroposition) over a large ventricular septal defect (VSD) and promotes obstruction to the right ventricular infundibular tract. The pulmonary valve is also stenotic, and the pulmonary trunk and arteries are, to some degree, hypoplastic. Severe obstruction to pulmonary blood flow (PBF) leads to more systemic unsaturation and, thus, prolonged hypoxia.

Open heart surgery is the traditional treatment modality, augmenting the right ventricular outflow tract (RVOT), closing the VSD, thus redirecting the aorta to the left ventricle, correcting the cardiac anatomy, and normalizing systemic flow saturation.¹

Some patients are not candidates for early surgery due to insufficient body weight, small pulmonary artery size (bad anatomy), prematurity, neurologic impairment, or associated defects.^{2,3} In those cases, palliative procedures are necessary to increase PBF and systemic oxygen saturation, reducing levels of hypoxia. Ideal palliation would offer a stable and symmetric pulmonary blood flow source and adequate growth of pulmonary arteries, leaving behind no residues that can impair corrective surgery.

The most traditional form of palliation is the Blalock-Taussig Shunt (BTS), idealized by Alfred Blalock and Helen Taussig and first performed in 1944 by Alfred Blalock.⁴ Classic BTS consists of right subclavian artery anastomosis to the right pulmonary artery when the aortic arch is left-sided. When the aorta is right-sided, the anastomosis is performed in the left subclavian artery.

Modified BTS using interposition of a PTFE tube graft was later developed in the '70s aiming to preserve subclavian flow to the ipsilateral arm.⁵ Although effective, BTS has some issues, including selective PBF, unequal development of pulmonary arteries, suture-mediated pulmonary branch stenosis, and shunt occlusion with consequent hypoxemia. In addition, it should be considered that transporting a severely ill patient to the operating room is a risk in itself.

Non-surgical palliation alternatives were pursued, and several strategies were offered, such as pulmonary balloon valvuloplasty (PBV) and ductal or RVOT stenting.

PBV is effective in cases where the main obstructive feature is the pulmonary valve, having reduced efficacy when significant infundibular stenosis is present. In that case, effective palliation has short-term efficacy.⁶

Ductal stenting is a safe and effective procedure when performed in experienced centers. It has comparable results to BTS in selected patients with ductal-dependent PBF. Glatz et al. report on 106 patients treated with ductal stenting versus 251 patients treated with BTS. Primary composite outcomes (death or reintervention) were more common in the BTS group (29.5% vs 17%, $p = 0.014$) due mainly to unplanned reinterventions for cyanosis relief (10.4% x 6.6%, $p = 0.26$). As anticipated, procedural complications were more commonly found in the BTS group, although without statistical significance. Pulmonary artery growth in the ductus stenting group was greater and more symmetric ($p = 0.015$).⁷ Possible complications of ductal stenting are in-stent re-stenosis, intimal proliferation, and stent obstruction.⁸

RVOT stenting emerged as a compelling technique for TOF palliation. Relief of infundibular obstruction and pulmonary valve stenosis by bare-metal stent implantation in the RVOT can lead to stable PBF and satisfactory growth of pulmonary arteries.⁹⁻¹³

RVOT stenting improves the pulsatile flow of systemic venous blood to the pulmonary artery, improving oxygen saturation without a decline in diastolic aortic pressure and resultant coronary perfusion. A systematic review and meta-analysis by Ghaderian et al. showed high clinical efficacy of RVOT stenting in achieving adequate pulmonary arterial growth during palliation and obtaining proper arterial oxygen saturation. They also showed low post-procedure morbidity and mortality following RVOT stenting and no significant difference in procedural outcomes.¹⁴ In small patients and complex anatomies, RVOT stenting allows for surgical correction in a later stage. Stent removal during surgery, albeit feasible, lengthens bypass time and, in most cases, determines the use of transannular patches at the time of definitive surgery.¹⁵

In the current issue of *Arquivos Brasileiros de Cardiologia*, Kupas et al.¹⁶ reported on six infants treated by RVOT stenting. The median age at the moment of the implant was 146.5 days and 367 days at the moment of stent implant and retrieval, respectively. Four patients had an infundibular obstruction, and two patients predominantly had a valvar obstruction. The immediate post-procedure evaluation showed a reduction of the peak systolic gradient, increased pulmonary arteries size and systemic oxygen saturation. Overall mortality was 33%. Thus, albeit constituting a very small case series, the authors propose stent implantation in RVOT as an interesting and appealing option for TOF palliation in very sick neonates.¹⁶

Transcatheter palliation may direct high-risk patients to the path for complete and physiologic resolution of TOF. New techniques on the horizon make TOF treatment very likely to be performed less invasively, with catheter-based and/or hybrid procedures.¹⁷

Keywords

Tetralogy of Fallot; Cyanosis; Cardiac Catheterization; Stents.

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References

1. Lillehei CW, Varco RL, Cohen M, Warden HE, Gott VL, DeWall RA, et al. The First Open Heart Corrections of Tetralogy of Fallot. A 26-31 Year Follow-up of 106 Patients. *Ann Surg.* 1986;204(4):490-502. doi: 10.1097/0000658-198610000-00017.
2. Reddy VM, McElhinney DB, Sagrado T, Parry AJ, Teitel DF, Hanley FL. Results of 102 Cases of Complete Repair of Congenital Heart Defects in Patients Weighing 700 to 2500 Grams. *J Thorac Cardiovasc Surg.* 1999;117(2):324-31. doi: 10.1016/S0022-5223(99)70430-7.
3. Memon MKY, Akhtar S, Mohsin M, Ahmad W, Arshad A, Ahmed MA. Short And Midterm Outcome Of Fallot's Tetralogy Repair In Infancy: A Single Center Experience In A Developing Country. *J Ayub Med Coll Abbottabad.* 2019;31(3):383-7.
4. Taussig HB. Neuhauser Lecture: Tetralogy of Fallot: Early History and Late Results. *AJR Am J Roentgenol.* 1979;133(3):422-31. doi: 10.2214/ajr.133.3.422.
5. Gazzaniga AB, Lamberti JJ, Siewers RD, Sperling DR, Dietrick WR, Arcilla RA, et al. Arterial Prosthesis of Microporous Expanded Polytetrafluoroethylene for Construction of Aorta-Pulmonary Shunts. *J Thorac Cardiovasc Surg.* 1976;72(3):357-63. doi: 10.1016/S0022-5223(19)40062-7.
6. Wu ET, Wang JK, Lee WL, Chang CC, Wu MH. Balloon Valvuloplasty as an Initial Palliation in the Treatment of Newborns and Young Infants with Severely Symptomatic Tetralogy of Fallot. *Cardiology.* 2006;105(1):52-6. doi: 10.1159/000089248.
7. Glatz AC, Petit CJ, Goldstein BH, Kelleman MS, McCracken CE, McDonnell A, et al. Comparison Between Patent Ductus Arteriosus Stent and Modified Blalock-Taussig Shunt as Palliation for Infants with Ductal-Dependent Pulmonary Blood Flow: Insights from the Congenital Catheterization Research Collaborative. *Circulation.* 2018;137(6):589-601. doi: 10.1161/CIRCULATIONAHA.117.029987.
8. Rosenthal E, Qureshi SA, Tabatabaie AH, Persaud D, Kakadekar AP, Baker EJ, et al. Medium-Term Results of Experimental Stent Implantation into the Ductus Arteriosus. *Am Heart J.* 1996;132(3):657-63. doi: 10.1016/S0002-8703(96)90252-5.
9. McGovern E, Morgan CT, Oslizlok P, Kenny D, Walsh KP, McMahon CJ. Transcatheter Stenting of the Right Ventricular Outflow Tract Augments Pulmonary Arterial Growth in Symptomatic Infants with Right Ventricular Outflow Tract Obstruction and Hypercyanotic Spells. *Cardiol Young.* 2016;26(7):1260-5. doi: 10.1017/S1047951115002231.
10. Quandt D, Ramchandani B, Penford G, Stickley J, Bhole V, Mehta C, et al. Right Ventricular Outflow Tract Stent Versus BT Shunt Palliation in Tetralogy of Fallot. *Heart.* 2017;103(24):1985-91. doi: 10.1136/heartjnl-2016-310620.
11. Sandoval JP, Chaturvedi RR, Benson L, Morgan G, Van Arsdell G, Honjo O, et al. Right Ventricular Outflow Tract Stenting in Tetralogy of Fallot Infants with Risk Factors for Early Primary Repair. *Circ Cardiovasc Interv.* 2016;9(12):e003979. doi: 10.1161/CIRCINTERVENTIONS.116.003979.
12. Stumper O, Ramchandani B, Noonan P, Mehta C, Bhole V, Reinhardt Z, et al. Stenting of the Right Ventricular Outflow Tract. *Heart.* 2013;99(21):1603-8. doi: 10.1136/heartjnl-2013-304155.
13. Tanidir IC, Bulut MO, Kamali H, Öztürk E, Yücel İK, Güzeltaş A, et al. Right Ventricular Outflow Tract Stenting During Neonatal and Infancy Periods: A Multi-center, Retrospective Study. *Türk Gogus Kalp Damar Cerrahisi Derg.* 2020;28(3):442-9. doi: 10.5606/tgkdc.dergisi.2020.18970.
14. Ghaderian M, Ahmadi A, Sabri MR, Behdad S, Dehghan B, Mahdavi C, et al. Clinical Outcome of Right Ventricular Outflow Tract Stenting Versus Blalock-Taussig Shunt in Tetralogy of Fallot: A Systematic Review and Meta-Analysis. *Curr Probl Cardiol.* 2021;46(3):100643. doi: 10.1016/j.cpcardiol.2020.100643.
15. Barron DJ, Ramchandani B, Murala J, Stumper O, Giovanni JV, Jones TJ, et al. Surgery Following Primary Right Ventricular Outflow Tract Stenting for Fallot's Tetralogy and Variants: Rehabilitation of Small Pulmonary Arteries. *Eur J Cardiothorac Surg.* 2013;44(4):656-62. doi: 10.1093/ejcts/ezt188.
16. Kupas KD, Oldoni I, Souza JM. Palliative Endovascular Intervention in Infants with Tetralogy of Fallot: A Case Series. *Arq Bras Cardiol.* 2021; 117(4):657-663.
17. Barron DJ, Vanderlaan RD. Predicting the Future: Tetralogy of Fallot Will Be Primarily Treated with Catheter Based Intervention Within Two Decades. Surgeon's Perspective. *Pediatr Cardiol.* 2020;41(3):546-52. doi: 10.1007/s00246-020-02298-y.



Impact of Serum Uric Acid Concentration on the Risk of Cardiovascular Disease: A Cohort Study Conducted in Northern China

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Abstract

Background: The results of previous studies of the relationship between serum uric acid (SUA) and the risk of cardiovascular disease (CVD) have been inconsistent due to confounding factors caused by other known cardiovascular risk factors.

Objectives: This study aimed to evaluate the relationship between SUA and incident CVD in middle-aged and elderly Chinese people, who were stratified according to body mass index (BMI).

Methods: This study recruited 5,721 participants of 40–75 years of age, who were free of CVD at baseline and who underwent follow-up from 2008 to 2017. Participants were categorized in SUA quintiles. Cox proportional hazard and Kaplan-Meier survival analysis were used to compare CVD incidence among the SUA groups. The correlations between SUA and CVD incidence in groups with differing BMI and waist circumference (WC) were also analyzed. A P value <0.05 was considered statistically significant.

Results: During a mean follow-up period of 7.6 years, CVD incidence increased with SUA (log-rank test $p < 0.001$). Compared with the first quintile, the adjusted hazard ratios (95% confidence interval (CI)) for the development of CVD were 1.08 (0.78–1.65), 1.17 (0.88–1.77), 1.47 (1.12–2.21), and 1.68 (1.28–2.44) for the second to fifth quintiles, respectively. This relationship was clearer in participants with normal BMI and WC. The adjusted hazard ratio for each 100 $\mu\text{mol/L}$ increase in SUA was 1.13 (95% CI: 1.02–1.39) for CVD events.

Conclusions: High SUA is an independent risk factor for CVD in middle-aged and elderly northern Chinese people. This effect is maintained even after stratification according to measures of leanness/obesity.

Keywords: Hyperuricemia; Uric Acid; Cardiovascular Diseases/incidence; Risk Factors; Body Weight.

Introduction

Hyperuricemia has become highly prevalent in recent years, most likely as a result of rapid economic development and changes in lifestyle.^{1,2} Some previous studies have shown that high serum uric acid (SUA) concentration is associated with higher incidences of conventional risk factors for cardiovascular disease (CVD), such as hypertension, diabetes, and arteriosclerosis.^{3–5} CVDs, including coronary artery disease, heart failure, and stroke, are well-known to be the most common causes of morbidity and mortality worldwide.^{6,7} In recent decades, increasing evidence has accumulated of a relationship between hyperuricemia and the occurrence and prognosis of CVD. In the Framingham heart study,⁸ a longitudinal observational study of 6,763 participants, the SUA concentration proved to have no causal role in the development of or death from coronary heart disease. However, other studies

have shown that hyperuricemia increases the risk of cardiovascular and cerebrovascular disease and mortality.^{9–11} In a cross-sectional study conducted in northeast China,¹² SUA was associated with coronary artery disease in women, and particularly in those who were >80 years old, but not in men. These contradictory findings may be explained by confounding factors caused by numerous other risk factors.

Hyperuricemia is common in the Chinese population, especially in economically developed regions.¹³ Therefore, it is important for public health that the status of SUA as a risk factor for CVD and the SUA concentration that requires intervention should be determined. Therefore, the present study aimed to determine the relationship between SUA concentration and the risk of CVD in a cohort of middle-aged and elderly Chinese people over a 10-year period.

Methods

Ethical standards

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was approved by the ethics committee of Hebei General Hospital (No. 190106).

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Informed consent was obtained from all the participants included in the study.

Study population

This cohort study recruited 40–75-year-old participants in comprehensive annual health screening at Hebei General Hospital, Shijiazhuang, China in 2008. These participants were employed by companies, universities, local governmental organizations, and hospitals. At the follow-up investigation until 2017, participants repeated the health screening each year, comprised of a questionnaire interview, physical examinations, and blood collection, similar to those during the baseline survey. This study was approved by the Human Ethics Committee of Hebei General Hospital (No.190106). Written informed consent was obtained from each participant.

For the analysis, CVD was defined as an ischemic heart disease (IHD), hemorrhagic stroke, or ischemic stroke. IHD was defined as myocardial infarction, angina pectoris, percutaneous coronary intervention, or coronary artery bypass surgery. The cohort consisted of 11,842 participants who had not experienced IHD, stroke, cancer, or kidney failure prior to enrollment, from 2008, and who had undergone annual medical examinations until 2017. This study excluded 4,892 participants due to incomplete data, the presence of comorbidities, or a lack of lifestyle assessment in any year. Participants were excluded because they developed cancer ($n=189$), chronic nephritis or renal failure ($n=106$), or a CVD event within the first year of the study ($n=68$); because they died from causes other than CVD ($n=45$); or because they were lost to follow-up ($n=821$). After the exclusion of these participants, data from a total of 5,721 participants (3,156 men and 2,565 women) were analyzed (Figure.1).

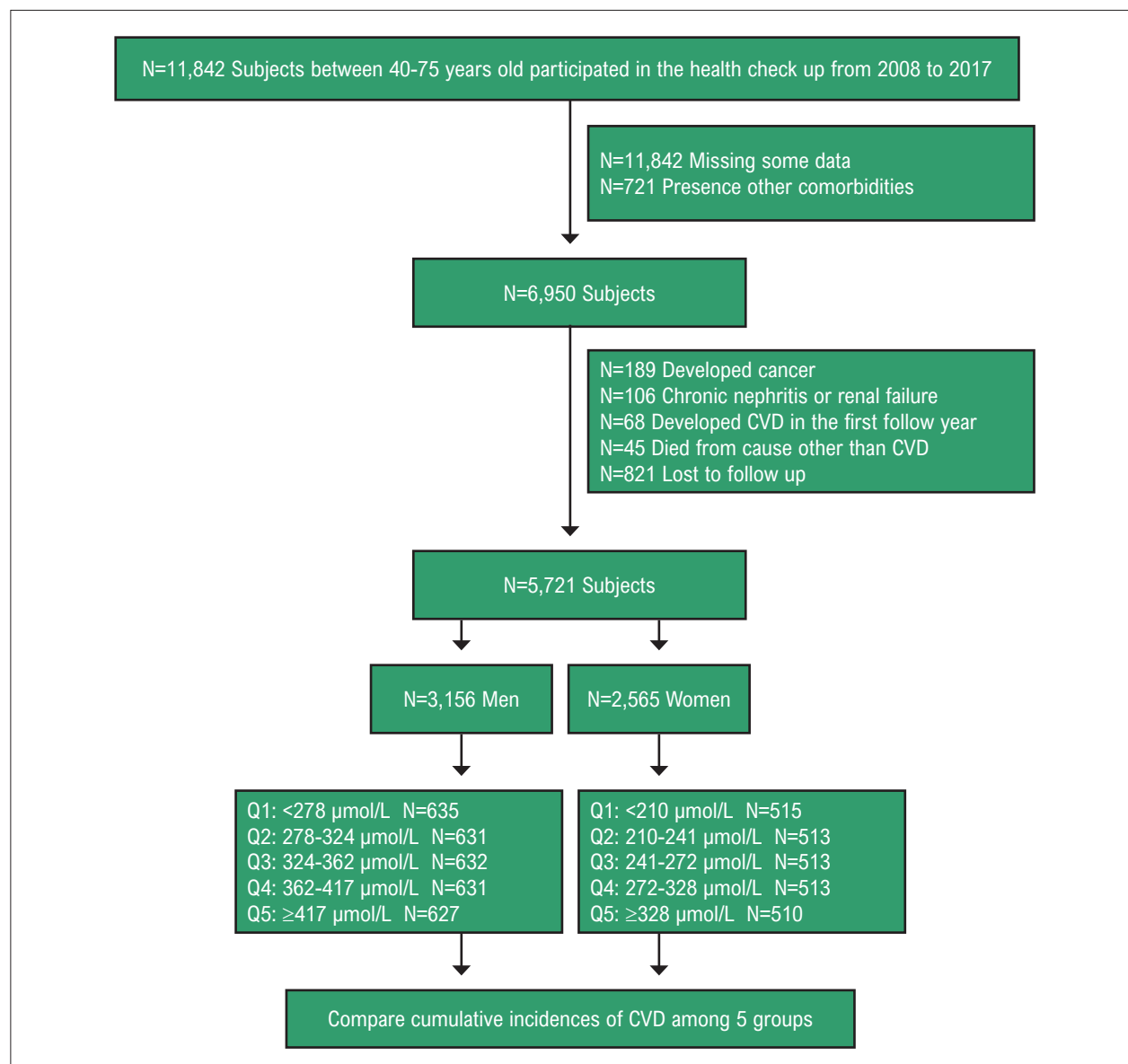


Figure 1 – Description of the study population. Participants of each sex were separately allocated to five groups (Q1-Q5) on the basis of their SUA concentration.

Data collection using questionnaires

Each participant underwent an annual physical examination and completed a structured questionnaire regarding their general medical history, use of medication, history of surgery, and family medical history. Questions regarding smoking (never, former, or current smoker) and alcohol consumption (never, former, or current drinker) were included.

Anthropometric measurements

Anthropometric data were collected annually, including height, body mass, waist circumference (WC), systolic blood pressure (SBP), and diastolic blood pressure (DBP), which were measured by well-trained nurses. The body mass index (BMI) was calculated as body mass in kilograms divided by the square of height in meters. Blood pressure was measured using a standard mercury sphygmomanometer (Omron HEM-7125, Dalian, China). The participants rested for >5 min before their blood pressure was measured. Height and body mass were measured while the participant was wearing light clothing and no shoes. These measurements were made twice during each physical examination, and the mean values were used in subsequent analyses.

Laboratory assessment

Venous blood samples were collected from all of the participants, following a 12-h overnight fast, and were used to measure white blood cell (WBC) and platelet (PLT) counts; hemoglobin (Hb), serum uric acid (SUA), fasting plasma glucose (FPG), creatinine (Cr), triglyceride (TG), total cholesterol (TC), low-density lipoprotein-cholesterol (LDL-C), and high-density lipoprotein-cholesterol (HDL-C) concentrations; and alanine aminotransferase (ALT) and aspartate aminotransferase (AST) activities. All of these measurements were made using standard methods with an automated biochemistry analyzer (Beckman Coulter AU5800, Tokyo, Japan). Estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease equation for Chinese patients with chronic kidney disease.¹⁴

Definitions

Participants of each sex were separately allocated to five groups on the basis of their SUA concentration: <278 $\mu\text{mol/L}$, 278–324 $\mu\text{mol/L}$, 324–362 $\mu\text{mol/L}$, 362–417 $\mu\text{mol/L}$, and $\geq 417 \mu\text{mol/L}$ for men; and <210 $\mu\text{mol/L}$, 210–241 $\mu\text{mol/L}$, 241–272 $\mu\text{mol/L}$, 272–328 $\mu\text{mol/L}$, $\geq 328 \mu\text{mol/L}$ for women. Hyperuricemia was defined as an SUA $\geq 420 \mu\text{mol/L}$ in men and $\geq 360 \mu\text{mol/L}$ in women.¹⁵

Hypertension was defined as an SBP $\geq 140 \text{ mmHg}$ and/or DBP $\geq 90 \text{ mmHg}$, or the current use of antihypertensive medication.¹⁶ Diabetes was defined as a physician-made diagnosis of diabetes reported by the participant, an FPG $\geq 7.0 \text{ mmol/L}$, or current use of antidiabetic medication.⁹ According to the recommended criteria for Chinese people, a BMI of 18.5–23.9 kg/m^2 was regarded as normal, a BMI of 24.0–27.9 kg/m^2 was regarded as indicating overweight, and a BMI $\geq 28 \text{ kg/m}^2$ was regarded as indicating obesity. Abdominal obesity was defined as a WC of >90 cm in

men and of >85 cm in women.¹⁷ The primary endpoints were the development of IHD (International Classification of Disease-10 codes I20–25), hemorrhagic stroke (I61), or ischemic stroke (I63).

Statistical analyses

The baseline characteristics of the participants were analyzed according to SUA quintile using descriptive statistics. Continuous variables are expressed as means $\pm$ standard deviations (SD) and categorical variables as percentages. The continuous variables were tested for normality through P-P plots. Comparisons between two groups were performed using unpaired Student's *t*-test for normally distributed data and the chi-square test for categorical data. Multiple comparisons were performed using one-way ANOVA and the *P*-value was corrected by post hoc Bonferroni test. The Kaplan-Meier survival analysis and the log-rank test were used to compare the incidences of CVD among the SUA groups. Cox proportional hazards analysis was used to assess the relationship between SUA and the incidence of CVD. Statistical analyses were conducted using SPSS version 22.0 (IBM Inc., Armonk, NY, USA) for Windows. A *p*-value <0.05 was considered statistically significant.

Results

Baseline characteristic of the participants

The baseline characteristics of the cohort participants, categorized according to sex and SUA quintile, are shown in Tables 1 and 2. BMI, WC, SBP, DBP, total cholesterol, triglycerides, LDL-C, ALT, Cr, FPG, and the prevalence of alcohol consumption, obesity, hypertension, and diabetes increased with higher serum uric acid levels in both sexes. Men with the highest SUA concentrations tended to be young, whereas women were older. In addition, a high SUA concentration was associated with low eGFR and HDL-C.

The relationship between SUA and the risk of CVD

The baseline and follow-up SUA concentrations are compared for each sex in Figure 2. SUA significantly increased from Q1 to Q5, both at baseline and during the follow-up period, according to ANOVA. The mean SUA concentration was lower at the end of the study than at baseline in men in Q5, but it still fulfilled the diagnostic criterion for hyperuricemia. The baseline characteristics of the participants, categorized according to incident CVD, are shown in Table 3. The mean follow-up period was 7.6 years, during which the cumulative CVD incidence was 14.3% ($n=821$) among the participants, with incidences of 13.9% ($n=438$) in men and 14.9% ($n=383$) in women. In addition, compared with participants who did not develop CVD, those who did develop CVD had higher BMI, WC, SBP, DBP, TC, TG, LDL-C, ALT, and FPG. There was no significant difference in Cr between the two groups.

As shown in Figure 3A, Kaplan-Meier analysis of CVD incidence in the SUA quintiles over the 10 years of the study showed significant differences between each group

Table 1 – Baseline characteristics of the male participants, categorized according to quintile of serum uric acid concentration

	All	Q1	Q2	Q3	Q4	Q5	p
N (participants)	3156	635	631	632	631	627	-
SUA($\mu\text{mol/L}$)	334.3 $\pm$ 40.5	240.2 $\pm$ 28.9	296.2 $\pm$ 11.8	337.5 $\pm$ 13.3	384.4 $\pm$ 13.4	456.3 $\pm$ 40.7	0.000
Age(years)	53.8 $\pm$ 9.6	53.2 $\pm$ 9.5	52.9 $\pm$ 9.6	52.0 $\pm$ 9.3	52.4 $\pm$ 9.5	51.7 $\pm$ 9.4	0.009
BMI(kg/m^2)	25.6 $\pm$ 2.9	24.5 $\pm$ 3.2	25.4 $\pm$ 2.8	25.7 $\pm$ 2.8	26.2 $\pm$ 2.7	26.9 $\pm$ 2.6	0.000
WC(cm)	89.1 $\pm$ 8.3	85.9 $\pm$ 8.9	88.3 $\pm$ 7.7	89.2 $\pm$ 8.2	90.2 $\pm$ 7.9	92.0 $\pm$ 8.3	0.000
SBP(mmHg)	123.8 $\pm$ 16.9	122.2 $\pm$ 16.5	122.3 $\pm$ 17.0	123.4 $\pm$ 16.8	123.0 $\pm$ 16.6	124.8 $\pm$ 16.7	0.012
DBP(mmHg)	79.5 $\pm$ 10.5	78.1 $\pm$ 11.3	78.2 $\pm$ 10.3	79.8 $\pm$ 10.5	80.2 $\pm$ 9.8	81.9 $\pm$ 10.6	0.004
TC(mmol/L)	4.92 $\pm$ 0.85	4.67 $\pm$ 0.85	4.76 $\pm$ 0.80	4.92 $\pm$ 0.83	5.00 $\pm$ 0.89	5.12 $\pm$ 0.85	0.000
TG(mmol/L)	1.85 $\pm$ 0.97	1.55 $\pm$ 0.91	1.66 $\pm$ 1.01	1.80 $\pm$ 1.04	2.06 $\pm$ 1.12	2.39 $\pm$ 1.23	0.000
HDL-C(mmol/L)	1.27 $\pm$ 0.27	1.32 $\pm$ 0.28	1.26 $\pm$ 0.24	1.25 $\pm$ 0.26	1.24 $\pm$ 0.25	1.23 $\pm$ 0.27	0.000
LDL-C(mmol/L)	2.8 $\pm$ 0.77	2.83 $\pm$ 0.72	2.85 $\pm$ 0.74	2.82 $\pm$ 0.82	2.83 $\pm$ 0.91	2.86 $\pm$ 0.83	0.132
ALT(U/L)	25.0 $\pm$ 11.8	23.3 $\pm$ 10.5	23.4 $\pm$ 10.8	25.4 $\pm$ 11.5	28.2 $\pm$ 11.3	28.7 $\pm$ 11.9	0.000
AST(U/L)	22.7 $\pm$ 8.5	22.2 $\pm$ 9.3	21.9 $\pm$ 6.7	23.1 $\pm$ 10.7	23.8 $\pm$ 10.2	23.9 $\pm$ 6.8	0.097
Cr($\mu\text{mol/L}$)	81.0 $\pm$ 9.2	75.5 $\pm$ 9.8	78.9 $\pm$ 9.6	82.4 $\pm$ 10.7	83.4 $\pm$ 10.6	87.0 $\pm$ 11.2	0.000
FPG(mmol/L)	5.96 $\pm$ 1.05	5.31 $\pm$ 1.81	5.96 $\pm$ 0.89	5.97 $\pm$ 0.91	6.02 $\pm$ 1.11	6.05 $\pm$ 0.85	0.000
eGFR($\text{ml/min}\cdot 1.73\text{m}^2$)	93.4 $\pm$ 12.4	97.8 $\pm$ 10.8	95.2 $\pm$ 10.9	92.8 $\pm$ 11.7	91.8 $\pm$ 12.4	87.5 $\pm$ 14.8	0.000
Current smokers (%)	40.67	40.39	42.77	41.83	39.98	41.48	0.326
Current drinkers (%)	37.23	35.69	36.66	38.02	41.86	42.78	0.000
Obesity (%)	20.8	13.72	16.08	19.44	24.42	31.82	0.000
Hypertension (%)	16.98	11.76	12.86	14.36	20.16	25.48	0.000
Diabetes (%)	11.08	7.42	8.38	9.79	9.98	13.23	0.000

SUA: serum uric acid; BMI: body mass index; WC: waist circumference; SBP: systolic blood pressure; DBP: diastolic blood pressure; TC: total cholesterol; TG: triglyceride; LDL-C: low-density lipoprotein-cholesterol; HDL-C: high-density lipoprotein-cholesterol; ALT: alanine aminotransferase; AST: aspartate aminotransferase; Cr: creatinine; FPG: fasting plasma glucose; eGFR: estimated glomerular filtration rate. Data are presented as means $\pm$ standard deviations (SD) if continuous and numbers (percentages) if categorical. Comparisons were performed using one-way ANOVA or the chi-square test for categorical data. The serum uric acid concentrations for each quintile were <278, 278–324, 324–362, 362–417, and $\geq 417 \mu\text{mol/L}$.

(log-rank test $p < 0.001$). Increases in SUA were associated with higher incidences of CVD. Because SUA is affected by renal function, we next categorized the participants according to eGFR and reanalyzed the data, and found that the relationship between SUA and CVD remained intact in participants who had eGFR values within the normal range (log-rank test $p < 0.001$; Figure 3B).

Cox proportional hazards analysis was used to further assess the relationship between SUA concentration and CVD incidence (Table 4). In the crude model, compared with SUA Q1, the hazard ratios (HRs) for CVD in the other four SUA quintiles were 1.18 (0.82–1.70), 1.41 (1.01–1.98), 1.95 (1.40–2.71), and 2.58 (1.84–3.61), respectively. The risks remained significantly different after adjustment for age in model 2, and age and sex in model 3. The HR decreased gradually as the number of adjusted covariates increased, but the association between SUA and CVD remained significant after adjustment for age, sex, eGFR, BMI, BP, total cholesterol, triglyceride, FPG, smoking, and alcohol intake (model 4). Compared with Q1, the HRs (95% CIs) for Q2–Q5 were 1.08 (0.78–1.65), 1.17 (0.88–1.77), 1.47

(1.12–2.21), and 1.68 (1.28–2.44). The adjusted HR for each 100 $\mu\text{mol/L}$ increase in SUA was 1.13 (95% CI: 1.02–1.39) for CVD events. We subsequently reanalyzed the data after stratification according to BMI and WC, and found that the significant association between SUA and CVD was more evident in participants with normal BMI and WC (Table 5).

Discussion

The present cohort study found a significant positive relationship between SUA concentration and the CVD incidence in middle-aged and elderly Chinese people. This relationship was regardless of the potential confounding factors of age, BMI, SBP, DBP, TC, TG, HDL-C, LDL-C, FBG, and a history of hypertension or diabetes. In addition, our study showed that a 100 $\mu\text{mol/L}$ increase in SUA increases the risk of CVD by 13%. These results demonstrate that SUA concentration is an independent risk factor for CVD.

Previous studies have also shown a relationship between SUA and CVD in other countries and regions. One previous meta-analysis showed that hyperuricemia increases the risk

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Table 2 – Baseline characteristics of the female participants, categorized according to quintile of serum uric acid concentration

	All	Q1	Q2	Q3	Q4	Q5	p
N (participants)	2565	515	513	513	514	510	-
SUA($\mu\text{mol/L}$)	259.8 $\pm$ 40.9	186.2 $\pm$ 18.2	226.0 $\pm$ 8.5	255.3 $\pm$ 10.9	290.5 $\pm$ 13.4	365.2 $\pm$ 30.7	0.000
Age(years)	52.1 $\pm$ 9.0	48.6 $\pm$ 7.7	50.3 $\pm$ 8.7	52.0 $\pm$ 8.6	53.5 $\pm$ 8.9	57.1 $\pm$ 9.2	0.000
BMI(kg/m^2)	24.2 $\pm$ 3.1	22.8 $\pm$ 2.6	23.7 $\pm$ 3.0	24.4 $\pm$ 3.3	24.7 $\pm$ 3.2	25.5 $\pm$ 3.1	0.000
WC(cm)	79.3 $\pm$ 9.5	75.1 $\pm$ 7.2	77.9 $\pm$ 8.3	79.6 $\pm$ 8.7	81.2 $\pm$ 8.6	83.6 $\pm$ 7.4	0.000
SBP(mmHg)	118.6 $\pm$ 19.3	110.7 $\pm$ 15.1	116.7 $\pm$ 17.6	118.8 $\pm$ 18.5	123.6 $\pm$ 19.6	124.0 $\pm$ 19.5	0.000
DBP(mmHg)	72.3 $\pm$ 9.7	69.1 $\pm$ 8.3	71.8 $\pm$ 9.8	73.0 $\pm$ 9.5	74.2 $\pm$ 10.0	74.6 $\pm$ 9.8	0.000
TC(mmol/L)	5.15 $\pm$ 0.92	4.86 $\pm$ 0.90	4.99 $\pm$ 0.86	5.21 $\pm$ 0.86	5.22 $\pm$ 0.93	5.58 $\pm$ 0.92	0.000
TG(mmol/L)	1.46 $\pm$ 0.95	1.03 $\pm$ 0.52	1.22 $\pm$ 0.61	1.45 $\pm$ 0.59	1.64 $\pm$ 0.60	2.09 $\pm$ 0.92	0.000
HDL-C(mmol/L)	1.56 $\pm$ 0.33	1.61 $\pm$ 0.32	1.60 $\pm$ 0.31	1.57 $\pm$ 0.32	1.50 $\pm$ 0.33	1.48 $\pm$ 0.36	0.006
LDL-C(mmol/L)	2.92 $\pm$ 0.78	2.89 $\pm$ 0.73	2.95 $\pm$ 0.73	2.99 $\pm$ 0.79	3.01 $\pm$ 0.81	3.04 $\pm$ 0.90	0.056
ALT(U/L)	16.3 $\pm$ 10.5	17.9 $\pm$ 8.6	17.9 $\pm$ 10.3	19.0 $\pm$ 8.6	20.6 $\pm$ 11.6	21.9 $\pm$ 9.3	0.013
AST(U/L)	21.6 $\pm$ 10.0	21.3 $\pm$ 9.8	20.6 $\pm$ 6.9	21.4 $\pm$ 7.1	22.3 $\pm$ 9.5	22.9 $\pm$ 6.0	0.087
Cr($\mu\text{mol/L}$)	61.3 $\pm$ 9.1	58.6 $\pm$ 8.1	59.6 $\pm$ 8.4	60.9 $\pm$ 8.6	61.9 $\pm$ 9.0	66.8 $\pm$ 10.02	0.000
FPG(mmol/L)	5.81 $\pm$ 1.00	5.61 $\pm$ 0.77	5.76 $\pm$ 0.91	5.87 $\pm$ 1.05	6.00 $\pm$ 1.15	6.18 $\pm$ 1.00	0.000
eGFR($\text{ml/min}\cdot 1.73\text{m}^2$)	97.7 $\pm$ 12.3	101.9 $\pm$ 11.3	99.9 $\pm$ 11.5	96.5 $\pm$ 12.6	94.2 $\pm$ 12.9	87.1 $\pm$ 14.0	0.000
Current smoker (%)	4.06	3.72	4.08	3.93	4.70	4.16	0.079
Current drinkers (%)	4.73	2.53	5.22	4.01	4.85	6.08	0.000
Obesity (%)	14.54	3.80	7.23	13.71	16.36	17.51	0.000
Hypertension (%)	20.34	8.86	16.87	18.39	23.05	26.72	0.000
Diabetes (%)	8.78	2.11	6.02	6.45	10.41	11.30	0.000

SUA: serum uric acid; BMI: body mass index; WC: waist circumference; SBP: systolic blood pressure; DBP: diastolic blood pressure; TC: total cholesterol; TG: triglyceride; LDL-C: low-density lipoprotein-cholesterol; HDL-C: high-density lipoprotein-cholesterol; ALT: alanine aminotransferase; AST: aspartate aminotransferase; Cr: creatinine; FPG: fasting plasma glucose; eGFR: estimated glomerular filtration rate. Data are presented as means $\pm$ standard deviations (SD) if continuous and numbers (percentages) if categorical. Comparisons were performed using one-way ANOVA or the chi-square test for categorical data. The serum uric acid concentrations for each quintile were <210 , 210–241, 241–272, 272–328, and ≥ 328 $\mu\text{mol/L}$.

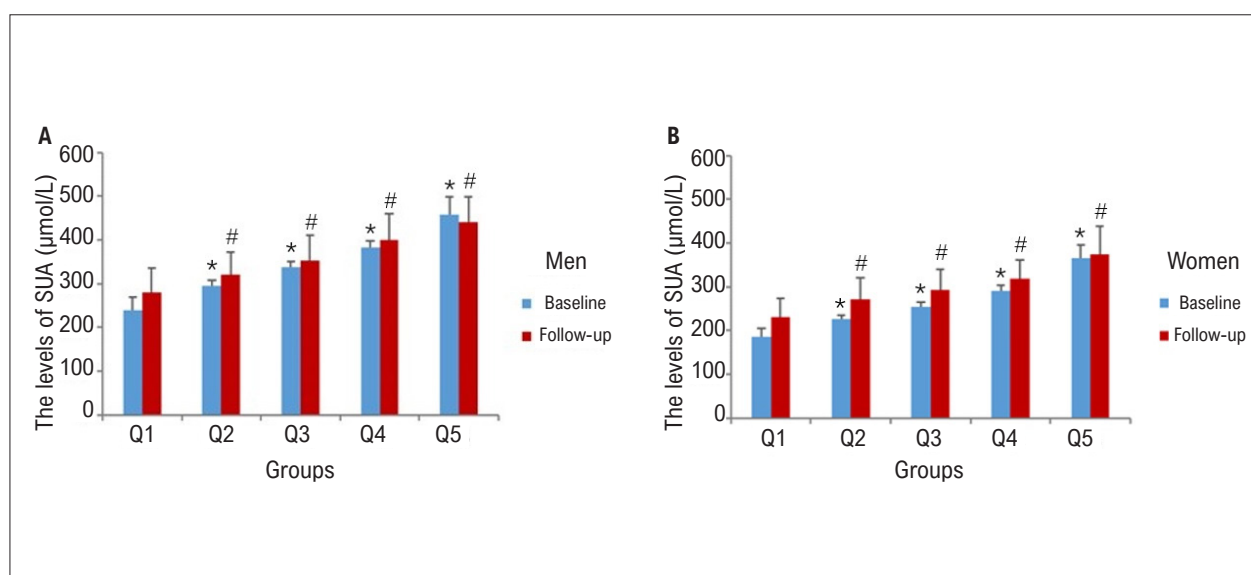


Figure 2 – Baseline and follow-up serum uric acid concentrations in participants of each sex. SUA, serum uric acid. Multiple comparisons were performed using one-way ANOVA and the P-value was corrected by post hoc Bonferroni test. In both men (A) and women (B), there were significant differences in SUA among the five groups at baseline and during follow-up. * $P<0.05$ (Q1 vs. other quintiles at baseline SUA concentrations); # $P<0.05$ (Q1 vs. other quintiles at follow-up SUA concentrations).

Table 3 – Baseline characteristics of the participants, categorized according to whether cardiovascular disease developed or not

	CVD (-)	CVD (+)	p
SUA (μmol/L)	299.4±75.1	319.5±73.6	0.012
Age (years)	52.2±9.2	59.6±9.1	0.000
Men (%)	47.1	53.4	–
BMI (kg/m ²)	24.9±3.1	25.7±3.2	0.001
WC(cm)	84.4±9.7	87.4±9.5	0.000
SBP (mmHg)	120.9±18.1	131.9±19.0	0.000
DBP (mmHg)	76.1±10.7	77.8±10.6	0.037
TC(mmol/L)	5.0±0.8	5.3±0.9	0.001
TG(mmol/L)	1.6±0.7	2.0±1.0	0.000
HDL-C(mmol/L)	1.41±0.3	1.27±0.3	0.000
LDL-C(mmol/L)	2.86±0.7	3.1±0.8	0.034
Cr(μmol/L)	71.8±14.3	72.1±14.1	0.061
FPG (mmol/L)	5.9±1.0	6.4±1.2	0.000
Smoker			
Never (%)	67.3	58.4	
Former (%)	11.6	17.7	
Current (%)	21.0	23.8	0.000
Alcohol intake			
Never (%)	76.1	69.5	
Former (%)	3.2	8.6	
Current (%)	20.6	21.8	0.000

SUA: serum uric acid; BMI: body mass index; WC: waist circumference; SBP: systolic blood pressure; DBP: diastolic blood pressure; TC: total cholesterol; TG: triglyceride; LDL-C: low-density lipoprotein-cholesterol; HDL-C: high-density lipoprotein-cholesterol; Cr: creatinine; FPG: fasting plasma glucose. Comparisons were performed using Student's t-test for continuous variables and the Chi-square test for categorical data. Data was presented as means ± standard deviations (SD) for continuous variable and numbers (percentage) for category variables.

of CVD: the risk of CVD was 2.1-fold higher in people with a high SUA than in those with a low SUA.¹⁸ Another meta-analysis of 16 cohort studies showed that hyperuricemia is associated with a higher risk of stroke (risk ratio: 1.41, 95% CI: 1.05–1.76) and higher stroke-related mortality (risk ratio: 1.36, 95% CI: 1.03–1.69), and these relationships remained significant after adjustment for other risk factors, such as sex, age, and the presence of hypertension or diabetes.¹⁹ There is also an increasing amount of evidence that hyperuricemia increases the risk of cardiovascular and cerebrovascular disease and mortality.^{9,11,20–22} In the present study, the participants were middle-aged and elderly people living in northern cities in China, but the findings were consistent with and extend previous findings.

However, most of the previous studies focused on the relationship between SUA and CVD-related mortality, and only a few focused on the relationship with CVD incidence. It is worth noting that a 10-year cohort study of 128,569 people conducted in Taiwan²² showed that hyperuricemia is a potential risk factor for IHD. However, a weakness of this study was that SUA was divided into only high or normal groups, and the relationship was only adjusted for a history of hypertension or diabetes, smoking, alcohol consumption, and the use of diuretics.

Thus, other important covariates, such as BMI, age, and eGFR were not adjusted for. The present study aimed to remedy these deficiencies by using quintiles of SUA to demonstrate the relationship between SUA and CVD after adjustment for a wide range of conventional risk factors. Furthermore, this relationship remained when SUA was treated as a continuous variable. Previous studies have also demonstrated a continuous relationship between SUA and CVD,⁹ and in the present study, the SUA values in Q4, which did not exceed the reference range, were associated with a significantly higher risk of CVD.

The mechanism by which a high SUA may increase the risk of CVD remains elusive. However, CVD is often closely related to atherosclerosis, and some previous studies have shown that a high SUA concentration accelerates its development.^{23,24} A large previous study of the relationship between SUA and early atherosclerosis showed that, compared with people in the lowest quartile of SUA, the carotid intima-media thickness (CIMT) was 37% higher in men and 48% higher in women in the highest SUA quartile.²⁵ Several potential mechanisms may account for the relationship between SUA and high CIMT and CVD. First, a high SUA concentration may promote endothelial dysfunction, and therefore the

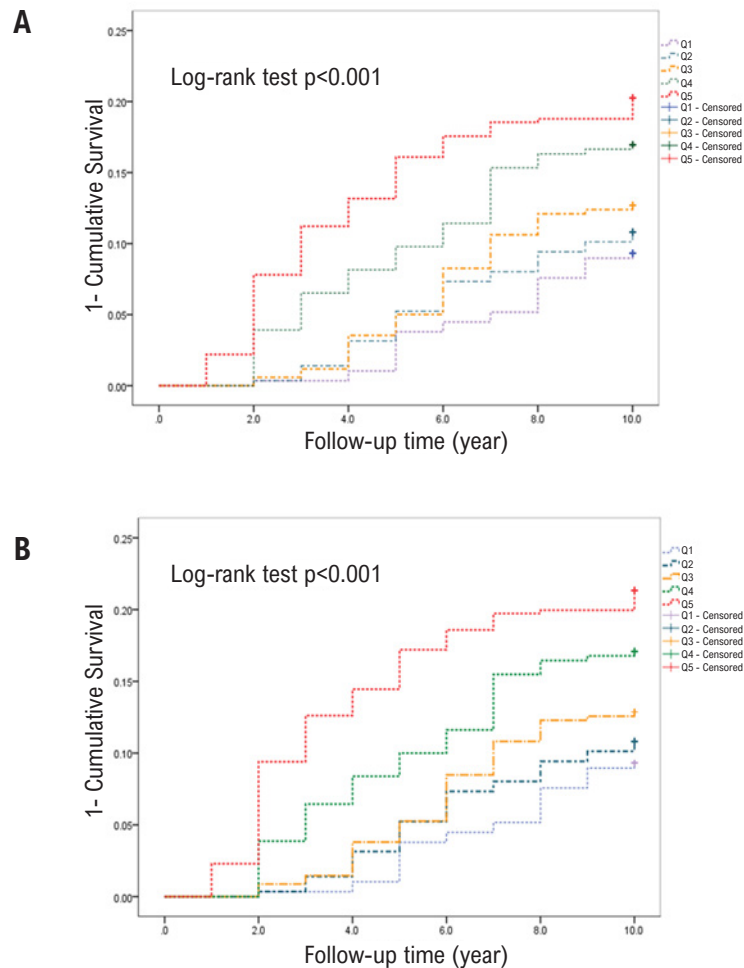


Figure 3 – Kaplan-Meier curves for incident cardiovascular disease for each quintile of serum uric acid (SUA) concentration. (A) All participants (log-rank test p -value < 0.01 , Q1 vs. other quintiles). (B) Participants with normal eGFR (log-rank test p -value < 0.01 , Q1 vs. other quintiles).

Table 4 – Hazard ratios for incident cardiovascular disease

SUA levels	Number of events	Hazard ratio (95% CI)			
		Model 1	Model 2	Model 3	Model 4
Q1	106/1150	1	1	1	1
Q2	124/1144	1.18(0.82-1.70)	1.56(0.80-1.66)	1.12(0.77-1.63)	1.08(0.78-1.65)
Q3	146/1145	1.41(1.01-1.98)	1.34(0.96-1.89)	1.27(0.91-1.79)	1.17(0.88-1.77)
Q4	203/1145	1.95(1.40-2.71)	1.73(1.25-2.41)	1.61(1.15-2.23)	1.47(1.12-2.21)
Q5	242/1137	2.58(1.84-3.61)	2.08(1.48-2.91)	1.89(1.34-1.34)	1.68(1.28-2.44)
SUA per 100 μ mol/L		1.25(1.11-1.42)	1.18(1.04-1.34)	1.16(1.09-1.29)	1.13(1.02-1.39)

CI: confidence interval; SUA: serum uric acid. Model 1 used the crude data. Model 2 was adjusted for age. Model 3 was adjusted for age and sex. Model 4 was adjusted for age, sex, eGFR, body mass index, blood pressure, total cholesterol, triglyceride, fasting plasma glucose, smoking, and alcohol intake.

Table 5 – Adjusted hazard ratios for the risk of CVD associated with serum uric acid concentration, stratified according to body mass index and waist circumference

	Hazards ratio(95%CI)				
	Q1	Q2	Q3	Q4	Q5
BMI (≤ 23.9)	Reference	1.15(0.92-1.29)	1.21(0.98-1.56)	1.26(1.01-1.64)	1.32(1.08-1.82)
BMI (24.0-27.9)	Reference	1.08(0.78-1.67)	1.13(0.69-1.89)	1.15(0.87-1.65)	1.18(0.98-1.83)
BMI (≥ 28)	Reference	0.92(0.74-1.56)	1.01(0.85-1.85)	0.98(0.78-1.49)	1.08(0.95-1.77)
WC (male<90,female<85)	Reference	0.89(0.78-1.45)	1.08(0.88-1.37)	1.12(1.01-1.43)	1.21(1.03-1.59)
WC (male ≥ 90 ,female ≥ 85)	Reference	1.02(0.72-1.78)	1.15(0.83-1.85)	1.23(0.75-1.91)	1.30(0.91-1.89)

The adjusted hazard ratios were calculated in Model 4 and were stratified according to body mass index (BMI, kg/m²) and waist circumference (WC, cm). SUA Q1 was used as the reference group. The covariates used in Model 4 were age, sex, eGFR, body mass index, blood pressure, total cholesterol, triglyceride, fasting plasma glucose, smoking, and alcohol intake.

development of CVD. Some previous studies have found that allopurinol-induced reductions in SUA correlate strongly with improvements in endothelial function.²⁶ In animal experiments, it was found that high SUA may cause endothelial dysfunction by means of a reduction in nitric oxide production.²⁷⁻²⁹ Second, SUA may induce greater secretion of proinflammatory substances, leading to increases in vascular inflammation and atherosclerosis.^{23,30,31} Third, a longitudinal study conducted at the National Institutes of Health showed a positive correlation between SUA and pulse wave velocity in men, which may have been mediated through a pro-inflammatory effect and/or by inducing the proliferation of smooth muscle cells.³² Thus, high SUA may not only have indirect effects on the progression of atherosclerosis, through its association with obesity, hypertension, diabetes, the metabolic syndrome, and other conventional cardiovascular risk factors, but may also increase the incidence and mortality associated with cardiovascular events.^{33,34}

In the present study, a stronger positive correlation was shown between SUA concentration and the CVD incidence in participants aged ≥ 40 years. This may be mediated through the effect of long-term exposure to hyperuricemia in the progression of atherosclerosis. It is worth noting that, in the present study, compared with participants in Q1, men and women in Q4, with mean SUA concentrations of 384.4 $\mu\text{mol/L}$ and 290.5 $\mu\text{mol/L}$, respectively, which are below the diagnostic criteria for hyperuricemia, still presented significantly higher risks of CVD. Therefore, we should be vigilant if patients have high-normal SUA concentrations. Notably, the relationship between SUA and the CVD incidence was present in participants with normal BMI and WC. The underlying mechanisms are unclear, but given that obesity is an important risk factor for CVD, it may also conceal an effect of high SUA on the CVD incidence in an obese population.

There were some limitations to the present study. SUA was only measured once, at baseline, as in almost all of the previous studies, so we could not exclude the possibility that some of the participants may have had only a brief increase in SUA at the time of enrollment. This study analyzed a population living in the northern cities of China who work in universities, hospitals, government departments,

or companies, and therefore had a high educational level and a stable income. Therefore, it is uncertain whether the results could be extrapolated to other regions. Thus, further large-scale, multi-center studies are required. Furthermore, although a variety of potential confounding factors were adjusted for, there remains a possibility of residual confounding due to factors such as daily exercise, diet, stress, and family history, which were not evaluated in the present study. However, despite the above limitations, we believe that our findings make a valuable contribution to knowledge of the link between SUA and the incidence of CVD.

Conclusion

In summary, the present study confirmed that high SUA concentration is an independent risk factor for CVD in middle-aged and elderly people. Hyperuricemia should be considered as a potential risk and considered in the prevention and treatment of CVD.

Author Contributions

Conception and design of the research and Obtaining financing: Nie Q, Song G; Acquisition of data, Analysis and interpretation of the data and Statistical analysis: Nie Q, Zhang X, Hao Z, Wang L, Liu H, Liu C, Wang Z; Writing of the manuscript: Nie Q; Critical revision of the manuscript for intellectual content: Zhang X, Hao Z, Song G.

Potential Conflict of Interest

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

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References

- Qiu L, Cheng XQ, Wu J, Liu JT, Xu T, Ding HT, et al. Prevalence of hyperuricemia and its related risk factors in healthy adults from Northern and Northeastern Chinese provinces. *BMC Public Health*. 2013 Jul 17;13:664.
- Liu H, Zhang XM, Wang YL, Liu BC. Prevalence of hyperuricemia among Chinese adults: a national cross-sectional survey using multistage, stratified sampling. *J Nephrol*. 2014;27(6):653-8.
- Kuwabara M, Kuwabara R, Hisatome I, Niwa K, Roncal-Jimenez CA, Bjornstad P, et al. "Metabolically Healthy" obesity and hyperuricemia increase risk for hypertension and diabetes: 5-year Japanese Cohort Study. *Obesity (Silver Spring)*. 2017;25(11):1997-2008.
- Yokoi Y, Kondo T, Okumura N, Shimokata K, Osugi S, Maeda K, et al. Serum uric acid as a predictor of future hypertension: Stratified analysis based on body mass index and age. *Prev Med*. 2016 Sep;90:201-6.
- Bener A, Al-Hamaq A, Öztürk M, Tewfik I. Vitamin D and elevated serum uric acid as novel predictors and prognostic markers for type 2 diabetes mellitus. *J Pharm Bioallied Sci*. 2019;11(2):127-32.
- Guan T, Ma J, Li M, Xue T, Lan Z, Guo J, et al. Rapid transitions in the epidemiology of stroke and its risk factors in China from 2002 to 2013. *Neurology*. 2017;89(1):53-61.
- Yang G, Wang Y, Zeng Y, Gao GF, Liang X, Zhou M, et al. Rapid health transition in China, 1990-2010: findings from the Global Burden of Disease Study 2010. *Lancet*. 2013;381(9882):1987-2015.
- Culleton BF, Larson MG, Kannel WB, Levy D. Serum uric acid and risk for cardiovascular disease and death: the Framingham Heart Study. *Ann Intern Med*. 1999;131(1):7-13.
- Lai X, Yang L, Légaré S, Angileri F, Chen X, Fang Q, et al. Dose-response relationship between serum uric acid levels and risk of incident coronary heart disease in the Dongfeng-Tongji Cohort. *Int J Cardiol*. 2016 Dec 1;224:299-304.
- Kanellis J, Feig DI, Johnson RJ. Does asymptomatic hyperuricaemia contribute to the development of renal and cardiovascular disease? An old controversy renewed. *Nephrology (Carlton)*. 2004;9(6):394-9.
- Purnima S, El-Aal BG. Serum uric acid as prognostic marker of coronary heart disease (CHD). *Clin Invest Arterioscler*. 2016;28(5):216-24.
- Sun Y, Zhang H, Tian W, Shi L, Chen L, Li J, et al. Association between serum uric acid levels and coronary artery disease in different age and gender: a cross-sectional study. *Aging Clin Exp Res*. 2019;31(12):1783-90.
- Liu R, Han C, Wu D, Xi X, Gu J, Guan H, et al. Prevalence of hyperuricemia and gout in Mainland China from 2000 to 2014: a systematic review and meta-analysis. *Biomed Res Int*. 2015;2015:762820.
- Ma YC, Zuo L, Chen JH, Luo Q, Yu XQ, Li Y, et al. Modified glomerular filtration rate estimating equation for Chinese patients with chronic kidney disease. *J Am Soc Nephrol*. 2006;17(10):2937-44.
- Wei F, Sun N, Cai C, Feng S, Tian J, Shi W, et al. Associations between serum uric acid and the incidence of hypertension: a Chinese senior dynamic cohort study. *J Transl Med*. 2016;14(1):110.
- Khera R, Lu Y, Lu J, Saxena A, Nasir K, Jiang L, et al. Impact of 2017 ACC/AHA guidelines on prevalence of hypertension and eligibility for antihypertensive treatment in United States and China: nationally representative cross sectional study. *BMJ*. 2018 Jul 11;362:k2357.
- Wei Y, Wang J, Han X, Yu C, Wan F, Yuan J, et al. Metabolically healthy obesity increased diabetes incidence in a middle-aged and elderly Chinese population. *Diabetes Metab Res Rev*. 2020;36(1):e3202.
- Kim SY, Guevara JP, Kim KM, Choi HK, Heitjan DF, Albert DA. Hyperuricemia and coronary heart disease: a systematic review and meta-analysis. *Arthritis Care Res (Hoboken)*. 2010;62(2):170-80.
- Kim SY, Guevara JP, Kim KM, Choi HK, Heitjan DF, Albert DA. Hyperuricemia and risk of stroke: a systematic review and meta-analysis. *Arthritis Rheum*. 2009;61(7):885-92.
- Wu J, Qiu L, Cheng XQ, Xu T, Wu W, Zeng XJ, et al. Hyperuricemia and clustering of cardiovascular risk factors in the Chinese adult population. *Sci Rep*. 2017;7(1):5456.
- Kuwabara M, Niwa K, Hisatome I, Nakagawa T, Roncal-Jimenez CA, Andres-Hernando A, et al. Asymptomatic hyperuricemia without comorbidities predicts cardiometabolic diseases: five-year Japanese Cohort Study. *Hypertension*. 2017;69(6):1036-44.
- Chuang SY, Chen JH, Yeh WT, Wu CC, Pan WH. Hyperuricemia and increased risk of ischemic heart disease in a large Chinese cohort. *Int J Cardiol*. 2012;154(3):316-21.
- Wijnands JM, Boonen A, Dagnelie PC, Greevenbroek MMJ, Kallen CJH, Ferreira I, et al. The cross-sectional association between uric acid and atherosclerosis and the role of low-grade inflammation: the CODAM study. *Rheumatology (Oxford)*. 2014;53(11):2053-62.
- Cicero AFG, Salvi P, D'Addato S, Rosticci M, Borghi C, Brisighella Heart Study Group. Association between serum uric acid, hypertension, vascular stiffness and subclinical atherosclerosis: data from the Brisighella Heart Study. *J Hypertens*. 2014;32(1):57-64.
- Chen Y, Xu B, Sun W, Wang T, Xu Y, Xu M, et al. Impact of the serum uric acid level on subclinical atherosclerosis in middle-aged and elderly Chinese. *J Atheroscler Thromb*. 2015;22(8):823-32.
- Doehner W, Schoene N, Rauchhaus M, Leyva-Leon F, Pavitt DV, Reaveley DA, et al. Effects of xanthine oxidase inhibition with allopurinol on endothelial function and peripheral blood flow in hyperuricemic patients with chronic heart failure: results from 2 placebo-controlled studies. *Circulation*. 2002;105(22):2619-24.
- Mazzali M, Kanellis J, Han L, Feng L, Xia YY, Chen Q, et al. Hyperuricemia induces a primary renal arteriopathy in rats by a blood pressure-independent mechanism. *Am J Physiol Renal Physiol*. 2002;282(6):F991-7.
- Choi YJ, Yoon Y, Lee KY, Hien TT, Kang KW, Kim KC, et al. Uric acid induces endothelial dysfunction by vascular insulin resistance associated with the impairment of nitric oxide synthesis. *FASEB J*. 2014;28(7):3197-204.
- Khosla UM, Zharikov S, Finch JL, Nakagawa T, Roncal C, Mu W, et al. Hyperuricemia induces endothelial dysfunction. *Kidney Int*. 2005;67(5):1739-42.
- Prasad M, Matteson EL, Herrmann J, Gulat R, Rihal C, Lerman LO, et al. Uric acid is associated with inflammation, coronary microvascular dysfunction, and adverse outcomes in postmenopausal women. *Hypertension*. 2017;69(2):236-42.
- Valle M, Martos R, Cañete MD, Valle R, Donkelaar EL, Bermudo F, et al. Association of serum uric acid levels to inflammation biomarkers and endothelial dysfunction in obese prepubertal children. *Pediatr Diabetes*. 2015;16(6):441-7.
- Canepa M, Viazzi F, Strait JB, Ameri P, Pontremoli R, Brunelli C, et al. Longitudinal association between serum uric acid and arterial stiffness: results from the Baltimore Longitudinal Study of Aging. *Hypertension*. 2017;69(2):228-35.
- Kanbay M, Jensen T, Solak Y, Le M, Roncal-Jimenez C, Rivard C, et al. Uric acid in metabolic syndrome: from an innocent bystander to a central player. *Eur J Intern Med*. 2016 Apr;29:3-8.
- Bombelli M, Quarti-Trevano F, Tadic M, Facchetti R, Cuspidi C, Mancia G, et al. Uric acid and risk of new-onset metabolic syndrome, impaired fasting glucose and diabetes mellitus in a general Italian population: data from the Pressioni Arteriose Monitorate E Loro Associazioni study. *J Hypertens*. 2018;36(7):1492-8.



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How Can We Favorably Modulate Serum Uric Acid?

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Short Editorial related to the article: *Impact of Serum Uric Acid Concentration on the Risk of Cardiovascular Disease: A Cohort Study Conducted in Northern China*

The study “Impact of Serum Uric Acid Concentration on the Risk of Cardiovascular Disease: A Cohort Study Conducted in Northern China”,¹ carried out with a cohort of middle-aged Chinese, discusses the influence of uric acid on cardiovascular outcomes. The study showed that serum uric acid was a risk factor for cardiovascular disease in middle-aged and elderly people in northern China.¹

Findings about this association are controversial. It has been proven in previous studies.²⁻⁵

Since 2018, the European Guideline for the management of hypertension recommends serum uric acid level as a parameter for assessing cardiovascular risk,⁶ and uric acid measurement should be included in the routine follow-up of patients with hypertension.

It should be considered that factors such as physical activity, diet, stress and family history influence serum uric acid levels and also cardiovascular risk; however, they were not evaluated in the study by Nie et al.¹ Among these factors, diet has an important influence and has been investigated in previous studies.

The Dietary Approaches to Stop Hypertension (DASH) diet, originally indicated for reducing blood pressure, characterized by high consumption of vegetables, whole grains and low-fat dairy, can also be suggested for reducing uric acid levels, as described by Gao et al.,⁷ with 71,893 Chinese participants in the Kailuan I study and the Kailuan II study, who did not have gout in a previous evaluation. Adherence to the DASH diet was independently associated with a low probability of having hyperuricemia. Another study with pre-hypertensive or hypertensive adults showed a reduction in severely high uric acid levels after 30 days of adherence to the DASH diet, and this effect was sustained for another 90 days.⁸

As for the vegetarian eating pattern, a study with 424 meat eaters, 425 fish eaters, 422 vegetarians and 422 vegans, participants of the EPIC-Oxford cohort, suggested that vegans had the highest serum levels of uric acid, followed by meat eaters, fish eaters and vegetarians.⁹ These results contrast with findings from

a study of 14,809 participants (6,932 men and 7,877 women) from the Third National Health and Nutrition Examination Survey (1988–1994), where a high consumption of meat and seafood was associated with higher blood uric acid levels, although there was no association with total dietary protein.¹⁰

This controversy between the findings and the fact that vegans and vegetarians had the extremes of uricemia values in the EPIC-Oxford study,⁹ 2013), may be due to the fact that a high consumption of total dairy products, total milk, low-fat dairy products, low-fat milk, low-fat yogurt, and cheese is associated with a lower risk of hyperuricemia.¹¹

The Mediterranean diet, widely studied in cardiovascular diseases, contributes to the prevention and treatment of hyperuricemia. Greater adherence to the diet was related to a lower probability of having hyperuricemia in 2,380 participants in the ATTICA study without previous cardiovascular risk factors.¹²

In addition to the dietary pattern, other factors can influence the increase in serum uric acid. In the Elderly-SEPHAR III Study, with a sample of 1,920 adults, of whom 447 were elderly patients (>65 years of age), age represented one of the factors contributing to the increased level of serum uric acid.¹³ In another study, body mass index, waist circumference, and waist-to-height ratio were positively associated with the risk of hyperuricemia in 2,895 participants in the China Health and Retirement Longitudinal Study with a 4-year follow-up.¹⁴

Cardiovascular diseases continue to be the leading cause of death in the world¹⁵ and dietary changes that are occurring and will continue to occur in all parts of the world, with a predominance of dietary patterns that in themselves have a nutritional profile related to development of chronic diseases and also a composition that favors an increase in serum uric acid, will aggravate the associated cardiovascular risk. Considering this context, the findings of the study by Nie et al., 2021, should be observed and used to support actions both in the clinical management of patients at cardiovascular risk, as well as to direct public health actions aimed at its prevention.

Keywords

Uric Acid/therapeutic use; Diet; Middle Aged; Risk Factors; Hypertension; Heredity; Hyperuricemia, Prevention and Control.

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References

- Nie Q, Zhang X, Hao Z, Wang L, Liu H, Liu C, Wang Z, Song G. Impact of Serum Uric Acid Concentration on the Risk of Cardiovascular Disease: A Cohort Study Conducted in Northern China. *Arq Bras Cardiol.* 2021; 117(4):666-675.
- Bener A, Al-Hamaq A, Öztürk M, Tewfik I. Vitamin D and elevated serum uric acid as novel predictors and prognostic markers for type 2 diabetes mellitus. *J Pharm Bioallied Sci.* 2019;11(2):127-32.
- Tian T, Wang Y, Xie W, Zhang J. Associations of Serum Uric Acid with Clustering of Cardiovascular Risk Factors and a 10-Year Atherosclerotic Cardiovascular Disease Risk Score in Jiangsu Adults, China. *Diabetes Metab Syndr Obes.* 2021;14:3447-60.
- Lai X, Yang L, Légaré S, Angileri F, Chen X, Fang Q, et al. Dose-response relationship between serum uric acid levels and risk of incident coronary heart disease in the Dongfeng-Tongji Cohort. *Int J Cardiol.* 2016 Dec 1;224:299-304.
- Purnima S, El-Aal BG. Serum uric acid as prognostic marker of coronary heart disease (CHD). *Clin Invest Arterioscler.* 2016;28(5):216-24.
- Williams B, Mancia G, Spiering W, Rosei EA, Azizi M, Burnier M, et al. 2018 ESC/ESH guidelines for the management of arterial hypertension. (Commentary). *Eur Heart J.* 2018;39(6):3021-104.
- Gao Y, Cui LF, Sun YY, Yang WH, Wang JR, Wu SL, Gao X. Adherence to the Dietary Approaches to Stop Hypertension Diet and Hyperuricemia: A Cross-Sectional Study. *Arthritis Care Res (Hoboken).* 2021 Apr;73(4):603-11.
- Tang O, Miller ER, Gelber AC, Choi HK, Appel LJ, Juraschek SP. DASH diet and change in serum uric acid over time. *Clin Rheumatol.* 2017 Jun;36(6):1413-7.
- Schmidt JA, Crowe FL, Appleby PN, Key TJ, Travis RC. Serum Uric Acid Concentrations in Meat Eaters, Fish Eaters, Vegetarians and Vegans: A Cross-Sectional Analysis in the EPIC-Oxford Cohort. *PLoS ONE.* 2013; 8(2): e56339.
- Choi HK, Liu S, Curhan G. Intake of purine-rich foods, protein, and dairy products and relationship to serum levels of uric acid: The Third National Health and Nutrition Examination Survey. *Arthritis & Rheumatism,* 2005, 52(1):283-9.
- Mena-Sánchez G, Babio N, Becerra-Tomás N, Martínez-González MÁ, Díaz-López A, Corella D, et al.; PREDIMED-PLUS investigators. Association between dairy product consumption and hyperuricemia in an elderly population with metabolic syndrome. *Nutr Metab Cardiovasc Dis.* 2020 Feb 10;30(2):214-22.
- Kontogianni MD, Chrysoshoou C, Panagiotakos DB, Tsetsekou E, Zeimbekis A, Pitsavos C, Stefanadis C. Adherence to the Mediterranean diet and serum uric acid: the ATTICA study. *Scand J Rheumatol.* 2012;41(6):442-9.
- Buzas R, Ivan V, Gheorghe-Fronea O, Morgovan AF, Ardelean M, Albulescu N, Dorobantu M, et al. Arterial Hypertension and Serum Uric Acid in Elderly-SEPHAR III Study. *Arq. Bras. Cardiol.* 2021;117(2):378-84.
- Zhou Z, Li K, Li X, Luan R, Zhou R. Independent and joint associations of body mass index, waist circumference, waist-height ratio and their changes with risks of hyperuricemia in middle-aged and older Chinese individuals: a population-based nationwide cohort study. *Nutr Metab (Lond).* 2021;18(1):62.
- World Health Organization. (WHO) Cardiovascular Diseases (CVDs). [Internet]. [Cited in 2020 ja 23] Available at: <https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-cvds>



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Relationship between Late Gadolinium Enhancement and Ventricular Repolarization Parameters in Heart Failure Patients with Reduced Ejection Fraction

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Abstract

Background: Heart failure with reduced ejection fraction (HFrEF) is a highly prevalent disease that requires repeating hospitalizations, causes significant morbidity and mortality. Therefore, early recognition of poor outcome predictors is essential for patient management.

Objective: The aim of the present study is to investigate the relationship between late gadolinium enhancement (LGE) detected by cardiac magnetic resonance (CMR) and repolarization parameters such as corrected QT (QTc) interval, Tp-e interval, frontal QRS-T angle detected by 12 lead electrocardiograph (ECG) in HFrEF.

Method: In this single-center, retrospective observational study included 97 consecutive HFrEF patients who had CMR scan. Study population was divided into two groups according to the presence of LGE. Echocardiographic and CMR measurements and demographic features were recorded. QTc intervals, Tp-e intervals, frontal QRS-T angles were calculated from the ECG. A p-value less than 0.05 was considered statistically significant.

Results: LGE was detected in 52 (53.6%) out of 97 HFrEF patients. QTc intervals ($p=0.001$), Tp-e intervals ($p<0.001$), frontal QRS-T angles ($p<0.001$) were found to be significantly higher in LGE group when compared to non-LGE group. In univariate regression analysis which was performed to investigate the predictors of LGE in HFrEF, all three repolarization parameters were reached significant values but in multivariate analysis the only repolarization parameter remained significant was Tp-e interval (OR=1.085 95% CI 1.032-1.140, $p=0.001$).

Conclusion: With the prolongation of the Tp-e interval, the presence of myocardial fibrosis which is an arrhythmogenic substrate, can be predicted in patients with HFrEF.

Keywords: Heart Failure; Gadolinium; Stroke Volume; Diagnostic, Imaging; Magnetic Resonance Spectroscopy; Electrocardiography/methods; Continuity of Patient Care/ethic.

Introduction

Heart failure (HF) is a highly prevalent disease in the general population that requires repeat hospitalizations and causes significant morbidity and mortality.^{1,2} As a consequence of these serious outcomes, HF results in a high economic burden for healthcare systems. Therefore, early recognition of poor outcome

predictors is essential for patient management. Mortality occurs commonly due to pump failure or arrhythmogenic episodes.^{3,4} Whether ischemic or nonischemic origin, patients with HF have more myocardial fibrosis than healthy subjects which is a substrate for arrhythmias and negative remodeling which gradually decreases left ventricular functions.⁵⁻⁷

Late gadolinium enhancement (LGE) from cardiac magnetic resonance (CMR) is capable of detecting tissue abnormalities, particularly myocardial fibrosis.⁸ Researchers recently discovered that, in addition to LVEF, LGE could be used as a marker of poor prognosis in patients with HF.⁹⁻¹¹

In clinical practices, ECG is widely used to predict the arrhythmogenic risk. QTc interval, Tp-e interval and QRS-T angle are ventricular repolarization parameters, recommended

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as predictors of malignant ventricular arrhythmias. Tp-e is a relatively new parameter for transmural repolarization dispersion and also related with the sudden cardiac death (SCD) risk.^{12,13} Frontal QRS-T angle defined as an angle between ventricular depolarization and repolarization directions, reflects electrical heterogeneity and abnormal changes in direction of repolarization sequence due to cardiac structural abnormalities and frontal QRS-T angle is a strong predictor of electrical instability and SCD.¹⁴⁻¹⁶

We aimed to investigate the relationship between LGE detected by CMR and repolarization parameters such as QTc interval, Tp-e interval, frontal QRS-T angle detected by 12 lead ECG in HFrEF patients and to determine which one of these parameters is more significant in this aspect.

Methods

Study population

This study included 97 HFrEF patients admitted to the cardiology clinic between January 2017 and June 2019, who had undergone CMR for various reasons (HF etiology research, viability research, EF calculation, etc.) and had an EF <40% on transthoracic echocardiography.

Data regarding patients' demographic characteristics (age, gender and body mass index), medical history [diabetes mellitus (DM), hypertension (HT), hyperlipidemia (HL) and coronary artery disease], medications [beta-blockers, angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB), spironolactone, diuretics, digoxin, statins], cardiac rhythm [sinus rhythm, atrial fibrillation, and left bundle branch block (LBBB)], echocardiographic examination results, 12-lead ECG and biochemical blood tests were recorded. The NYHA functional class of each patient was determined.

Patients who were aged <18 years or >90 years; who had a history of acute coronary syndrome or primary coronary intervention within the past 6 months; and who had hypotension, pulmonary edema, or cardiogenic shock were excluded from the study. In addition, patients with stage 4-5 chronic kidney disease (CKD); those with an active focus of infection, neurological illness severe enough to affect biochemical and hematological results, chronic obstructive pulmonary disease (COPD), malignancy or liver function impairment/liver failure were excluded.

The study was approved by the ethics committee of Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Training Research Hospital. This study was performed in accordance with the requirements of the Declaration of Helsinki.

Electrocardiography

12-lead ECG was performed at paper speed of 25 mm/second with the patient at rest in supine position. Resting heart rate was then measured from ECG data. All ECG data were scanned and transferred to personal computer and used for x400% magnification with Adobe Photoshop software (Adobe Systems, Inc., San Jose, CA, USA). ECG measurements of QTc, Tp-e intervals and

frontal QRS-T angle were performed by 2 cardiologists who were blinded to the patient's CMR data. Subjects with U wave on their ECG were excluded from the study. Average value of 3 examinations was calculated for each lead. QT interval was measured from beginning of QRS complex to end of T wave. In patients with LBBB, the formula $[QT = QTLBBB - (0.86 \times QRS_{LBBB} - 71)]$ recommended by Wang et al was used¹⁷ and QT interval was corrected by heart rate using Bazett's formula $[QT_c = QT / \sqrt{R-R \text{ interval}}]$. Tp-e interval was defined as interval from peak of T wave to end of T wave. Measurements of Tp-e interval were performed from precordial leads. Tp-e/QT ratio and Tp-e/QTc ratio were calculated from these measurements. The frontal QRS-T angle was calculated as the absolute value of the difference between the frontal plane QRS and T axes. If such a difference was more than 180°, QRS-T angle was adjusted to the minimal angle as 360° minus the absolute value of the difference between the frontal plane QRS and T axes.¹⁸ The intra-researcher and inter-researcher differences for QTc, Tp-e intervals and QRS-T angle were less than 5%.

Image acquisition

Images were acquired using 1.5 T scanners (MAGNETON Aera, Siemens, Erlangen, Germany) with full myocardial coverage. Balanced steady-state free-precession sequences were used to obtain breath-hold cine images in three long-axis planes, followed by a contiguous stack of short-axis slices from the atrioventricular ring to the apex.¹⁹ Late enhancement images were acquired 10 min after the administration of 0.1 mmol/kg intravenous gadolinium contrast agent (gadopentetate dimeglumine/gadobutrol, Bayer, Berlin, Germany) with an inversion recovery-prepared gradient-echo sequence.²⁰ Inversion times were optimised to null normal myocardium with images acquired in two orthogonal phase-encoding directions to exclude artefact.

Image analysis

Images were transferred to a workstation (Leonardo, Siemens Medical Solutions, Erlangen, Germany) for analysis. For the functional analysis, commercially available software program, Argus (Siemens Healthcare, Erlangen, Germany) was used.

CMR data analysis

The endocardial and epicardial borders were traced manually using both software systems and functional analysis was performed.

Analysis using Argus (Siemens Healthcare, Erlangen, Germany) Software for each study, the end-diastolic and end-systolic phases were determined. For the detection of each phase, the largest and narrowest diameters of the ventricular cavity at the middle of the ventricle were used. The endocardial and epicardial borders were traced manually in short axis images in both phases. The borders of the endocardium were traced by using the intensity difference between the chamber when filled with blood and the moderate intensity of the myocardium. The papillary

muscles were included in the LV volumetric analysis. While the epicardial border was being detected, the interventricular septum was included in the LV volume. The most basal slice that was surrounded by at least 50% of the myocardium with filled blood was defined as the basal segment of the left ventricle. This was included in the LV chamber volume. The apex was defined as the last slice with a visible lumen throughout the entire cardiac cycle. The end-systolic volume (ESV), end-diastolic volume (EDV) and EF were determined according to the Simpson's rule. The elapsed time from inputting of the data to obtaining the results was calculated for each patient.

CMR images were reanalyzed and documented using the 17-segment cardiac model recommended by the American Heart Association to improve standardization of the results. The left ventricle was evaluated from the short-axis images from basal, mid, and apical segments. The basal and mid cavity were divided into 6 equal segments: anterior, anteroseptal, inferoseptal, inferior, inferolateral, and anterolateral. The apical segment was divided into 4 segments: anterior, septal, inferior, and lateral. The apical cap was termed the apex and constituted the 17th segment. The contrast-enhanced images were analyzed visually by two experienced observers who were blinded to other MRI, echocardiographic, and clinical data. Late gadolinium enhancement was rated by visual assessment, and each segment was graded on a 2-point scale (segmental fibrosis score; 0 = absence of late gadolinium enhancement, 1 = presence of late gadolinium enhancement), using the method of Kaandorp et al. because of the frequency of linear and patchy enhancement in patients with nonischemic dilated cardiomyopathy.

Statistical analysis

Data was analyzed using the Statistical Package for the Social Sciences, version 24.0 (SPSS Inc., Chicago, Illinois, USA). Whether the variables show normal distribution; was evaluated using visual (histograms, probability curves) and analytical (Kolmogorov-Smirnov) methods. Continuous variables showing normal distribution were mean $\pm$ standard deviation (SD), continuous variables not showing normal distribution were expressed as median (interquartile range) and categorical variables as percentage (%). Continuous variables such as QTc, Tp-e interval and QRS-T angle were evaluated using unpaired Student's t-test and the Mann-Whitney U-test between the two groups. Chi-Square or Fisher exact test were used to compare categorical variables. The correlation between QTc, Tp-e interval and QRS-T angle and the other continuous variables were identified using Pearson or Spearman tests. Logistic regression analysis was performed to determine the independent predictors of LGE presence with CMR in HFrEF patients. Firstly, univariate logistic regression analysis was performed, parameters which were significant in this analysis ($p < 0.05$) were included in the multivariate logistic regression analysis. Receiver operator characteristic (ROC) curve analysis was carried out to determine the cutoff values. Significant prediction was accepted when the area under the ROC curve was more than 0.5; $p < 0.05$ was accepted as statistically significant.

Results

The mean age of the 97 HFrEF patients was 54.8 ± 13.8 . Our study population included 75 (77.3%) male and 22 (22.7%) female patients. We divided our patients into two groups according to the presence of LGE with CMR. LGE was detected in 52 (53.6%) patients. Basal demographics and laboratory results for both groups were in Table 1.

Comparison of parameters calculated from ECG and variables detected by CMR were shown in Table 2. Reflection of repolarization on ECG such as QT, QTc, Tp-e interval, Tp-e/QTc ratio and QRS-T angle were significantly higher in LGE group. In LGE group, mean 6.48 ± 3.54 enhanced segments were detected.

The correlation analysis of QTc, Tp-e interval and QRS-T angle with other variables was shown in Table 3. There were poor correlations between QTc interval and LVEF, LVEDD and LVESD and also there were poor correlations between QRS-T angle and LVEF, LVEDD, LVESD, LVEDV index and LVESV index. Although there wasn't any correlation between Tp-e and CMR parameters show cardiac structures and functions, the best correlation coefficient between LGE segment number was obtained with Tp-e interval. There were medium correlation with Tp-e interval ($r=0.564$, $p<0.001$) and poor correlations with QTc interval ($r=0.262$, $p=0.009$) and QRS-T angle ($r=0.369$, $p<0.001$). Another finding of our study, there were various degrees of correlations between QTc, Tp-e interval, QRS-T angle themselves.

Univariate regression analysis was performed to determine the variables which predict the LGE with CMR in HFrEF patients (Table 4). Age, male sex, hyperlipidemia, coronary artery disease, QTc interval, Tp-e interval, QRS-T angle and plasma creatinine level were found to be significant. With these variables four different models were generated and multivariate regression analysis was done. In the first model all three QTc, Tp-e interval and QRS-T angle and other significant variables were included (Table 4). In other three models, these parameters were evaluated separately (Table 5). In first model male sex ($p=0.032$), coronary artery disease ($p=0.009$), plasma creatinine level ($p=0.037$) and Tp-e interval [$p=0.001$, OR (95% CI) = 1.085 (1.032-1.140)] remained significant and they were independent predictors of LGE presence. In this model QTc interval ($p=0.185$) and QRS-T angle ($p=0.944$) lost their significance. In the model which evaluated only the QTc interval, QTc interval ($p=0.007$) was also found to be an independent predictor as well as male sex, coronary artery disease, plasma creatinine level. In the model which evaluated only the Tp-e interval, Tp-e interval remained significant ($p<0.001$) as in first model. In the model which evaluated only the QRS-T angle, male sex and coronary artery disease were found to be independent predictors but QRS-T angle couldn't reach the significance ($p=0.058$).

ROC curves for QTc, Tp-e interval and QRS-T angle were generated for LGE presence with CMR in HFrEF patients (Figure 1). Although there is a need for confirmation with prospective studies, according to the ROC curves we obtained, the best QTc interval cut off value was 460.5 ms, Tp-e interval cut off value was 101.5 ms, and QRS-T angle cut off value was

110 degrees in the determination of HFrEF patients with LGE. When the patients were divided into two groups according to the Tp-e cut off which had the best AUC value, there were 54 patients (55.7%) in Tp-e $\leq$ 101.5 group, 43 patients (44.3%) in Tp-e>101.5 group. In Tp-e>101.5 group, patients with LGE ratio were significantly higher than other group (Figure 2). Similar to these findings, LGE segment numbers median values were significantly higher [5.0 (3.0-9.0) vs 0.0 (0.0-2.25), p<0.001] in Tp-e>101.5 group.

Discussion

In our study, we stated significantly higher QTc interval, Tp-e interval and QRS-T angle in HFrEF patients with LGE by CMR when compared to HFrEF patients without LGE. Also in correlation analysis, it was seen that the best correlation coefficients were found between CMR measurements which show cardiac structure and function and QRS-T angle; number of left ventricular segments with LGE and Tp-e intervals. In multivariate regression analysis which was performed by different models, Tp-e interval was found to be the best

parameter within three parameters to predict the LGE presence in HFrEF patients. Also, Tp-e interval had the highest AUC value in ROC analysis performed for the LGE presence.

HF patients were divided into three groups according to the EF in latest European Society of Cardiology (ESC) guideline published in 2016. Group with EF under 40% was classified as HFrEF, group with EF 50% and more was classified as preserved EF HF (HFpEF), group with EF 40–49% was classified as mid-range EF HF (HFmrEF).¹ The highest mortality rates are seen in HFrEF group.²¹ One of the important reasons of mortality is malignant arrhythmias. Myocardial fibrosis which is a substrate for these arrhythmias can be detected with LGE by CMR.⁸ In literature there are several studies showed the relationship between LGE presence and adverse cardiovascular events in HF patients.^{9-11,22}

Liu et al. showed the relationship between LGE amount detected by CMR and major adverse cardiac events (MACE) in 84 stage C or D HF patients whether ischemic or not [p = 0.022, HR (95% CI) = 1.045 (1.001-1.084)].¹¹ Shi et al.²² stated in their meta analysis which contained five studies and 545 dilated cardiomyopathy (DCM) patients,

Table 1 – Baseline demographic, clinical, and laboratory characteristics of the study groups

Variable	HFrEF without LGE (n=45)	HFrEF with LGE (n=52)	p-value
Age, years	50.2 $\pm$ 15.6	58.7 $\pm$ 10.7	0.002
Male, n (%)	26 (57.8%)	49 (94.2%)	<0.001
Body mass index, kg/m ²	27.7 $\pm$ 4.2	26.6 $\pm$ 3.7	0.171
Diabetes mellitus, n (%)	11 (24.4%)	17 (32.7%)	0.371
Hypertension, n (%)	40 (88.9%)	46 (88.5%)	0.947
Coronary artery disease, n (%)	20 (44.4%)	45 (86.5%)	<0.001
Hyperlipidemia, n (%)	20 (44.4%)	36 (69.2%)	0.014
Heart rate, bpm	78.2 $\pm$ 18.9	76.8 $\pm$ 16.1	0.691
Atrial fibrillation, n (%)	5 (11.1%)	3 (5.8%)	0.466
LBBB, n (%)	8 (17.8)	8 (15.4)	0.751
NYHA class I, n (%)	10 (22.2%)	9 (17.3%)	0.543
NYHA class II, n (%)	32 (71.1%)	36 (69.2%)	0.840
NYHA class III, n (%)	3 (6.7%)	7 (13.5%)	0.331
Creatinine, mg/dL	0.80 (0.70-0.90)	1.10 (0.80-1.40)	<0.001
Glomerular filtration rate, ml/dk	91.3 $\pm$ 25.1	71.9 $\pm$ 26.3	0.001
Beta blockers, n (%)	42 (93.3%)	50 (96.2%)	0.661
ACEi or ARB, n (%)	40 (88.9%)	42 (80.8%)	0.270
Statins, n (%)	16 (35.6%)	36 (69.2%)	0.001
Diuretics, n (%)	25 (55.6%)	31 (59.6%)	0.686
Spironolactone, n (%)	31 (68.9%)	29 (55.8%)	0.185
Digoxin, n (%)	5 (11.1%)	2 (3.8%)	0.244
Diltiazem, n (%)	3 (6.7%)	2 (3.8%)	0.661
Verapamil, n (%)	0 (0.0%)	1 (1.9%)	1.0

Data are presented as percentage, mean $\pm$ standard deviation or median (interquartile range). HFrEF: heart failure with reduced ejection fraction; LGE: late gadolinium enhancement; LBBB: left bundle branch block; NYHA: New York Heart Association; ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker.

Table 2 – Comparison of study groups in terms of some parameters calculated from CMR and ECG

Variable	HFrEF without LGE (n=45)	HFrEF with LGE (n=52)	p-value
QRS duration, ms	103.6±26.2	101.4±20.9	0.650
QT interval, ms	391.6±53.3	418.9±50.3	0.011
QTc interval, Bazett	438.2±42.3	467.3±42.9	0.001
Tp-e interval, ms	91.4±12.3	108.3±14.6	<0.001
Tp-e/QT ratio	0.235±0.034	0.261±0.042	0.001
Tp-e/QTc ratio	0.208±0.025	0.233±0.038	<0.001
QRS-T angle, degree	61 (28-112)	136 (82-159)	<0.001
LVEF, %	30.9±10.7	28.8±8.3	0.275
LVEDD, mm	57.3±8.8	57.7±7.7	0.826
LVESD, mm	45.9±10.5	45.6±8.7	0.891
LVEDV index, mL/m ²	110.1±40.8	113.9±36.7	0.641
LVESV index, mL/m ²	73.8±40.1	77.1±31.1	0.661
Number of LV segments with LGE		6.48±3.54	

Data are presented as percentage, mean ± standard deviation or median (interquartile range). HFrEF: heart failure with reduced ejection fraction; LGE: late gadolinium enhancement; LVEF: left ventricular ejection fraction; LVEDD: left ventricular end diastolic diameter; LVESD: left ventricular end systolic diameter; LVEDV: left ventricular end diastolic volume; LVESV: left ventricular end systolic volume; LV: left ventricle.

Table 3 – Correlation analysis of QTc, Tp-e interval and QRS-T angle with other variables

Variable	QTc interval		Tp-e interval		QRS-T angle	
	r	p	r	p	r	p
Age	0.204	0.045	0.309	0.002	0.396	<0.001
Body mass index	-0.001	0.990	-0.019	0.860	-0.014	0.896
NYHA class	0.022	0.831	0.051	0.657	0.020	0.846
Creatinine	0.149	0.165	0.272	0.010	0.389	<0.001
Glomerular filtration rate	-0.184	0.087	-0.294	0.005	-0.412	<0.001
LVEF	-0.328	0.001	0.028	0.788	0.341	0.001
LVEDD	0.256	0.013	0.089	0.398	0.442	<0.001
LVESD	0.269	0.009	0.080	0.446	0.401	<0.001
LVEDV index	0.149	0.157	0.060	0.568	0.280	0.007
LVESV index	0.171	0.103	-0.015	0.890	0.333	0.001
Number of LV segments with LGE	0.262	0.009	0.564	<0.001	0.369	<0.001
QTc interval			0.338	0.001	0.505	<0.001
Tp-e interval	0.338	0.001			0.368	<0.001
QRS-T angle	0.505	<0.001	0.368	<0.001		

NYHA: New York Heart Association; LVEF: left ventricular ejection fraction; LVEDD: left ventricular end diastolic diameter; LVESD: left ventricular end systolic diameter; LVEDV: left ventricular end diastolic volume; LVESV: left ventricular end systolic volume; LV: left ventricle.

LGE presence was the predictor of high cardiovascular mortality [$p=0.03$, OR (95% CI) = 2.67 (1.12-6.35)], aborted SCD [$p=0.007$, OR (95% CI) = 5.26 (1.57-17.55)] and hospitalization due to HF [$p<0.001$, OR (95% CI) = 3.91 (1.99-7.69)].²² In Duan et al.⁹ meta analysis which evaluated 13 studies and included 1675 DCM patients,

investigated the effects of LGE presence on MACE. In these 13 studies LGE presence ratios were between 18% and 71%. Results of analysis showed that LGE was associated with all cause mortality [$p<0.001$, OR (95% CI) = 3.43 (2.26-5.22)], cardiac death [$p<0.001$, OR (95% CI) = 3.65 (1.80-7.40)], hospitalization due to HF [$p=0.001$, OR (95% CI) =

Table 4 – Univariate and multivariate regression analysis to determine the predictability of LGE in HF patients

Variable	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p	OR (95% CI)	p
Age	1.051 (1.016-1.086)	0.004	0.960 (0.901-1.023)	0.209
Male	11.936 (3.230-44.114)	<0.001	6.348 (1.172-34.392)	0.032
Body mass index	0.927 (0.831-1.034)	0.173		
Diabetes mellitus	1.501 (0.615-3.668)	0.373		
Hypertension	0.958 (0.272-3.379)	0.947		
Hyperlipidemia	2.812 (1.224-6.464)	0.015	0.484 (0.105-2.226)	0.352
Coronary artery disease	8.036 (2.986-21.624)	<0.001	12.355 (1.851-82.445)	0.009
LBBB	0.841 (0.288-2.459)	0.752		
Atrial fibrillation	0.490 (1.110-2.176)	0.348		
QRS duration	0.996 (0.979-1.013)	0.646		
QTc interval	1.016 (1.006-1.027)	0.002	1.011 (0.995-1.028)	0.185
Tp-e interval	1.099 (1.055-1.144)	<0.001	1.085 (1.032-1.140)	0.001
QRS-T angle	1.017 (1.008-1.026)	<0.001	0.999 (0.984-1.015)	0.944
LVEF	0.976 (0.935-1.019)	0.273		
LVEDV index	1.003 (0.992-1.013)	0.637		
LVESV index	1.003 (0.991-1.013)	0.657		
Creatinine	18.678 (3.460-100.82)	0.001	12.501 (1.170-133.63)	0.037

OR: odds ratio; CI: confidence interval; LBBB: left bundle branch block; LVEF: left ventricular ejection fraction; LVEDV: left ventricular end diastolic volume; LVESV: left ventricular end systolic volume.

Table 5 – Multivariate regression analysis to determine the independent predictor of LGE in HF patients

Variable	Multivariate analysis					
	QTc interval		Tp-e interval		QRS-T angle	
	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Age	0.974 (0.921-1.030)	0.359	0.964 (0.905-1.027)	0.252	0.980 (0.927-1.036)	0.469
Male	6.393 (1.468-27.84)	0.013	7.405 (1.383-39.64)	0.019	7.369 (1.617-33.58)	0.010
Hyperlipidemia	0.643 (0.169-2.452)	0.518	0.513 (0.118-2.226)	0.626	0.727 (0.202-2.621)	0.398
Coronary artery disease	11.676 (2.43-56.09)	0.002	10.989 (1.89-63.69)	0.008	7.227 (1.605-32.55)	0.010
Creatinine	9.551 (1.548-58.92)	0.015	10.892 (1.26-94.01)	0.030	5.299 (0.947-29.66)	0.058
QTc, Tp-e, QRS-T angle	1.018 (1.005-1.032)	0.007	1.097 (1.045-1.152)	<0.001	1.010 (1.000-1.021)	0.058

OR: odds ratio; CI: confidence interval.

2.87 (1.53-5.39)], major arrhythmic events [$p < 0.001$, OR (95% CI) = 4.24 (2.95-6.08)] and SCD [$p < 0.001$, OR (95% CI) = 3.33 (1.80-6.17)].⁹

Although CMR gives great informations to the clinicians, it has some limitations. CMR is not widely available, CMR interpretations need speciality, costs are high and safety for patients with metallic implants is still debated, can be less reliable in tachyarrhythmic patients, claustrophobia and contrast agent gadolinium usage in severe renal failure patients are other important limitations. So it can be a great convenience to predict myocardial fibrosis with repolarization

parameters calculated from ECG which is easily available and interpretable. We built our study on this aim and we investigated whether QTc interval, Tp-e interval and frontal QRS-T angle are related with LGE presence and which one these parameters can be a better predictor.

QT and QTc intervals are the well known and largely used parameters of myocardial repolarization and are related to ventricular arrhythmia and cardiovascular mortality.²³ In some studies it is shown that the duration between peak and end-point of T wave (Tp-e interval) is a new marker to evaluate the ventricular repolarization and because it isn't

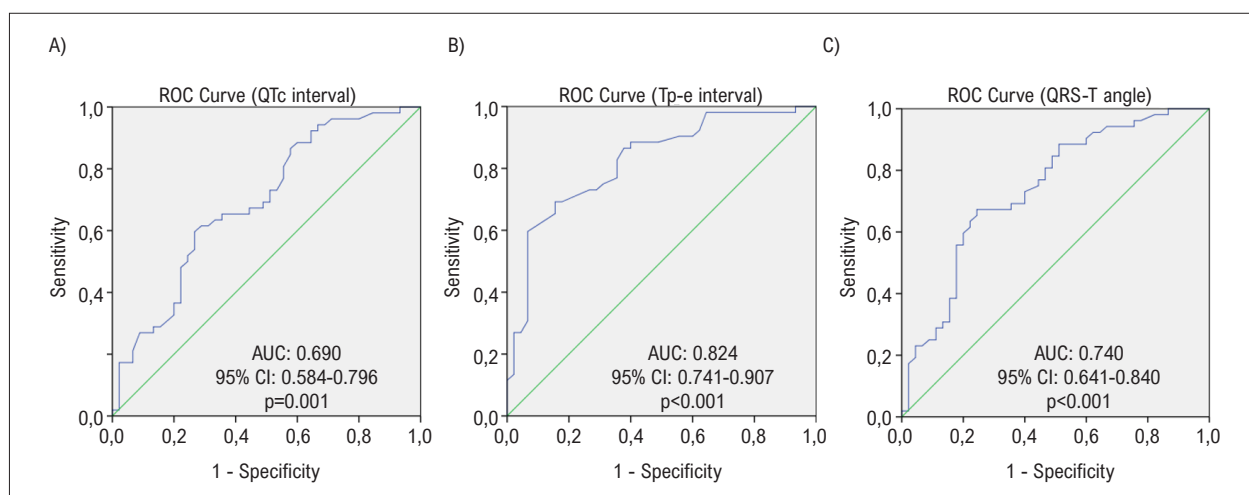


Figure 1 – Receiver operating characteristics curve showing the distinguishing ability of the QTc, Tp-e interval and QRS-T angle for LGE presence with CMR in HFrEF.

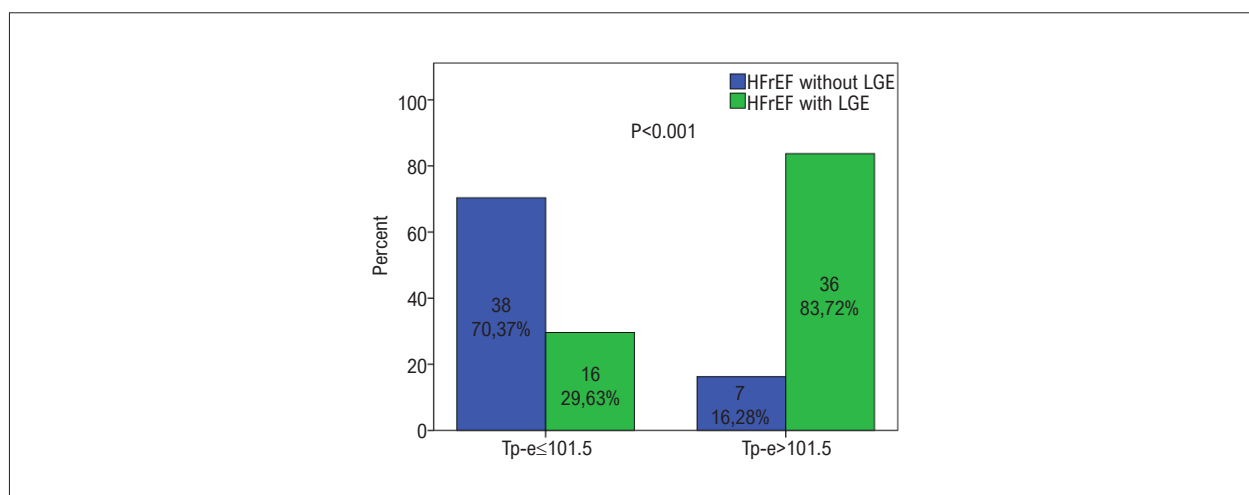


Figure 2 – Comparison of LGE rates in low and high Tp-e groups. HFrEF: Heart failure with reduced ejection fraction; LGE: late gadolinium enhancement.

affected by heart rate variability, Tp-e interval can be more reliable to evaluate the ventricular repolarization. Moreover, Tp-e/QT and Tp-e/QTc ratio were shown to be a sensitive index of ventricular repolarization and arrhythmogenesis, as it provided an estimate of the dispersion of repolarization relative to the total duration of repolarization.^{24,25} Another new marker is spatial QRS-T angle. It is defined as angle difference between ventricular depolarization (QRS wave) direction and ventricular repolarization (T wave) direction.¹⁸ But calculation of the spatial QRS angle is too complicated and needs advanced computer programming.²⁶ Conversely frontal QRS angle can be measured easily from automatic reports of ECG devices and has a good correlation with spatial QRS angle in risk stratification.²⁷ That's reason why we used frontal QRS-T angle in our study.

Previous studies revealed in HF patients repolarization parameters were associated with all cause mortality, cardiac

death, hospitalization due to HF, SCD and proper shocking in patients with ICD.²⁸⁻³¹ Best of our knowledge there isn't any study investigating the relation of LGE with CMR and repolarization parameters so we aimed to meet the deficit. In our study, similar to the literature LGE ratio was 53.6% in HFrEF patients. All the repolarization parameters were significantly higher in patients with LGE. In univariate analysis all three parameters predicted LGE presence separately. In multivariate analysis firstly a model was generated which included all three repolarization parameters and the other significant variables. In this model only Tp-e interval from repolarization parameters remained significant and found to be an independent predictor of LGE presence [$p=0.001$, OR (95% CI) = 1.085 (1.032-1.140)]. With a different point of view, when we inserted the parameters separately to the models QTc interval and Tp-e interval remained significant but the significance level of Tp-e interval was better than the

QTc interval ($p < 0.001$ vs $p = 0.007$). On the other hand Tp-e interval had medium correlation ($r = 0.564$, $p < 0.001$) with number of LV segments with LGE and other two parameters had poor correlations. As a result in our study Tp-e interval was found to be more related with the LGE in HFrEF patients when compared to other two repolarization parameters. Risk estimation of MACE in HFrEF patients can be possible with this parameter which can be easily measured from standard 12 lead ECG.

Our study had some limitations. First of all this study designed as a retrospective, single center and contained a small study population. No healthy volunteers were included to the study. There wasn't any clinical follow up data. HF patients were included to the study independent from the etiology. Evaluation of the patients separately according to the ischemic or non ischemic etiology could give more information. Our CMR data is limited in our study. LGE is only given as presence-absence and the number of segments showing involvement. The availability of additional data showing scar transmural, percentage of LV scar and regional strain could enrich the study. Finally, in this study, cut-off values of repolarization parameters were developed using ROC curves. Therefore, our results must be interpreted carefully until they are confirmed in subsequent studies.

Conclusion

In our study we found higher QTc interval, Tp-e interval and frontal QRS-T angle in HFrEF patients with LGE by CMR when compared to HFrEF patients without LGE. Tp-e interval was the best independent predictor of LGE presence. This information with the prolongation of the Tp-e interval allows us to predict

the presence of myocardial fibrosis which is an arrhythmogenic substrate, in patients with HFrEF. As a result, we believe with a standard 12 lead ECG which is easily available and interpreted, it can be possible to predict the risk of adverse cardiovascular events in HFrEF patients and also we think decrease in MACE ratios can be obtained with intensive medical therapy, close follow-ups and ICD therapy. We know there should be more prospective, randomized, large populated studies to support our opinions.

Author Contributions

Conception and design of the research: Demir AR, Celik O, Ustündağ S; Acquisition of data: Demir AR, Ustündağ S, Avcı Y, Demirci G; Analysis and interpretation of the data: Demir AR, Uygur B, Somuncu MU; Statistical analysis: Demir AR; Writing of the manuscript: Demir AR, Yilmaz E; Critical revision of the manuscript for intellectual content: Kahraman S, Ertürk M.

Potential Conflict of Interest

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

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References

1. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, et al (2016). ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail*. 2016;18(8),891-975.
2. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Colvin MM, et al. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *J Am Coll Cardiol*. 2017;70(6),776-803.
3. Goldstein S, Hjalmarson A. The mortality effect of metoprolol CR/XL in patients with heart failure: results of the MERIT-HF Trial. *Clin Cardiol*. 1999;22,V30-5.
4. Narang R, Cleland JGF, Erhardt L, Ball SG, Coats, AJS, Cowley AJ, et al. Mode of death in chronic heart failure: a request and proposition for more accurate classification. *Eur Heart J*. 1996;17(9),1390-403.
5. Bernardo BC, Weeks KL, Pretorius L, McMullen JR. Molecular distinction between physiological and pathological cardiac hypertrophy: experimental findings and therapeutic strategies. *Pharmacol Therap*. 2010;128(1),191-227.
6. Piek A, De Boer RA, Silljé HHW. The fibrosis-cell death axis in heart failure. *Heart Fail Rev*. 2016;21(2),199-211.
7. Weeks KL, McMullen JR. The athlete's heart vs. the failing heart: can signaling explain the two distinct outcomes?. *Physiology*. 2011;26(2),97-105.
8. Nanjo S, Yoshikawa K, Harada M, Inoue Y, Namiki A, Nakano H, et al. Correlation between left ventricular diastolic function and ejection fraction in dilated cardiomyopathy using magnetic resonance imaging with late gadolinium enhancement. *Circulation*. 2009;73(10),1939-44.
9. Duan, X, Li J, Zhang Q, Zeng Z, Luo Y, Jiang J, et al. Prognostic value of late gadolinium enhancement in dilated cardiomyopathy patients: a meta-analysis. *Clin Radiol*. 2015;70(9),999-1008.
10. Becker MA, Cornel JH, Van de Ven PM, van Rossum AC, Allaart CP, Germans, T. The prognostic value of late gadolinium-enhanced cardiac magnetic resonance imaging in nonischemic dilated cardiomyopathy: a review and meta-analysis. *JACC: Cardiovasc Imag*. 2019;11(9),1274-84.
11. Liu T, Ma X, Liu W, Ling S, Zhao L, Xu L, et al. Late gadolinium enhancement amount as an independent risk factor for the incidence of adverse cardiovascular events in patients with stage C or D heart failure. *Front Physiol*. 2016;7,484.
12. Taşolar H, Ballı M, Çetin M, Otlı YÖ, Altun B, Bayramoğlu A. Effects of the Coronary Collateral Circulation on the Tp-e Interval and Tp-e/QT Ratio in Patients with Stable Coronary Artery Disease. *Ann Noninvas Electrocard* 2015;20(1),53-61.
13. Kors JA, van Eck HJR, van Herpen G. The meaning of the Tp-Te interval and its diagnostic value. *J Electrocard*. 2008;41(6),575-80.

14. Aro AL, Huikuri HV, Tikkanen JT, Junttila MJ, Rissanen HA, Reunanen A, et al. QRS-T angle as a predictor of sudden cardiac death in a middle-aged general population. *Europace*. 2011;14(6):872-6.
15. Chua KC, Teodorescu C, Reinier K, Uy-Evanado A, Aro AL, Nair SG, et al. Wide QRS-T Angle on the 12-Lead ECG as a Predictor of Sudden Death Beyond the LV Ejection Fraction. *J Cardiovasc Electrophys*. 2016;27(7):833-9.
16. Borleffs CJW, Scherptong RW, Man SC, van Welsenes GH, Bax JJ, van Erven L, et al. Predicting ventricular arrhythmias in patients with ischemic heart disease: clinical application of the ECG-derived QRS-T angle. *Circulation: Arrhythm Electrophysiol*. 2009;2(5):548-54.
17. Wang B, Zhang LI, Cong P, Chu H, Liu Y, Liu J, et al. A new formula for estimating the true QT interval in left bundle branch block. *J Cardiovasc Electrophys*. 2017;28(6):684-9.
18. Oehler A, Feldman T, Henrikson CA, Tereshchenko LG. QRS-T angle: a review. *Ann Noninvas Electr*. 2014;19(6):534-42.
19. Kramer CM, Barkhausen J, Flamm SD, Kim RJ, Nagel E. Standardized cardiovascular magnetic resonance imaging (CMR) protocols, society for cardiovascular magnetic resonance: board of trustees task force on standardized protocols. *J Cardiovasc Magn Reson*. 2008;10(1):35.
20. Simonetti OP, Kim RJ, Fieno DS, Hillenbrand HB, Wu E, Bundy JM, et al. An improved MR imaging technique for the visualization of myocardial infarction. *Radiology*. 2001;218(1):215-23.
21. Lam CS, Solomon SD. The middle child in heart failure: heart failure with mid-range ejection fraction (40–50%). *Eur Heart J*. 2014;16(10):1049-55.
22. Shi HW, Pu P, Deng W, Zhou H, Bian ZY, Shen DF, et al. Prognostic value of late gadolinium enhancement in dilated cardiomyopathy patients. A meta-analysis. *Saudi Med J*. 2016;34(7):719.
23. Algra A, Tijssen JG, Roelandt JR, Pool J, Lubsen J. QTc prolongation measured by standard 12-lead electrocardiography is an independent risk factor for sudden death due to cardiac arrest. *Circulation*. 1991;83(6):1888-94.
24. Antzelevitch C, Sicouri S, Di Diego JM, Burashnikov A, Viskin S, Shimizu W, et al. Does Tpeak–Tend provide an index of transmural dispersion of repolarization?. *Heart Rhythm*. 2007;4(8):1114-6.
25. Gupta P, Patel C, Patel H, Narayanaswamy S, Malhotra B, Green JT, et al. Tp-e/QT ratio as an index of arrhythmogenesis. *Journal of electrocardiology*. 2008;41(6):567-574.
26. Okin PM. Electrocardiography in women: taking the initiative. *Circulation*. 2006;113(4):464-6.
27. Zhang ZM, Prineas RJ, Case D, Soliman EZ, Rautaharju PM, ARIC Research Group. Comparison of the prognostic significance of the electrocardiographic QRS/T angles in predicting incident coronary heart disease and total mortality (from the atherosclerosis risk in communities study). *Am J Cardiol*. 2007;100(5):844-9.
28. Zhu TY, Teng SE, Chen YY, Liu SR, Meng SR, Peng J. Correlation of Tp-e interval and Tp-e/QT ratio with malignant ventricular arrhythmia in patients with implantable cardioverter-defibrillator for primary prevention. *Nan fang yi ke da xue xue bao=J South Med Univ*. 2016;36(3):401-4.
29. Sen Ö, Yilmaz S, Sen F, Balci KG, Akboga MK, Yayla C, et al. T-peak to T-end Interval Predicts Appropriate Shocks in Patients with Heart Failure Undergoing Implantable Cardioverter Defibrillator Implantation for Primary Prophylaxis. *Ann Noninvasa Electrol*. 2016.
30. Gotsman I, Shauer A, Elizur Y, Zwas DR, Lotan C, Keren A. Temporal changes in electrocardiographic frontal QRS-T angle and survival in patients with heart failure. *PloS One*. 2018;13(3):e0194520.
31. Li SN, Zhang XL, Cai GL, Lin RW, Jiang H, Chen JZ, et al. Prognostic sMed J. Significance of frontal QRS-T angle in patients with idiopathic dilated cardiomyopathy. *Chin*. 2016;129(16): 1904.



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Myocardial Scar and Ventricular Repolarization on the electrocardiogram: Insights from Cardiac Magnetic Resonance Imaging

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Short Editorial related to the article: Relationship between Late Gadolinium Enhancement and Ventricular Repolarization Parameters in Heart Failure Patients with Reduced Ejection Fraction

Myocardial fibrosis is a final common feature of most inflammatory pathway and is frequently seen in patients with heart failure with reduced ejection fraction (HFrEF).^{1,2} Myocardial scar, detected by contrast enhanced magnetic resonance imaging (ce-MRI), has been shown to be a predictor of prognosis and sudden cardiac death in patients with HFrEF.³⁻⁶ Cardiac MRI has emerged as a non-invasive gold standard for the assessment of scar and risk prediction of ventricular arrhythmias.^{3,5,7,8} Nevertheless, cardiac MRI can be time consuming, expensive, and not easily available.

The 12-lead surface electrocardiogram (ECG) is a simple and inexpensive diagnostic tool that is widely used in clinical practice for the diagnosis of cardiac arrhythmias. The ECG waveform is the expression of the transmembrane action potentials and is composed of two distinct processes: depolarization and repolarization.⁹ Ventricular repolarization is a complex electrical phenomenon which in clinical practice is measured from the beginning of the QRS complex to the end of the T-wave.¹⁰ Cardiac structural and electrical changes may cause action potential abnormalities, affecting the refractory period and thus favoring the onset of ventricular arrhythmias.¹⁰

In this issue of the *Arquivos Brasileiros de Cardiologia*, Erturk et al.¹¹ conducted an observational, retrospective study evaluating the relationship between myocardial scar by ce-MRI and several electrocardiographic parameters of ventricular repolarization in patients with HFrEF. The authors observed prolonged measurements of QTc interval, Tp-e interval, and frontal QRS-T angle in patients with HFrEF who exhibited myocardial scar on ceMRI compared to those who did not.

Based on multivariable analysis, Tp-e interval was the best parameter to predict the presence of myocardial scar. The authors concluded that it is possible to predict myocardial scar in HFrEF using ECG parameters.¹¹

There are limited reports concerning the relationship between the presence of myocardial scar and changes in the

ECG. In experimental models, the induction of subendocardial scar formation has been shown to prolong repolarization time of the M cells,^{9,12} which determines the QT interval. Previous studies have shown a strong association between the presence of subendocardial scar and the abnormal ventricular repolarization in patients with coronary artery disease.¹³ Interestingly, community-based cardiac MRI studies have also demonstrated that the presence of subclinical scar detected by ceMRI was associated with increased mortality.¹⁴ Therefore, abnormal ventricular repolarization detected by ECG may be useful in predicting subclinical myocardial scar and identifying high risk patients.

Although the study presents encouraging results that add important information to prior reports,^{11,13,15} it has several limitations, including the small sample size, single-center patient selection and the retrospective and observational design. Large prospective studies are needed to validate the ventricular repolarization parameters proposed here. The investigators established a solid basis of information that will move forward the electrocardiography field in future studies.

This study, Erturk et al.¹¹ also highlights the intimate relationship between myocardial fibrosis and disturbances in electrical conduction. There has been a substantial effort in understanding scar composition and related electrical instability.^{3,5,7} It is well known that areas of scarred tissue exhibit regions of slow conduction that favor reentry circuits and predispose to ventricular tachycardia. However, the underlying mechanism that yield ventricular fibrillation is less clear. Electrical instability is rarely the consequence of a single abnormality but rather a dynamic process involving a group of factors that together lead to a fatal event. Consequently, new methods incorporating different modalities are needed to characterize ventricular electrical instability. The current study motivates the development of larger, prospective study to evaluate the use of ECG for screening of myocardial scar and consequent evaluation of ventricular arrhythmia risk.

Keywords

Endomyocardial Fibrosis; Heart Failure; Stroke Volume; Prognosis; Death Sudden, Cardiac; Electrocardiography/methods; Magnetic Resonance Spectroscopy/methods.

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References

1. Macedo R, Schmidt A, Rochitte CE, Lima JAC, Bluemke DA. MRI to assess arrhythmia and cardiomyopathies [Internet]. Vol. 24, *Journal of Magnetic Resonance Imaging*. 2006;24(6):1197-206. doi.org/10.1002/jmri.20739
2. Mello RP de, Szarf G, Schwartzman PR, Nakano EM, Espinosa MM, Szejnfeld D, et al. Delayed enhancement cardiac magnetic resonance imaging can identify the risk for ventricular tachycardia in chronic Chagas' heart disease. *Arq Bras Cardiol*. 2012 May;98(5):421-30.
3. Mewton N, Liu CY, Croisille P, Bluemke D, Lima JAC. Assessment of myocardial fibrosis with cardiovascular magnetic resonance. *J Am Coll Cardiol*. 2011 Feb 22;57(8):891-903.
4. Boyé P, Abdel-Aty H, Zacharzowsky U, Bohl S, Schwenke C, van der Geest RJ, et al. Prediction of life-threatening arrhythmic events in patients with chronic myocardial infarction by contrast-enhanced CMR. *JACC Cardiovasc Imaging*. 2011 Aug;4(8):871-9.
5. Schmidt A, Azevedo CF, Cheng A, Gupta SN, Bluemke DA, Foo TK, et al. Infarct tissue heterogeneity by magnetic resonance imaging identifies enhanced cardiac arrhythmia susceptibility in patients with left ventricular dysfunction. *Circulation*. 2007 Apr 17;115(15):2006-14.
6. Desjardins B, Crawford T, Good E, Oral H, Chugh A, Pelosi F, et al. Infarct architecture and characteristics on delayed enhanced magnetic resonance imaging and electroanatomic mapping in patients with postinfarction ventricular arrhythmia. *Heart Rhythm*. 2009 May;6(5):644-51.
7. Nazarian S, Bluemke DA, Lardo AC, Zviman MM, Wu KC, Watkins S, et al. Magnetic resonance assessment of the substrate for inducible ventricular tachycardia in patients with non-ischemic dilated cardiomyopathy. *Heart Rhythm*. 2005 May;2(5):S81.
8. de Haan S, Meijers TA, Knaapen P, Beek AM, van Rossum AC, Allaart CP. Scar size and characteristics assessed by CMR predict ventricular arrhythmias in ischaemic cardiomyopathy: comparison of previously validated models. *Heart*. 2011 Dec;97(23):1951-6.
9. Yan G-X, Lankipalli RS, Burke JF, Musco S, Kowey PR. Ventricular repolarization components on the electrocardiogram. *J Am Coll Cardiol*. 2003 Aug;42(3):401-9.
10. Monitillo F, Leone M, Rizzo C, Passantino A, Iacoviello M. Ventricular repolarization measures for arrhythmic risk stratification. *World J Cardiol*. 2016 Jan 26;8(1):57-73.
11. Demir AR, Celik O, Ustündağ S, Uygur B, Somuncu MU, Yılmaz E, et al. Relação entre o Realce Tardio pelo Gadolínio e os Parâmetros de Repolarização Ventricular em Pacientes com Insuficiência Cardíaca com Fração de Ejeção Reduzida. *Arq Bras Cardiol*. 2021; 117(4):678-687.
12. Yan GX, Antzelevitch C. Cellular basis for the normal T wave and the electrocardiographic manifestations of the long-QT syndrome. *Circulation*. 1998 Nov 3;98(18):1928-36.
13. Scott PA, Rosengarten JA, Shahed A, Yue AM, Murday DC, Roberts PR, et al. The relationship between left ventricular scar and ventricular repolarization in patients with coronary artery disease: insights from late gadolinium enhancement magnetic resonance imaging. *Europace*. 2013 Jun;15(6):899-906.
14. Kwong RY, Chan AK, Brown KA, Chan CW, Glenn Reynolds H, Tsang S, et al. Impact of Unrecognized Myocardial Scar Detected by Cardiac Magnetic Resonance Imaging on Event-Free Survival in Patients Presenting With Signs or Symptoms of Coronary Artery Disease [Internet]. Vol. 113, *Circulation*. 2006.113(23): 2733-43. doi.org/10.1161/circulationaha.105.570648
15. Mewton N, Strauss DG, Rizzi P, Verrier RL, Liu CY, Tereshchenko LG, et al. Screening for cardiac magnetic resonance scar features by 12-lead ECG, in patients with preserved ejection fraction. *Ann Noninvasive Electrocardiol*. 2016;21(1):49-59. Doi:10.1111/anec.12264



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Can we Trust in Routine Echocardiography to Assess the Right Ventricle and Pulmonary Insufficiency? A Comparative Study with Cardiac Magnetic Resonance

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Abstract

Background: Cardiac magnetic resonance (CMR) is the method of choice for assessing right ventricular (RV) dimensions and function, and pulmonary insufficiency (PI).

Objectives: To assess the accuracy of two-dimensional echocardiography (2D ECHO) in estimating RV function and dimensions, and the degree of PI, and compare the 2D ECHO and CMR findings.

Methods: We compared ECHO and CMR reports of patients whose indication for CMR had been to assess RV and PI. A p-value < 0.05 was considered statistically significant.

Results: We included 51 congenital heart disease patients, with a median age of 9.3 years (7-13.3 years). There was poor agreement between 2D ECHO and CMR for classification of the RV dimension (Kappa 0.19; 95% CI 0.05 to 0.33, p 0.004) and function (Kappa 0.16; 95% CI -0.01 to +0.34; p 0.034). The RV was undersized by 2D ECHO in 43% of the cases, and RV function was overestimated by ECHO in 29% of the cases. The degree of agreement between the methods in the classification of PI was not significant (Kappa 0.014; 95% CI -0.03 to +0.06, p 0.27). 2D ECHO tended to overestimate the degree of PI.

Conclusions: The 2D ECHO showed a low agreement with CMR regarding the RV dimensions and function, and degree of PI. In general, ECHO underestimated the dimensions of the RV and overestimated the function of the RV and the degree of PI as compared with CMR.

Keywords: Diagnostic, Imaging; Magnetic Resonance, Imaging; Echocardiography/methods; Ventricular Function, Right; Lung Diseases; Pulmonary Valve, Insufficiency; Heart Defects, Congenital.

Introduction

Cardiac magnetic resonance imaging (CMR) is considered the method of choice to assess dimensions and function of the right ventricle (RV), as well as to quantify pulmonary insufficiency (PI). Patients with congenital heart disease (CHD) and involvement of the right ventricular outflow tract or pulmonary valve are subject to develop dilation and dysfunction of the RV and PI at some stage in their lives, as a result of either the natural history or surgical or hemodynamic procedures. In this type of patient, indication for CMR is part of the multi-imaging approach recommended today.^{1,2} However, CMR is less available than two-dimensional echocardiogram (2D ECHO), especially for young children, when sedation is frequent. Thus, it is crucial to optimize CMR indications and referrals for CMR.

In turn, 2D ECHO is a widely available and relatively low-cost method but limited in assessing the RV and the degree of PI.³⁻¹⁰ Despite this, in daily practice, indication for CMR is made based on the evaluation of clinical and echocardiographic features.

In our study, we sought to retrospectively assess the accuracy of transthoracic 2D ECHO in estimating the function and dimensions of the RV and the degree of PI, comparing its findings with those of CMR.

Methods

This study was carried out in a reference center for the treatment of CHD. We selected, from the pediatric/congenital CMR database, patients whose indication for CMR had been to assess the RV and PI. Patients who underwent CMR between April 2015 and August 2018 were included. We compared the closest (in terms of the date of the tests) 2D ECHO and CMR reports, excluding patients who underwent some type of invasive treatment between the two tests.¹¹ This study was approved by the institutional review board.

Two-dimensional echocardiogram

The examinations were performed by five different echocardiographers, trained in pediatric cardiology and

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CHD, with at least five years of experience, using either HD 11 or iE33 cardiac ultrasound systems (Philips Medical Systems, Bothell, USA). All information was collected from ECHO reports, with no review of the images or analysis of the methods to conclude the report. In our service, the report is issued only by the performing physician, and there is no mandatory review of the reports by other physicians.

Subjective analysis or Z-score of measurements of the RV obtained in two-dimensional mode (four-chamber window) or M-mode (parasternal window) according to the American Society of Echocardiography guidelines are generally used to assess right ventricular dimensions.^{12,13} In our service, the main methods to assess the function of the RV are: qualitative analysis (eyeball method), TAPSE (tricuspid annular plane systolic excursion), fractional area change (FAC) and the S' wave peak systolic velocity by pulsed-wave tissue Doppler imaging (TDI). TAPSE and RV TDI s' are also plotted in Z-scores.^{14,15} The set of these parameters determines the examiner's final impression. To assess PI, the following parameters are generally used: diameter of the regurgitant jet / diameter of the RV outflow tract, location of the pulmonary artery tree where reflux is detected, pressure half-time of the flow curve and integral velocity-time (IVT). After this analysis, the examiner uses a four-level stratification to classify right ventricular function (normal, or mild, moderate, or severe dysfunction), size of the RV (normal, or mild dilation, moderate, or severe dilation) and the degree of PI (absent, or mild, moderate, or severe insufficiency). For analysis of the left ventricular (LV) function, the ejection fraction (LVEF), obtained by the Teichholz and/or Simpson method, was used.

Cardiac magnetic resonance

The CMR examinations were carried using a 1.5 Tesla scanner (General Electric SIGNA™). Ventricular volumes were determined after acquisition of two-dimensional images in cine-SSFP (steady state free precession) in the short axis of the heart or axial section of the chest, from the atrioventricular ring to the cardiac apex. Ventricular volumes and EF were determined after manual tracing in offline analysis using the MASS R MR Analytical Software System, version 5.1 (Leiden University Medical Center and MEDIS Medical Imaging system). The images were obtained in free breathing with number of excitations (NEX) of three, or in apnea (NEX of 1), depending on patient's clinical situation and quality of the images. The indexed end diastolic volume of the RV (RVEDVi), the right ventricular EF, the indexed end diastolic volume of the left ventricle (LVEDVi) and the LVEF were evaluated.

Indexed ventricular volumes were transformed into a Z-score, based on the normal values published by the Society for Cardiovascular Magnetic Resonance (Table 1),¹⁶ using the following formula: $Z\text{-score} = (\text{patient measurement} - \text{expected average}) / \text{standard deviation [SD]}$. For patients younger than eight years old, calculations were made based on the study by Valsangiacomo-Buechel (Table 2),¹⁷ using the formula: $Z = \log_{10} (\text{measured/expected}) / \text{SD}$ ($\text{SD} = 0.05$). A Z-score between -2 and +2 was considered normal; a Z-score between +2.01 and +3 a mild dilation; a Z-score between +3.01 and +4 moderate dilation, and a Z-score > +4 was considered severe dilation.

Regarding EF classification, it was performed as follows:

- Right ventricle: EF > 45% = normal; EF from 36 to 45% = mild dysfunction; EF from 25 to 35% = moderate dysfunction; EF < 25% = severe dysfunction.
- Left ventricle: EF > 50% = normal; EF from 40 to 50% = mild dysfunction; EF from 30 to 39% = moderate dysfunction; EF < 30% = severe dysfunction.

PI was evaluated by phase contrast imaging performed perpendicular to the pulmonary trunk and perpendicular to the pulmonary branches, in free breathing (NEX of 2 or 3), adjusting the number of views per segment according to patient's heart rate, allowing the reconstruction of 30 phases per RR interval. Pulmonary regurgitation volume and fraction were analyzed using the FLOW R MR Flow Quantification software, version 3.1 (MEDIS Medical Imaging system and Leiden University Medical Center). As there are two possible methods to classify the degree of PI by CMR (regurgitant volume and fraction of regurgitation), discrepancies were resolved by analysis of the data by the observer. The following values were considered for classification:

- Mild PI: regurgitant volume = 0.3-1.0 L/min/m² or regurgitation fraction = 5-20%.
- Moderate PI: regurgitant volume = 1.01-2.50 L/min/m² or regurgitation fraction = 21-40%.
- Severe PI: regurgitant volume > 2.5 L/min/m² or regurgitation fraction > 40%.

Statistical analysis

Continuous variables were expressed as mean $\pm$ standard deviation or median with interquartile range (25-75), depending on data distribution. Data distribution can be considered normal when around 95% of the data fall within 1.96 standard deviations from the mean (bilaterally). Categorical variables were presented in absolute numbers and percentages. Agreement was analyzed using the Kappa coefficient, with the aid of the StatsDirect program, version 2.7.2, 2008 (Cheshire, UK). Statistical significance was considered as $p < 0.05$ (bilateral test).

Results

Out of 178 children or adults with CHD undergoing CMR during the study period, 51 (29%) were included in the analysis. The main characteristics of the study population are shown in Table 3.

Echocardiographic findings

The dimensions of the RV were classified as abnormal in 96% of the cases, with mild dilation in 16%, moderate dilatation in 43% and severe dilatation in 37%. Had the echocardiographers considered only the right ventricular end-diastolic diameter RVEDD Z-score, there would be worsening in classification in 42 patients (82%), no changes in five patients (10%) and a better or more appropriate classification in four patients (8%) compared to CMR. Right ventricular dysfunction was reported in 20% of

Table 1 – Values for normal indexed ventricular volumes in adults and children older than eight years of age

	Adults (> 18 years)		Children (8-17 years)	
	Male	Female	Male	Female
LVEDVi (ml/m ²)	81 ± 12	76 ± 10	80 ± 11	75 ± 11
RVEDVi (ml/m ²)	91 ± 15	80 ± 16	84 ± 10	76 ± 10

LVEDV: left ventricular end-diastolic volume; RVEDV: right ventricular end diastolic volume.

Table 2 – Values for normal ventricular volumes in children under 8 years of age

	Children (< 8 years)	
	Boys	Girls
LVEDV (mL)	77.5xBSA ^{1.38}	67.8xBSA ^{1.38}
RVEDV (mL)	83.8xBSA ^{1.47}	72.7xBSA ^{1.47}

BSA: body surface area; LVEDV: left ventricular end-diastolic volume; RVEDV: right ventricular end diastolic volume.

Table 3 – Characteristics of the study population (n=51) and their diagnoses

Characteristics	
Male sex	30 (58%)
Weight (Kg) (SD)	33.0 ± 16.7
Body surface area (m ²) (IQR)	1.0 (0.8-1.4)
Age at the time of surgical treatment (years) (IQR)	1.3 (0.8-2.4)
Age on the day of CMR (years) (IQR)	9.2 (6.9-13.3)
Age on the day of echocardiogram (years) (IQR)	9.0 (6.8-13.0)
Time between surgical treatment and CMR (years) (IQR)	7.2 (5.4-11.1)
Interval between CMR and echocardiogram (days) (IQR)	124 (70-188)
Main diagnoses	
Tetralogy of Fallot	35 (68%)
Pulmonary valve stenosis	6 (12%)
Common arterial trunk	3 (6%)
Pulmonary atresia with ventricular septal defect	2 (4%)
Tetralogy of Fallot with absent pulmonary valve	2 (4%)
Congenital pulmonary insufficiency	1 (2%)
Atrioventricular septal defect with pulmonary stenosis	1 (2%)
Pulmonary atresia with intact interventricular septum	1 (2%)

IQR: interquartile range; CMR: cardiac magnetic resonance.

cases, being mild in 10%, moderate in 8% and severe in 2%. Out of the 51 patients, 29 (57%) had values of TAPSE, FAC or TDI in their reports, and among these 29 patients, 18 (62%) had measurements below the normal range. Despite this finding, nine of these 18 patients were classified as having normal systolic RV function. The agreement between these echocardiographic indices of RV systolic function and CMR right ventricular EF was

38%. Had the echocardiographer considered only these abnormal indices, disregarding the eyeball method, there would be misclassifications in nine more cases and a correct classification in five more cases. Echocardiographic measurements are presented in Table 4. PI was mild in 2%, moderate in 2% and severe in 94%; in one case, PI was not classified. In none of the cases, LV systolic dilation or dysfunction was observed (Table 5).

Table 4 – Echocardiographic measurements of the study patients

Parameters	Values
RV end-diastolic diameter (mm)	30.5 ± 7.48
RV end-diastolic diameter Z-score	2 (1.48-2.53)
TAPSE (mm) (n = 15)	17.9 ± 3.59
TAPSE Z-score	-2.3 (-3.28 a -0.94)
FAC (%) (n = 7)	41 ± 12.3
RV peak S' cm/s (n = 23)	9.1 ± 1.89
RV peak S' cm/s Z-score	-2.4 (-3.22 a -1.69)
RV diameter / LV diameter (mm)	0.8 (0.71-0.99)

RV: right ventricular; TAPSE: tricuspid annular plane systolic excursion; fractional area change: FAC; RV peak S': S' wave peak systolic velocity of the right ventricle CMR findings.

Table 5 – Comparison between two-dimensional echocardiogram (2D ECHO) and cardiac magnetic resonance (CMR) findings

			Normal	Mild dilation	Moderate dilation	Severe dilation
DIMENSION	RV	ECHO	2 (4%)	8 (16%)	22 (44%)	19 (38%)
		CMR	3 (6%)	3 (6%)	6 (12%)	39 (76%)
	LV	ECHO	51 (100%)	0	0	0
		CMR	38 (76%)	5 (10%)	3 (6%)	5 (10%)
			Normal	Mild dysfunction	Moderate dysfunction	Severe dysfunction
FUNCTION	RV	ECHO	41 (80%)	5 (10%)	4 (8%)	1 (2%)
		CMR	30 (59%)	15 (29%)	4 (8%)	2 (4%)
	LV	ECHO	51 (100%)	0	0	0
		CMR	35 (69%)	14 (27%)	1 (2%)	1 (2%)
			None	Mild	Moderate	Severe
PULMONARY INSUFFICIENCY		ECHO	0	1 (2%)	1 (2%)	48 (96%)
		CMR	1 (2%)	8 (16%)	32 (64%)	9 (18%)

RV: right ventricle; LV: left ventricle.

CMR findings

The examination was performed under anesthesia in 16 patients (31%). The RVEDVi varied between 84.7 and 275.6 mL/m², which corresponded to an average Z-score of $+5.6 \pm 2$. Three patients (6%) had a RVEDVi Z-score within normal limits (91.4 ± 7.9 mL/m²), another three (6%) presented mild dilation (110.6 ± 4.8 mL/m²), six (12%) moderate dilation (120 ± 10.9 mL/m²) and 39 (76%) severe dilation (151.8 ± 31.5 mL/m²). The LVEDVi varied between 66.4 and 155.2 mL/m² (Table 6). Dilation of the left ventricle was observed in 25% of patients and LV systolic dysfunction was found in 31% (Table 5). Of the 16 patients with LV dysfunction, in 12 (75%) the exam was performed under anesthesia.

Agreement analysis between 2D ECHO and CMR

Dimension of the right ventricle

A significant agreement was observed between the methods for the classification of right ventricular dimensions (Kappa 0.19; 95% CI 0.05 to 0.33, p 0.004), although the degree of this agreement was low. The difference in classification was of one degree in 74% of the discordant cases, with an underestimation of the dimensions of the RV by ECHO in 22 cases (43%) and overestimation in five cases (10%) (Figure 1). Of the 39 cases of severe dilation, ECHO made the correct diagnosis in 17 (44%). The sensitivity of the ECHO to detect moderate or severe dilations of the RV was 87% and the specificity was 67%.

Table 6 – Main cardiac magnetic resonance findings in the study patients (n=51)

Parameters analyzed	Values
RV end-diastolic volume indexed (ml/m ²)	142.1 ± 33.4
RV end-systolic volume indexed (ml/m ²)	76.1 ± 27.4
RV ejection fraction (%)	46.9 ± 10.2
Pulmonary insufficiency (L/min/m ²)	1.5 (1.01-1.99)
Pulmonary insufficiency (%)	31.1 ± 10.7
LV end diastolic volume indexed (mL/m ²)	87.4 ± 18.5
LV end systolic volume indexed (mL/m ²)	42.4 ± 12.8
LV ejection fraction (%)	53.6 ± 8.4%
RV volume / LV volume ratio	1.6 (1.43-1.86)

RV: right ventricle; LV: left ventricle.

Right ventricular systolic function

There was a weak agreement between the methods for classification of the RV function (Kappa 0.16; 95% CI -0.01 to +0.34; p 0.034). The difference in classification was of one degree in 86% of the discordant cases, with the RV function overestimated by ECHO in 15 cases (29%) and underestimated in six cases (12%) (Figure 2). The two cases with severe RV dysfunction were not detected by ECHO: one was classified as normal and the other as moderate dysfunction.

Pulmonary insufficiency

The degree of agreement between the methods for classification of PI was not statistically significant (Kappa 0.014; 95% CI -0.03 to +0.06, p 0.27). There was disagreement in 80% of the cases, with ECHO tending to overestimate the degree of PI. There was disagreement above one degree in 20% of the cases (Figure 3).

Left ventricular systolic function and dimension

ECHO did not identify any of the 16 cases (31%) of LV dysfunction and none of the 13 cases (25%) of LV dilation, preventing the assessment of agreement between the methods. Of the 16 cases of LV dysfunction, 10 (62%) also had RV dysfunction and only one had normal-sized RV.

Discussion

Residual PI and remodeling of the RV over time are important elements in the long-term course of patients who have undergone RV outflow tract repair in childhood. Decision making regarding the time to perform a new surgical intervention in these cases is still challenging. Clinical and electrocardiographic criteria, in addition to findings of image examinations, such as ECHO and CMR, are used to assist in this decision, seeking to determine the optimal time to perform surgical treatment.

The 2D ECHO is the most used imaging method to monitor the course of these patients, guiding, in most cases, the decision-making. Given the difficulties in performing a

2D echocardiographic assessment of the RV with objective parameters, qualitative assessment (eyeball) of the dimensions and function of the RV is still widely used. However, the accuracy of this assessment is questionable and still motivates further studies. Our study sought to assess the accuracy of 2D ECHO, performed during the outpatient routine, in quantifying the dimensions and function of the RV and the degree of PI. We selected patients with CHD at risk to develop RV dilation and dysfunction and PI.

We observed that there was a certain, albeit weak, agreement between ECHO and CMR for the classification of right ventricular dimensions. This finding is similar to that found by Lai et al.,⁴ when they applied the guidelines for the assessment of the RV using 2D ECHO in normal patients, in patients with atrial septal defects and in patients who had undergone tetralogy of Fallot repair. In their article, the authors postulate that 2D ECHO inaccuracies are inherent to the application of linear or area measurements in a complex geometry chamber. Puchalski et al.,¹⁸ in a study with a design similar to ours, obtained similar results and emphasized the great interobserver variability as a potential source of disagreement between ECHO and CMR. It is suggested that the adding of objective to subjective measures would increase the agreement between the methods.^{7,19} In this sense, Greutmann et al.²⁰ observed, in an adult population, that the linear measurement with the best correlation with the RV diastolic volume was the RV area in the four-chamber apical view. By measuring this area, Alghandi et al.²¹ were able to discriminate patients with RVEDVi > 170 ml/m². More recent studies have investigated the use of 3D ECHO to assess the RV and, even so, it is generally observed underdimensioning of the RV^{7,22-24} is explained by its incomplete visualization, especially in cases of severe RV dilation, when the cardiac apex is dislocated and difficult to access by ECHO inspection. In our study, although we analyzed a young population, 86% of the patients had moderate or severe dilation of the RV. This could explain the lack of accuracy, if we consider that the bigger the RV, the greater the difficulties in evaluating it. However, in our study, 2D ECHO was able to detect 96% of cases of moderate and / or severe dilation, which may serve the purpose of screening patients who would need to undergo CMR.

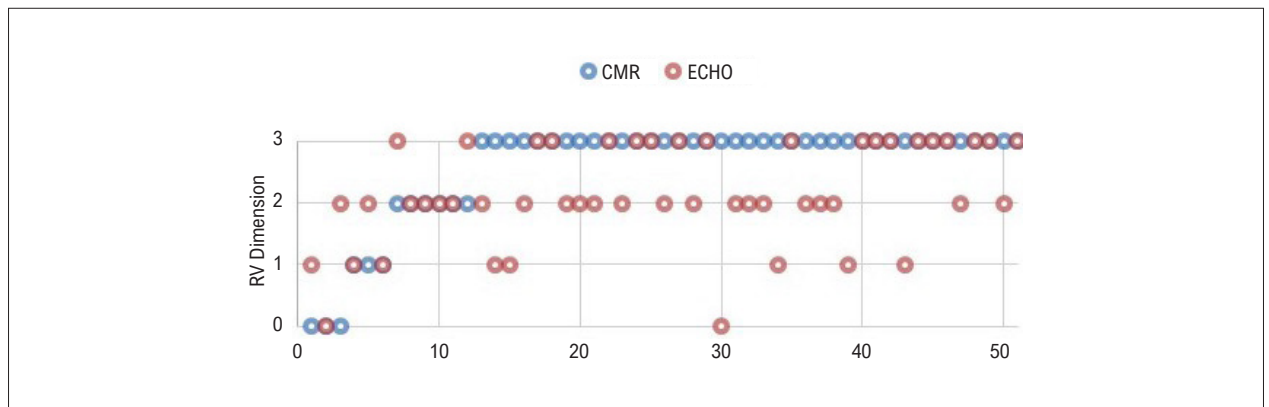


Figure 1 – Graph comparing the classification of RV dimension by CMR and ECHO for each patient.

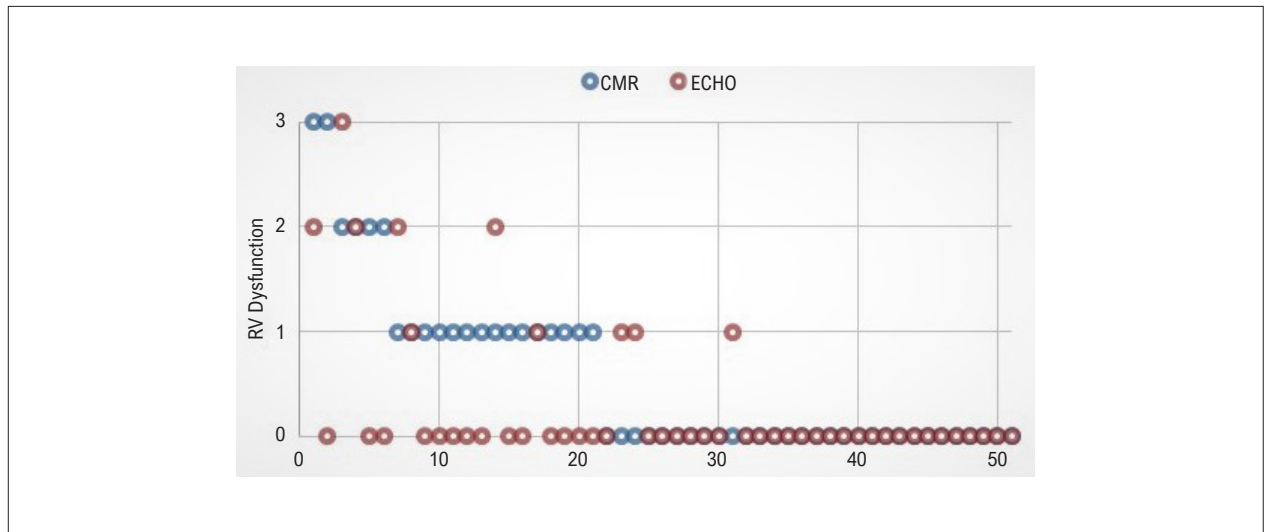


Figure 2 – Graph comparing the classification of RV systolic function by CMR and ECHO for each patient.

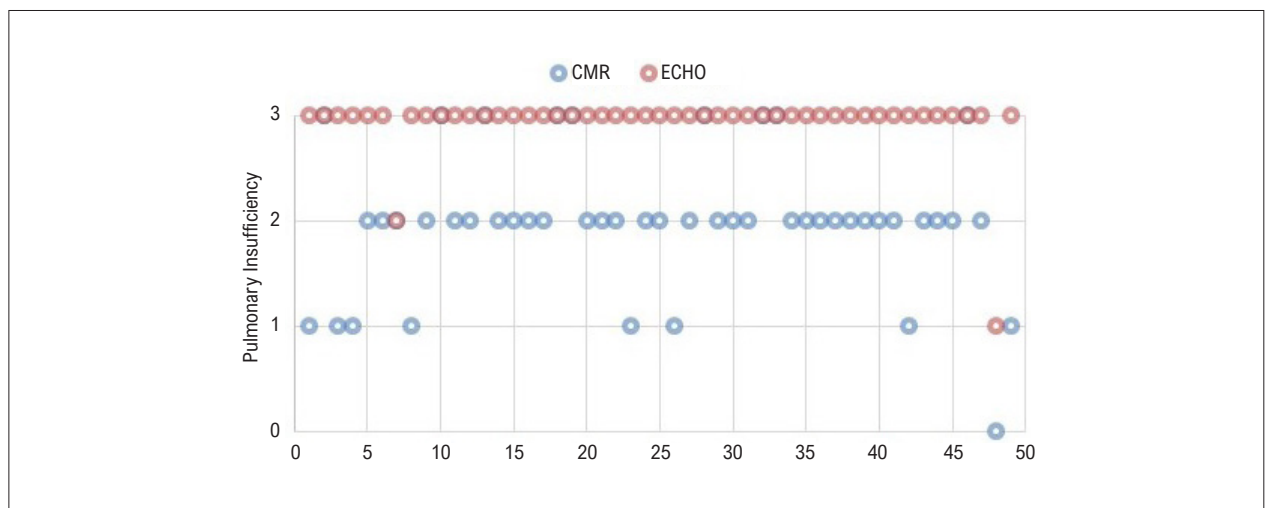


Figure 3 – Graph comparing the classification of pulmonary insufficiency by CMR and ECHO for each patient.

Regarding RV systolic function, our results are in line with those of the study by Puchalski,¹⁸ who reported a poor agreement between 2D ECHO and CMR. However, the degree of disagreement between the stratification classes was only of one grade in 86% of the cases, and this difference occurred mainly in the zone between mild dysfunction and normal function. Several echocardiographic methods have been used to assess right ventricular function, including TAPSE, FAC, TDI, Tei index, among others. Although some of them are reproducible, none of them has shown a strong correlation with the right ventricular EF in the pediatric population, especially in patients with CHD.^{3,7-10,25-27} Methods with unidimensional measurements, such as TAPSE, or bidimensional measurements such as FAC, do not take into account the complex geometry of the RV. These two methods do not consider the RV outflow tract, for example, commonly compromised in patients undergoing tetralogy of Fallot correction.²¹ In addition, there are other factors influencing these measurements, such as previous pericardiectomy, preload, ultrasound beam angulation, echocardiographic window quality, LV function, etc. In the study by Mercer-Rosa et al.¹⁶ TAPSE was not correlated to right ventricular EF by CMR, nor to the peak VO_2 . The same author, in 2012, observed a weak correlation between the tissue Doppler of the right ventricular free wall and the right ventricular EF by CMR, and the lack of correlation between the Tei index and the right ventricular EF by CMR in patients post-tetralogy of Fallot repair.⁵ In the study by Leong et al.²⁸ in an adult population with heart failure, right ventricular speckle tracking strain showed the strongest correlation ($r = 0.77$) with CMR right ventricular EF, compared with other techniques including TAPSE, FAC and TDI. However, one has to consider that this population usually does not present with severe RV dilatation. 3D ECHO is perhaps the method that best correlates with CMR,²⁹ but it is still far from becoming a method as available as the 2D ECHO, especially in the young population.³⁰ In practice, many services end up using qualitative evaluation (eyeball) of the right ventricular function, combined with some of the aforementioned indices to corroborate the final impression. The assessment of the function of the RV by 2D ECHO, therefore, becomes an examiner-dependent method and subject to different interpretations.

With regard to the degree of PI, we did not find any agreement between ECHO and CMR in our study. In 38 patients (75% of the sample), PI was classified as severe by ECHO, but as moderate or mild by CMR. In other words, ECHO overestimated the degree of PI in most cases, a data similar to that observed by Mercer-Rosa et al.⁵ In that study,⁵ many patients with mild PI by CMR were classified as having moderate or severe PI by ECHO, when using the diastolic VTI / systolic VTI ratio obtained in the pulmonary trunk. In turn, Renella et al.³¹ observed that ECHO had great sensitivity in identifying cases of severe PI in different methods used and recommend the evaluation of Doppler curves in the pulmonary branches, instead of in the pulmonary trunk, to increase the specificity of the method. In practice, the literature has shown that ECHO is able to discriminate cases of mild PI from cases of moderate or severe PI, which is corroborated by our findings.

LV dysfunction has been described in patients with RV disease repair and linked to major adverse events.³²⁻³⁷ Therefore, LV assessment cannot be neglected. In our sample, although the 2D ECHO showed normal LV function in all patients, CMR identified LV dysfunction in 31% of cases, which indicates the limitations of 2D ECHO in assessing LV function in this situation. Of the patients with LV dysfunction, 62% also had some degree of RV dysfunction, which may be related to ventricular interdependence.^{38,39} In our view, the evaluation of LV function in cases of RV dilation or dysfunction is more difficult to the ECHO due to the paradoxical movement of the interventricular septum and the LV dislodgement by a dilated or dysfunctional RV, making its visibility more difficult.

Study limitations

This was a retrospective, single-center study with a limited number of patients. The possibility of inclusion bias should be considered, since the decision to submit the patient to CMR is often made after analysis of ECHO findings. Analysis of ECHO results was based on the reports only, without image review. Considering that five echocardiographers performed the exams, there is the possibility of intraobserver and interobserver disagreements. Also, time interval between ECHO and CMR was relatively large. Although there was no surgical or percutaneous interventional procedure between ECHO and CMR, ideally the exams should have been performed within 24 hours of each other. The use of Z-score of ventricular measurements obtained by CMR is not a common approach in the literature, and the classification range, as well as the clinical impact of these measurements, need to be better evaluated in future studies.

Conclusions

In our practice, and considering the study limitations, 2D ECHO showed a low agreement with CMR regarding right ventricular dimensions and systolic function, and degree of PI. In general, ECHO underestimated the dimensions of the RV and overestimated the function of the RV and the degree of PI. We understand that the incorporation of more objective echocardiographic parameters is necessary for a better agreement with the CMR. However, the real impact of this analysis in relation to clinical decision-making is still uncertain.

Author contributions

Conception and design of the research: Cabral MB, Kozak MF, Afiune JY. Acquisition of data: Cabral MB, Kozak MF. Analysis and interpretation of the data: Cabral MB, Kozak MF, Afiune JY. Statistical analysis: Kozak MF. Writing of the manuscript: Kozak MF, Afiune JY. Critical revision of the manuscript for intellectual content: Kozak MF, Afiune JY.

Potential Conflict of Interest

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

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Study Association

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

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Instituto de Cardiologia do Distrito Federal under the protocol number 4.207.712. 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. Geva T. Repaired tetralogy of Fallot: the roles of cardiovascular magnetic resonance in evaluating pathophysiology and for pulmonary valve replacement decision support. *J Cardiovasc Magn Reson*. 2011;13(1):9.
2. Sachdeva R, Valente AM, Armstrong AK, Cook SC, Han BK, Lopez L. ACC/AHA/ASE/HRS/ISACHD/SCAI/SCCT/SCMR/SOPE 2020 Appropriate Use Criteria for Multimodality Imaging During the Follow-Up Care of Patients With Congenital Heart Disease: A Report of the American College of Cardiology Solution Set Oversight Committee and Appropriate Use Criteria Task Force, American Heart Association, American Society of Echocardiography, Heart Rhythm Society, International Society for Adult Congenital Heart Disease, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, Society for Cardiovascular Magnetic Resonance, and Society of Pediatric Echocardiography. *J Am Coll Cardiol*. 2020;75(6):657-703.
3. Di Lorenzo MP, Bhatt SM, Mercer-Rosa L. How best to assess right ventricular function by echocardiography. *Cardiol Young*. 2015;25(8):1473-81.
4. Lai WW, Gauvreau K, Rivera ES, Saleeb S, Powell AJ, Geva T. Accuracy of guideline recommendations for two-dimensional quantification of the right ventricle by echocardiography. *Int J Cardiovasc Imaging*. 2008;24(7):691-8.
5. Mercer-Rosa L, Yang W, Kutty S, Rychik J, Fogel M, Goldmuntz E. Quantifying Pulmonary Regurgitation and Right Ventricular Function in Surgically Repaired Tetralogy of Fallot. A Comparative Analysis of Echocardiography and Magnetic Resonance Imaging. *Circ Cardiovasc Imaging*. 2012;5(5): 637-43.
6. Mercer-Rosa L, Parnell A, Forfia PR, Yang W, Goldmuntz E, Kawut SM. Tricuspid Annular Plane Systolic Excursion in the Assessment of Right Ventricular Function in Children and Adolescents after Repair of Tetralogy of Fallot. *J Am Soc Echocardiogr*. 2013;26(11):1322-9.
7. Portnoy SG, Rudski LG. Echocardiographic evaluation of the right ventricle: a 2014 perspective. *Curr Cardiol Rep*. 2015;17(4):21.
8. Koestenberger M, Nagel B, Ravekes W, Everett AD, Stueger HP, Heinzl B et al. Systolic right ventricular function in pediatric and adolescent patients with tetralogy of Fallot: echocardiography versus magnetic resonance imaging. *J Am Soc Echocardiogr*. 2011;24(1):45-52.
9. Koestenberger M, Nagel B, Avian A, Ravekes W, Sorantin E, Cvirn G et al. Systolic right ventricular function in children and young adults with pulmonary artery hypertension secondary to congenital heart disease and tetralogy of Fallot: Tricuspid annular plane systolic excursion (TAPSE) and Magnetic Resonance Imaging data. *Congenit Heart Dis*. 2012;7(3):250-8.
10. Koestenberger M, Nagel B, Ravekes W, Avian A, Heinzl B, Fandl A et al. Tricuspid annular peak systolic velocity (S') in children and young adults with pulmonary artery hypertension secondary to congenital heart diseases, and in those with repaired tetralogy of Fallot: echocardiography and MRI data. *J Am Soc Echocardiogr*. 2012;25(10):1041-9.
11. Wald RM, Valente AM, Gauvreau K, Babu-Narayan SV, Assenza GE, Schreier J et al. Cardiac magnetic resonance markers of progressive RV dilation and dysfunction after tetralogy of Fallot repair. *Heart*. 2015;101(21):1724-30.
12. Lopez L, Colan SD, Frommelt PC, Ensing CJ, Kendall K, Younoszai AK et al. Recommendations for Quantification Methods during the Performance of a Pediatric Echocardiogram. *J Am Soc Echocardiogr*. 2010;23(5):465-95.
13. Pettersen MD, Du W, Skeens ME, Humes RA. Regression equations for calculation of z scores of cardiac structures in a large cohort of healthy infants, children, and adolescents: an echocardiographic study. *J Am Soc Echocardiogr* 2008;21(8):922-34. doi: 10.1016/j.echo.2008.02.006.
14. Koestenberger M, Ravekes W, Everett AD, Stueger HP, Heinzl B, Gamillscheg A et al. Right Ventricular Function in Infants, Children and Adolescents: Reference Values of the Tricuspid Annular Plane Systolic Excursion (TAPSE) in 640 Healthy Patients and Calculation of z Score Values. *J Am Soc Echocardiogr*. 2009 Jun;22(6):715-9.
15. Koestenberger M, Nagel B, Ravekes W, Avian A, Heinzl B, Cvirn G et al. Reference values of tricuspid annular peak systolic velocity in healthy pediatric patients, calculation of z score, and comparison to tricuspid annular plane systolic excursion. *Am J Cardiol*. 2012;109(1):116-21.
16. Kawel-Boehm N, Maceira A, Valsangiacomo-Buechel ER, Vogel-Claussen J, Turkbey EB, Williams R et al. Normal values for cardiovascular magnetic resonance in adults and children. *J Cardiovasc Magn Reson*. 2015;17:17-29.
17. Valsangiacomo-Buechel ER, Kaiser T, Jackson C, Schmitz A, Kellenberger CJ. Normal right and left ventricular volumes and myocardial mass in children measured by steady state free precession cardiovascular magnetic resonance. *J Cardiovasc Magn Reson*. 2019;11(1):19.
18. Puchalski MD, Williams RV, Askovich B, Minich LA, Mart C, Tani LY. Assessment of right ventricular size and function: echo versus magnetic resonance imaging. *Congenit Heart Dis*. 2007;2(1):27-31.
19. Ling LF, Obuchowski NA, Rodriguez L, Popovic Z, Kwon D, Marwick TH. Accuracy and interobserver concordance of echocardiographic assessment of right ventricular size and systolic function: a quality control exercise. *J Am Soc Echocardiogr*. 2012;25(7):709-13.
20. Greutmann M, Tobler D, Biaggi P, Mah ML, Crean A, Oechslin EN et al. Echocardiography for assessment of right ventricular volumes revisited: A cardiac magnetic resonance comparison study in adults with repaired tetralogy of Fallot. *J Am Soc Echocardiogr*. 2010;23(9):905-11.
21. Alghamdi MH, Grosse-Wortmann L, Ahmad N, Mertens L, Friedberg MK. Can Simple Echocardiographic Measures Reduce the Number of Cardiac Magnetic Resonance Imaging Studies to Diagnose Right Ventricular Enlargement in Congenital Heart Disease? *J Am Soc Echocardiogr*. 2012;25(5):518-23.
22. Dragulescu A, Grosse-Wortmann L, Fackoury C, Mertens L. Echocardiographic assessment of right ventricular volumes: A comparison of different techniques in children after surgical repair of tetralogy of Fallot. *Eur Heart J – Cardiovasc Imaging* 2012;13(7):596-604.
23. Crean AM, Maredia N, Ballard G, Menezes R, Wharton G, Forster J. 3D Echo systematically underestimates right ventricular volumes compared to cardiovascular magnetic resonance in adult congenital heart disease patients with moderate or severe RV dilatation. *Journal of Cardiovascular Magnetic Resonance*. 2011;13(1):78.
24. Knight DS, Grasso AE, Quail MA, Muthurangu V, Taylor AM, Toumpanakis C et al. Accuracy and reproducibility of right ventricular quantification in patients with pressure and volume overload using single-beat three-dimensional echocardiography. *J Am Soc Echocardiogr*. 2015;28(3):363-74.

25. Bonnemains L, Stos B, Vaugrenard T, Marie PY, Odille F, Boudjemline Y. Echocardiographic right ventricle longitudinal contraction indices cannot predict ejection fraction in post-operative Fallot children. *Eur Heart J – Cardiovasc Imaging*. 2012;13(3):235-42.
26. Koca B, Öztunç F, GülerEroglu Ayse, Gökalp S, Dursun M, Yilmaz R. Evaluation of right ventricular function in patients with tetralogy of Fallot using the myocardial performance index and isovolumic acceleration: a comparison with cardiac magnetic resonance imaging. *Cardiol Young*. 2014;24(3):422-9.
27. Kutty S, Zhou J, Gauvreau K, Trincado C, Powell AJ, Geva T. Regional dysfunction of the right ventricular outflow tract reduces the accuracy of Doppler tissue imaging assessment of global right ventricular systolic function in patients with repaired tetralogy of Fallot. *J Am Soc Echocardiogr*. 2011;24(6):637-43.
28. Leong DP, Grover S, Molaee P, Chakrabarty A, Shirazi M, Cheng YH et al. Nonvolumetric echocardiographic indices of right ventricular systolic function: validation with cardiovascular magnetic resonance and relationship with functional capacity. *Echocardiography*. 2012;29(4):455-63. Doi: 10.1111/j.1540-8175.2011.01594.x
29. Hamilton-Craig CR, Stedman K, Maxwell R, Anderson B, Stanton T, Chan J, Yamada A, Scalia GM, Burstow DJ. Accuracy of quantitative echocardiographic measures of right ventricular function as compared to cardiovascular magnetic resonance. *Int J Cardiol Heart Vasc*. 2016;12:38-44.
30. Renella P, Marx GR, Zhou J, Gauvreau K, Geva T. Feasibility and reproducibility of three-dimensional echocardiographic assessment of right ventricular size and function in pediatric patients. *J Am Soc Echocardiogr*. 2014;27(8):903-10.
31. Renella P, Aboulhosn J, Lohan DG, Jonnala P, Finn JP, Satou GM et al. Two-dimensional and Doppler echocardiography reliably predict severe pulmonary regurgitation as quantified by cardiac magnetic resonance. *J Am Soc Echocardiogr*. 2010;23(8):880-6.
32. Ait Ali L, Trocchio G, Crepaz R, Stuefer J, Stagnaro N, Siciliano V, Molinaro S, Sicari R, Festa P. Left ventricular dysfunction in repaired tetralogy of Fallot: incidence and impact on atrial arrhythmias at long term-follow up. *Int J Cardiovasc Imaging*. 2016;32(9):1441-9.
33. Li Y, Xie M, Wang X, Lu Q, Zhang L, Ren P. Impaired right and left ventricular function in asymptomatic children with repaired tetralogy of Fallot by two-dimensional speckle tracking echocardiography study. *Echocardiography*. 2015;32(1):135-43.
34. Roche SL, Grosse-Wortmann L, Friedberg MK, Redington AN, Stephens D, Kantor PF. Exercise echocardiography demonstrates biventricular systolic dysfunction and reveals decreased left ventricular contractile reserve in children after tetralogy of Fallot repair. *J Am Soc Echocardiogr*. 2015;28(3):294-301.
35. Geva T, Mulder B, Gauvreau K, Babu-Narayan SV, Wald RM, Hickey K et al. Preoperative predictors of death and sustained ventricular tachycardia after pulmonary valve replacement in patients with repaired tetralogy of Fallot enrolled in the INDICATOR cohort. *Circulation*. 2018;138(19):2106-15.
36. Geva T, Sandweiss BM, Gauvreau K, Lock JE, Powell AJ. Factors associated with impaired clinical status in long-term survivors of tetralogy of Fallot repair evaluated by magnetic resonance imaging. *J Am Coll Cardiol*. 2004;43(6):1068-74.
37. Tretter JT, Redington AN. The Forgotten Ventricle? The Left Ventricle in Right-Sided Congenital Heart Disease. *Circ Cardiovasc Imaging*. 2018;11(3):e007410.
38. Penny DJ, Redington AN. Function of the Left and Right Ventricles and the Interactions Between Them. *Pediatr Crit Care Med*. 2016;17(8 Suppl 1):S112-8.
39. Friedberg MK, Redington AN. Right versus left ventricular failure: differences, similarities, and interactions. *Circulation*. 2014 Mar 4;129(9):1033-44.



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The Challenge of Echocardiography in the Accurate Assessment of the Right Ventricle and Pulmonary Insufficiency

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Short Editorial related to the article: Can We Trust in Routine EOCardiography to Assess the Right Ventricle and Pulmonary Insufficiency? A Comparative Study with Cardiac Magnetic Resonance

The current recognition of the importance of the right ventricle (RV) role in the evolution and prognosis of various cardiovascular conditions is indisputable and the proper assessment of its dimension and function has a direct impact on clinical management.

Pulmonary insufficiency (PI) is common after tetralogy of Fallot repair (POTF) and approach of congenital heart disease with pulmonary obstruction, being is an important determinant of outcome due to its consequences, causing RV dilation and dysfunction, exercise intolerance, increased risk of arrhythmias and sudden death.¹

Multimodality imaging methods are the pillars for assessing these patients. The relevance of nuclear magnetic resonance (NMR) in the quantification of PI and evaluation of the RV is unquestionable, emphasizing its limitations related to accessibility, cost and need for sedation, especially in children.² It is undeniable the contribution of echocardiography in clinical practice, despite the difficulties in quantifying PI and evaluating the RV, considered significant challenges that have encouraged a growing number of studies.^{3,4}

Studies to validate the quantification of IP by echocardiography (2D) tend to overestimate the value compared to MRI.⁵ The greater efficacy for quantification by 2D is determined by the joint analysis of several indices established in the literature.⁶ Mercer-Rosa et al.,⁵ showed a moderate correlation between the the ratio of diastolic and systolic time-velocity integrals and the regurgitant fraction by MRI, establishing a cutoff value to stratify the important degree and suggesting the incorporation of this index to the other parameters for greater efficacy.

Regarding the RV dimension assessment, the literature shows weak agreement between the linear measurements assessed by

the 2D and the MRI, with the 2D tending to underestimate.⁷ However, given the complex geometry of the RV that prevents visualization in a single plane, it is clear that the isolated linear measure impair the evaluation. The inclusion of planimetry at the end-diastolic area, associated with two-dimensional measurements in the apical four-chamber and parasternal short axis planes for evaluating the outflow tract, contributes to the accuracy. In the studies carried out by both authors, Shiran et al.⁸ and Alghamdi et al.³ in adults with pulmonary hypertension and children with congenital heart disease, it was possible to estimate the volumes by measuring the diastolic area indexed in the 2D with good correlation.

Three-dimensional (3D) echocardiography has contributed to volumetric and functional assessment, enabling the analysis of all segments with no contraindication, but it requires specific equipment not available in all services. There is a significant correlation between 3D and MRI and a certain tendency for 3D to underestimate volumes when there is pronounced dilatation.⁹ Reference values for children and adults are available in the literature.^{10,11}

The assessment of RV systolic function is always based on the integrated approach of qualitative analysis with quantitative parameters that reflect global function, fractional area change (FAC) and also longitudinal function, tricuspid annular plane systolic excursion (TAPSE) measurement and systolic velocity by Tissue Doppler.¹¹ The interpretation of the TAPSE value as an isolated measure in congenital heart diseases should be cautious, as it only reflects the longitudinal shortening and is influenced by pericardiotomy.¹² In contrast, the FAC value, global assessment index, has a good correlation with the ejection fraction, despite the difficulties inherent in the delineation of the ventricular cavity.⁸

The evaluation of peak systolic longitudinal strain has enabled greater accuracy in the functional analysis of the RV, with the peculiarity of enabling the early detection of the dysfunction and preceding the reduction of the ejection fraction.¹³ In POTF, the incorporation of strain to other conventional evaluation parameters has contributed to the accuracy, advancing on the echocardiography challenge for RV assessment.¹⁻¹⁴

In the article,¹⁵ the authors evidenced weak agreement between the 2D and the MRI in evaluating the RV dimension and function, in addition to the degree of PI, and noted that the 2D underestimated the dimension and overestimated the PI function and degree. It is important to note that in the study the measurement of the end-diastolic area and right ventricular outflow tract in paraesternal short-axis were not included, which may have contributed

Keywords

Heart Defects, Congenital; Ventricular Function, Right; Pulmonary Valve Insufficiency; Magnetic Resonance Spectroscopy/methods; Tetralogy of Fallot/surgery.

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to the underestimated value by 2D. However, an important finding was the screening of most cases with moderate to severe dilation, pointing out the relevance in clinical practice of 2D in the follow-up and the precise indication of MRI. Regarding the overestimated value of the function by 2D, we could speculate that the non-inclusion of the two-dimensional strain that enables the early detection of

the dysfunction before the reduction of the ejection fraction may have corroborated the result.

In this context, it is noteworthy that the clinical attitude towards decision-making depends on the integrated approach between clinical data and different imaging methods, which are complementary, thus seeking the best perspective for the patient.

References

1. Larios G, Yim D, Dragulescu A, Mertens L, Grosse-Wortmann L, Friedberg MK. Right ventricular function in patients with pulmonary regurgitation with versus without tetralogy of Fallot. *Am Heart J*. 2019;213:8-17. doi:10.1016/j.ahj.2019.03.012
2. Valente AM, Cook S, Festa P, Ko HH, Krishnamurthy R, Taylor AM, et al. Multimodality imaging guidelines for patients with repaired tetralogy of fallot: a report from the American Society of Echocardiography: developed in collaboration with the Society for Cardiovascular Magnetic Resonance and the Society for Pediatric Radiology. *J Am Soc Echocardiogr*. 2014;27(2):111-41.
3. Alghamdi MH, Grosse-Wortmann L, Ahmad N, Mertens L, Friedberg MK. Can simple echocardiographic measures reduce the number of cardiac magnetic resonance imaging studies to diagnose right ventricular enlargement in congenital heart disease? *J Am Soc Echocardiogr*. 2012;25(5):518-23.
4. Sanz J, Sánchez-Quintana D, Bossone E, Bogaard HJ, Naeije R. Anatomy, Function, and Dysfunction of the Right Ventricle: JACC State-of-the-Art Review. *J Am Coll Cardiol*. 2019;73(12):1463-82.
5. Mercer-Rosa L, Yang W, Kutty S, Rychik J, Fogel M, Goldmuntz E. Quantifying pulmonary regurgitation and right ventricular function in surgically repaired tetralogy of Fallot: a comparative analysis of echocardiography and magnetic resonance imaging. *Circ Cardiovasc Imaging*. 2012;5(5):637-43.
6. Zoghbi WA, Enriquez-Sarano M, Foster E, Grayburn PA, Kraft CD, Levine RA, et al. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. *J Am Soc Echocardiogr*. 2003;16(7):777-802.
7. Lai WW, Gauvreau K, Rivera ES, Saleeb S, Powell AJ, Geva T. Accuracy of guideline recommendations for two-dimensional quantification of the right ventricle by echocardiography. *Int J Cardiovasc Imaging*. 2008;24(7):691-8.
8. Shiran H, Zamanian RT, McConnell MV, Liang DH, Dash R, Heidary S, et al. Relationship between echocardiographic and magnetic resonance derived measures of right ventricular size and function in patients with pulmonary hypertension. *J Am Soc Echocardiogr*. 2014;27(4):405-12.
9. Leibundgut G, Rohner A, Grize L, Bernheim A, Kessel-Schaefer A, Bremerich J, et al. Dynamic assessment of right ventricular volumes and function by real-time three-dimensional echocardiography: a comparison study with magnetic resonance imaging in 100 adult patients. *J Am Soc Echocardiogr*. 2010;23(2):116-26.
10. Laser KT, Karabiyik A, Körperich H, Horst JP, Barth P, Kececioglu D, et al. Validation and Reference Values for Three-Dimensional Echocardiographic Right Ventricular Volumetry in Children: A Multicenter Study. *J Am Soc Echocardiogr*. 2018;31(9):1050-63.
11. Rudski LG, Lai WW, Afalalo J, Hua L, Handschumacher MD, Chandrasekaran K, et al. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. *J Am Soc Echocardiogr*. 2010;23(7):685-713; quiz 86-8.
12. Mercer-Rosa L, Parnell A, Forfia PR, Yang W, Goldmuntz E, Kawut SM. Tricuspid annular plane systolic excursion in the assessment of right ventricular function in children and adolescents after repair of tetralogy of Fallot. *J Am Soc Echocardiogr*. 2013;26(11):1322-9.
13. Scherptong RW, Mollema SA, Blom NA, Kroft LJ, de Roos A, Vliegen HW, et al. Right ventricular peak systolic longitudinal strain is a sensitive marker for right ventricular deterioration in adult patients with tetralogy of Fallot. *Int J Cardiovasc Imaging*. 2009;25(7):669-76.
14. DiLorenzo MP, Elci OU, Wang Y, Banerjee A, Sato T, Ky B, et al. Longitudinal Changes in Right Ventricular Function in Tetralogy of Fallot in the Initial Years after Surgical Repair. *J Am Soc Echocardiogr*. 2018;31(7):816-21.
15. Cabral MB, Kozak MF, Afiune JY. Can we Trust in Routine Echocardiography to Assess the Right Ventricle and Pulmonary Insufficiency? A Comparative Study with Cardiac Magnetic Resonance. *Arq Bras Cardiol*. 2021; 117(4):690-698.



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Individual and Combined Performance of Indicators of Overall and Central Obesity to Estimate Coronary Risk in ELSA-Brasil Participants

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Abstract

Background: Anthropometric indicators have been used in clinical practice and epidemiological studies for screening of health risk factors.

Objectives: To evaluate the individual discriminatory power of body adiposity index (BAI), body mass index (BMI), waist circumference (WC) and waist-hip-ratio (WHR) to identify individuals at risk for coronary heart disease and to evaluate whether combinations of anthropometric indicators of overall obesity with indicators of central obesity improve predictive ability in adults.

Methods: A total of 15,092 participants (54.4% women) aged 35-74 years were assessed at baseline of the ELSA-Brasil study. Individuals at risk for coronary heart disease were identified using the Framingham risk score and divided into very-high risk (VHR 20%) and high risk (HR10%). Measures of diagnostic accuracy and area under the ROC curves (AUC) were analyzed. Associations were tested using Poisson regression analysis with robust variance, according to age and sex. Statistical significance was set at 5%.

Results: WHR showed the highest discriminatory power for VHR20% in all groups, with higher predictive ability in women (AUC: 0.802; 95%CI: 0.748-0.856 vs 0.657; 95%CI: 0.630-0.683 in the age range of 35-59 years, and AUC: 0.668; 95%CI: 0.621-0.715 vs 0.611; 95%CI: 0.587-0.635 in the age range of 60-74 years). BAI + WHR and BMI + WHR had the highest predictive power in men and women, respectively. Combinations of indicators of overall obesity with indicators of central obesity were more strongly associated with VHR20% and HR10% in all subgroups.

Conclusion: Combined indicators had greater predictive ability than indicators taken individually. BAI + WHR and BMI + WHR were the best estimators of coronary risk in men and women, respectively, and WHR had the best individual performance.

Keywords: Cardiovascular Diseases; Anthropometry; Obesity; Risk Factors; Epidemiology; Adiposity; Body Mass Index; Waist Circumference.

Introduction

Anthropometric indicators of obesity have been widely used in clinical practice and epidemiological studies for the screening for health risk factors.¹⁻³

Body mass index (BMI), devised by Lambert Adolphe Jaques Quetelet in 1832,⁴ is one of the most popular strategies used to indirectly measure obesity in populations. Although it has been extensively used in studies on cardiovascular diseases,^{3,5} this tool may not be able to describe the variation in body composition among individuals.³

In recent years, new indicators have been proposed as more accurate indirect measures of obesity. In 2011, Bergman et al.⁶ proposed the body adiposity index (BAI) as a better indicator of body fat as compared with BMI. However, the accuracy of this index in measuring adiposity has varied among populations,⁷⁻⁹ and results of its performance as a screening strategy for cardiometabolic risk factors are still controversial.¹⁰⁻¹⁶ Indicators of body fat distribution, waist circumference (WC), waist-to-hip ratio (WHR), waist-to-hip ratio (WHtR), and the conicity index (C index) have shown good performance as predictors of health risk.^{12,17} A recent study with participants of the ELSA-Brasil study demonstrated a positive association of WC and WHR with carotid intima-media thickness.¹⁷ In addition, the use of these indicators has been strengthened by epidemiological studies and does not require complex mathematical calculations.

It is controversial whether anthropometric indicators of overall and central obesity have higher predictive ability and usefulness to identify cardiometabolic risk factors in large populations.¹⁸⁻²² Besides, while some studies have shown that

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the combined use of indicators can improve their predictive capacity for adverse health outcomes,^{18,23–25} others have shown the opposite.^{19,26} Few studies evaluating the combined performance of indicators of overall and central obesity have been performed in the Brazilian adult population.

Therefore, the aims of the present study were to evaluate the individual discriminatory power of BAI, WC, WHR to assess coronary risk; to investigate whether the combination of anthropometric indicators of overall obesity (BMI and BAI) with indicators of central obesity (WC and WHC) improves the predictive ability of coronary risk in a large sample of Brazilian adults.

Methods

Source of data and study population

The Brazilian Longitudinal Study of Adult Health (ELSA-Brasil), evaluated, at baseline (2008–2010), 15,105 servants of educational and research institutions of six Brazilian cities (Belo Horizonte, Porto Alegre, Rio de Janeiro, Salvador, São Paulo and Vitória), aged between 35 and 74 years. Of these, nine did not have complete information on the variables analyzed, and four reported using silicone hip implants, and were then excluded. Thus, the present study investigated 15,092 patients. Methodological details of the ELSA-Brasil study were published by Aquino et al.²⁷

Demographic, anthropometric, and clinical data

Demographic, anthropometric, and clinical data were collected by interviews or measured, by trained personnel and supervised by highly qualified professionals. Age, sex, smoking and previous history of diabetes mellitus were collected using standardized procedures. Anthropometric measures were obtained after a 12-hour overnight fasting, with patients standing barefoot, wearing standard clothing provided by the ELSA-Brasil group. The measurements were taken based on a standardized protocol developed for the study, following the recommendations of the International Society for the Advancement of Kinanthropometry (ISAK).²⁸

Weight was measured at the nearest 0.1 Kg using a calibrated scale (Toledo 2096PP). Height was measured using a stadiometer (Seca-SE0216), and WC and hip circumference measured at the nearest 0.1 cm using an inelastic tape. WC was measured at the midpoint between the lowest rib and the iliac crest, and HC was measured at the level of the greatest gluteus protuberance. Measures were taken in triplicate and the mean of the three measurements considered for analysis.

Blood samples were collected in dry tubes for determination of glycemia, and total cholesterol and fractions at the study centers after 12-hour overnight fasting. Plasma glucose levels were determined by a hexokinase (enzymatic) method, and cholesterol levels determined by the cholesterol oxidase method (enzymatic colorimetric method), both using standard calibrated equipment (Siemens ADVIA 1200). In order to ensure the quality and standardization of results, all samples were sent to ELSA-Brasil central laboratory for processing and analysis.

Three blood pressure measures were taken with a one-minute interval after five minutes of rest, using an automated device (OMRON – HEM-705 CP), with participants sitting in a quiet room at controlled temperature (20°C – 24°C), under fasting conditions and with an empty bladder, following the protocol developed for the study. The mean of the last two measurements was considered for analysis.

Anthropometric indicators

The anthropometric indicators of obesity evaluated were BMI (Kg/m²), which was calculated by dividing weight (Kg) by height (m) squared, and BAI, calculated using the equation: $BAI = ([\text{hip circumference in cm} / \text{height in meters}] 1.5) - 18$.⁶ Central obesity was estimated by measurements of WC (cm) and the WHR, the latter calculated by dividing WC (cm) by hip circumference (cm).

Cardiovascular risk

The risk for cardiovascular events were calculated using the Framingham risk score (FRS), which included age, systolic blood pressure (SBP), systolic diastolic pressure (SDP), total cholesterol, high-density lipoprotein (HDL)-cholesterol, smoking and diabetes for its calculation.²⁹

Diabetes was defined as a history of diabetes, fasting glucose ≥ 126 mg/dL, or a two-hour glucose ≥ 200 mg/dL (oral glucose tolerance test) or glycated hemoglobin $\geq 6.5\%$.

Current smokers were those who reported to smoke regularly in the interview.

An increased risk for cardiovascular events was classified as: “very high” (VH), for individuals with 20% or more 10-year coronary artery disease risk (VHR20%), of “high” for individuals with 10–20% 10-year coronary artery disease risk (HR10%).

Statistical analysis

Central tendency and dispersion measures were used for initial analyses of patient distribution. Descriptive analysis was used to analyze normality of data, by graphic (histogram and P-Plot) and the Shapiro Wilk test. The F-test was used to analyze the homogeneity of variance. Continuous variables with normal distribution were expressed as mean and standard deviation and assessed using the unpaired t-Student test. Continuous variables with non-normal distribution were expressed as median and interquartile range and assessed by the Mann-Whitney U test. Categorical variables were expressed as absolute and relative frequencies and tested by the Pearson's chi-square test.

Then, the cutoff points for the anthropometric indicators (BMI, BAI, WHR and WC) to identify individuals at 20% or more 10-year coronary artery disease risk (VHR20%) were determined by ROC (Receiver Operating Characteristic) curves by age and sex. The maximum value of the Youden index (sensitivity + specificity – 1) was used as the criterion for selecting the optimum cut-off point. Areas under the ROC curves (AUCs) and respective 95% confidence intervals (95% CI) were used to evaluate individual predictive ability of the indicators. The AUCs were compared by the non-parametric test proposed by Delong et al.,³⁰ and differences in the

indicators alone and combined were compared between sexes and age ranges. Also, the AUC of the best combination of indicators was compared with that of the best individual indicator in each group.

Discriminatory ability of indicators was tested either alone or in combinations (indicator of overall obesity with indicator of central obesity. First, four combinations were analyzed (BAI + WC, BMI + WC, BAI + WHR and BMI + WHR), rated and grouped as follows: "0 = both indicators are within normal range"; "1 = indicator of overall obesity only is increased"; "2 = indicator of central obesity only is increased"; "3 = both indicators are increased". For example, in the combination BAI + WC, the groups were: "0 = $BAI_0 + WC_0$ "; "1 = $BAI_1 + WC_0$ "; "2 = $BAI_0 + WC_1$ "; and "3 = $BAI_1 + WC_1$ ".

Subsequently, to determine the adjusted association of indicators of overall obesity with those of central obesity and combinations, another grouping into four categories was made, varying from none to at least one indicator (either overall or central obesity) was increased, i.e., 00, 01, 10, 11. For this purpose, dummies variables were created: 0 = participants without any increased indicator; 1 = participants with at least one indicator of overall obesity increased and indicators of central obesity within normal range; 2 = participants with at least one indicator of central obesity increased and indicators of central obesity within normal range; 3 = the other possible combinations between at least one indicator of central obesity increased and at least one indicator of overall obesity increased.

Associations were tested by Poisson regression models with robust variance, with analysis of the prevalence ratio (PR)

and the 95% CI between the combinations of indicators and VHR20%. Due to the low frequency of VHR20% among young women (0.8%), and the small number of participants at risk in some combinations, an additional analysis was conducted to confirm or not the associations of the anthropometric indicators (alone or in combination) with cardiovascular risk, with HR10% as the outcome.

Model adjustments were assessed by analysis of Pearson residuals.

The significance level was set at 5% ($p < 0.05$), and the statistical analyses were performed using the STATA software program version 12.0.

Results

A total of 6,881 men (28.5% aged between 60 and 74 years) and 8,211 women (26.7% aged between 60 and 74 years) at baseline of the ELSA-Brasil study. Mean values of total cholesterol, SBP, DBP and median age and HDL-cholesterol were higher in participants of both sexes aged 60-74 years compared with younger ones, except DBP and total cholesterol in men.

The prevalence of VHR20% was 6.3% and 40.6% in men aged 35-59 years and 60-74 years, respectively, and 0.8% and 6.1% in women aged 35-59 years and 60-74 years, respectively. A higher prevalence of men with central obesity (WC_1 and WHR_1) was observed compared with women, in both age ranges, with higher prevalence in older (60-74 years) subjects of both sexes. Differences in the percentage of patients with overall obesity varied according to the indicator (Table 1).

Table 1 – Characteristics of participants by sex and age range – ELSA-Brasil (2008-2010)

Variable	Men		Women	
	35-59 years (n= 5,354)	60-74 years (n= 1,527)	35-59 years (n= 6,478)	60-74 years (n= 1,733)
Age, median (IQR)	48 (44-54)*	65 (62-69)*†	49 (44-54)	64 (61-68)†
Total cholesterol, mean (SD)	214.1 (44.6)	207.1 (42.4)*†	214.5 (39.8)	224.2 (45.4)†
HDL-Cholesterol, median (IQR)	48 (42-56)*	50 (43-59)*†	59 (51-70)	62 (52-73)†
Systolic blood pressure, mean (SD)	124.0 (15.7)*	131.1 (19.2)*†	115.1 (15.3)	127.4 (19.1)†
Diastolic blood pressure, mean (SD)	79.2 (10.8)*	77.9 (10.9)*†	73.8 (10.2)	74.8 (10.2)†
HR,10%, n (%)	1.711 (32.0)*	1.285 (84.2)*†	542 (8.4)	613 (35.4%)*†
VHR,20%, n (%)	340 (6.3)*	620 (40.6)*†	52 (0.8)	106 (6.1)†
Diabetes, n (%)	1.301 (19.3)*	569 (37.3)*†	882 (13.6)	484 (27.9)†
Smoking, n (%)	813 (15.2)*	171 (11.2)*†	855 (13.2)	138 (7.9)†
BAI ₁ , n (%)	1.521 (28.4)*	524 (34.3)†	2.468 (38.1)	585 (33.8)†
BMI ₁ , n (%)	2.425 (45.3)*	542 (35.5)†	2.269 (35.0)	583 (33.6)
WC ₁ , n (%)	2.491 (46.5)*	871 (57.0)*†	2.346 (36.2)	682 (39.3)†
WHR ₁ , n (%)	1.761 (32.9)*	892 (58.4)*†	1.351 (20.9)	598 (34.5)†

HDL: high-density lipoprotein; HR10%: high risk (individuals with 10-20% 10-year coronary artery disease risk); VHR20%: very high risk (individuals with 20% or more 10-year coronary artery disease risk); BAI: body adiposity index; BMI: body mass index; WC: waist circumference; WHR: waist-hip ratio; SD: standard deviation; IQR: interquartile range; n (%): number of observations (frequency). * $p < 0.05$ compared with women within the same age group; † $p < 0.05$ compared with younger individuals of the same sex.

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The best cutoff point of each indicator to detect VHR20% and define the groups is listed in Table 2, where 0 means “normal” and 1 “increased”.

Among the anthropometric indicators, WHR showed the highest discriminatory ability for VHR20% in all groups. The AUC for the combination BAI + WHR was higher in men and the AUC for BMI + WHR was higher in women in both age ranges. The performance of all indicators, either alone or in combinations, was better in women than men, except the BAI₁ that did not show statistically significant difference. Likewise, in the comparison of participants between age groups, only BAI₁ in both sexes and BMI₁ in men did not show statistically significant difference.

Compared with individual analyses of the indicators, combined analyses yielded higher sensitivity, except for the BAI + WC and BMI + WC combinations in older men, which had lower sensitivity than the WHR. Sensitivity of all combinations were higher than 70%, reaching values higher than 90% (Table 3) in women aged 35-59 years (Table 3).

Combinations of two indicators had greater predictive capacity than the indicators alone. For example, while AUCs of BMI₁ and WHR₁ in women aged 60-74 years were 0.632 and 0.668, respectively, the AUC of BMI + WHR was 0.710, i.e., an increase of at least 0.042 (0.042/0.668 = 6.3%). The increment with the best combinations varied from 2.1% to 6.3% (Figure 1).

Combinations of one indicator of overall obesity with one indicator of central obesity (BAI₁+WC₁, BAI₁ + WHR₁, BMI₁+WC₁ and BMI₁+WHR₁) were positively associated with VHR20% in men and women in both, regardless of the presence of only one indicator, be it of overall or central obesity. The prevalence ratios of these combinations were also higher than in all other groups (Table 4).

Although the prevalence of women with VHR20% was low (<1%) in the group aged 35-59 years, the number of women

taken as reference (without risk) was very small, which may have explained the wide confidence intervals. Besides, in some strata, the number of participants at risk was small, as in the combination BMI₁+WC₀ in elderly men and women, which made difficult the analyses in these groups. For this reason, we also evaluated the associations of the combinations of anthropometric indicators with HR10%, which confirmed the results that individuals with an increased indicator of overall obesity (BAI or BMI) and an increased indicator of central obesity (WC or WHR) have higher 10-year coronary disease risk (Table 5).

The presence of central obesity (WC₁ and/or WHR₁), in absence of overall obesity (BMI₁ and/or BAI₁) was more strongly associated with VHR20% and HR10% than the reverse combination. The magnitude of the effect of the combined presence of overall and central obesity was greater in all strata, except in the association with VHR20% in younger men (Table 6).

Discussion

BAI₁ showed a modest predictive ability in all groups, with an AUC varying between 0.547 (95%CI: 0.522-0.571) in men aged 60-74 years and 0.628 (95%CI:0.562-0.694) in younger women. This result was similar to BMI₁, since despite the slightly greater AUC values compared with the AUCs of BAI₁ only in the group of younger women, such difference was statistically significant (p<0.05). Of all anthropometric indicators analyzed, the WHR was the one with the best individual performance.

The ROC curves are frequently used to evaluate the performance of a diagnostic test, and probably the most used statistical analysis to measure the predictive ability of anthropometric indicators. Many studies, however, instead of performing a statistical comparison between indicators or the groups, they have been restricted to observing the largest

Table 2 – Cutoff points of anthropometric indicators and respective classifications – ELSA-Brasil (2008-2010)

Indicator	Cutoff point	Categories	Class*
BAI	28 (men)	BAI < 28 (men) or	BAI ₀
	34 (women 35-59 years)	BAI < 34 (women 35-59 years) or BAI < 36 (women 60-74 years)	
	36 (women 60-74 years)	BAI ≥ 28 (men) or	BAI ₁
		BAI ≥ 34 (women 35-59 years) or BAI ≥ 36 (women 60-74 years)	
BMI	27 (men 35-59 years)	BMI < 27 (men 35-59 years) or BMI < 28 (men 60-74 years) or	BMI ₀
	28 (men 60-74 years)	BMI < 34 (women 35-59 years) or BMI < 36 (women 59-74 years)	
	28 (women 35-59 years)	BMI ≥ 27 (men 35-59 years) or BMI ≥ 28 (men 60-74 years) or	BMI ₁
	29 (women 60-74 years)	BMI ≥ 34 (women 35-59 years) or BMI ≥ 36 (women 60-74 years)	
WC	95 (men)	WC < 95 (men) or	WC ₀
	90 (women 35-59 years)	WC < 90 (women 35-59 years) or WC < 93 (women 60-74 years)	
	93 (women 60-74 years)	WC ≥ 95 (men) or	WC ₁
		WC ≥ 90 (women 35-59 years) or WC ≥ 93 (women 60-74 years)	
WHR	0.97 (men)	WHR < 0.97 (men) or	WHR ₀
	0.90 (women 35-59 years)	WHR < 0.90 (women 35-59 years) or WHR < 0.91 (women 60-74 years)	
	0.91 (women 60-74 years)	WHR ≥ 0.97 (men) or	WHR ₁
		WHR ≥ 0.90 (women 35-59 years) or WHR ≥ 0.91 (women 60-74 years)	

BAI: body adiposity index; BMI: body mass index; WC: waist circumference; WHR: waist-hip ratio; * “0 = normal” and “1 = increased”.

Table 3 – Measures of diagnostic accuracy of individual and combined anthropometric indicators of obesity to estimate 20% of coronary risk in 10 years, according to sex and age group. ELSA-Brasil (2008-2010).

	Men 35-59 years (n=5,354)			Men 60-74 years (n=1,527)			
Indicators	SEN (%)	SPE (%)	AUC (95%CI)	SEN (%)	SPE (%)	AUC (95%CI)	p
Individual							
<i>BAI₁</i>	43.2	72.6	0.578 (0.551 – 0.605)	39.8	69.5	0.547 (0.522 – 0.571)	0.080
<i>BMI₁</i>	62.9	55.9	0.594 (0.568 – 0.621)	43.2	69.8	0.565 (0.541 – 0.590)	0.116
<i>WC₁</i>	64.9	54.7	0.598 (0.572 – 0.624)	64.2	47.9	0.560 (0.535 – 0.585)	0.041
<i>WHR₁</i>	62.2	69.1	0.657 (0.630 – 0.683)^{abc}	71.6	50.6	0.611 (0.587 – 0.635)^{abc}	0.013
Combinations							
<i>BAI + WC</i>	70.9	49.3	0.618 (0.589 – 0.647)	70.3	41.7	0.574 (0.549 – 0.601)	0.029
<i>BAI + WHR</i>	75.3	55.7	0.680 (0.652 – 0.707)^{1,3#}	80.3	40.0	0.624 (0.597 – 0.650)^{1,3}	0.004
<i>BMI + WC</i>	71.2	48.3	0.610 (0.583 – 0.638)	64.6	46.6	0.578 (0.550 – 0.605)	0.010
<i>BMI + WHR</i>	77.9	48.4	0.672 (0.645 – 0.700) ^{2,4}	76.0	44.4	0.623 (0.596 – 0.650) ^{2,4}	0.013
	Women 35-59 years (n=6,478)			Women 60-74 years (n=1,733)			
Indicators	SEN (%)	SPE (%)	AUC (95%CI)	SEN (%)	SPE (%)	AUC (95%CI)	p
Individual							
<i>BAI₁</i>	63.5	62.1	0.628 (0.562 – 0.694)	50.9	67.4	0.592 (0.542 – 0.641)	0.389
<i>BMI₁</i>	78.9	65.3	0.721 (0.665 – 0.777) ^{e*}	58.5	68.0	0.632 (0.584 – 0.681) [*]	0.020
<i>WC₁</i>	92.3	64.2	0.783 (0.746 – 0.820) ^{df*}	68.9	62.6	0.657 (0.611 – 0.703) ^{d*}	<0.001
<i>WHR₁</i>	80.8	79.6	0.802 (0.748 – 0.856)^{ab*}	66.0	67.6	0.668 (0.621 – 0.715)^{a*}	<0.001
Combinations							
<i>BAI + WC</i>	94.2	51.6	0.777 (0.734 – 0.820) [*]	75.5	52.6	0.667 (0.618 – 0.717) [*]	0.001
<i>BAI + WHR</i>	98.1	53.2	0.846 (0.810 – 0.882) ^{1,3*}	85.8	48.1	0.709 (0.663 – 0.754) [*]	<0.001
<i>BMI + WC</i>	92.3	59.0	0.786 (0.743 – 0.829) [*]	70.8	57.9	0.668 (0.618 – 0.717) [*]	<0.001
<i>BMI + WHR</i>	96.2	59.4	0.850 (0.811 – 0.889)^{2,4#}	82.1	52.1	0.710 (0.663 – 0.757)^{4#}	<0.001

BAI: body adiposity index; BMI: body mass index; WC: waist circumference; WHR: waist-hip ratio; 95%CI: 95% confidence interval; p: p value when comparing age groups of the same sex. Bold: Highest AUC values in each grouping. $p \leq 0.05$ between individual indicators by sex – SEN: sensitivity; SPE: specificity; AUC: Area under the ROC curves. ^a WHR > BAI; ^b WHR > BMI; ^c WHR > WC; ^d WC > BAI; and BMI > BAI; ^e WC > BMI; between combinations by sex ¹ BAI+WHR > BAI+WC; ² BMI+WHR > BAI+WC; ³ BAI+WHR > BMI+WC; ⁴ BMI+WHR > BMI+WC. * with men of the same age group; # best match with best individual.

AUC, making it difficult to evaluate its performance. In a Chinese study by Xiao et al.,¹² the AUCs were compared, showing that the discriminatory abilities of type 2 diabetes mellitus (DM2), BAI and BMI were not statistically different between men and women. Also, central obesity indicators – WC, WHtR and WHR – were better predictors than DM2 in women than in men.¹² These findings are similar to our results that demonstrated a comparable performance of BMI and BAI in both sexes, and that both WC and WHR were better predictors of coronary risk in women.

Leal Neto et al.¹⁴ did not find statistically significant differences between the AUCs of BAI and BMI ($p=0.885$) in discriminating hypertension in Brazilian elderly (men and women), despite slightly larger AUCs of BAI than BMI. Similar results in the comparison of the discriminatory ability of BAI and BMI were reported in a Colombian study,¹⁰ in identifying elevated blood pressure and glycemia, and metabolic syndrome in women,¹⁰ and in identifying hypertension in a sample of adult men participating in the Olivetti Heart Study.³¹ Nevertheless, BMI was a better discriminator of metabolic syndrome in Korean women.³²

On the other hand, Alvim et al.¹³ pointed out that BAI, compared with WC and BMI, was a better predictor of DM2

in male and female Amerindians in Brazil. However, in a sample of the general population, residents of a capital city, the performance of BAI, BMI and WC was similar in men and WC was a better predictor of DM2 than BAI and BMI in women.

A study conducted with 2,981 Iranians, BAI and BMI had comparable performance as predictors of DM2 in men, whereas BAI was not a good predictor in women (AUC=0.527; 95%CI: 0.484-0.569). A reasonable predictive power of WHR was seen in both men and women; worse than WC and WHtR in men and similar to the other indicators in women.³³

Few studies exist investigating global coronary risk as an outcome, which makes comparison of our results with others difficult. However, Felix-Redondo et al.,²² in a study with 28,743 individuals from Spain, reported a positive association of BMI, WC and WHR with future coronary events, calculated by the REGICOR score, adapted from the FRS and validated for the Spanish population. Almeida et al.¹⁵ identified a positive association between BAI and FRS in 14,673 participants of the ELSA-Brasil study.

Wang et al.,³⁴ evaluated the individual performance of eight anthropometric indicators to estimate coronary risk (using the FRS) in 11,247 Chinese people, and identified a reasonable

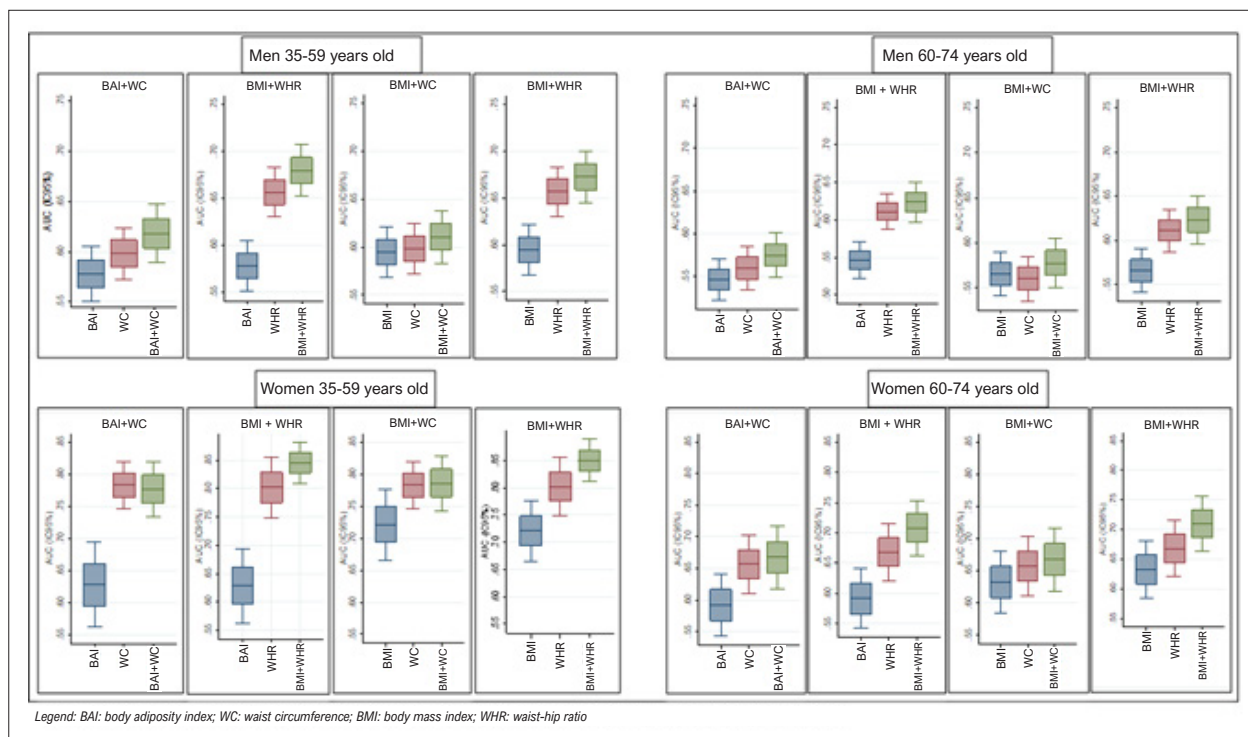


Figure 1 – Graphic representation of areas under the ROC curve of individual and combined anthropometric indicators to identify very-high risk for coronary artery disease by sex and age ranges, ELSA-Brasil 2008-2010.

predictive power. The AUCs varied between 0.59 and 0.70 in women and between 0.52 and 0.60 in men, which was similar to our results. However, largest AUCs were found for the Body Shape Index in men and the WHtR and Body Roundness Index in women, which was not evaluated in the present study.

Some studies^{2,12,19} have suggested that indicators of body fat distribution are better predictors of health risk than indicators of overall obesity, as they provide a better estimate of abdominal fat, which is correlated with the amount of visceral adipose tissue, and consequently to greater production of pro-inflammatory adipokines. Nevertheless, the performance of these indicators in population studies has varied depending on characteristics like age, ethnicity, and sex, as well as on the cut-off points and outcomes analyzed.^{19,23,34} Likewise, studies^{10,14-16} on indicators of overall obesity have shown that genetic, environmental and behavioral components of different ethnic groups may explain differences in their performance, reinforcing the need for more appropriate parameters for screening health risk factors in each population.

In addition, there is no consensus that the combination of anthropometric indicators improves the diagnosis of adverse health effects, and studies using this methodology are scarce.^{19,23-26} Experts continue to search for better indicators or methodological strategies aiming at more accurate screening for diseases in different populations. Combinations of at least one indicator of overall obesity with one indicator of central obesity were more strongly associated with an increased risk of coronary artery disease, even after adjustments for

the presence of either one indicator of overall obesity or of central obesity. All combinations showed higher sensitivity and larger AUCs than the indicators analyzed individually. The combinations BAI + WHR and BMI + WHR showed the largest AUC for men and women, respectively. These findings indicate that this method of analysis seems to be a good alternative to improve the screening for coronary risk factors.

Even considering certain degree of collinearity between indicators of overall and central obesity, which would indicate a reduction in the magnitude of the effect, in all associations, both HR10% and VHR20% were more prevalent in those individuals with increased values of one indicator of overall obesity and one indicator of central obesity concomitantly (BAI₁+WC₁, BAI₁+WHR₁, BMI₁+WC₁, and BMI₁+WHR₁) than the presence of only one indicator increased.

The study by Lam et al.²³ partly corroborate these results in that two indicators combined improve the detection of individuals with cardiometabolic risk factors. However, in their study, the combination of BMI with WHtC, was the one with the best performance in employees of a hospital in Singapore. Likewise, Tao et al.²⁵ showed that two indicators combined improved the predictive ability by up to 19.45% as compared with one indicator alone. The combination of BMI plus WC was the one with the largest AUC to detect hypertension and metabolic syndrome in Chinese men and women, DM2 in men and dyslipidemia in women. Also, this combination was more strongly associated with cardiovascular risk factors in a sample of white individuals from the Third National Health and Nutrition Examination Survey (NHANES III) than any of

Table 4 – Adjusted prevalence ratios of combinations of anthropometric indicators of obesity to estimate very-high risk for coronary artery disease, by sex and age ranges – ELSA-Brasil (2008-2010)

Combinations of indicators	Men				Women			
	35-59 years (n=5,354)		60-74 years (n=1,527)		35-59 years (n=6,478)		60-74 years (n=1,733)	
	n (risk)	PR (95%CI)	n (risk)	PR (95%CI)	n (risk)	PR (95%CI)	n (risk)	PR (95%CI)
BAI ₀ + WC ₀	2,573 (99)	1.0	562 (184)	1.0	3,321 (3)	1.0	881 (26)	1.0
BAI ₁ + WC ₀	290 (20)	1.79 (1.13 – 2.85)	94 (38)	1.23 (0.94 – 1.62)	811 (1)	1.36 (0.14 – 13.11)	170 (7)	1.40 (0.62 – 3.16)
BAI ₀ + WC ₁	1,260 (94)	1.94 (1.47 – 2.55)	441 (189)	1.31 (1.12 – 1.54)	689 (16)	25.70 (7.51 – 87.99)	267 (26)	3.30 (1.95 – 5.58)
BAI ₁ + WC ₁	1,231 (126)	2.66 (2.06 – 3.43)	430 (209)	1.48 (1.27 – 1.73)	1,657 (32)	21.38 (6.55 – 69.72)	415 (47)	3.84 (2.41 – 6.11)
BAI ₀ + WHR ₀	2,876 (84)	1.0	485 (122)	1.0	3,420 (1)	1.0	798 (15)	1.0
BAI ₁ + WHR ₀	717 (44)	2.10 (1.47 – 3.00)	150 (54)	1.43 (1.10 – 1.86)	1,707 (9)	18.03 (2.29 – 142.22)	337 (21)	3.32 (1.73 – 6.35)
BAI ₀ + WHR ₁	957 (109)	3.90 (2.96 – 5.13)	518 (251)	1.93 (1.61 – 2.30)	590 (18)	104.33 (13.95 – 780.18)	350 (37)	5.62 (3.13 – 10.11)
BAI ₁ + WHR ₁	804 (102)	4.34 (3.29 – 5.74)	374 (193)	2.05 (1.71 – 2.46)	761 (24)	107.85 (14.62 – 796.13)	248 (33)	7.08 (3.91 – 12.82)
BMI ₀ + WC ₀	2,521(98)	1.0	642 (219)	1.0	3,795 (4)	1.0	973 (31)	1.0
BMI ₁ + WC ₀	342 (21)	1.58 (1.00 – 2.50)	14 (3)	0.63 (0.23 – 1.72)	337 (0)	----	78 (2)	0.80 (0.20 – 3.30)
BMI ₀ + WC ₁	408 (28)	1.76 (1.17 – 2.65)	343 (133)	1.14 (0.96 – 1.35)	414 (7)	16.04 (4.71 – 54.61)	177 (13)	2.31 (1.23 – 4.32)
BMI ₁ + WC ₁	2,083 (192)	2.37 (1.87 – 3.00)	528 (265)	1.47 (1.28 – 1.69)	1,932 (41)	20.14 (7.22 – 56.19)	505 (60)	3.73 (2.45 – 5.68)
BMI ₀ + WHR ₀	2,500 (75)	1.0	552 (149)	1.0	3,820 (2)	1.0	866 (19)	1.0
BMI ₁ + WHR ₀	1,093 (53)	1.62 (1.15 – 2.28)	83 (27)	1.21 (0.86 – 1.69)	1,307 (8)	11.69 (2.48 – 54.99)	269 (17)	2.88 (1.52 – 5.46)
BMI ₀ + WHR ₁	429 (51)	3.96 (2.82 – 5.57)	433 (203)	1.74 (1.46 – 2.06)	389 (9)	44.19 (9.58 – 203.82)	284 (25)	4.01 (2.24 – 7.18)
BMI ₁ + WHR ₁	1,332 (160)	4.00 (3.07 – 5.22)	459 (241)	1.95 (1.65 – 2.19)	962 (33)	65.52 (15.75 – 272.60)	314 (45)	6.53 (3.88 – 10.99)

BAI: body adiposity index; BMI: body mass index; WC: waist circumference; WHR: waist-hip ratio; PR: prevalence ratio; 95%CI: 95% confidence interval; n: number of participants in the subgroup; risk: number of participants at very-high risk for coronary events

Table 5 – Adjusted prevalence ratios of combinations of anthropometric indicators of obesity to estimate high risk for coronary artery disease, by sex and age ranges – ELSA-Brasil (2008–2010)

Combinations of indicators	Men				Women			
	35–59 years (n=5,354)		60–74 years (n=1,527)		35–59 years (n=6,478)		60–74 years (n=1,733)	
	n (risk)	PR (95%CI)	n (risk)	PR (95%CI)	n (risk)	PR (95%CI)	n (risk)	PR (95%CI)
BAI₀ + WC₀	2,573 (559)	1.0	562 (430)	1.0	3,321 (137)	1.0	881 (213)	1.0
BAI₁ + WC₀	290 (94)	1.49 (1.24 – 1.79)	94 (77)	1.07 (0.96 – 1.19)	811 (35)	1.05 (0.73 – 1.50)	170 (49)	1.19 (0.92 – 1.55)
BAI₀ + WC₁	1,260 (485)	1.77 (1.60 – 1.96)	441 (386)	1.14 (1.08 – 1.21)	689 (106)	3.73 (2.93 – 4.74)	267 (132)	2.04 (1.73 – 2.42)
BAI₁ + WC₁	1,231 (572)	2.14 (1.94 – 2.35)	430 (209)	1.19 (1.13 – 1.26)	1,657 (264)	3.86 (3.17 – 4.71)	415 (219)	2.18 (1.88 – 2.53)
BAI₀ + WHR₀	2,876 (607)	1.0	485 (345)	1.0	3,420 (125)	1.0	798 (161)	1.0
BAI₁ + WHR₀	717 (239)	1.58 (1.39 – 1.79)	150 (127)	1.19 (1.09 – 1.30)	1,707 (117)	1.88 (1.47 – 2.40)	337 (122)	1.79 (1.47 – 2.19)
BAI₀ + WHR₁	957 (437)	2.16 (1.96 – 2.39)	518 (471)	1.28 (1.20 – 1.36)	590 (118)	5.47 (4.32 – 6.93)	350 (184)	2.61 (2.20 – 3.09)
BAI₁ + WHR₁	804 (427)	2.52 (2.29 – 2.77)	374 (342)	1.29 (1.20 – 1.37)	761 (182)	6.54 (5.28 – 8.10)	248 (146)	2.92 (2.45 – 3.47)
BMI₀ + WC₀	2,521 (562)	1.0	642 (498)	1.0	3,795 (146)	1.0	973 (233)	1.0
BMI₁ + WC₀	342 (91)	1.19 (0.99 – 1.44)	14 (9)	0.83 (0.56 – 1.23)	337 (26)	2.00 (1.34 – 3.00)	78 (29)	1.55 (1.14 – 2.12)
BMI₀ + WC₁	408 (154)	1.69 (1.47 – 1.96)	343 (299)	1.12 (1.06 – 1.19)	414 (57)	3.58 (2.68 – 4.78)	177 (85)	2.01 (1.66 – 2.42)
BMI₁ + WC₁	2,083 (903)	1.94 (1.78 – 2.12)	528 (479)	1.17 (1.11 – 1.23)	1,932 (313)	4.21 (3.49 – 5.09)	505 (266)	2.20 (1.91 – 2.53)
BMI₀ + WHR₀	2,500 (512)	1.0	552 (401)	1.0	3,820 (131)	1.0	866 (172)	1.0
BMI₁ + WHR₀	1,093 (334)	1.49 (1.33 – 1.68)	83 (71)	1.18 (1.06 – 1.30)	1,307 (111)	2.48 (1.94 – 3.16)	269 (111)	2.08 (1.71 – 2.53)
BMI₀ + WHR₁	429 (204)	2.32 (2.05 – 2.63)	433 (396)	1.26 (1.19 – 1.34)	389 (72)	5.40 (4.13 – 7.06)	284 (146)	2.59 (2.17 – 3.08)
BMI₁ + WHR₁	1,332 (660)	2.42 (2.20 – 2.66)	459 (417)	1.25 (1.18 – 1.33)	962 (228)	6.91 (5.64 – 8.47)	314 (184)	2.95 (2.51 – 3.47)

BAI: body adiposity index; BMI: body mass index; WC: waist circumference; WHR: waist-hip ratio; PR: prevalence ratio; 95%CI: 95% confidence interval; n: number of participants in the subgroup; risk: number of participants at very-high risk for coronary events

Table 6 – Prevalence ratios of anthropometric indicators of overall and central obesity to estimate very high and high 10-year coronary artery disease risk by sex and age range – ELSA-Brasil (2008-2010)

Combinations of indicators	Very-high risk (VHR20%)					
	Men			Women		
	35-59 years (n=5,354)	60-74 years (n=1,527)	35-59 years (n=6,478)	60-74 years (n=1,733)		
	n (risk)	PR (95%CI)	n (risk)	PR (95%CI)	n (risk)	PR (95%CI)
Without risk	2,201 (63)	1.0	421 (111)	1.0	721 (13)	1.0
Overall obesity only	438 (23)	1.83 (1.15 – 2.92)	81 (28)	1.31 (0.93 – 1.84)	168 (7)	2.31 (0.97 – 5.70)
Central obesity only	585 (55)	3.28 (2.31 – 4.66)	440 (199)	1.72 (1.42 – 2.07)	303 (25)	4.58 (2.37 – 8.83)
Central + Overall	2,130 (198)	3.25 (2.46 – 4.28)	585 (282)	1.83 (1.53 – 2.19)	541 (61)	6.25 (3.47 – 11.26)
	High risk (HR10%)					
Without risk	2,201 (425)	1.0	421 (300)	1.0	721 (135)	1.0
Overall obesity only	438 (118)	1.40 (1.17 – 1.66)	81 (63)	1.09 (0.96 – 1.24)	168 (48)	1.53 (1.15 – 2.03)
Central obesity only	585 (242)	2.14 (1.88 – 2.47)	440 (393)	1.25 (1.17 – 1.34)	303 (144)	2.54 (2.09 – 3.08)
Central + Overall	2,130 (925)	2.25 (2.04 – 2.48)	585 (529)	1.27 (1.19 – 1.36)	541 (286)	2.82 (2.38 – 3.35)

PR: prevalence ratio; 95%CI: 95% confidence interval; n: number of participants in the subgroup; risk: number of participants at risk for future coronary events

the indicators alone.²⁴ It is worth mentioning that these two last studies did not evaluate BAI.

The main strength of the present study is the fact that this is the first study to test combinations of BAI with other indicators of central obesity to estimate coronary risk, including separate analysis of men and women in different age ranges. The results indicated that the combined use of an indicator of overall obesity with another of central obesity improves the identification of adult people or populations at higher 10-year risk of coronary events. Also, the study presents statistical comparisons of AUCs of the indicators (individually and combined) between sexes and age ranges.

However, there are potential limitations that should be considered. First, the cross-sectional design of the study does not allow inferences about the causal relationship between anthropometric measures of obesity and future coronary risk. Nevertheless, a reverse causality seems improbable, and strong evidence supports that obesity is a risk factor for cardiovascular disease.^{5,20-22} The follow-up of participants of the ELSA-Brasil study will allow to assess whether the combination of obesity indicators is a better predictor of coronary risk than the indicator alone. Another limitation is the external validity, since the sample population from the ELSA-Brasil study is not representative of the Brazilian population, as it does not include extreme segments such as the richer and poorer income groups. However, this is a large, multicenter and heterogeneous sample, able to provide new insights of the relationship of overall and central obesity indicators with coronary risk in heterogeneous populations. Therefore, further investigations with other populations, as well as longitudinal studies and examination of other combinations of obesity indicators are warranted.

Conclusion

The WHR showed the best individual performance in both sexes and both age ranges. Combinations of at least one indicator of overall obesity with another of central obesity were more strongly associated with the risk of coronary artery disease. The combinations BAI+WHR and BMI + WHR yielded the largest AUCs in men and women, respectively. Thus, the combined use of one indicator of overall obesity

(BAI or BMI, according to sex) with WHR is recommended as a screening strategy for coronary risk in adults. However, in low-income settings or in cases where a weighing scale for body weight is not available, a measuring tape can be used to measure hip circumference, WC and height, calculate BAI and WHR and perform risk assessment, since the performance of this combination was comparable to that of BMI + WHR in women.

Author Contributions

Conception and design of the research, Acquisition of data, Analysis and interpretation of the data, Writing of the manuscript and Critical revision of the manuscript for intellectual content: Almeida RT, Matos SMA, Aquino EML; Statistical analysis: Almeida RT; Obtaining financing: Aquino EML.

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, Fiocruz, Hospital Universitário –USP, UFMG, UFES e Hospital as Clínicas de Porto Alegre under the protocol number 027/06, 343/06, 669/06, 186/06, 041/06, 194/06. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

References

1. Almeida RT, Almeida MMG, Araújo TM. Obesidade Abdominal e risco Cardiovascular: Desempenho de Indicadores Antropométricos em mulheres. *Arq Bras Cardiol.* 2009;92(5):375–80.
2. Pitanga FJG, 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.
3. Rezende F, Rosado L, Franceschini S, Rosado G, Ribeiro R, Marins JCB. Revisão crítica dos métodos disponíveis para avaliar a composição corporal em grandes estudos populacionais e clínicos. *Arch Latinoam Nutr.* 2007;57(4):327–34.
4. Eknoyan G. Adolphe Quetelet (1796-1874) the average man and indices of obesity. *Nephrol Dial Transplant.* 2007;23(1):47–51.
5. Dwivedi AK, Dubey P, Cistola DP, Reddy SY. Association Between Obesity and Cardiovascular Outcomes: Updated Evidence from Meta-analysis Studies. *Curr Cardiol Rep.* 2020;22(4).
6. Bergman RN, Stefanovski D, Buchanan TA, Sumner AE, Reynolds JC, Sebring NG, et al. A better index of body adiposity. *Obesity.* 2011;19(5):1083–9.
7. Lam BCC, Lim SC, Wong MTK, Shum E, Ho CY, Bosco JIE, et al. A method comparison study to validate a novel parameter of obesity, the body adiposity index, in Chinese subjects. *Obesity.* 2013;21(12):E634–9.
8. Kuhn PC, Vieira Filho JPB, Franco L, Dal Fabbro A, Franco LJ, Moises RS. Evaluation of body adiposity index (BAI) to estimate percent body fat in an indigenous population. *Clin Nutr.* 2014;33(2):287–90.
9. López AA, Cespedes ML, Vicente T, Tomas M, Bannasar-Veny M, Tauler P, et al. Body adiposity index utilization in a Spanish Mediterranean population: comparison with the body mass index. *PLoS One.* 2012;7(4):e35281.

10. Mora-García GJ, Gómez-Camargo D, Mazenett E, Alario Á, Fortich Á, Gómez-Alegría C, et al. Anthropometric parameters' cut-off points and predictive value for metabolic syndrome in women from Cartagena, Colombia. *Salud Publica Mex.* 2014;56(2):146–53.
11. Bennasar-Veny M, Lopez-Gonzalez AA, Tauler P, Cespedes ML, Vicente-Herrero T, Yañez A, et al. Body Adiposity Index and Cardiovascular Health Risk Factors in Caucasians: A Comparison with the Body Mass Index and Others. *PLoS One.* 2013;8(5):e63999.
12. Xiao X, Liu YY, Sun C, Gang X, Cheng J, Tian S, et al. Evaluation of different obesity indices as predictors of type 2 diabetes mellitus in a Chinese population. *J Diabetes.* 2015;7(3):386–92.
13. Alvim RO, Mourao-Junior CA, Oliveira CM, Krieger JE, Mill JG, Pereira AC. Body mass index, waist circumference, body adiposity index, and risk for type 2 diabetes in two populations in Brazil: General and Amerindian. *PLoS One.* 2014;9(6):e100223.
14. Leal Neto JS, Coqueiro RS, Freitas RS, Fernandes MH, Oliveira DS, Barbosa AR. Anthropometric indicators of obesity as screening tools for high blood pressure in the elderly. *Int J Nurs Pract.* 2013;19(4):360–7.
15. Almeida RT, Pereira AC, Fonseca MJM, Matos SMA, Aquino EML. Association between body adiposity index and coronary risk in the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil). *Clin Nutr.* 2020;39(5):1423–31.
16. Mussi RFF, Petroski EL. Indicadores de obesidade: capacidade preditiva para síndrome metabólica em adultos quilombolas. *Cien Saude Colet.* 2019;24(7):2471–80.
17. Eickemberg M, Amorim LDAF, Almeida MCC, Aquino EML, Fonseca MJM, Santos IS, et al. 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):220–7.
18. Coutinho T, Goel K, Corrêa de Sá D, Carter RE, Hodge DO, Kragelund C, et al. Combining body mass index with measures of central obesity in the assessment of mortality in subjects with coronary disease: Role of "normal weight central obesity". *J Am Coll Cardiol.* 2013;61(5):553–60.
19. Lee CMY, Huxley RR, Wildman RP, Woodward M. Indices of abdominal obesity are better discriminators of cardiovascular risk factors than BMI: a meta-analysis. *J Clin Epidemiol.* 2008;61(7):646–53.
20. Wormser D, Kaptoge S, Di Angelantonio E, Wood AM, Pennells L, Thompson A, et al. Separate and combined associations of body-mass index and abdominal adiposity with cardiovascular disease: collaborative analysis of 58 prospective studies. *Lancet.* 2011;377(9771):1085–95.
21. Van-Dijk SB, Takken T, Prinsen EC, Wittink H. Different anthropometric adiposity measures and their association with cardiovascular disease risk factors: a meta-analysis. *Neth Hear J.* 2012;20(5):208–18.
22. Félix-Redondo FJ, Grau M, Baena-Díez JM, Dégano IR, De León AC, Guembe MJ, et al. Prevalence of obesity and associated cardiovascular risk: The DARIOS study. *BMC Public Health.* 2013;13(1).
23. Lam BCC, Koh GCH, Chen C, Wong MTK, Fallows SJ. Comparison of Body Mass Index (BMI), Body Adiposity Index (BAI), Waist Circumference (WC), Waist-To-Hip Ratio (WHR) and Waist-To-Height Ratio (WHtR) as predictors of cardiovascular disease risk factors in an adult population in Singapore. *PLoS One.* 2015;10(4):e0122985.
24. Zhu S, Heshka S, Wang Z, Shen W, Allison DB, Ross R, et al. Combination of BMI and Waist Circumference for Identifying Cardiovascular Risk Factors in Whites. *Obes Res.* 2004;12(4):633–45.
25. Tao Y, Yu J, Tao Y, Pang H, Yu Y, Yu Y, et al. Comparison of the Combined Obesity Indices to Predict Cardiovascular Diseases Risk Factors and Metabolic Syndrome in Northeast China. *Int J Environ Res Public Health.* 2016;13(8):801.
26. Whitlock G, Lewington S, Sherliker P, Clarke R, Emberson J, Halsey J, et al. Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies. *Lancet.* 2009;373(9669):1083–96.
27. Aquino EML, Barreto SM, Bensenor IM, Carvalho MS, Chor D, Duncan BB, et al. Brazilian Longitudinal Study of Adult Health (ELSA-Brasil): objectives and design. *Am J Epidemiol.* 2012;175(4):315–24.
28. International Society for the Advancement of Kinanthropometry (ISAK). International Standards for Anthropometric Assessment. Adelaide: National Library of Australia; 2001.
29. Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. *Circulation.* 1998;97(18):1837–47.
30. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics.* 1988;44(3):837–45.
31. D'Elia L, Manfredi M, Sabino P, Strazzullo P, Galletti F. The Olivetti Heart Study: Predictive value of a new adiposity index on risk of hypertension, blood pressure, and subclinical organ damage. *Nutr Metab Cardiovasc Dis.* 2016;26(7):630–6.
32. Sung Y-A, Oh J-Y, Lee H. Comparison of the body adiposity index to body mass index in Korean women. *Yonsei Med J.* 2014;55(4):1028–35.
33. Talaie M, Sadeghi M, Marshall T, Thomas GN, Iranipour R, Nazarat N, et al. Anthropometric indices predicting incident type 2 diabetes in an Iranian population: the Isfahan Cohort Study. *Diabetes Metab.* 2013;39(5):424–31.
34. Wang F, Chen Y, Chang Y, Sun G, Sun Y. New anthropometric indices or old ones: which perform better in estimating cardiovascular risks in Chinese adults. *BMC Cardiovasc Disord.* 2018;18(1):14.



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A Key Strategy to Predict Cardiovascular Diseases: A Combination of Anthropometric Indices

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Short Editorial related to the article: Individual and Combined Performance of Indicators of Overall and Central Obesity to Estimate Coronary Risk in ELSA-Brazil Participants

The obesity pandemic is one of the most pressing health concerns of the 21st century. Prevalent even among developed and developing countries, this disease has been related to cardiovascular events, dyslipidemia, type 2 diabetes, sleep disorders, and cancer. It has recently been considered a risk factor for critical illness in coronavirus disease-2019 (COVID-19) pandemic.^{1,2}

In Brazil, the National Health Survey, in partnership with the Ministry of Health, found that obesity has gradually increased over the last 17 years in adult women (14.5% to 30.2%) and men (9.6% to 22.8%). Its prevalence has more than doubled between 2003 and 2019.³ A collaborative effort between the government, public health officers, and medical staff is needed to manage the complex and multifactorial obesity issue.

In everyday clinical practice, obesity is assessed using body weight and excessive fat measurement. In addition to the body mass index (BMI), independent anthropometric indices, including the waist circumference (WC), waist-to-hip ratio (WHR), and body adiposity index (BAI), are accessible means for evaluating abdominal obesity. Despite the availability and safety when obtaining these parameters, the appropriate indices for predicting the development of cardiovascular disease (CVD) across different ages, genders, and ethnicity, remain unknown.⁴

Several Brazilian studies have obtained conflicting results when evaluating the anthropometric measures and risk of CVD development in adults. Barroso et al. found that central obesity, but not BMI, was a predictor of CVD in adult women.⁵ WC was considered the most appropriate alternative screening tool to identify Quilombola women with the most significant risk for CVD.⁶ Another study reported that the BMI, WC, and WHR were viable predictors of CVD in men, while BMI was the most reliable predictor for women.⁷ Hachbardt et al.⁸ recently showed that BMI was associated with WC, related to CVD risk, but not WHR.⁸ By resolving the conflicting results of these studies, the gold standard anthropometric indicator of adiposity for predicting CVD can

be established. These studies were conducted in different time periods, and their sample sizes were not representative of the country's entire population.

The Brazilian Longitudinal Study of Adult Health (ELSA-Brazil) has reported the association between anthropometric indicators of obesity and CVD in a large sample of women and men.⁹ The neck circumference parameter and BAI index have been proposed as predictors of a 10-year risk for developing coronary disease.^{10,11}

In this issue of the *Arquivos Brasileiros de Cardiologia*, the ELSA-Brazil team has proposed a novel CVD prediction method based on the combination of the anthropometric parameters. The first merit of the study was that Almeida et al.¹² were the first group to investigate the predictive ability of individual or combined anthropometric parameters for coronary risk in 15,092 Brazilian individuals.¹² In addition to the individual analysis of obesity parameters, the authors created four combinations (BAI plus WC, BMI plus WC, BAI plus WHR, and BMI plus WHR) to test their hypotheses. The second positive point of the study was to associate one overall obesity parameter with one central obesity indicator. To characterize an increased risk for cardiovascular events, individuals were classified in the following groups: VHR20% - for those with 20% or more of a 10-year coronary artery disease risk; and HR10%, for subjects with 10-20% of a 10-year coronary artery disease risk.

Below are the main findings of the study: For individual parameters, WHR was the most reliable parameter for VHR20% in both sexes. When analyzing combinations, WHR plus BAI was the most reliable predictor for men, while WHR plus BMI was the most reliable predictor for women with VHR20%. In addition, individuals with HR10% had a higher 10-year coronary disease risk when an increased BAI or BMI was combined with a higher WC or WHR.¹² In summary, the combinations of at least one overall obesity parameter and one central obesity parameter were the main predictors of coronary risk development in 10 years.

These data highlighted the importance of including grouped measures for analyzing CVD profiles. The information obtained in this study is essential for reviewing and updating the clinical guidelines and public health policies. The Brazilian population is heterogeneous in terms of social, economic, and health conditions.¹² Thus, future analyses should include a representative sample size to better understand this disease and its management. Also, the research of Almeida et al.¹² can open up ways for new studies that will identify the ideal markers in other groups, as the Brazilian youth population, comparing the association of combined anthropometric parameters on CVD risk development.

It is time to act to protect our hearts.

Keywords

Anthropometry; Cardiovascular Diseases; Obesity; Pandemics; Risk Factors.

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References

1. KY SK, Bhat PKR, Sorake CJ. Double Trouble: A Pandemic of Obesity and COVID-19. *Lancet Gastroenterol Hepatol*. 2021;6(8):608. doi: 10.1016/S2468-1253(21)00190-4.
2. Jardim PCBV. Overweight, the Cardiovascular Risk of the Century. *Arq Bras Cardiol*. 2019;113(2):185-7. doi: 10.5935/abc.20190171.
3. Instituto Brasileiro de Geografia e Estatística. Pesquisa Nacional de Saúde 2019: Atenção Primária à Saúde e Informações Antropométricas. Rio de Janeiro: IBGE. 2020.
4. Ross R, Neeland IJ, Yamashita S, Shai I, Seidell J, Magni P, et al. Waist Circumference as a Vital Sign in Clinical Practice: A Consensus Statement from the IAS and ICCR Working Group on Visceral Obesity. *Nat Rev Endocrinol*. 2020;16(3):177-89. doi: 10.1038/s41574-019-0310-7.
5. Barroso TA, Marins LB, Alves R, Gonçalves ACS, Barroso SG, Rocha GS. Association of Central Obesity with The Incidence of Cardiovascular Diseases and Risk Factors. *Int J Cardiovasc Sci*. 2017;30(5):416-24. <https://doi.org/10.5935/2359-4802.20170073>.
6. Ferreira HS, Soares ML, Krakauer NY, Santos EA, Krakauer JC, Uchôa TC, et al. What is the Best Anthropometric Predictor for Identifying Higher Risk for Cardiovascular Diseases in Afro-Descendant Brazilian Women? A Cross-Sectional Population-Based Study. *Am J Hum Biol*. 2021:e23652. doi: 10.1002/ajhb.23652.
7. Martins MV, Ribeiro AQ, Martinho KO, Franco FS, Souza JD, Morais KBD, et al. Anthropometric Indicators of Obesity as Predictors of Cardiovascular Risk in the Elderly. *Nutr Hosp*. 2015;31(6):2583-9. doi: 10.3305/nh.2015.31.6.8372.
8. Hachbardt NB, Hattori TY, Nascimento VF, Silva JH, Terças-Trettel ACP, Oliveira VKV, et al. Cardiovascular Risk in Women Deprived of Freedom from a Public Prison in Mato Grosso, Brazil. *High Blood Press Cardiovasc Prev*. 2020;27(2):139-50. doi: 10.1007/s40292-020-00365-2.
9. Eickemberg M, Amorim LDAF, Almeida MDCC, Aquino EML, Fonseca MJMD, Santos IS, et al. Indicators of Abdominal Adiposity and Carotid Intima-Media Thickness: Results from the Longitudinal Study of Adult Health (ELSA-Brazil). *Arq Bras Cardiol*. 2019;112(3):220-7. doi: 10.5935/abc.20180273.
10. Silva AAGO, Araujo LF, Diniz MFHS, Lotufo PA, Bensenor IM, Barreto SM, et al. Neck Circumference and 10-Year Cardiovascular Risk at the Baseline of the ELSA-Brasil Study: Difference by Sex. *Arq Bras Cardiol*. 2020;115(5):840-8. doi: 10.36660/abc.20190289.
11. Almeida RT, Pereira ADC, Fonseca MJMD, Matos SMA, Aquino EML. Association Between Body Adiposity Index and Coronary Risk in the Brazilian Longitudinal Study of Adult Health (ELSA-Brazil). *Clin Nutr*. 2020;39(5):1423-31. doi: 10.1016/j.clnu.2019.06.001.
12. Almeida RT, Matos SMA, Aquino EML. Individual and Combined Performance of Indicators of Overall and Central Obesity to Estimate Coronary Risk in ELSA-Brasil Participants. *Arq Bras Cardiol*. 2021;117(4):701-712.



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Novel Cardioprotective Effect of L-Carnitine on Obese Diabetic Mice: Regulation of Chemerin and CMKLRI Expression in Heart and Adipose Tissues

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Abstract

Background: L-carnitine (LC) has many beneficial effects on diabetic animals and humans, but its regulatory effect on chemerin as an inflammatory cytokine, and its receptor in diabetes status is unknown.

Objectives: The present study aimed to investigate the regulatory effect of LC on the expression of chemerin and chemokine-like receptor 1 (CMKLRI) in adipose and cardiac tissues of diabetic mice.

Methods: Sixty NMRI mice were divided into four groups including control, diabetic, diabetic + LC supplementation and control + LC supplementation. Diabetes was induced by feeding the animals a high-calorie diet for 5 weeks and injection of Streptozotocin. The animals were treated with 300 mg/kg LC for 28 days. On days 7, 14, and 28 after treatment, the mRNA and protein levels of chemerin and CMKLRI in the cardiac and adipose tissues of the animals were determined using qPCR analysis and ELISA. Insulin resistance indices were also measured in all experimental groups. Differences with $p < 0.05$ were considered significant.

Results: Chemerin and CMKLRI expressions levels were increased in cardiac and adipose tissues of diabetic mice on days 14 and 28 after diabetes induction, concurrent with the incidence of insulin resistance and increased levels of circulating chemerin ($p < 0.05$). The treatment with LC caused a significant decrease in the expression of both genes in studied tissues and the reduction of insulin resistance symptoms and serum chemerin levels ($p < 0.05$).

Conclusion: The results suggest that LC treatment were able to downregulate the expression of chemerin and CKLR1 in cardiac and adipose tissues of obese, diabetic experimental animals.

Keywords: Diabetes Mellitus; Carnitine; Chemokines.

Introduction

A growing body of evidence has shown the existence of a complex and multifaceted biochemical and molecular relationship between diabetes mellitus (DM), obesity and cardiovascular diseases (CVDs).¹ One possible mechanism linking DM and obesity with subsequent CVDs is low-grade inflammation in adipose tissue.² The adipose tissue of animals or humans with DM and insulin resistance secretes a variety of cytokines or adipocytokines. The abnormal secretion of these adipocytokines contributes to increased inflammation and lipid accumulation and can lead to the development of endothelial and myocardial dysfunction and cardiomyopathies.^{2,3} The alterations in the expression or secretion of pro-inflammatory and anti-inflammatory

adipokines in cardiomyocytes and adipose tissue have been implicated in the pathogenesis of metabolic syndrome and CVDs in obese animals or humans.²

Chemerin is a recently identified adipokine that acts as a chemoattractant protein and mediates its effects through a G-protein coupled receptor, the chemokine-like receptor 1 (CMKLRI), also known as ChemR23.⁴⁻⁷ Previous studies demonstrated that chemerin had a role in various cardiovascular pathologies, including the development of hypertension, progression of atherosclerotic lesions, and impaired heart function in patients with dilated cardiomyopathy.⁸ Chemerin can promote endothelial inflammation, and induce apoptosis in murine cardiomyocytes, demonstrating the potential role of chemerin in cardiomyocyte dysfunctions.^{9,10}

Recently, mitochondrial-targeting nutrients, such as lipoic acid, L-carnitine (LC), nicotinamide and biotin have been given more attention regarding the improvement of diabetes-related inflammatory and cardiovascular complications.^{11,12} L-carnitine (LC) is a conditionally essential nutrient that facilitates fatty acid transport to the oxidation sites in the mitochondria.^{13,14}

There is increasing evidence that LC supplementation may be beneficial in treating insulin-resistance and obesity-related metabolic disturbances in diabetic patients.¹¹ Various studies have shown that LC has beneficial effects on the prevention and improvement of cardiovascular disease, including

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chronic heart failure, anterior acute myocardial infarction, coronary artery disease, myocardial remodeling and atrial fibrillation.^{12,14} Several mechanisms have been reported regarding the protective role of LC in cardiac cells under hyperglycemic conditions, including improvement of cardiac energy homeostasis, oxidative stress attenuation and hypoxic cell damage and apoptosis reduction.^{15,16} Limited evidence has also shown that LC may affect serum chemerin levels in obese children.¹⁷ Based on our knowledge, a few studies have focused on the role of LC supplementation on chemerin expression regulation, particularly in cardiac and adipose tissues of diabetic animals. The aim of the present study was to investigate the effects of LC supplementation on chemerin and CMKLRI expression in adipose and cardiac tissues in an experimental model of obesity and diabetes induced by a high-calorie diet fed to mice.

Materials and methods

Animals

Sixty male NMARI mice (25 ± 2 g) were selected from the Center of Laboratory Animals of the School of Veterinary Medicine of Shahid Chamran University of Ahvaz, Iran. All the mice were kept under controlled environmental conditions, with an average temperature of 23 ± 1 °C, a 12:12 h light/darkness cycle and free access to water and special diet for mice prepared as pellet (Pars, Tehran, Iran). All experimental protocols were approved by the Ethics Committee for Research in Animals and Humans of Shahid Chamran University of Ahvaz (EE/98.24.3.26209/SCU.AC.IR). All animal experimentations were carried out in accordance with the guidelines for the care and use of laboratory animals (NIH publication n. 86-23). There was an adaptation period of 7 days before the start of the experiment.

Experimental design

The animals ($n=60$) were randomly divided into four equal groups. Randomization was achieved by allocating the animals of the same sex, age and weight in different experimental groups using random number tables. Two groups were fed a high-energy diet, which was prepared by adding 20% sucrose (w/w) and 10% lard (w/w) into the diets for 5 weeks and described as HF/HC ($n=30$), whereas the other ones continued to consume normal diets for the same period, serving as a control groups ($n=30$). After 5-weeks receiving the HF/HC diets, the diabetic groups were treated with a single intraperitoneal injection of STZ (Sigma, Germany) (30 mg/kg body weight) prepared in a citrate buffer solution.^{18,19}

Blood glucose was measured five days after STZ treatment using a hand-held glucometer (Medisign, China) and the presence of diabetes was confirmed if serum glucose was over 6.5 mmol/L and if the HOMA-IR was high in comparison to the control group.²⁰ The day following the confirmation of diabetes was considered as day 0 of LC treatment. One diabetic group was treated with LC at a dose of 300 mg/kg ($n=15$) in drinking water, while concomitantly being fed the HF/HC diets for 28 days, while the other diabetic group ($n=15$) (diabetic control) were fed only HF/HC diets for the same period.^{18,19}

One control group ($n=15$) that received a normal diet and the other control group ($n=15$) (LC-treated control) that consumed LC at dose of 300 mg/kg in drinking water for 28 days were also considered for the analyses.

Sampling

Animal euthanasia was carried out with a combination of ketamine (100 mg/kg) and xylazine (10 mg/kg) respectively, on days 0, 14 and 28 of LC treatment. Blood samples were collected, and sera were separated and stored at -20°C for later use. Hearts and visceral adipose tissues were separated and kept at -70°C until use.

Biochemical parameter measurements

Serum insulin and chemerin levels were determined using the species-specific ELISA kits (EastBioPharm, China). Serum glucose was measured by commercial kits (PishtazTeb, Iran) according to the manufacturer's recommendations. Serum IL1- β and TNF- α levels were determined using species-specific ELISA kits, as recommended by the manufacturer (Biovision Inc. USA)

HOMA-IR Estimation

The HOMA-IR factor was calculated using the following formula:

$$\text{HOMA index} = \frac{\text{Fasting insulin } (\mu\text{U/ml}) \times \text{Fasting glucose (mmol/L)}}{22.5}$$

The rising and falling of HOMA-IR values in relation to control, healthy animals indicate increase and decrease in insulin sensitivity, respectively.²⁰

RNA isolation and cDNA synthesis

Total RNA was extracted from 100 mg of heart and adipose tissues using RNXTM isolation reagent according to the manufacturer's procedure (SinaClon, Tehran, Iran). The samples were treated with DNase I enzyme to avoid DNA contamination. The purity of RNA at a 260/280 OD ratio and RNA integrity were evaluated using an Eppendorf $\mu\text{Cuvette G1.0}$ microvolume measuring cell (Eppendorf BioPhotometer D30, Eppendorf, Germany). Reverse transcription was performed with the YTA cDNA synthesis kit (Yekta tajhiz, Iran) and Eppendorf Thermal Cycler (Germany) using 1 μg of RNA and random hexamer, as recommended by the manufacturer.

Real-time quantitative RT-PCR

Real-time PCR was performed using the Roche Light-Cycler detection system (Basel, Switzerland) with the qPCRTM Green Master Kit for SYBR Green I[®] (Yektatajhiz, Iran). The relative expression level of the chemerin and CMKLRI transcripts were compared to mice GAPDH as the housekeeping gene. Specific sets of primers (Pishgam BioTech, Co, Tehran, Iran) designed for this study were: chemerin (GenBank:NC-007299): 5'- TCTTCACTACGACCAGTATCAG -3' and 5'- ACATTATCTGCATAGACCCCATG -3' and CMKLRI (GenBank:NM-008153.3): 5'- GTACGACGCTTACAACGACT -3' and 5'- GCACACCAAGCTGTAGATCA -3', GAPDH (GenBank:NM-001034055): 5'-

CTCATCTACCTCTCCATCGTCTG -3' and 5'-CCTGCTTGTCTGCCGGTGCTTG -3' The PCR protocol used consisted of a 5 min denaturation at 94°C followed by 45 cycles at 94°C for 15 sec, 60°C for 30 sec. Two separate reactions without cDNA or with RNA were performed in parallel as controls. The relative quantification was performed according to the comparative $2^{-\Delta\Delta C_t}$ method and using Lightcycler 96® software. Assay validation to check whether the primer for chemerin and CMKLRI and GAPDH had similar amplification efficiencies was performed as previously described. All qPCR analyses were performed according to The Minimum Information for Publication of Quantitative Real-Time PCR Experiments (MIQE) guideline.²¹

Determination of tissue chemerin protein

Cardiac and adipose tissues were homogenized in 500 μ l RIPA lysis buffer (NaCl; 150 mM, SDS 0.1%, Tris; 25 mM, pH 7.4, NaF; 1 mM, Phenylmethylsulfonyl fluoride 1 mM) with a homogenizer (Heidolph, Schwabach, Germany). The homogenate was centrifuged at 10000×RPM for 15 min at 4°C (Centrifuge 5415 R; Eppendorf AG, Hamburg, Germany). The supernatant was collected and stored at -70°C for subsequent analysis. Protein concentration in the supernatant was estimated using the Bradford method. Chemerin concentration was determined using the species-specific ELISA kits (East Biopharm, China) and expressed as ng/mg of tissue protein.

Statistical analyses

Statistical analysis was conducted using the SPSS 22 software (SPSS Inc., Chicago, IL, USA). All data were presented as mean $\pm$ standard deviation (SD). The Shapiro–Wilk or Levene's test was used to determine the normality of data or equality of error variances. All parameters were statistically analyzed by three-way analysis of variance (ANOVA) with sampling times, LC treatment and diabetic condition as factors. When the interaction and/or the main effects were significant, means were compared between different experimental groups at different time points using Tukey's multiple-comparison post-hoc test. Graphs were drawn using Graphpad Prism 8 (GraphPad Software Inc., San Diego, CA, USA). We did not use any statistical methods to predetermine sample size. Samples sizes were estimated based on sample availability, ethical issues about accomplishing experimental aims without having to use numerous animals and previous experimental studies.^{11,16} A *p*-value below 0.05 was considered statistically significant.

Results

Our results showed that consumption of a 5-week high calorie diet, concurrent with low-dose injection of STZ induced a T2DM phenotype that was characterized by hyperinsulinemia and hyperglycemia. The effect of the main factors (Diabetic condition, 2 levels; LC treatment, 2 levels; and sampling time, 3 levels) and their interaction with each variable are shown in Table 1. A three-way ANOVA analysis indicated a main effect of sampling time ($p = 0.0031$), LC treatment ($p = 0.0001$), diabetic condition ($p = 0.0001$)

and the interaction of sampling time $\times$ LC treatment $\times$ diabetic condition ($p = 0.0018$) on insulin levels in different experimental groups (Table 1). Changes in serum insulin levels in diabetic mice treated with LC are shown in Figure 1A. Serum levels of insulin were significantly increased at day 7 after diabetes induction (day 0 of LC treatment) in relation to healthy, control animals and it remained high until day 28 of the experiment ($p < 0.05$). Serum insulin levels were significantly decreased in diabetic mice after two and four weeks of treatment with LC, when compared to untreated diabetic mice ($p < 0.05$) (Figure 1A). Treatment of diabetic mice with LC for a longer period, between 14 and 28 days of treatment, was no more effective in reducing insulin levels ($p > 0.05$) (Figure 1A).

A three-way ANOVA analysis indicated a main effect of sampling time ($p = 0.0002$), LC treatment ($p = 0.0005$), diabetic condition ($p = 0.0002$) and interaction of sampling time $\times$ LC treatment $\times$ diabetic condition ($p = 0.0002$) on serum glucose levels in different experimental groups. The serum glucose levels were found to be significantly higher in diabetic mice on days 14 and 28 after diabetes induction compared with healthy animals ($p < 0.05$), while administration of HF/HC supplemented diet and STZ injection had no significant effect on serum glucose levels during the first one week of experimental induction of diabetes ($p > 0.05$) (Figure 1B). It was observed that the treatment of *diabetic mice with LC* resulted in a significant reduction of blood sugar levels, as observed on days 14 and 28 when compared with diabetic, untreated mice ($p < 0.05$) (Figure 1B). LC intake had no obvious effect on serum glucose levels in healthy mice ($p > 0.05$) (Figure 1B).

A three-way ANOVA analysis indicated a main effect of sampling time ($p = 0.0019$), LC treatment ($p = 0.0017$), diabetic condition ($p = 0.0005$) and interaction of sampling time $\times$ LC treatment $\times$ diabetic condition ($p = 0.0015$) on HOMA-IR in different experimental groups. HOMA-IR in diabetic animals was found to significantly increase on days 14 and 28 of the experimental period in relation to healthy mice ($p < 0.05$), while it showed no significant change in the first week after the experimental induction of diabetes ($p > 0.05$) (Figure 1C). Oral administration of LC had a significant lowering effect on HOMA-IR on days 14 and 28 of the experimental period in diabetic mice ($p < 0.05$) (Figure 1C). As shown in Fig. 2, higher body weight was observed in mice that received HF/HC supplemented diet at all times of the experiment, when compared with healthy mice ($p < 0.05$). During the four weeks of observation of the LC-treated diabetic mice, the latter showed weight loss, relative to day 0, i.e., before the start of the treatment ($p < 0.05$) (Figure 2).

Regarding serum chemerin levels, a three-way ANOVA analysis showed a main effect of sampling time ($p = 0.0003$), LC treatment ($p = 0.0005$), diabetic condition ($p = 0.0003$) and interaction of sampling time $\times$ LC treatment $\times$ diabetic condition ($p = 0.0003$). Our results showed that serum chemerin levels were significantly higher in the diabetic group than in the control group at all sampling times, with the highest level being observed on day 28 of the experiment ($p < 0.05$). After two weeks of LC treatment, serum chemerin levels of

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Table 1 – Results of three-way ANOVA analysis to determine the effects of the diabetic condition (D), Sampling time (ST) and LC treatment (LC) and their interactions (D × ST × LC) on each variable.

Variable	Main factors						Interactions of main factors	
	Diabetic condition (D)		LC treatment (LC)		Sampling times (ST)		D×LC×ST	
	p value	F (1.48)	p value	F (1.48)	p value	F (2.48)	p value	F (2.48)
Insulin	p = 0.0001	305.92	p = 0.0001	17.41	p = 0.0031	4.89	p = 0.0018	3.73
Glucose	p = 0.0002	6182.2	p = 0.0005	1248.2	p = 0.0002	634.6	p = 0.0002	67.59
HOMA-IR	p = 0.0005	447.02	p = 0.0017	12.95	p = 0.0019	8.12	p = 0.0015	8.91
Adipose chemerin mRNA	p = 0.0003	1761.2	p = 0.0003	1040.3	p = 0.0008	125.45	p = 0.0007	319.21
Cardiac chemerin mRNA	p = 0.0002	5546.3	p = 0.0001	187.6	p = 0.0002	73.36	p = 0.0002	67.9
Adipose chemerin protein	p = 0.0002	2267.2	p = 0.0002	762.21	p = 0.0002	70.23	p = 0.0003	64.22
Cardiac chemerin protein	p = 0.0003	1651.4	p = 0.0002	641.22	p = 0.0003	62.27	p = 0.0004	64.12
Adipose CMKLR1 mRNA	p = 0.0001	8376.2	p = 0.0001	306.99	p = 0.0001	96.51	p = 0.0001	65.73
Cardiac CMKLR1 mRNA	p = 0.0001	2172.3	p = 0.0002	65.04	p = 0.0003	75.59	p = 0.0002	7.37
Serum chemerin	p = 0.0003	3759.4	p = 0.0005	183.59	p = 0.0003	423.2	p = 0.0003	91.87
IL1-β	p = 0.0005	2042.1	p = 0.0002	53.12	p = 0.0004	375.6	p = 0.0008	68.46
TNF-α	p = 0.0001	4644.3	p = 0.0002	475.6	p = 0.0002	2516.2	p = 0.0002	439.17

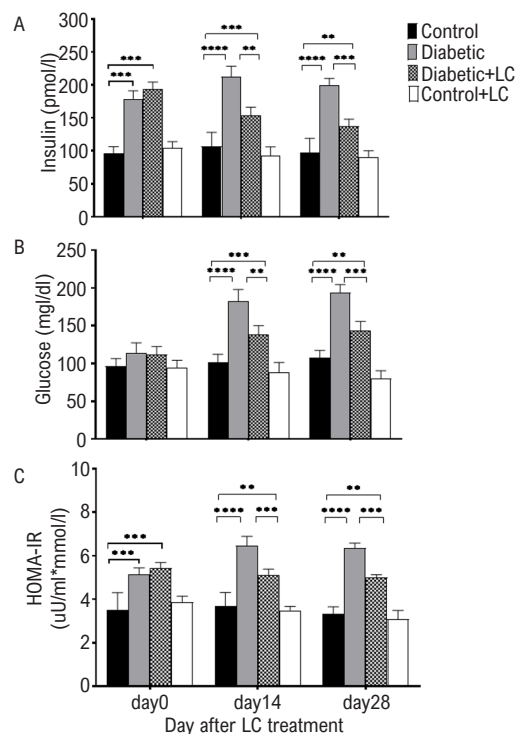


Figure 1 – Serum levels of insulin (A), Glucose (B) and HOMA-IR in different experimental groups on days 0, 14 and 28 of LC treatment. Data are shown as means ± SD. The level of significance between groups at each sampling time was set at *p < 0.05, **p < 0.01, ***p < 0.001, ****p < 0.0001.

diabetic mice showed no significant difference with those of untreated diabetic mice ($p > 0.05$), while a significant lowering effect on serum chemerin levels was observed when diabetic mice consumed LC for 28 days ($p < 0.05$) (Figure 3).

As for the chemerin and CMKLR1 mRNA levels in cardiac muscle, a three-way ANOVA analysis showed a main effect of sampling time (chemerin $p = 0.0001$, CMKLR1 $p = 0.0003$), LC treatment (chemerin; $p = 0.0002$, CMKLR1 $p = 0.0002$), diabetic condition (chemerin; $p = 0.0002$, CMKLR1 $p = 0.0001$) and interaction between the three factors (chemerin; $p < 0.0001$, CMKLR1 $p = 0.0002$). The mRNA and protein levels of chemerin and CMKLR1 in cardiac tissue of diabetic mice were higher than that in normal animals at all sampling times after diabetes induction ($p < 0.05$) (Figure 4 and Table 2). Oral consumption of LC for two weeks had no significant effect on the reduction of chemerin or CMKLR1 expression in cardiac tissue of diabetic mice ($p > 0.05$), while the expression of the studied genes was reduced in cardiac tissue of diabetic mice after 28 days of LC treatment, when compared with that in diabetic, untreated animals ($p < 0.05$) (Figure 4, Table 2).

Regarding adipose chemerin and CMKLR1 mRNA and protein levels, a three-way ANOVA analysis showed a main effect of sampling time (chemerin; $p = 0.0008$, CMKLR1 $p = 0.0001$), LC treatment (chemerin; $p = 0.0003$, CMKLR1

$p = 0.0001$), diabetic condition (chemerin; $p = 0.0003$, CMKLR1 $p = 0.0001$) and interaction between three factors (chemerin; $p = 0.0007$, CMKLR1 $p = 0.0001$). It was observed that animals that received HF/HC supplemented diet had higher protein and mRNA levels of chemerin and CMKLR1 in adipose tissue on days 7, 14 and 28 after the final feeding when compared with animals that received a normal diet ($p < 0.05$) (Figure 5 A-B, Table 3). The treatment of diabetic mice with LC for 14 or 28 days resulted in a significant reduction in chemerin protein and mRNA levels in adipose tissue of diabetic animals when compared with untreated, diabetic mice ($p < 0.05$) (Figure 5A, Table 2). Animals that received LC for 14 days showed no significant change in CMKLR1 expression ($p > 0.05$), while those that were treated with LC for 28 days had a lower expression of CMKLR1 when compared with untreated, diabetic mice ($p < 0.05$) (Figure 5B).

Regarding serum IL1- β and TNF- α levels, a three-way ANOVA analysis showed a main effect of sampling time (IL1- β ; $p = 0.0004$ and TNF- α ; $p = 0.0002$), treatment (IL1- β ; $p = 0.0002$ and TNF- α ; $p = 0.0002$) diabetic condition (IL1- β ; $p = 0.0005$, TNF- α $p = 0.0001$) and interaction between the three factors (IL1- β ; $p = 0.0008$, TNF- α $p = 0.0002$). Serum IL1- β and TNF- α levels were significantly increased in the diabetic group when compared to the control group on days 14 and 28 after induction of diabetes ($p < 0.05$) (Tables 4 and 5). The treatment of diabetic mice with LC for

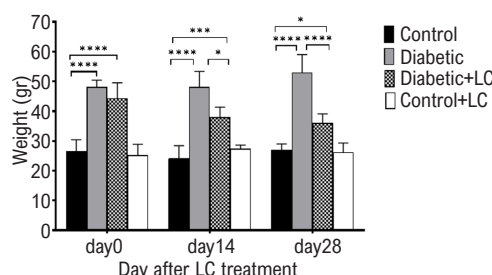


Figure 2 – Changes in body weight in different experimental groups on days 0, 14 and 28 of LC treatment. Data are means $\pm$ SD. The level of significance between groups at each sampling time was set at * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$.

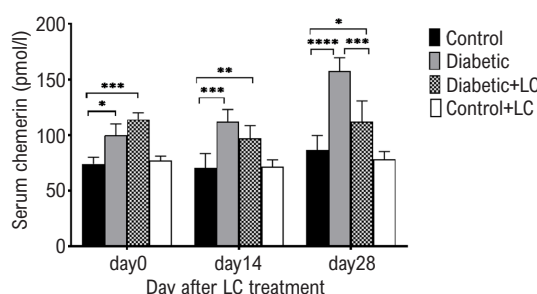


Figure 3 – Serum levels of chemerin in different experimental groups on days 0, 14 and 28 of LC treatment. Data are shown as means $\pm$ SD. The level of significance between groups at each sampling time was set at * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$.

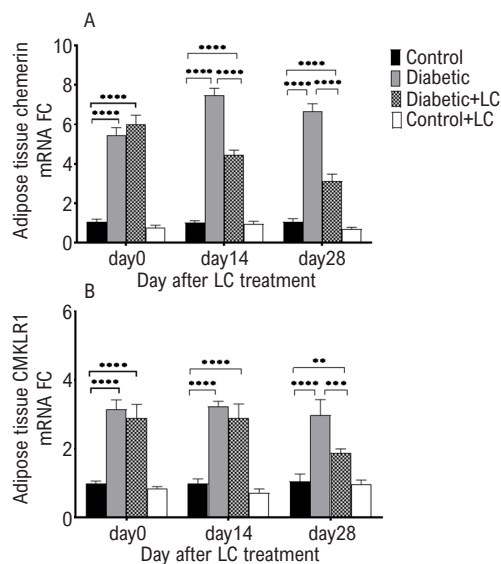


Figure 4 – Gene expression levels of chemerin (A) and CMKLR1 (B) in adipose tissue of different experimental groups on days 0, 14 and 28 of LC treatment. The qRT-PCR method was used for the analysis of the relative expression of studied genes. GAPDH was used as the housekeeping gene. The level of significance between the groups at each sampling time was set at * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$.

Table 2 – Concentration of chemerin in cardiac tissue of experimental groups. Data are shown as mean $\pm$ SD. Different lower-case letters (a,b) demonstrate significant differences between groups in each day of the experiment ($p < 0.05$). Different upper-case letters (A,B) demonstrate significant differences between times of treatment in each group ($p < 0.05$)

	Cardiac tissue chemerin level (ng/mg protein)		
	Days of LC treatment		
	0	14	28
Control	2.47 $\pm$ 0.42 ^{aA}	2.56 $\pm$ 0.27 ^{aA}	2.27 $\pm$ 0.22 ^{aA}
Diabetic	3.01 $\pm$ 0.31 ^{aA}	4.97 $\pm$ 0.48 ^{bB}	5.51 $\pm$ 0.41 ^{bB}
Diabetic + LC	2.81 $\pm$ 0.16 ^{aA}	4.42 $\pm$ 0.38 ^{bB}	3.13 $\pm$ 0.29 ^{aA}
Control + LC	2.32 $\pm$ 0.38 ^{aA}	2.67 $\pm$ 0.33 ^{aA}	2.37 $\pm$ 0.28 ^{aA}

LC: L-carnitine.

14 days had no significant effects on serum levels of IL-1 β and TNF- α compared to untreated diabetic mice ($p > 0.05$). However, four weeks after treatment with LC, serum levels of both inflammatory factors were significantly reduced, when compared to untreated diabetic mice.

Discussion

In the current study, the effect of LC supplementation on the expression of chemerin and its receptor in adipose and cardiac tissues of experimentally-induced obese and insulin resistant mice were studied. In accordance with previous studies using rodent models of type 2 diabetes, our results showed that a five week-consumption of a HF/HC supplemented diet, together with injection of a single low dose of STZ in mice resulted in insulin resistance and obesity, which

was characterized by hyperglycemia, hyperinsulinemia and increased HOMA-IR and body weight.^{16,18,19} It was observed that the HF/HC diet supplementation for five weeks resulted in hyperinsulinemia, with no obvious change in blood sugar levels, while after two weeks being fed a high calorie diet, the animals showed serum symptoms of insulin resistance, including hyperinsulinemia and hyperglycemia. These findings suggest that the serum metabolic alterations induced by this treatment were more similar to those of type 2 diabetes than of type 1 diabetes.

Our results showed that expression of chemerin and its receptor, CMKLR1, in adipose and cardiac tissues of diabetic mice were increased after induction of experimental diabetes. It was also observed that diabetic animals had higher serum levels of chemerin when compared with healthy animals. This finding suggests that simultaneous changes that occur in

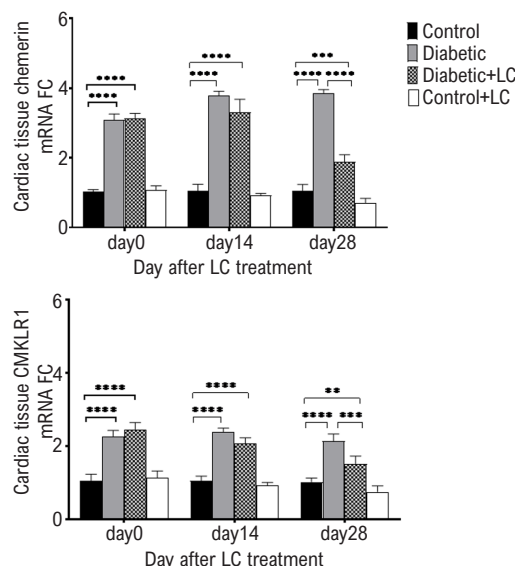


Figure 5 – Gene expression levels of chemerin (A) and CMKLR1 (B) in cardiac tissue of different experimental groups on days 0, 14 and 28 of LC treatment. The qRT-PCR method was used for the analysis of the relative expression of studied genes. GAPDH was used as the housekeeping gene. Data are shown as means $\pm$ SD. The level of significance between groups at each sampling time was set at * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$.

Table 3 – Concentration of chemerin in adipose tissue of different experimental groups. Data are presented as mean $\pm$ SD. Different lower-case letters (a,b) demonstrate significant differences between groups in each day of the experiment ($p < 0.05$). Different upper-case letters (A,B) demonstrate significant differences between times of treatment in each group ($p < 0.05$)

	Adipose tissue chemerin level (ng/mg protein)		
	Days of LC treatment		
	0	14	28
Control	7.62 $\pm$ 2.58 ^{aA}	8.11 $\pm$ 1.32 ^{aA}	6.49 $\pm$ 1.07 ^{aA}
Diabetic	13.22 $\pm$ 3.61 ^{ba}	14.78 $\pm$ 2.59 ^{ba}	16.72 $\pm$ 97 ^{bb}
Diabetic + LC	12.64 $\pm$ 2.09 ^{ba}	10.36 $\pm$ 1.78 ^{cb}	10.97 $\pm$ 3.12 ^{bb}
Control + LC	6.82 $\pm$ 1.94 ^{aA}	7.09 $\pm$ 2.06 ^{aA}	7.44 $\pm$ 1.19 ^{aA}

LC: L-carnitine.

Table 4 – Serum concentration of IL1- β in different experimental groups. Data are presented as mean $\pm$ SD. Different lower-case letters (a,b) demonstrate significant differences between groups on each day of the experiment ($p < 0.05$). Different upper-case letters (A,B) demonstrate significant differences between times of treatment in each group ($p < 0.05$)

	Serum TNF- α (pmol/L)		
	Days of LC treatment		
	0	14	28
Control	0.71 $\pm$ 0.19 ^{aA}	0.65 $\pm$ 0.10 ^{aA}	0.75 $\pm$ 0.09 ^{aA}
Diabetic	0.65 $\pm$ 0.11 ^{aA}	3.92 $\pm$ 0.38 ^{bb}	7.10 $\pm$ 0.68 ^{bc}
Diabetic + LC	1.33 $\pm$ 0.16 ^{ba}	3.34 $\pm$ 0.50 ^{bb}	3.94 $\pm$ 0.43 ^{cb}
Control + LC	0.78 $\pm$ 0.18 ^{aA}	0.98 $\pm$ 0.16 ^{aA}	0.57 $\pm$ 0.11 ^{dB}

LC: L-carnitine.

Table 5 – Serum concentration of TNF- α in different experimental groups on days 0, 14 and 28 of LC treatment. Data are presented as mean $\pm$ SD. Different lower-case letters (a,b) demonstrate significant differences between groups in each day of the experiment ($p < 0.05$). Different upper-case letters (A,B) demonstrate significant differences between times of treatment in each group ($p < 0.05$)

	Serum IL1- β (pmol/L)		
	Days of LC treatment		
	0	14	28
Control	0.93 $\pm$ 0.11 ^{aA}	1.02 $\pm$ 0.14 ^{aA}	0.89 $\pm$ 0.31 ^{aA}
Diabetic	1.23 $\pm$ 0.33 ^{aA}	2.96 $\pm$ 0.12 ^{bB}	5.78 $\pm$ 0.21 ^{bB}
Diabetic + LC	1.33 $\pm$ 0.26 ^{aA}	2.23 $\pm$ 0.27 ^{bB}	3.46 $\pm$ 0.12 ^{cC}
Control + LC	1.07 $\pm$ 0.24 ^{aA}	0.98 $\pm$ 0.19 ^{aA}	0.82 $\pm$ 0.41 ^{aA}

LC: L-carnitine.

the levels of chemerin and its receptor in the diabetic state exacerbates the function of this hormone in the target tissues and this may play an important role in the development of functional disturbances of adipose and cardiac tissues in the diabetic status. The bulk of human and animal data supports a relationship between chemerin, obesity and metabolic syndrome, a cluster of metabolic disorders that increase the risk of CVDs. In accordance with our results, human and animal studies reported the parallel findings that obese and diabetic animals have elevated circulating levels of chemerin compared with healthy or lean subjects or animals.^{22,23} Several possible mechanisms may be assumed about the effects of increased expression of chemerin and CMKLR1 on the initiation and progression of insulin resistance in diabetic animals. It is now known that inflammation has an important role in adipose tissue insulin resistance and cardiac muscle dysfunction.²⁴ Obesity is correlated with a significant increase in the production of proinflammatory cytokines, such as IL1 β and TNF α , which can induce insulin resistance and cell death in the cardiac muscle.^{25,26} Our findings showed the presence of increased serum levels of IL1 β and TNF α following diabetes induction. Serum chemerin levels correlate with levels of proinflammatory cytokines, such as TNF- α , IL1 β and IL-6.^{6,7,25} Chemerin also has adverse effects on cardiomyocyte by induction of caspase-9 and Akt-mediated cell apoptosis.¹⁰ Taken together, it is concluded that the observed overexpression of chemerin and its receptor in adipose and cardiac tissues of diabetic mice may have an important role in the progression of insulin resistance and cardiac dysfunctions in the diabetic status.

Our results showed that LC administration for 4 weeks can attenuate the expression of chemerin and its receptor in adipose and cardiac tissues of diabetic mice. These alterations were associated with an improvement in insulin resistance symptoms and a reduction in serum chemerin and some inflammatory factors' levels. According to the results of the current study, previous studies showed that the use of LC leads to an increase in overall insulin sensitivity and whole body insulin-mediated glucose uptake in animals or humans with type 2 diabetes.^{16,26} Considerable evidence supports the fact that fatty acid oversupply and obesity leads to an ectopic accumulation of several lipid metabolites in heart muscle and

possibly other tissues, which are detrimental to insulin signaling and leads to insulin resistance.²⁷ Cardiac muscle cells cannot synthesize LC *de novo* and must acquire it exogenously via the carnitine/organic cation transporter 2.²⁸ Based on these finding we suggest that LC supplementation in the diet may restore the LC pool and reduce lipid metabolites and lipotoxicity in cardiac and adipose tissues.

Based on our knowledge, the effects of LC on systemic chemerin level or its tissue expression in cardiac tissue of diabetic animals or humans have not been investigated so far. Our results, for the first time, show that protein and mRNA levels of chemerin and its receptor were reduced in the cardiac tissue of diabetic mice, concurrently with increased whole-body insulin sensitivity. Previous findings showed that chemerin mRNA and protein levels were elevated in the epicardial adipose tissue of patients with coronary artery disease.²⁹ Serum chemerin levels are also elevated in patients with coronary artery disease and correlated with the severity and extent of coronary stenosis and several cardiometabolic parameters.³⁰ It has been observed that chemerin increases apoptosis and caspase-9 activity in murine cardiomyocytes and improve the cardioprotective parameters in isolated perfused rat heart.^{10,31} Chemerin treatment also alters the outcome of myoblast cells, from myogenesis to adipogenesis, which is characterized by increased ROS levels and TG content in treated cells.³² Taken together, it was concluded that the reduction in chemerin levels and its receptor expression in cardiac tissue of diabetic mice after LC treatment may attenuate the adverse effect of chemerin on cardiomyocytes in diabetic animals. Further studies are needed to confirm this opinion.

Although the results of the current study showed that LC treatment can attenuate the increase of chemerin expression in target tissues, the molecular mechanisms regulating its expression remain poorly understood. Our results showed that LC treatment can reduce the serum levels of TNF α and IL1 β in obese, diabetic rats. It was observed that these proinflammatory cytokines induce chemerin mRNA expression and secretion from 3T3-L1 adipocytes.³³ Serum chemerin levels are also associated with serum levels of TNF α in obese patients.³⁴ Based on these findings, the reduction in chemerin expression in diabetic mice may be due to a decrease in

the secretion of inflammatory mediators. Hyperinsulinemia improvement may also be another mechanism caused by LC in reducing chemerin expression. Our results showed that LC could attenuate the increase in insulin levels in obese, diabetic mice. Because insulin can increase chemerin secretion from adipose tissue *in vitro* and in tissue explants,³⁵ we suggest that insulin reduction in LC-treated animals may have a regulatory role on chemerin expression in adipose and cardiac tissues of diabetic mice.

There are some possible limitations to this study. In our study, gene expression was measured in total cardiac tissue in experimental animals. In light of the fact that various cardiac cell types, such as cardiomyocytes and cardiac fibroblasts, may have different actions on the pathogenesis of cardiac disease, our data did not allow differentiating expression profiles between the different cell types. Furthermore, differences in gene expression profiles between cardiac tissues from the right and left ventricles and atria have been confirmed, in addition to differences between cardiac cell types. Thus, we did not differentiate the gene expression between different parts of cardiac tissue in experimental animals. A further limitation is related to the fact that we measured all factors in young adult animals and within a short period of an experimental diabetes model. In this regard, it is of interest recalling that aging and long-term diabetes is by far the dominant risk factor for the development of cardiovascular diseases and the prevalence of cardiovascular diseases increases dramatically with increasing age. We did not determine whether LC treatment in aged rats or those with long-term diabetes leads to a similar downregulation of the expression of chemerin and its receptor in cardiac tissue of diabetic rats.

Conclusion

In summary, our data showed that the consumption of a high-calorie diet resulted in obesity, insulin resistance and

upregulation of chemerin and its receptor, CMKLR1, in adipose and cardiac tissues of mice. The treatment of diabetic mice with LC can attenuate symptoms of insulin resistance and suppress the overexpression of chemerin in diabetic animals. The results of the current experiment aid in the understanding of the novel regulatory effect of LC on cardiac gene expression in obesity and diabetes conditions. Further studies are needed to provide more evidence about nutrition therapy using LC for the non-pharmacological management of patients with diabetes and CVD based on the regulation of chemerin components in cardiac muscle.

Author Contributions

Conception and design of the research: Tabandeh MR, Hosseini SA; Acquisition of data: Amiri R; Analysis and interpretation of the data: Amiri R, Tabandeh MR, Hosseini SA; Statistical analysis: Amiri R, Tabandeh MR, Hosseini SA; Obtaining financing and Critical revision of the manuscript for intellectual content: Tabandeh MR; Writing of the manuscript: Amiri R, Tabandeh MR.

Potential Conflict of Interest

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

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Study Association

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References

- Francesquet M, Silva PTD, Schneiders LB, Silveira JFCD, Soares SS, Tornquist D, et al. Youth overweight/obesity and its relationship with cardiovascular disease and parental risk factors. *Arch Endocrinol Metab.* 2019;63(4):411-416. doi: 10.20945/2359-3997000000156.
- Nakamura K, Fuster JJ, Walsh K. Adipokines: a link between obesity and cardiovascular disease. *J Cardiol.* 2014;63(4):250-9. doi: 10.1016/j.jjcc.2013.11.006.
- Moussa K, Gurung P, Adams-Huet B, Devaraj S, Jialal I. Increased eosinophils in adipose tissue of metabolic syndrome. *J Diabetes Complications.* 2019;33(8):535-538. doi: 10.1016/j.jdiacomp.2019.05.010.
- Nagpal S, Patel S, Jacob H, DiSepio D, Ghosh C, Malhotra M, et al. Tazarotene-induced gene 2 (TIG2), a novel retinoid-responsive gene in skin. *J Invest Dermatol.* 1997;109(1):91-5. doi: 10.1111/1523-1747.ep12276660.
- El Husseny MW, Mamdouh M, Shaban S, Ibrahim Abushouk A, Zaki MM, Ahmed OM, et al. Adipokines: Potential Therapeutic Targets for Vascular Dysfunction in Type II Diabetes Mellitus and Obesity. *J Diabetes Res.* 2017;2017:8095926. doi: 10.1155/2017/8095926.
- El-Deeb TS, Bakkar SM, Eltoony L, Zakhary MM, Kamel AA, Nafee AM, et al. The adipokine chemerin and fetuin-a serum levels in type 2 diabetes mellitus: relation to obesity and inflammatory markers. *Egypt J Immunol.* 2018;25(1):191-202.
- Weigert J, Neumeier M, Wanninger J, Filarsky M, Bauer S, Wiest R, et al. Systemic chemerin is related to inflammation rather than obesity in type 2 diabetes. *Clin Endocrinol.* 2010;72(3):342-8. doi: 10.1111/j.1365-2265.2009.03664.x.
- Kostopoulos CG, Spiroglou SG, Varakis JN, Apostolakis E, Papadaki HH. Chemerin and CMKLR1 expression in human arteries and periaortic fat: a possible role for local chemerin in atherosclerosis? *BMC Cardiovasc Disord.* 2014;14:56. doi: 10.1186/1471-2261-14-56.
- Dimitriadis GK, Kaur J, Adya R, Miras AD, Mattu HS, Hattersley JG, et al. Chemerin induces endothelial cell inflammation: activation of nuclear factor-kappa beta and monocyte-endothelial adhesion. *Oncotarget.* 2018;9(24):16678-16690. doi: 10.18632/oncotarget.24659.
- Rodríguez-Penas D, Feijóo-Bandín S, García-Rúa V, Mosquera-Leal A, Durán D, Varela A, et al. The adipokine chemerin induces apoptosis in cardiomyocytes. *Cell Physiol Biochem.* 2015;37(1):176-92. doi: 10.1159/000430343.
- Hao J, Shen W, Tian C, Liu Z, Ren J, Luo C, et al. Mitochondrial nutrients improve immune dysfunction in the type 2 diabetic Goto-Kakizaki rats. *J Cell Mol Med.* 2009;13(4):701-11. doi: 10.1111/j.1582-4934.2008.00342.x.

12. Malone JJ, Schocken DD, Morrison AD, Gilbert-Barnes E. Diabetic cardiomyopathy and carnitine deficiency. *J Diabetes Complications*. 1999;13(2):86-90. doi: 10.1016/s1056-8727(99)00039-2.
13. Bavari M, Tabandeh MR, Varzi HN, Bahramzadeh S. Neuroprotective, antiapoptotic and antioxidant effects of L-carnitine against caffeine-induced neurotoxicity in SH-SY5Y neuroblastoma cell line. *Drug Chem Toxicol*. 2016;39(2):157-66. doi: 10.3109/01480545.2015.1063062.
14. Guimarães SMS, Cruz WMS, Weigert CS, Scalco FB, Colafranceschi AS, Ribeiro MG, et al. Decompensated Chronic Heart Failure Reduces Plasma L-carnitine. *Arch Med Res*. 2018;49(4):278-281. doi: 10.1016/j.arcmed.2018.09.004.
15. Vacante F, Senesi P, Montesano A, Frigerio A, Luzi L, Terruzzi I. L-Carnitine: An Antioxidant Remedy for the Survival of Cardiomyocytes under Hyperglycemic Condition. *J Diabetes Res*. 2018;9;2018:4028297. doi: 10.1155/2018/4028297.
16. Kohan Nr, Nazifi S, Tabandeh MR, Lari MA. Effect of L-Carnitine supplementation on apelin and apelin receptor (Apj) expression in cardiac muscle of obese diabetic rats. *Cell J*. 2018;20(3):427-434. doi: 10.22074/cellj.2018.5408.
17. Hamza RT, Elkabbany ZA, Shedi AM, Hamed AI, Ebrahim AO. Serum chemerin in obese children and adolescents before and after L-Carnitine therapy: relation to nonalcoholic fatty liver disease and other features of metabolic syndrome. *Arch Med Res*. 2016;47(7):541-549. doi: 10.1016/j.arcmed.2016.11.010.
18. Gilbert ER, Fu Z, Liu D. Development of a nongenetic mouse model of type 2 diabetes. *Exp Diabetes Res*. 2011;2011:416254. doi: 10.1155/2011/416254.
19. Barrière DA, Noll C, Roussy G, Lizotte F, Kessai A, Kirby K, et al. Combination of high-fat/high-fructose diet and low-dose streptozotocin to model long-term type-2 diabetes complications. *Sci Rep*. 2018;8(1):424. doi: 10.1038/s41598-017-18896-5.
20. Antunes LC, Elkfury JL, Jornada MN, Fioletto KC, Bertoluci MC. Validation of HOMA-IR in a model of insulin-resistance induced by a high-fat diet in Wistar rats. *Arch Endocrinol Metab*. 2016;60(2):138-42. doi: 10.1590/2359-3997000000169.
21. Bustin SA, Benes V, Garson JA, Hellemans J, Huggett J, Kubista M, et al. The MIQE guidelines: minimum information for publication of quantitative real-time PCR experiments. *Clin Chem*. 2009;55(4):611-22. doi: 10.1373/clinchem.2008.112797.
22. Bozaoglu K, Segal D, Shields KA, Cummings N, Curran JE, Comuzzie AG, et al. Chemerin is associated with metabolic syndrome phenotypes in a Mexican-American population. *J Clin Endocrinol Metab*. 2009;94(8):3085-8. doi: 10.1210/jc.2008-1833 8.
23. Ernst MC, Issa M, Goralski KB, Sinal CJ. Chemerin exacerbates glucose intolerance in mouse models of obesity and diabetes. *Endocrinology*. 2010;151(5):1998-2007. doi: 10.1210/en.2009-1098.
24. Abate N. Obesity and cardiovascular disease. Pathogenetic role of the metabolic syndrome and therapeutic implications. *J Diabetes Complications*. 2000;14(3):154-74. doi: 10.1016/s1056-8727(00)00067-2.
25. Parolini S, Santoro A, Marcenaro E, Luini W, Massardi L, Facchetti F, et al. The role of chemerin in the colocalization of NK and dendritic cell subsets into inflamed tissues. *Blood*. 2007;109(9):3625-32. doi: 10.1182/blood-2006-08-038844.
26. Bene J, Hadziszewski K, Melegh B. Role of carnitine and its derivatives in the development and management of type 2 diabetes. *Nutr Diabetes*. 2018;7;8(1):8. doi: 10.1038/s41387-018-0017-1.
27. Aroor AR, Mandavia CH, Sowers JR. Insulin resistance and heart failure: molecular mechanisms. *Heart Fail Clin*. 2012;8(4):609-17. doi: 10.1016/j.hfc.2012.06.005.
28. Iwata D, Kato Y, Wakayama T, Sai Y, Kubo Y, Iseki S, et al. Involvement of carnitine/organic cation transporter OCTN2 (SLC22A5) in distribution of its substrate carnitine to the heart. *Drug Metab Pharmacokin*. 2008;23(3):207-15. doi: 10.2133/dmpk.23.207.
29. Gao X, Mi S, Zhang F, Gong F, Lai Y, Gao F, et al. Association of chemerin mRNA expression in human epicardial adipose tissue with coronary atherosclerosis. *Cardiovasc Diabetol*. 2011;10:87. doi: 10.1186/1475-2840-10-87.
30. Hah YJ, Kim NK, Kim MK, Kim HS, Hur SH, Yoon HJ, et al. Relationship between chemerin levels and cardiometabolic parameters and degree of coronary stenosis in Korean patients with coronary artery disease. *Diabetes Metab J*. 2011;35(3):248-54. doi: 10.4093/dmj.2011.35.3.248.
31. Kutlay Ö, Kaygısız Z, Kaygısız B. The Effect of chemerin on cardiac parameters and gene expressions in isolated perfused rat heart. *Balkan Med J*. 2019;1;36(1):43-8. doi: 10.4274/balkanmedj.2017.1787.
32. Li HX, Chen KL, Wang HY, Tang CB, Xu XL, Zhou GH. Chemerin inhibition of myogenesis and induction of adipogenesis in C2C12 myoblasts. *Mol Cell Endocrinol*. 2015;414:216-23. doi: 10.1016/j.mce.2015.07.006.
33. Kralisch S, Weise S, Sommer G, Lipfert J, Lossner U, Bluher M, et al. Interleukin-1 β induces the novel adipokine chemerin in adipocytes in vitro. *Regul Pept*. 2009;154(1-3):102-6. doi: 10.1016/j.regpep.2009.02.010.
34. Parlee SD, Ernst MC, Muruganandan S, Sinal CJ, Goralski KB. Serum chemerin levels vary with time of day and are modified by obesity and tumor necrosis factor- α . *Endocrinology*. 2010;151(6):2590-602. doi: 10.1210/en.2009-0794.
35. Tan BK, Chen J, Farhatullah S, Adya R, Kaur J, Heutling D, et al. Insulin and metformin regulate circulating and adipose tissue chemerin. *Diabetes*. 2009;58(9):1971-7. doi: 10.2337/db08-1528.



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L-Carnitine Supplementation in the Diabetic Heart

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Short Editorial related to the article: Novel Cardioprotective Effect of L-Carnitine on Obese Diabetic Mice: Regulation of Chemerin and CMKLR1 Expression in Heart and Adipose Tissues

Carnitine is a non-essential nutrient, which is derived from amino acids. The main food source of carnitine is red meat, poultry and dairy products. Part of the carnitine can be produced endogenously, from lysine and methionine mainly by the liver and kidneys.¹ It acts primarily as an enzymatic cofactor for the transport of long-chain fatty acids from the cytoplasm into the mitochondria, and subsequent degradation to beta-oxidation, being a very important energy metabolism pathway. Therefore, carnitine is essential as fuel for muscles, and more than 95% of the total body carnitine is found in skeletal muscle.¹ The liver, heart, brain and kidneys have the remainder of the body's carnitine reserves or are able to synthesize it.¹ This distribution shows the importance of carnitine in these organs. L-carnitine supplementation has been studied in sarcopenia,² in liver diseases,³ in heart failure,⁴ in kidney diseases⁵ and in neurological diseases.^{6,7}

Most studies have shown the benefit of L-carnitine on cardiovascular risk factors. L-carnitine supplementation reduces hypertension, hyperlipidemia, hyperglycemia, insulin-dependent diabetes mellitus, insulin resistance, obesity, inflammation and oxidative stress.^{4,8-12}

In addition to attenuating risk factors for atherosclerosis, L-carnitine supplementation can improve the energy metabolism of the “diabetic” heart. The improvement can occur by normalizing the manipulation of the acetyl and acyl groups by the mitochondria, as L-carnitine is responsible for their transfer through the mitochondrial membrane.¹³ Another proposed mechanism is that L-carnitine supplementation can improve the inflammatory and oxidative cardiac microenvironment caused by hyperglycemia.¹⁴ Thus, a

systematic review article and meta-analysis of randomized clinical trials showed that L-carnitine supplementation was associated with a reduction in the levels of CRP, Interleukin-6 (IL-6), tumor necrosis factor- α (TNF- α) and plasma malondialdehyde, and increased plasma levels of superoxide dismutase.⁹

Regarding obesity, a systematic review showed that L-carnitine supplementation reduced body weight, body mass index (BMI) and fat mass, and the subgroup analysis based on the participants' basal BMI range showed more reductions in overweight or obese adults than in those within the normal BMI range.¹²

The article published in this issue of the *Arquivos Brasileiros de Cardiologia* is based on obesity, diabetes and inflammation.¹⁵

The authors presented results of an experimental study, in which obese mice with induced diabetes received L-carnitine. Chemerin protein and Chemokine-like Receptor 1 (CMKLR1) levels in serum, cardiac and adipose tissue, as well as other inflammatory markers were evaluated, in addition to insulin resistance.¹⁵

Chemerin is a new adipokine that participates in the early stages of acute inflammation and participates in the development of hypertension, progression of atherosclerotic lesions, possibly acting through its CMKLR1 receptor.¹⁶ The authors were able to demonstrate an association between L-carnitine consumption and a reduction in serum chemerin values and in cardiac and adipose tissue in treated diabetic mice, in addition to a reduction in the levels of other inflammatory markers (IL-1 β and TNF- α) after 4 weeks of treatment. They also observed that the group submitted to the intervention had a better insulin resistance profile.¹⁵

The decrease in the levels of chemerin and other inflammatory markers may be showing the importance of the inflammatory process in the diabetic heart. However, it is still too early to recommend L-carnitine supplementation. Some studies have shown that carnitine degradation products by the intestinal microbiota can generate Trimethylamine N-oxide (TMAO).¹⁷ A systematic review showed that TMAO was associated with an increase in cardiovascular events and mortality in a dose-dependent manner.¹⁷ Thus, more studies are necessary to understand the role of L-carnitine supplementation in the adjuvant treatment of the diabetic heart.

Keywords

Carnitine; Energy Metabolism; Polymerase Chain Reaction.

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References

1. Dahash BA, Sankararaman S. Carnitine deficiency. Treasure Island: StatPearls Publishing LLC; 2021.
2. Ebadi M, Bhanji RA, Mazurak VC, Montano-Loza AJ. Sarcopenia in Cirrhosis: From Pathogenesis to Interventions. *J Gastroenterol*. 2019;54(10):845-59. doi: 10.1007/s00535-019-01605-6.
3. Ishikawa H, Takaki A, Tsuzaki R, Yasunaka T, Koike K, Shimomura Y, et al. L-carnitine Prevents Progression of Non-Alcoholic Steatohepatitis in a Mouse Model with Upregulation of Mitochondrial Pathway. *PLoS One*. 2014;9(7):e100627. doi: 10.1371/journal.pone.0100627.
4. Wang ZY, Liu YY, Liu GH, Lu HB, Mao CY. L-Carnitine and Heart Disease. *Life Sci*. 2018;194:88-97. doi: 10.1016/j.lfs.2017.12.015.
5. Morgans HA, Chadha V, Warady BA. The Role of Carnitine in Maintenance Dialysis Therapy. *Pediatr Nephrol*. 2021;36(8):2545-51. doi: 10.1007/s00467-021-05101-z.
6. Kpka A, Ochociska A, Chojnowska S, Borzym-Kluczyk M, Skorupa E, Kna M, et al. Potential Role of L-Carnitine in Autism Spectrum Disorder. *J Clin Med*. 2021;10(6):1202. doi: 10.3390/jcm10061202.
7. Kpka A, Ochocinska A, Borzym-Kluczyk M, Skorupa E, Stasiewicz-Jarocka B, Chojnowska S, et al. Preventive Role of L-Carnitine and Balanced Diet in Alzheimer's Disease. *Nutrients*. 2020;12(7):1987. doi: 10.3390/nu12071987.
8. Abbasnezhad A, Hasanavand A, Falahi E, Kashkooli S, Asbaghi O, Choghakhori R. Effect of L-Carnitine Supplementation on Lipid Profiles of Patients with Liver Disease: A Systematic Review and Meta-Analysis. *Prev Nutr Food Sci*. 2020;25(2):124-32. doi: 10.3746/pnf.2020.25.2.124.
9. Fathizadeh H, Milajerdi A, Reiner Ž, Amirani E, Asemi Z, Mansournia MA, et al. The Effects of L-Carnitine Supplementation on Indicators of Inflammation and Oxidative Stress: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *J Diabetes Metab Disord*. 2020;19(2):1879-94. doi: 10.1007/s40200-020-00627-9.
10. Alanazi WA, Al-Harbi NO, Imam F, Ansari MA, Alhoshani A, Alasmari AF, et al. Role of Carnitine in Regulation of Blood Pressure (MAP/SBP) and Gene Expression of Cardiac Hypertrophy Markers (α-MHC) During Insulin-Induced Hypoglycaemia: Role of Oxidative Stress. *Clin Exp Pharmacol Physiol*. 2021;48(4):478-89. doi: 10.1111/1440-1681.13455.
11. Serban MC, Sahebkar A, Mikhailidis DP, Toth PP, Jones SR, Muntner P, et al. Impact of L-Carnitine on Plasma Lipoprotein(a) Concentrations: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Sci Rep*. 2016;6:19188. doi: 10.1038/srep19188.
12. Talenezhad N, Mohammadi M, Ramezani-Jolfaie N, Mozaffari-Khosravi H, Salehi-Abargouei A. Effects of L-Carnitine Supplementation on Weight Loss and Body Composition: A Systematic Review and Meta-Analysis of 37 Randomized Controlled Clinical Trials with Dose-Response Analysis. *Clin Nutr ESPEN*. 2020;37:9-23. doi: 10.1016/j.clnesp.2020.03.008.
13. Savic D, Ball V, Curtis MK, Fialho MDLS, Timm KN, Hauton D, et al. L-Carnitine Stimulates In Vivo Carbohydrate Metabolism in the Type 1 Diabetic Heart as Demonstrated by Hyperpolarized MRI. *Metabolites*. 2021;11(3):191. doi: 10.3390/metabo11030191.
14. Vacante F, Senesi P, Montesano A, Frigerio A, Luzi L, Terruzzi I. L-Carnitine: An Antioxidant Remedy for the Survival of Cardiomyocytes under Hyperglycemic Condition. *J Diabetes Res*. 2018;2018:4028297. doi: 10.1155/2018/4028297.
15. Amiri R, Tabandeh MR, Hosseini SA. Novel Cardioprotective Effect of L-Carnitine on Obese Diabetic Mice: Regulation of Chemerin and CMKLR1 Expression in Heart and Adipose Tissues. *Arq Bras Cardiol*. 2021;117(4):715-725.
16. Kostopoulos CG, Spiroglou SG, Varakis JN, Apostolakis E, Papadaki HH. Chemerin and CMKLR1 Expression in Human Arteries and Periadventitial Fat: A Possible Role for Local Chemerin in Atherosclerosis? *BMC Cardiovasc Disord*. 2014;14:56. doi: 10.1186/1471-2261-14-56.
17. Schiattarella GG, Sannino A, Toscano E, Giugliano G, Gargiulo G, Franzone A, et al. Gut Microbe-Generated Metabolite Trimethylamine-N-Oxide as Cardiovascular Risk Biomarker: A Systematic Review and Dose-Response Meta-Analysis. *Eur Heart J*. 2017 Oct 14;38(39):2948-2956. doi: 10.1093/eurheartj/ehx342.



Relationship between Right Ventricular Strain Signs in Electrocardiography and Levels of Biomarkers Associated with COVID-19 Pneumonia Severity

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Abstract

Background: The novel coronavirus disease (COVID-19) may lead to severe disease that can cause death. COVID-19 is known to affect the cardiovascular system. Early detection of the progression to the severe disease stage that affects the cardiovascular system may play a critical role in the treatment of COVID-19.

Objectives: To explore the possible relationship between the COVID-19 pneumonia and right ventricular strain findings on electrocardiography (ECG).

Methods: We conducted a retrospective study of 141 hospitalized patients with COVID-19. Spearman's correlation and logistic regression analyses were applied to assess relationships between ECG manifestations of right ventricular strain and levels of biomarkers and other laboratory and chest imaging findings. The significance level was considered as < 0.05 .

Results: The ECG signs of right ventricular stress were significantly more frequent and the levels of fibrinogen, CRP, and ferritin were significantly higher in COVID-19 patients with elevated levels of hs-cTnI, procalcitonin and D-dimer. The univariate analysis showed there are significant relations between the presence of bilateral pneumonia, most of the ECG signs of right ventricular strain and cardiac injury and inflammatory and thrombotic biomarkers. The multivariate analysis revealed that ST-segment elevation in V_1 and the $S_1Q_3T_3$ pattern are independent predictors of cardiac damage (odds ratio=0.23; 95% CI, 0.06 to 0.90; $p=0.035$) and elevated procalcitonin levels (odds ratio=0.19; 95% CI, 0.06 to 0.62; $p=0.006$), respectively.

Conclusion: The findings of the present study suggest that right heart damage is prevalent in COVID-19. In addition, our study shows the clinical value of ECG in evaluating and monitoring the patients with COVID-19 pneumonia.

Keywords: COVID-19; Betacoronavirus; Cardiovascular Diseases; Ventricular Function Right; Stress; Eletrocardiography/methods; Biomarkers; Pneumonia/complications.

Introduction

The 2019 novel coronavirus disease (COVID-19) pneumonia, which first emerged in Wuhan, China's Hubei province, in December 2019, has rapidly spread across the world. Although respiratory symptoms are primary clinical signs of COVID-19, several patients also develop cardiovascular injury, which is predominantly detected as an increase in high-sensitivity cardiac troponin assays.¹ Moreover, it has been demonstrated that the COVID-19 pneumonia has a worse clinical course in patients with cardiovascular disease.² In this context, disclosing the ways in which the novel

coronavirus affects the cardiovascular system is crucial to the treatment of these patients in a timely and efficient fashion and for the reduction of ominous outcomes such as death.

In the present study, we assess the abnormal electrocardiogram (ECG) manifestations in COVID-19. Specifically, we aimed to investigate the possible relationship between the severity of COVID-19 pneumonia and the right ventricular strain findings in the ECG. Additionally, we intent to explore possible relationships between the electrocardiographic abnormalities, cardiac injury, as well as elevated biomarkers of inflammation and thrombosis in COVID-19 patients.

Materials and methods

Study Patients

This retrospective, single-center and observational study was conducted at Bakirkoy Dr. Sadi Konuk Training and Research Hospital. Between April 1 and April 30, 2020, 141 consecutive hospitalized patients who were diagnosed with COVID-19 pneumonia according to the World Health

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Organization interim guidance³ were enrolled in the present study. The diagnosis of COVID-19 infection was also confirmed by the positive result of real-time reverse-transcriptase-polymerase chain reaction analysis of the patient's nasal or pharyngeal swab samples. The ECGs of the patients were obtained on admission. All of the study patients were adults (over 18 years old) and the diagnosis of pulmonary embolism was excluded by the findings of contrast-enhanced chest computed tomography (CT) in all patients.

Data Collection

The demographic, epidemiological, clinical, and radiological data, as well as comorbidities and laboratory findings at admission were recorded in the electronic medical records for each study patient. Laboratory data included the high-sensitive cardiac troponin I (hs-cTnI), creatine kinase-myocardial brain fraction (CK-MB), complete blood count, C-reactive protein (CRP), procalcitonin, fibrinogen, D-dimer, ferritin, kidney and liver function tests. All of the patients were clinically followed up to May 25, 2020. Two investigators controlled all study data.

Elevated hs-cTnI levels, which is the sign of cardiac damage, was considered when $>$ the 99th percentile upper reference limit. The levels of procalcitonin and D-dimer were considered elevated when ≥ 0.5 ng/mL and ≥ 0.5 μ g/mL, respectively.⁴

Electrocardiographic Evaluation

The 12-lead ECGs obtained at the time of admission were independently interpreted regarding the right ventricular strain signs by two experienced cardiologists who were blinded to patient data. ECG signs were determined based on the ECG manifestations due to right ventricular stress secondary to pulmonary hypertension in pulmonary embolism.^{5,6} The following ECG signs of right ventricular strain were evaluated: (1) sinus tachycardia (heart rate > 100 beats/minute),⁵ (2) incomplete or complete right bundle branch block (RBBB),⁵ (3) T-wave inversion in leads V_1 to V_4 ,⁵ (4) $S_1Q_3T_3$ pattern,⁵ (5) Qr in lead V_1 (existence of a prominent Q wave ≥ 0.2 millivolts while QRS duration is < 120 milliseconds)⁶, (6) ST-segment elevation ≥ 0.1 millivolt in lead V_1 .⁶

Statistical Analysis

Descriptive statistics were performed using mean $\pm$ standard deviation (SD) for normally-distributed or median and interquartile ranges (IQR) for skewed-distributed continuous variables and percentage for categorical variables. The distribution of variables was assessed by the Kolmogorov-Smirnov test. Continuous variables were compared by the independent-samples *t* test when normally distributed or the Mann-Whitney-U test when not normally distributed. Categorical variables were compared with the chi-square (χ^2) test or Fisher's exact test, where appropriate. Correlations between the levels of hs-cTnI, procalcitonin, D-dimer, CRP, fibrinogen, ferritin and neutrophil count were assessed by Spearman's correlation coefficient analysis. The

univariate logistic regression analysis was performed to test the relationship between the variables and the elevated hs-cTnI, procalcitonin and D-dimer levels. Additionally, odds ratios and 95% confidence intervals (CIs) were calculated for each variable. The multivariate logistic regression analysis was performed to assess the independent predictors of cardiac damage (elevated levels of hs-cTnI), elevated levels of procalcitonin and D-dimer. The variables that were significant in the univariate analysis were included in the multivariate analysis. A *p* value < 0.05 was considered as statistically significant. All statistical analyses were carried out using IBM SPSS software version 26.0.

Results

One-hundred and forty-one consecutive patients hospitalized with COVID-19 pneumonia were analyzed in the present study. The study patients' median age was 64 years (range, 26-91 years), and 84 (59.6%) were males. Five patients died during hospital stay and 136 patients were discharged. Comorbidities, electrocardiographic signs of right ventricular strain, radiographic findings, and the clinical outcome of all study patients are shown in Table 1.

Clinical and Electrocardiographic Characteristics

Table 2 shows a summary of the comparison of the demographic data, signs of ECG, CT findings, clinical outcome, and laboratory data by categorizing as elevated or normal the levels of hs-cTnI, procalcitonin and D-dimer in patients with COVID-19 pneumonia. Smoking status, gender and the presence of comorbidities were similar between patients with elevated or normal levels of hs-cTnI, procalcitonin and D-dimer.

In patients with elevated levels of hs-cTnI, procalcitonin, and D-dimer, the ECG signs of right ventricular stress, including sinus tachycardia, complete RBBB, T-wave inversion in V_1 - V_4 , $S_1Q_3T_3$ pattern, Qr morphology in lead V_1 and ST-segment elevation in V_1 were significantly more prevalent when compared to the patients with normal levels of hs-cTnI, procalcitonin, and D-dimer. The ratio of bilateral pneumonia based on the findings of the chest CT was significantly higher in patients with elevated levels of hs-cTnI, procalcitonin, and D-dimer. Patients with elevated levels of hs-cTnI, procalcitonin, and D-dimer also had significantly higher levels of fibrinogen, CRP, ferritin, CK-MB and a higher neutrophil-to-leukocyte ratio, while they had significantly lower lymphocyte count (Table 2).

In-hospital mortality was significantly higher in the patients with elevated hs-cTnI and procalcitonin levels. Incomplete RBBB was significantly frequent in the patients who only had cardiac damage. Patients with elevated procalcitonin levels had significantly higher neutrophil count than those with normal procalcitonin levels. Patients with elevated levels of procalcitonin and D-dimer were significantly older, and their lymphocyte-to-leukocyte ratios were significantly lower (Table 2).

Moreover, patients with cardiac damage presented with significantly higher levels of D-dimer and procalcitonin than those without cardiac damage. D-dimer and hs-

Table 1 – Comorbidities, clinical outcome, electrocardiographic and radiographic findings of patients with COVID-19 pneumonia

	Patients (n=141)
Smoking	21 (14.9%)
Comorbidities	
Hypertension	44 (31.2%)
Diabetes	36 (25.5%)
Coronary artery disease	27 (19.1%)
Chronic obstructive pulmonary disease	5 (3.5%)
Malignancy	2 (1.4%)
ECG signs	
Sinus tachycardia	87 (61.7%)
Incomplete RBBB	62 (44.0%)
Complete RBBB	28 (19.9%)
T-wave inversion in V ₁ to V ₄	37 (26.2%)
S ₁ Q ₃ T ₃ pattern	52 (36.9%)
Qr in V ₁	35 (24.8%)
ST-segment elevation in V ₁	54 (38.3%)
Chest computed tomography findings	7 (5%)
Unilateral pneumonia	55 (39.0%)
Bilateral pneumonia	86 (61.0%)
Clinical outcome	35 (24.8%)
In-hospital death	5 (3.5%)

ECG: electrocardiogram; RBBB: right bundle branch block.

cTnI levels were significantly increased in patients with elevated procalcitonin levels, when compared to patients with normal procalcitonin levels. Procalcitonin and hs-cTnI levels were also found to be significantly higher in patients with elevated D-dimer levels, when compared to those with normal D-dimer levels (Table 2).

Univariate and Multivariate Logistic Regression Analyses

The univariate logistic regression analysis showed that sinus tachycardia, incomplete RBBB, complete RBBB, T-wave inversion in V₁-V₄, S₁Q₃T₃ pattern, Qr morphology in V₁, ST-segment elevation in V₁, presence of bilateral pneumonia, neutrophil count, CRP, procalcitonin, ferritin, fibrinogen, D-dimer and CK-MB levels were significantly associated with cardiac damage in patients with COVID-19 pneumonia (Table 3). However, at the multivariate logistic regression analysis, only the ST-segment elevation in V₁ was determined as an independent predictor of cardiac damage in patients with COVID-19 pneumonia (odds ratio=0.23; 95% CI, 0.06 to 0.90; p=0.035).

The patients' age, complete RBBB, T-wave inversion in V₁-V₄, S₁Q₃T₃ pattern, Qr morphology in V₁, ST-segment elevation in V₁, presence of bilateral pneumonia, lymphocyte-to-leukocyte ratio, neutrophil count, neutrophil-to-leukocyte ratio, CRP, ferritin, fibrinogen, D-dimer, hs-cTnI, and CK-MB levels were significantly associated with the elevated procalcitonin levels in the univariate logistic regression analysis. The multivariate

logistic regression analysis revealed that the S₁Q₃T₃ pattern (odds ratio=0.19; 95% CI, 0.06 to 0.62; p=0.006), neutrophil count (odds ratio=1.35; 95% CI, 1.07 to 1.71; p=0.011) and presence of bilateral pneumonia (odds ratio=0.15; 95% CI, 0.03 to 0.84; p=0.031) were independently associated with the elevated levels of procalcitonin (Table 4).

According to the univariate analysis, the patients' age, presence of bilateral pneumonia, the lymphocyte-to-leukocyte ratio, neutrophil and lymphocyte counts, levels of CRP, ferritin, fibrinogen, procalcitonin, hs-cTnI, CK-MB and the presence of ECG signs, including complete RBBB, T-wave inversion in V₁-V₄, S₁Q₃T₃ pattern, and Qr morphology in V₁ were significantly associated with the elevated levels of D-dimer (Table 5). Nonetheless, among these determinants, only fibrinogen was found to be an independent predictor of the elevated levels of D-dimer in the multivariate analysis (odds ratio=1.05; 95% CI, 1.03 to 1.07; p<0.001).

The Spearman's correlation analysis also revealed that neutrophil count, hs-cTnI, procalcitonin, D-dimer, CRP, fibrinogen and ferritin levels were significantly and positively correlated with each other (Table 6).

Discussion

Cardiac damage detected by the increase of cardiac biomarkers in COVID-19 has been associated with a fatal prognosis. However, the pathophysiological mechanisms

Table 2 – Comparison of the characteristics of patients with COVID-19 pneumonia according to elevated or normal hs-cTnI, procalcitonin and D-dimer levels

Characteristics	Normal hs-cTnI (n = 69)	Elevated hs-cTnI (n = 72)	p Value	Procalcitonin < 0.5 ng/mL (n = 74)	Procalcitonin ≥ 0.5 ng/mL (n = 67)	p Value	D-dimer < 0.5 µg/mL (n = 39)	D-dimer ≥ 0.5 µg/mL (n = 102)	p Value
Age	62.6 ± 12.3	63.4 ± 12.5	0.69 [†]	60.1 ± 12.1	66.3 ± 11.1	0.003 [†]	57.0 ± 12.6	65.3 ± 11.5	< 0.001 [†]
Female	29 (42%)	28 (38.9%)	0.70 [*]	29 (39.2%)	28 (41.8%)	0.75 [*]	13 (33.3%)	44 (43.1%)	0.289 [*]
ECG signs									
Sinus tachycardia	34 (49.3%)	53 (73.6%)	0.003 [*]	30 (40.5%)	57 (85.1%)	< 0.001 [*]	9 (23.1%)	78 (76.5%)	< 0.001 [*]
Incomplete RBBB	21 (30.4%)	41 (56.9%)	0.002 [*]	28 (37.8%)	34 (50.7%)	0.123 [*]	16 (41%)	46 (45.1%)	0.66 [*]
Complete RBBB	8 (11.6%)	20 (27.8%)	0.016 [*]	4 (5.4%)	24 (35.8%)	< 0.001 [*]	2 (5.1%)	26 (25.5%)	0.007 [*]
T inversion in V1 to V4	3 (4.3%)	34 (47.2%)	< 0.001 [*]	4 (5.4%)	33 (49.3%)	< 0.001 [*]	1 (2.6%)	36 (35.3%)	< 0.001 [*]
S ₁ Q ₃ T ₃ pattern	14 (20.3%)	38 (52.8%)	< 0.001 [*]	8 (10.8%)	44 (65.7%)	< 0.001 [*]	2 (5.1%)	50 (49%)	< 0.001 [*]
Qr in V ₁	1 (1.4%)	34 (47.2%)	< 0.001 [*]	3 (4.1%)	32 (47.8%)	< 0.001 [*]	1 (2.6%)	34 (33.3%)	< 0.001 [*]
ST elevation in V ₁	5 (7.2%)	49 (68.1%)	< 0.001 [*]	5 (6.8%)	49 (73.1%)	< 0.001 [*]	0 (0.0%)	54 (52.9%)	< 0.001 [*]
Chest CT findings									
Unilateral pneumonia	40 (58%)	15 (20.8%)	< 0.001 [*]	52 (70.3%)	3 (4.5%)	< 0.001 [*]	31 (79.5%)	24 (23.5%)	< 0.001 [*]
Bilateral pneumonia	29 (42%)	57 (79.2%)		22 (29.7%)	64 (95.5%)		8 (20.5%)	78 (76.5%)	
Clinical outcome									
In-hospital death	0 (0.0%)	5 (6.9%)	0.026 [†]	0 (0.0%)	5 (7.5%)	0.017 [*]	0 (0.0%)	5 (4.9%)	0.322 [†]
Laboratory data									
Leukocyte count ×10 ³ /µL	6.6 (5.6-7.8)	6.9 (5.3-8.9)	0.66 [†]	6.5 (5.3-8.2)	7.3 (5.7-8.6)	0.104 [†]	6.8 (5.4-7.7)	6.7 (5.6-6.6)	0.269 [†]
Neutrophil count ×10 ³ /µL	4.9 (3.3-5.9)	4.7 (3.9 – 6.8)	0.22 [†]	4.7 (3.2-5.7)	5.4 (4-7.8)	0.004 [†]	4.9 (3.2-5.8)	4.9 (3.8-6.8)	0.203 [†]
Neutrophil/ Leukocyte ratio, %	70.5 ± 8.9	74.0 ± 10.2	0.033 [†]	69.6 ± 9.2	75.3 ± 9.5	< 0.001 [†]	69.4 ± 9.4	73.4 ± 9.7	0.03 [†]
Lymphocyte count ×10 ³ /µL	1.1 (0.9- 1.3)	0.9 (0.8-1.2)	0.006 [†]	1.05 (0.9-1.1)	0.96 (0.9-1.2)	0.019 [†]	1.10 (0.9-1.6)	0.97 (1-1.2)	0.009 [†]
Lymphocyte / Leukocyte ratio, %	15.6 (13.6 -20)	15 (10-19.7)	0.06 [†]	16.7 (14.3-20)	13.6 (9.5 -19)	0.003 [†]	17 (14-17)	15 (10-18)	0.007 [†]

Continuation

Platelets $\times 10^3/\mu\text{L}$	220 (168 – 256)	221 (163-285)	0.98 [†]	219 (167-256)	220 (166-306)	0.82 [†]	218 (163-243)	220 (167-291)	0.411 [†]
Creatinine (mg/dL)	0.86 (0.7-1)	0.98 (0.8-1.2)	0.16 [†]	0.86 (0.7-1.1)	0.98 (0.8-1.3)	0.09 [†]	0.83 (0.7-1)	0.97 (0.8-1.2)	0.13 [†]
ALT (U/L)	31 (25-45)	31.5 (20-49)	0.74 [†]	30 (21-45)	32 (23-47)	0.55 [†]	31 (25-43)	31 (21-45)	0.32 [†]
AST (U/L)	30 (24-38)	35.5 (26-47)	0.11 [†]	30 (23-39)	36 (26-46)	0.23 [†]	30 (23-40)	34 (26-44)	0.37 [†]
Fibrinogen, mg/dL	472 (413-542)	590 (505-736)	< 0.001 [†]	449 (409-507)	626 (550-740)	< 0.001 [†]	415 (396-428)	577 (505-683)	< 0.001 [†]
D-dimer, $\mu\text{g/mL}$	0.45 (0.2-0.9)	1.40 (0.7-3.7)	< 0.001 [†]	0.41 (0.2-0.8)	2.04 (1-3.8)	< 0.001 [†]	0.24 (0.2-0.3)	1.20 (0.7-2.8)	< 0.001 [†]
CRP, mg/L	58 (44-88)	136 (89-203)	< 0.001 [†]	54 (43-87)	153 (153-204)	< 0.001 [†]	49 (41-61)	114 (77-179)	< 0.001 [†]
Ferritin, $\mu\text{g/L}$	294 (236-400)	612 (397-975)	< 0.001 [†]	282 (232-382)	662 (450-980)	< 0.001 [†]	254 (226-292)	532 (356-806)	< 0.001 [†]
Procalcitonin, ng/mL	0.06 (0.02-0.38)	2.76 (0.31-6.69)	< 0.001 [†]	0.055 (0.02-0.07)	2.76 (1-7.7)	< 0.001 [†]	0.05 (0.02-0.06)	0.96 (0.07-5.30)	< 0.001 [†]
CK-MB, ng/mL	3 (2-3)	8.5 (5-15.5)	< 0.001 [†]	3 (2-4)	9 (4-16)	< 0.001 [†]	3 (2-4)	5.5 (3-12)	< 0.001 [†]
hs-cTnI, ng/L	15 (12-16)	62.5 (26-348)	< 0.001 [†]	16 (13-18)	67 (18-356)	< 0.001 [†]	16 (13-16)	31 (16-173)	< 0.001 [†]

Data are presented as mean $\pm$ SD or median (IQR) or N. (%). ECG: electrocardiogram; hs-cTnI: highly-sensitive cardiac troponin I; CT: computed tomography; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; CRP: C-reactive protein; CK-MB: creatine kinase-myocardial brain fraction. [†] Compared using the independent sample t test, [‡] Compared using the Mann-Whitney U test, * Compared using the X2 test, [‡] Compared using Fisher's exact test.

underlying cardiac damage associated with COVID-19 have not been clearly demonstrated. The possible mechanisms that other studies have suggested to explain the myocardial damage caused by COVID-19 are myocarditis due to direct infection with SARS-CoV-2 or secondary to the vigorous systemic inflammatory response induced by COVID-19, plaque instability that leads to acute coronary syndrome, and hypoxemia due to respiratory failure.^{7,8} Recently, pulmonary microvascular thrombosis has been reported with diffuse alveolar damage in COVID-19 pneumonia.^{9,10}

McGonagle et al. have proposed a pulmonary intravascular coagulopathy model to explain myocardial injury and cardiovascular mortality in COVID-19 pneumonia. According to this model, COVID-19 induces diffuse pulmonary intravascular coagulopathy through diffuse lung inflammation, similar to the macrophage activation syndrome. Both the immunothrombosis of the extensive pulmonary vascular bed and the alveolar hypoxemia may trigger right ventricular stress by causing pulmonary hypertension and may play a role in the fatal outcome. In COVID-19 pneumonia, elevated D-dimer levels may reflect wide pulmonary microthrombosis, while elevated cardiac biomarker levels may indicate right ventricular strain triggered by pulmonary hypertension.¹¹ The findings of our current study support this model. All of the ECG signs of right ventricular strain in the study, except incomplete RBBB, were significantly more prevalent in COVID-19 patients with cardiac damage and elevated procalcitonin and D-dimer levels. As we expected, all of the ECG signs of right ventricular strain, including incomplete RBBB, were significantly more common in COVID-19 patients with cardiac damage. We also observed a significant and direct association among the levels of hs-cTnI, procalcitonin and D-dimer, neutrophil count, levels of CRP, ferritin and fibrinogen in patients with COVID-19 pneumonia. These results indicate that inflammation, thrombosis and cardiac damage are directly related with each other in COVID-19 patients.

The univariate regression analysis revealed that four of the seven ECG signs of right ventricular strain were significantly associated with cardiac injury and elevated levels of procalcitonin and D-dimer in patients with COVID-19 pneumonia. However, all of these seven ECG signs were significantly associated only with cardiac injury in COVID-19 patients. These findings suggest that the possible cause of elevated hs-cTnI levels or cardiac injury in COVID-19 is right ventricular stress, which is induced by sudden-onset pulmonary hypertension due to diffuse pulmonary vascular thrombosis triggered by COVID-19 pneumonia.

The multivariate analysis revealed that among the ECG signs and other variables, only the ST-segment elevation in V₁ was an independent predictor of cardiac damage in patients with COVID-19 pneumonia. Therefore, the existence of ST-segment elevation in V₁ on the admission ECG may indicate a poor prognosis in patients with COVID-19, when we consider that the cardiac injury is associated with poor prognosis in these patients. Moreover, the existence of ST-segment elevation in V₁ was also significantly associated with

Table 3 – Determinants of cardiac damage in patients with COVID-19 by univariate and multivariate logistic regression analyses

	Univariate		Multivariate	
	OR (95% CI)	p Value	OR (95% CI)	p Value
Sinus tachycardia	0.35 (0.17-0.70)	0.003		
Incomplete RBBB	0.33 (0.17-0.66)	0.002		
Complete RBBB	0.34 (0.14-0.84)	0.019		
T inversion in V ₁ -V ₄	0.05 (0.01-0.18)	< 0.001		
S ₁ Q ₃ T ₃ pattern	0.23 (0.11-0.48)	< 0.001		
Qr in V ₁	0.02 (0.00-0.12)	< 0.001		
ST elevation in V ₁	0.04 (0.01-0.10)	< 0.001	0.23 (0.06-0.90)	0.035
Presence of bilateral pneumonia	0.19 (0.09-0.40)	< 0.001		
Neutrophil count	1.04 (1.00-1.08)	0.036		
Fibrinogen, mg/dL	1.01 (1.01-1.01)	< 0.001		
D-dimer, µg/mL	3.14 (1.91-5.17)	< 0.001		
CRP, mg/L	1.02 (1.01-1.03)	< 0.001		
Ferritin, µg/L	1.01 (1.00-1.01)	< 0.001		
Procalcitonin, ng/mL	2.03 (1.45-2.83)	< 0.001		
CK-MB, ng/mL	2.09 (1.58-2.76)	< 0.001		

OR: Odds ratio; CI: confidence interval; RBBB: right bundle branch block; CRP: C-reactive protein.

Table 4 – Determinants of the elevated levels of procalcitonin (≥ 0.5 ng/mL) in patients with COVID-19 by univariate and multivariate logistic regression analyses

	Univariate		Multivariate	
	OR (95% CI)	p Value	OR (95% CI)	p Value
Age	1.04 (1.01-1.08)	0.004		
Complete RBBB	0.10 (0.03-0.32)	< 0.001		
T inversion in V ₁ -V ₄	0.06 (0.02-0.18)	< 0.001		
S ₁ Q ₃ T ₃ pattern	0.06 (0.03-0.15)	< 0.001	0.19 (0.06-0.62)	0.006
Qr in V ₁	0.05 (0.01-0.16)	< 0.001		
ST elevation in V ₁	0.03 (0.01-0.08)	< 0.001		
Presence of bilateral pneumonia	0.02 (0.01-0.07)	< 0.001	0.15 (0.03-0.84)	0.031
Neutrophil count	1.27 (1.09-1.48)	0.002	1.35 (1.07-1.71)	0.011
Neutrophil/Leukocyte ratio	1.07 (1.03-1.11)	0.001		
Lymphocyte/Leukocyte ratio	0.93 (0.88-0.98)	0.009		
Fibrinogen, mg/dL	1.02 (1.01-1.02)	< 0.001		
D-dimer, µg/mL	8.64 (3.67-20.35)	< 0.001		
CRP, mg/L	1.03 (1.02-1.04)	< 0.001		
Ferritin, µg/L	1.01 (1.01-1.01)	< 0.001		
CK-MB, ng/mL	1.35 (1.18-1.53)	< 0.001		
hs-cTnI, ng/L	1.02 (1.01-1.02)	< 0.001		

OR: Odds ratio; CI: confidence interval; RBBB: right bundle branch block; CRP: C-reactive protein.

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Table 5 – Determinants of the elevated levels of D-dimer ($\geq 0.5 \mu\text{g/mL}$) in patients with COVID-19 by univariate and multivariate logistic regression analyses

	Univariate		Multivariate	
	OR (95% CI)	p Value	OR (95% CI)	p Value
Age	1.06 (1.02-1.10)	0.001		
Complete RBBB	0.16 (0.04-0.70)	0.015		
T inversion in V_1 - V_4	0.05 (0.01-0.37)	0.003		
$S_1Q_3T_3$ pattern	0.06 (0.01-0.25)	< 0.001		
Qr in V_1	0.05 (0.01-0.40)	0.004		
Presence of bilateral pneumonia	0.08 (0.03-0.20)	< 0.001		
Neutrophil count	1.04 (1.00-1.09)	0.033		
Lymphocyte count	0.41 (0.17-0.96)	0.041		
Lymphocyte/Leukocyte ratio	0.93 (0.88-0.98)	0.007		
Fibrinogen, mg/dL	1.04 (1.02-1.06)	< 0.001	1.05 (1.03-1.07)	< 0.001
Procalcitonin, ng/mL	17.73 (2.82-111.30)	0.002		
CRP, mg/L	1.05 (1.03-1.07)	< 0.001		
Ferritin, $\mu\text{g/L}$	1.01 (1.01-1.02)	< 0.001		
CK-MB, ng/mL	1.34 (1.12-1.61)	0.001		
hs-cTnI, ng/L	1.10 (1.03-1.18)	0.006		

OR: Odds ratio; CI: confidence interval; RBBB: right bundle branch block; CRP: C-reactive protein.

Table 6 – Spearman's correlations of biomarkers with each other in patients with COVID-19

	hs-cTnI		Procalcitonin		D-dimer		CRP		Neutrophil count		Fibrinogen		Ferritin	
	r	p	r	p	r	p	r	p	r	p	r	p	r	p
hs-cTnI	1	.	0.666	< 0.001	0.633	< 0.001	0.599	< 0.001	0.175	0.04	0.618	< 0.001	0.625	< 0.001
Procalcitonin	0.666	< 0.001	1	.	0.776	< 0.001	0.811	< 0.001	0.213	0.01	0.748	< 0.001	0.841	< 0.001
D-dimer	0.633	< 0.001	0.776	< 0.001	1	.	0.821	< 0.001	0.172	0.04	0.924	< 0.001	0.842	< 0.001
CRP	0.599	< 0.001	0.811	< 0.001	0.821	< 0.001	1	.	0.271	0.001	0.811	< 0.001	0.962	< 0.001
Neutrophil count	0.175	0.04	0.213	0.01	0.172	0.04	0.271	0.001	1	.	0.174	0.04	0.222	0.008
Fibrinogen	0.618	< 0.001	0.748	< 0.001	0.924	< 0.001	0.811	< 0.001	0.174	0.04	1	.	0.832	< 0.001
Ferritin	0.625	< 0.001	0.841	< 0.001	0.842	< 0.001	0.962	< 0.001	0.222	0.008	0.832	< 0.001	1	.

CRP: C-reactive protein; hs-cTnI: highly-sensitive cardiac troponin I; r: Spearman's correlation coefficient.

elevated procalcitonin levels, according to our results of the regression analyses. The $S_1Q_3T_3$ pattern, which is a well-known electrocardiographic manifestation of acute right heart strain, particularly developed due to massive pulmonary embolism, was found to be one of the independent predictors of elevated procalcitonin levels in patients with COVID-19 pneumonia in our multivariate regression analyses. Unsurprisingly, the other two independent predictors of elevated procalcitonin levels in COVID-19 patients were the presence of bilateral pneumonia, and neutrophil count. As both of these predictors are related to the extensiveness and severity of the disease, we suggest that the $S_1Q_3T_3$ pattern may also reflect disease extent and severity.

Interestingly, there was no relationship between the patients' age and cardiac damage. Yet, the univariate regression analysis demonstrated a positive relationship between age and elevated levels of procalcitonin and D-dimer. The multivariate analysis indicated that fibrinogen was the only independent predictor of elevated D-dimer levels. However, none of the ECG signs of the right ventricular strain was an independent predictor of elevated D-dimer levels. Although elevated D-dimer levels may be the reflection of the diffuse pulmonary intravascular thrombosis in COVID-19, elevated D-dimer levels are not specific and can occur due to many other conditions. Therefore, we concluded that we did not find an

independent relationship between the elevated D-dimer levels and the ECG signs on the multivariate analysis.

Very recently, Ackermann et al.¹² have published an article that investigated the fundamental pathological mechanisms of severe COVID-19 infection by examining the morphological and molecular changes of the lungs obtained during the autopsy of patients who died due to COVID-19 infection. They have reported that both COVID-19 and influenza exhibits diffuse alveolar damage and infiltrating perivascular lymphocytes, although COVID-19 is distinct with its three angiocentric characteristics. These characteristics are the extensive vascular thrombosis with microangiopathy and occlusion of alveolar capillaries, vascular angiogenesis via intussusceptive angiogenesis, and endothelial cell damage possibly due to the direct invasion by SARS-CoV-2.¹² Their findings support ours by showing widespread pulmonary vascular thrombosis, which is accompanied by endothelial injury and angiogenesis caused by COVID-19. Therefore, it can be stated that widespread pulmonary intravascular thrombus and angiogenesis induced by COVID-19 may lead to pulmonary hypertension, which may result in sudden right ventricular strain. Therefore, it can be estimated that right ventricular stress may appear in the ECG and echocardiography findings. In agreement with this suggestion, we have shown that right ventricular stress can be determined by the ECG in patients with COVID-19 for the first time. Our findings were also supported by a recent study that demonstrated a prevalence of right ventricular dilation, which was also detected by echocardiographic examination, in hospitalized patients with COVID-19 infection.¹³ However, the relationships between right ventricular dilation, cardiac damage and biomarkers of both inflammation and thrombosis were not investigated in the aforementioned study.

Our study has some limitations that need to be stated. First, this is a single-center study, with a small sample size. Second, as a retrospective study, specific laboratory investigations such as other thrombotic and cardiac biomarkers or echocardiographic examinations, and ECG monitoring for possible reversion of the ECG signs were not available. Third, as the study included patients with COVID-19 only, patients without COVID-19 could not be compared, especially regarding ECG signs.

References

1. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;395(10223):497-506.
2. Li B, Yang J, Zhao F, Zhi L, Wang X, Liu L, et al. Prevalence and impact of cardiovascular metabolic diseases on COVID-19 in China. *Clin Res Cardiol*. 2020;109(5):531-8.
3. World Health Organization. (WHO). Global surveillance for COVID-19 caused by human infection with COVID-19 virus: interim guidance. [Cited in 2020 March 20]. Available from: <https://extranet.who.int/iris/restricted/handle/10665/331506>.
4. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med*. 2020;382(18):1708-20.
5. Daniel KR, Courtney DM, Kline JA. Assessment of cardiac stress from massive pulmonary embolism with 12-lead ECG. *Chest*. 2001;120:474-481.
6. Kucher N, Walpoth N, Wustmann K, Noveanu M, Gertsch M. QR in V1 - an ECG sign associated with right ventricular strain and adverse clinical outcome in pulmonary embolism. *Eur Heart J*. 2003;24(1):1113-9.
7. Akhmerov A, Marbán E. COVID-19 and the Heart. *Circ Res*. 2020;126(10):1443-55.

Conclusions

To the best of our knowledge, the present study is the first one to show the right ventricular strain manifestations on the ECG and its relationship with inflammation and thrombosis in patients with COVID-19 pneumonia. Additionally, the findings of this study reveal that COVID-19 infection affects the heart, especially through the right side of the heart. In doing so, our study eventually suggests that the ECG, which is a feasible, cost-effective, safe and rapid test, can be used in both the assessment and monitoring of patients with COVID-19 in terms of cardiac damage, severity of the inflammation and perhaps prognosis. Finally, our findings need to be validated by prospective and larger clinical trials.

Author Contributions

Conception and design of the research and Critical revision of the manuscript for intellectual content: Polat V, Bozcali E; Acquisition of data: Polat V, Akturk IF; Analysis and interpretation of the data: Polat V, Bozcali E, Yasar KK, Karaosmanoglu HK; Statistical analysis and Obtaining financing: Polat V; Writing of the manuscript: Polat V, Bozcali E, Akturk IF.

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 Bakirkoy Dr. Sadi Konuk Training and Research Hospital under the protocol number 2020/255. 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.

8. Guo T, Fan Y, Chen M, Wu X, Zhang L, He T, et al. Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19). *JAMA Cardiol.* 2020;5(7):811-8.
9. Zhang T, Sun LX, Feng RE. Comparison of clinical and pathological features between severe acute respiratory syndrome and coronavirus disease 2019. *Zhonghua Jie He He Hu Xi Za Zhi.* 2020;43(6):496-502.
10. Yao XH, Li TY, He ZC, Ping YF, Liu HW, Yu SC, et al. A pathological report of three COVID-19 cases by minimally invasive autopsies. *Zhonghua Bing Li Xue Za Zhi.* 2020;49(5):411-7.
11. McGonagle D, O'Donnell JS, Sharif K, Emery P, Bridgewood C. Immune mechanisms of pulmonary intravascular coagulopathy in COVID-19 pneumonia. *Lancet Rheumatol.* 2020;2(7):e437-e445.
12. Ackermann M, Verleden SE, Kuehnel M, Haverich A, Welte T, Laenger F, et al. Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in Covid-19. *N Engl J Med.* 2020;383(2):120-8.
13. Argulian E, Sud K, Vogel B, Bohra C, Garg V, Talebi S, et al. Right ventricular dilation in hospitalized patients with COVID-19 infection. *JACC Cardiovasc Imaging.* 2020;13(11):2459-61.



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Atorvastatin Attenuates Vascular Remodeling in Mice with Metabolic Syndrome

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Abstract

Background: Metabolic syndrome is characterized by an array of comorbidities. During this syndrome, structural changes are observed in the cardiovascular system, especially vascular remodeling. One of the predisposing causes for these changes is chronic inflammation resulting from changes in the structure and composition of perivascular adipose tissue. Atorvastatin is effective in the treatment of dyslipidemias. However, its pleiotropic effects have not been completely understood. We hypothesize that metabolic syndrome may lead to vascular remodeling and that atorvastatin therapy may be able to attenuate this condition.

Objectives: To assess the effects of atorvastatin therapy on vascular remodeling in an experimental model of metabolic syndrome.

Methods: Swiss mice received a control diet or a hyperglycemic diet for 18 weeks. After 14 weeks of diet, mice were treated with vehicle or atorvastatin (20mg/kg) during for 4 weeks. Nutritional and metabolic profiles were assessed by biochemical tests; moreover, a histological assessment of aorta structure was conducted, and cytokine levels were determined by the immunoenzyme assay. The acceptable level of significance for the results was set at $p < 0.05$.

Results: Hyperglycemic diet promoted the development of metabolic syndrome. It indeed culminated in hypertrophic remodeling of vascular smooth muscle and perivascular adipose tissue. Furthermore, there were increases in the levels of circulating TNF- α and IL-6 and in the perivascular adipose tissue. Atorvastatin therapy significantly reduced metabolic damages, vascular remodeling, and cytokine levels.

Conclusion: Atorvastatin attenuate metabolic damages associated with metabolic syndrome induced by hyperglycemic diet, in addition to attenuating vascular remodeling; both effects are associated with reduced levels of pro-inflammatory cytokines.

Keywords: Dyslipidemias; Dietary Carbohydrates; Metabolic Syndrome; Vascular Remodeling; Atorvastatin; Inflammation; Mice.

Introduction

Cardiovascular diseases pose great risks for the quality of life of the world population. In Brazil, nearly 350 thousand individuals die from cardiovascular diseases every year.^{1,2} One of the most important predisposing causes for cardiovascular risks is metabolic syndrome (MS), characterized by an array of comorbidities involving increased abdominal circumference (≥ 89 cm for women and ≥ 102 cm for men), increased levels of triglycerides (≥ 150 mg/dL), reduced levels of HDL cholesterol (≤ 50 mg/dL for women and ≤ 40 mg/dL for men), increased levels of blood pressure ($\geq 130/85$ mmHg), and increased levels of fasting glucose (≥ 100 mg/dL). The presence of at least three of these comorbidities is pivotal for the diagnosis of MS.^{3,4}

During MS there are structural and functional changes in components of the vascular system.⁵⁻⁷ Individuals with MS present endothelial dysfunction, in addition to increased migration and proliferation of smooth muscle cells. An expansion of perivascular adipose tissue (PVAT) is also observed, as shown by morphological increase of adipocytes and by the replacement of brown adipose tissue with white adipose tissue, resulting in a reduction in the release of PVAT-derived relaxing factors and consequent lack of anti-contractile capacity.⁸⁻¹¹

Hypertrophy and replacement of adipocytes in the PVAT may favor the production and accumulation of pro-inflammatory cytokines.¹² Rodents that underwent a high-calorie diet and developed MS showed increase in and accumulation of PVAT in the aorta and the carotid arteries. This fact promoted the release of chemokines and recruitment of monocytes and T-cells to PVAT.¹³ In this inflammatory environment, increased production of interleukin-6 (IL-6) and infiltrate of tumor necrosis factor-alpha (TNF- α) releasing macrophages may also be observed in the PVAT.¹⁴ This set triggers chronic vascular system inflammation, impairing the structure and the function of the constituents of this system.

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Blood vessel inflammation indeed contributes to vascular remodeling, increased peripheral resistance, and circulatory disorders.^{7,15,16} In this context, vascular remodeling is a chronic adaptive process characterized by changes in blood vessel structure derived from pro-inflammatory cytokines, in addition to growth factors, hemodynamic stimulation, and reactive oxygen species. It encompasses changes in cell growth, death, and migration and in synthesis and degradation of the extracellular matrix.¹⁷⁻¹⁹

An important factor to be considered in the vascular changes found during MS is dyslipidemia, a condition characterized by increased circulating levels of cholesterol and triglycerides and reduced levels of HDL.²⁰ Numerous studies established that dyslipidemia leads to an inflammatory vascular response, reflected in the activation of endothelial cells, recruitment of leukocytes, and production of pro-inflammatory cytokines.^{21,22} Hypercholesterolemic mice fed with a high-fat diet showed remodeling in the medial layer of the femoral artery, associated with recruitment of macrophages.²³ In this context, there is a positive correlation between levels of circulating cholesterol, chronic inflammation, and vascular remodeling.

Atorvastatin, an inhibitor of β -hydroxy- β -methylglutaryl-coenzyme A reductase, has shown to be one of the most effective statins in the treatment of dyslipidemias, reducing the production of LDL-cholesterol and increasing the production of high density lipoprotein (HDL) cholesterol.^{24,25} However, over the last decades, a growing body of evidence, both experimental and clinical, has accumulated to support the idea that atorvastatin exerts beneficial cardiovascular effects, regardless of its primary effects.²⁶ In an experimental MS model, atorvastatin was able to improve reactivity and reduce structural remodeling of resistance arteries, both of which were associated with reduced inflammation and reduced oxidative stress.²⁷ Furthermore, atorvastatin is able to inhibit the secretion of matrix metalloproteinase 9 in vascular cells and suppress the expression of transforming growth factor beta, thus reducing vascular fibrosis.²⁸⁻³⁰ These *in vitro* effects of atorvastatin also associated with its anti-inflammatory capacity.³¹ In the clinical context, atorvastatin reduces atherosclerotic processes³² and clinical manifestations of acute coronary syndrome.³³ Indeed, one of the several pleiotropic effects of atorvastatin is its robust vasoprotective capacity. Nevertheless, there is no sufficient evidence to confirm the effects and the possible mechanisms involved in the actions of atorvastatin from the perspective of the vascular smooth muscle and, unprecedentedly, of PVAT as inflammatory tissues in conditions of MS. Therefore, in this study we hypothesize that MS leads to vascular remodeling of vascular smooth muscle and of PVAT, resulting from increased vascular inflammation. Moreover, atorvastatin therapy may be able to reduce vascular inflammation and thus revert the damages associated with MS.

Methods

Animals and experimental design

All experimental procedures were analyzed by the Ethics Committee on Animal Use of Universidade Federal de Jataí (Protocol 02/2019). Three-week old male Swiss mice were

obtained from the Central Vivarium of Universidade Federal de Goiás – Regional Goiânia and housed in the Animal Experimentation Vivarium of Universidade Federal de Jataí, under a controlled temperature of $22 \pm 2^\circ\text{C}$, humidity of $50 \pm 5\%$, and 12-hour light/dark cycles, and ad libitum access to water and food. During the entire experimental period, mice were kept in polypropylene cages (30 cm long x 20 cm wide x 13 cm high), in groups of 3 mice per cage.

After one week of acclimatization, mice received a control diet or a hyperglycemic diet for 18 weeks. After 14 weeks of diet, mice were treated (daily in the afternoon) by gavage with vehicle (saline) or atorvastatin (20mg/kg, Sigma-Aldrich, #PZ0001, Germany) for 4 weeks.³⁴ The control diet consisted of 22% of protein, 70% of carbohydrate, and 8% of fat, whereas the hyperglycemic diet consisted of 10% of protein, 80% of carbohydrate, and 10% of fat. The hyperglycemic diet included 33% of control diet (Nuvilab® CR1, Nuvital, Brazil), 33% of condensed milk, and 7% of sucrose by weight, the remaining being water.⁶ The energy density was 12.16 kJ/g for the control diet and 13.35 kJ/g for the hyperglycemic diet. Mice were euthanized by overdose anesthesia (ketamine and xylazine, 140 mg/kg and 12 mg/kg, respectively, administered intraperitoneally).

Nutritional and murinometric profile of the experimental model

The nutritional profile was determined by food consumption and consequent caloric intake, in addition to feed efficiency. Caloric intake (by mouse) was calculated based on weekly food intake multiplied by the energy content of the diet (g x kcal). In order to analyze the capacity of each mouse to convert the ingested calories into body mass, feed efficiency was calculated by dividing the overall body mass gain (g) by the overall energy intake (kcal), in percent. The murinometric profile was determined by analysis of body mass and fat. Mice's body mass was measured every week using a high accuracy analytical balance, and obesity was characterized by the adiposity index $\{[\text{body fat (g)} / \text{final body weight (g)}] \times 100\}$ at the end of the diets and treatments, and body fat was calculated by the sum of epididymal, retroperitoneal and visceral fats.³⁵

Collection of serum and PVAT

Mice were subjected to an 8-hour fasting. After euthanasia, blood samples were collected through cardiac puncture and transferred into dry tubes. Blood was centrifuged at 2,500 rpm for 15 minutes to separate the serum to be used in the determination of mice's biochemical and cytokine levels. PVAT was mechanically removed from segments of the thoracic aorta, frozen in liquid nitrogen, pulverized and homogenized in cold phosphate buffer solution (PBS). The tissue specimen was centrifuged at 13,000 rpm for 20 minutes to separate the insoluble material. The supernatant was collected for determination of cytokine levels.

Assessment of lipid and glucose profiles

Serum levels of total cholesterol total, triglycerides, and HDL-cholesterol were determined by enzymatic methods (kits Labtest, Brazil) in blood samples obtained after whole

blood centrifugation. The concentration of very low-density lipoproteins (VLDL) was calculated based on the serum concentration of triglycerides, using the following formula: $VLDL \text{ (mg/dL)} = \text{Triglycerides (mg/dL)}/5$. The concentration of low-density lipoproteins (LDL) was calculated based on HDL and VLDL concentrations, using the following formula: $LDL \text{ (mg/dL)} = \text{Total cholesterol total} - \text{HDL} - \text{VLDL}$.³⁶ Glucose was determined after treatment with the diets. A drop of blood was applied to individual test strips specific for blood glucose measurement (Accu-Check Active, Germany).

Oral glucose tolerance test (OGTT)

On the day before the end of the 18th week of diets and treatments, after 8-hour fasting, mice's blood glucose was measured by a glucometer (Accu-Check Active, Germany), in order to determine baseline blood glucose levels. Subsequently, a 2 g/kg dose of glucose was administered to mice by gavage. From this moment on, a chronometer was started and new blood glucose measurements were conducted at 30, 60, 90 and 120 minutes.³⁷

Morphostructural assessment of vascular smooth muscle and PVAT

Specimens of thoracic aortas were removed and then fixed in 4% paraformaldehyde for 24 hours. The next stages involved dehydration in increasing concentrations of ethyl alcohol (70%, 80%, 90% and 100%) for 120 minutes, with subsequent diaphanization in absolute ethyl alcohol (1:1) 1, 2 and 3 for 120 minutes and in xylol 1, 2 and 3 for 30 minutes, with subsequent inclusion in paraffin. Aorta specimens were included in paraffin and sectioned in a microtome at a thickness of 4.5 μm for subsequent staining.

For hematoxylin and eosin staining, slides were deparaffinized, kept in a greenhouse at 65°C, and then immersed in xylol 1 and 2 for 20 minutes. Subsequently, slides were immersed in decreasing concentrations of ethyl alcohol (100%, 90%, 70% and 50%) for 5 minutes and immersed in distilled water for 10 minutes. After hydration, slides were immersed in hematoxylin for 6 minutes and immediately after washed in running water for 10 minutes. Subsequently, they were immerse in eosin for 6 minutes. Sections were dehydrated and diaphanized again and then mounted with Permount® Mounting Medium (Fisher Scientific, USA) and glass slides.

Stained images were obtained by a digital camera coupled to an optical microscope and analyzed with the ImageJ software (National Institutes of Health, USA). For the analysis of images, lumen, tunica media, and tunica adventitia were delimited in order to calculate the following morphometric variables: cross-sectional area (CSA) and thickness of tunica media. The volume of adipocytes (v) were calculated by the formula $v = \pi d^3/6$, where (d) represents the diameter of adipocytes. The mass of adipocytes was calculated by volume multiplied by density (0.92 g/cm³). The number of adipocytes was determined by dividing the mass of PVAT by mean mass of adipocytes.³⁸

Determination of levels of inflammatory cytokines

The levels of TNF- α and IL-6 in serum and in the PVAT were assessed by the immunoenzyme assay (ELISA) using DuoSet ELISA Development Systems kits (R&D Systems, USA) according to manufacturer's instructions. Microtiter 96-well plates were covered with 50 μl /well of specific anti-TNF- α and anti-IL-6 antibodies at the concentrations described by the manufacturer, diluted in PBS, and incubated overnight at 4°C. Plates were washed with PBS/Tween-20 (0.05%), and nonspecific binding sites were blocked with 100 μl of PBS containing 1% bovine serum albumin for 2 hours at room temperature. Subsequently, samples were added, and a new incubation was conducted for 2 hours at room temperature. After this period, plates were washed and 50 μl of biotinylated antibodies specific for each cytokine were added. After 2 hours, plates were washed, and streptavidin-peroxidase conjugate diluted at 1:40 was added to each well. Plates were incubated for 1 hour at room temperature. Subsequently, plates were washed and 100 μl of tetramethylbenzidine substrate were added. Optical density was measured at 630 nm in a SpectraMAX 190 Microplate Reader spectrophotometer (Molecular Devices, USA). The levels of cytokines in the samples were calculated based on an 11-point standard curve obtained by serial dilution. Results were expressed in pg/mL for serum samples and pg/mg of protein for samples of PVAT.

Statistical analysis

Results were expressed as mean $\pm$ standard deviation (SD). Data followed a normal distribution, according to the Kolmogorov-Smirnov test. Results were analyzed by two-way analysis of variance (ANOVA), followed by Tukey post-hoc test. The minimum acceptable level of significance was $p < 0.05$. For convenience reasons, the number of mice for each experimental group was 6. The Prisma software, version 8.0 (GraphPad Software Inc., USA) was used to analyze these parameters and to design the graphs.

Results

Nutritional and murinometric profile

Food intake and, consequently, calorie intake were higher in mice fed with the hyperglycemic diet, as well as feed efficiency. However, this last parameter was reduced after atorvastatin therapy. Murinometric parameters, such as mass gain, deposits of epididymal, retroperitoneal and visceral fats were higher in mice that received the hyperglycemic diet compared with those that received the control diet. Atorvastatin therapy led to a decrease in these parameters (Table 1). Mice on the hyperglycemic diet showed a greater increase in body mass compared to those on the control diet. Furthermore, mice fed with the hyperglycemic diet and treated with atorvastatin had a decrease in their body mass (Figure 1A). The adiposity index, the parameter used to determine obesity, was higher in mice that received the hyperglycemic diet compared to those that received the control diet. Atorvastatin therapy led to a decrease in the adiposity index among mice on the hyperglycemic diet (Figure 1B).

Table 1 – Eating behavior and weight assessment of body fat deposits

	CD + Vehicle	CD + Atorvastatin	HD + Vehicle	HD + Atorvastatin
Food intake (g/week)	22.6 ± 0.3	21.3 ± 0.4	31.7 ± 0.2	31.1 ± 0.5
Calorie intake (kcal/week)	274.8 ± 3.7	259.1 ± 4.9	423.1 ± 2.67*	415.2 ± 6.7
Feed efficiency (%)	0.51 ± 0.01	0.53 ± 0.01	0.64 ± 0.02*	0.47 ± 0.03 [#]
Mass gain (g)	25.0 ± 2.31	24.5 ± 2.25	37.3 ± 1.52*	27.9 ± 1.22 [#]
Epididymal fat (g)	0.97 ± 0.12	1.13 ± 0.11	2.68 ± 0.24*	1.31 ± 0.09 [#]
Retroperitoneal fat (g)	0.32 ± 0.06	0.61 ± 0.19	1.88 ± 0.12*	0.93 ± 0.19 [#]
Visceral fat (g)	0.75 ± 0.15	0.94 ± 0.13	1.67 ± 0.11*	1.01 ± 0.17 [#]

Dados expressed as mean ± SD. *, $p < 0.05$ vs. CD + Vehicle; [#], $p < 0.05$ vs. HD + Vehicle ($n = 6$ for each experimental group). CD: Control Diet, HD: Hyperglycemic Diet.

Lipid profile

Mice fed with the hyperglycemic diet had dyslipidemia compared with those fed with the control diet. Dyslipidemia may be observed based on increased levels of total cholesterol (Figure 2A), in which LDL (Figure 2B) and VLDL (Figure 2C) fractions were increased and HDL fraction (Figure 2D) was reduced. There was also an increase in the levels of triglycerides of mice that received the hyperglycemic diet compared to those that received the control diet (Figure 2E). Mice on the hyperglycemic diet and treated with atorvastatin showed a decrease in these lipid parameters.

Glucose profile

Fasting serum glucose of mice fed with the hyperglycemic diet was increased when compared to that of mice fed with the control diet. Mice that received the hyperglycemic diet and atorvastatin therapy did not show a decrease in glucose concentration (Figure 3A). In the OGTT (Figure 3B), mice on the hyperglycemic diet had an increased glucose concentration compared with mice on the control diet, and blood glucose levels did not return to baseline levels over time, as observed in mice on control diet. Moreover, mice fed with the hyperglycemic diet and treated with atorvastatin had lower blood glucose levels over time. The area under the curve shows the above mentioned effects (Figure 3C).

Morphology of smooth muscle

Mice fed with the hyperglycemic diet had an increase in vascular CSA compared to those fed with the control diet. Mice that received the hyperglycemic diet and were treated with atorvastatin showed decreased CSA (Figure 4A). Similarly, there was an increase in the thickness of vessel tunica media among mice on the hyperglycemic diet compared to those on the control diet. Atorvastatin therapy was able to reduce this increase in thickness of tunica media (Figure 4B).

Morphology of perivascular adipose tissue

In order to investigate whether there were changes in PVAT morphology, the present study assessed the size and the number of adipocytes presents in the tunica adventitia. It was possible to observe that mice fed with the hyperglycemic diet had larger adipocytes (Figure 5A) and in a smaller number

(Figure 5B) compared to mice fed with the control diet. The group that received the hyperglycemic diet and atorvastatin therapy showed a reduction in the size of adipocytes and an increase in their number.

Inflammatory profile

Concentrations of the pro-inflammatory cytokines called TNF- α (Figures 6A and 6C) and IL-6 (Figures 6B and 6D) were determined in the serum and in PVAT. Mice on the hyperglycemic diet showed higher concentration of TNF- α and IL-6, both in serum and in PVAT, compared to mice on the control diet. Atorvastatin therapy reduced the levels of TNF- α and IL-6 both in the serum and in the PVAT of mice fed with the hyperglycemic diet.

Discussion

The hyperglycemic diet resulted in murinometric and metabolic changes in mice. Silva et al.³⁹ subjected an experimental group to a similar diet and found increases in parameters identical to those used in this study.³⁹ In this context, Leopoldo et al.,⁴⁰ using experimental models, defined the categories of adiposity after study participants received a hyperglycemic diet, which vary from: normal – adiposity index (%) 4.17-4.55; overweight – adiposity index (%) 5.69-6.23; and obesity – adiposity index (%) 7.53-10.02.⁴⁰ Our results showed an adiposity index of nearly 10% for mice fed with the hyperglycemic diet, which classifies the experimental group as obese.

Glucose is a carbohydrate that represents one of the main energy sources for the body and, when in excess, through metabolic pathways, is stored as glycogen. If the capacity to store carbohydrate intake exceeds glycogenesis, the remaining excess is converted into triacylglycerol and incorporated into cholesterols obtained from the diet and into apolipoproteins, responsible to transport triglycerides to storage tissues, such as adipose tissue.⁴¹ Thus, carbohydrate excess in the diet of mice contributes to increases in body mass and adiposity index.

Mice that received the hyperglycemic diet showed dyslipidemia and increased fasting serum glucose. Mullugeta et al.⁴² showed that hyperglycemia and insulin resistance are associated with dyslipidemia in individuals

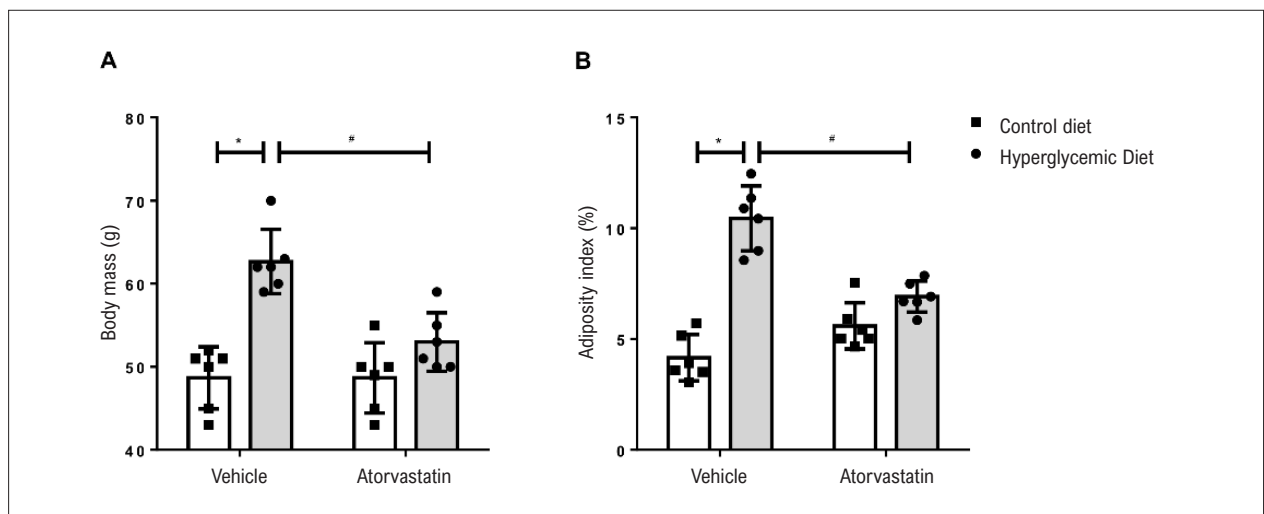


Figure 1 – Atorvastatin attenuates obesity associated with metabolic syndrome induced by hyperglycemic diet. The figures show body mass (A) and adiposity index (B) of mice fed with a control diet or with a hyperglycemic diet for 18 weeks and treated with vehicle solution or atorvastatin (20 mg/kg for 4 weeks). Results expressed as mean $\pm$ SD. *, $p < 0.05$ vs. Control Diet_Vehicle; #, $p < 0.05$ vs. Hyperglycemic Diet_Vehicle ($n = 6$ for each experimental group).

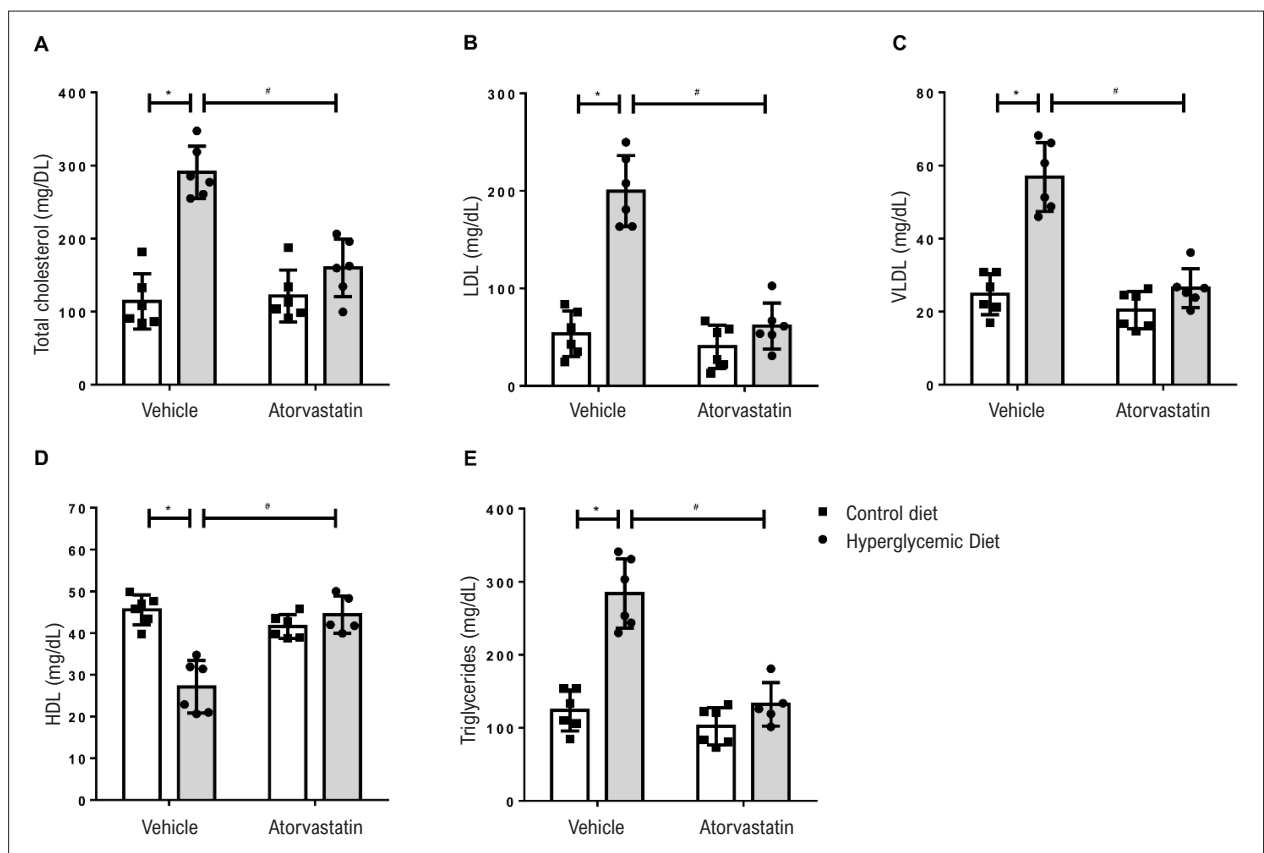


Figure 2 – Atorvastatin attenuates dyslipidemia associated with metabolic syndrome induced by hyperglycemic diet. The figures show the levels of total cholesterol (A), LDL (B), VLDL (C), HDL (D), and triglycerides (E) of mice fed with a control diet or with a hyperglycemic diet for 18 weeks and treated with vehicle solution or atorvastatin (20 mg/kg for 4 weeks). Results expressed in mean $\pm$ SD. *, $p < 0.05$ vs. Control Diet_Vehicle; #, $p < 0.05$ vs. Hyperglycemic Diet_Vehicle ($n = 6$ for each experimental group).

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with type II diabetes mellitus, i.e., hyperglycemia leads to impaired lipid metabolism. Furthermore, it was found that hyperglycemic individuals had increased serum levels of triglycerides, total cholesterol and its fractions compared to normoglycemic individuals.^{42,43}

Atorvastatin therapy proved to be efficient to control the levels of total cholesterol and its fractions. Moreover, atorvastatin reduced the levels of triglycerides, body mass, and adiposity index. Silva et al.⁴⁴ also showed the effectiveness of atorvastatin in daily doses of 10 mg or 20 mg on the correction of individuals' lipid profile, in which cholesterol therapy led also to a decrease in the level of triglycerides.⁴⁴ It is known that VLDL and LDL are lipoproteins consisting significant amounts of triacylglycerols; thus, we propose that by reducing the levels of VLDL and LDL through atorvastatin therapy may lead to reduced levels of triglycerides. Parhofer et al.⁴⁵ describes the lowering effect of triglycerides, especially by the inhibition of cholesterol synthesis, and also highlight that VLDL and LDL have the same removal mechanism; hence, the reduction in the number of circulating LDL particles may also significantly reduce VLDL levels.⁴⁵

According to the OGTT, the hyperglycemic diet induced glucose intolerance in mice. Chronic exposure to hyperglycemia

is known to eventually affect insulin activity with regard to synthesis, secretion of action of this hormone, which is indeed observed in type II diabetes mellitus.⁶ Therefore, it is possible to suggest that the results found for the glucose profile of mice on the hyperglycemic diet contribute to the development of type II diabetes mellitus. Kissebah et al.⁴⁶ showed that increased visceral fat is associated with glucose intolerance and insulin resistance, and Taylor et al.⁴⁷ found that visceral fat is related to the development of diabetes mellitus.^{46,47} Previous studies described that increased visceral fat predisposes to production and secretion of cytokines, such as IL-6 and TNF- α , and adipokines, such as resistin and adiponectin, which are associated with the development of insulin resistance and disorders in glucose metabolism and control, due to interference with insulin intracellular signaling.^{48,49} Increased visceral fat, as well and increased levels of TNF- α and IL-6, justify the imbalances in glucose profile.

Atorvastatin therapy was able to attenuate glucose intolerance in mice fed with the hyperglycemic diet. Huptas et al.⁵⁰ obtained promising results with atorvastatin therapy in individuals with MS, showing improvements in glucose metabolism through reduced glucose intolerance and reduced insulin resistance. Using experimental models of glucose

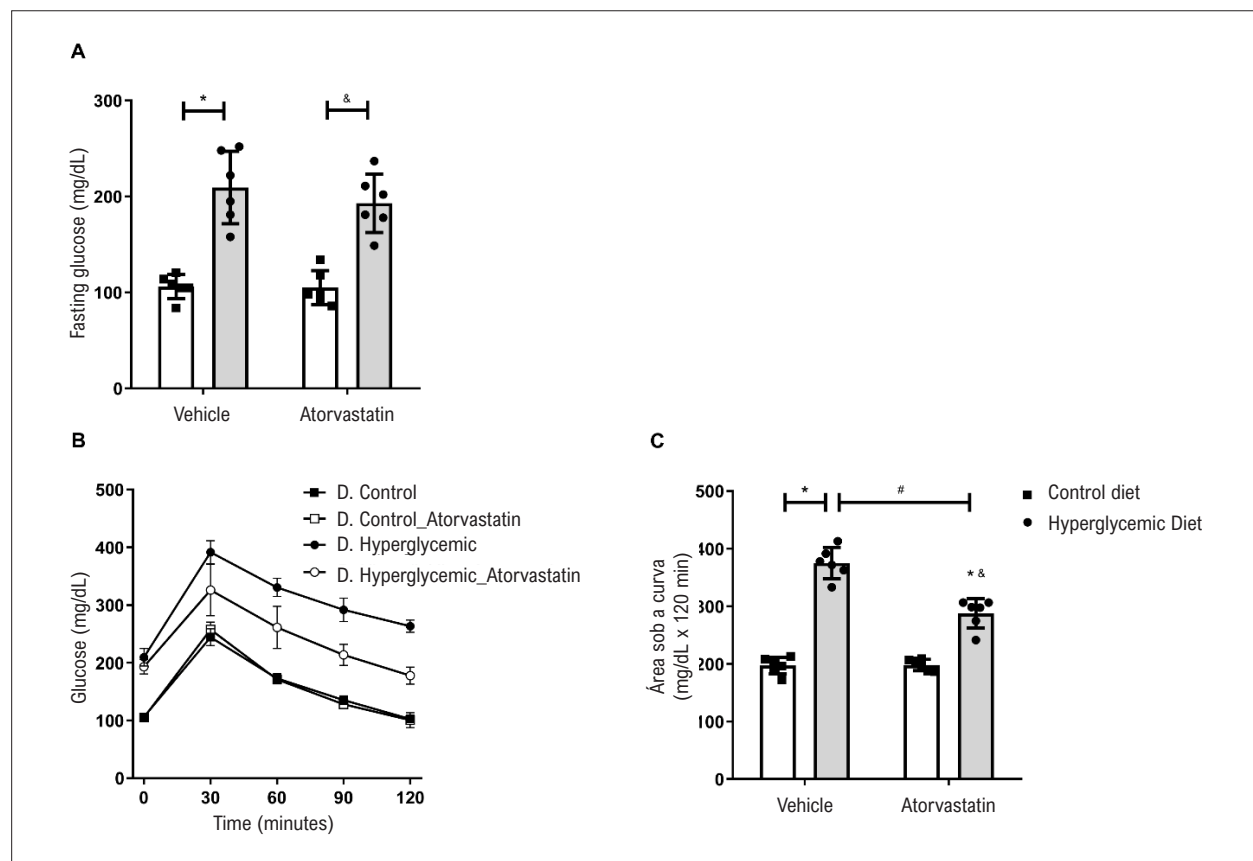


Figure 3 – Atorvastatin attenuates glucose intolerance associated with metabolic syndrome induced by hyperglycemic diet. The figures show the levels of fasting glucose (A), glucose curves (B), and area under the curve (C) obtained in the oral glucose tolerance tests of mice fed with a control diet or with a hyperglycemic diet for 18 weeks and treated with vehicle solution or atorvastatin (20 mg/kg for 4 weeks). Results expressed as mean $\pm$ SD. *, $p < 0.05$ vs. Control Diet_Vehicle; &, $p < 0.05$ vs. Control Diet_Atorvastatin; #, $p < 0.05$ vs. Hyperglycemic Diet_Vehicle ($n = 6$ for each experimental group).

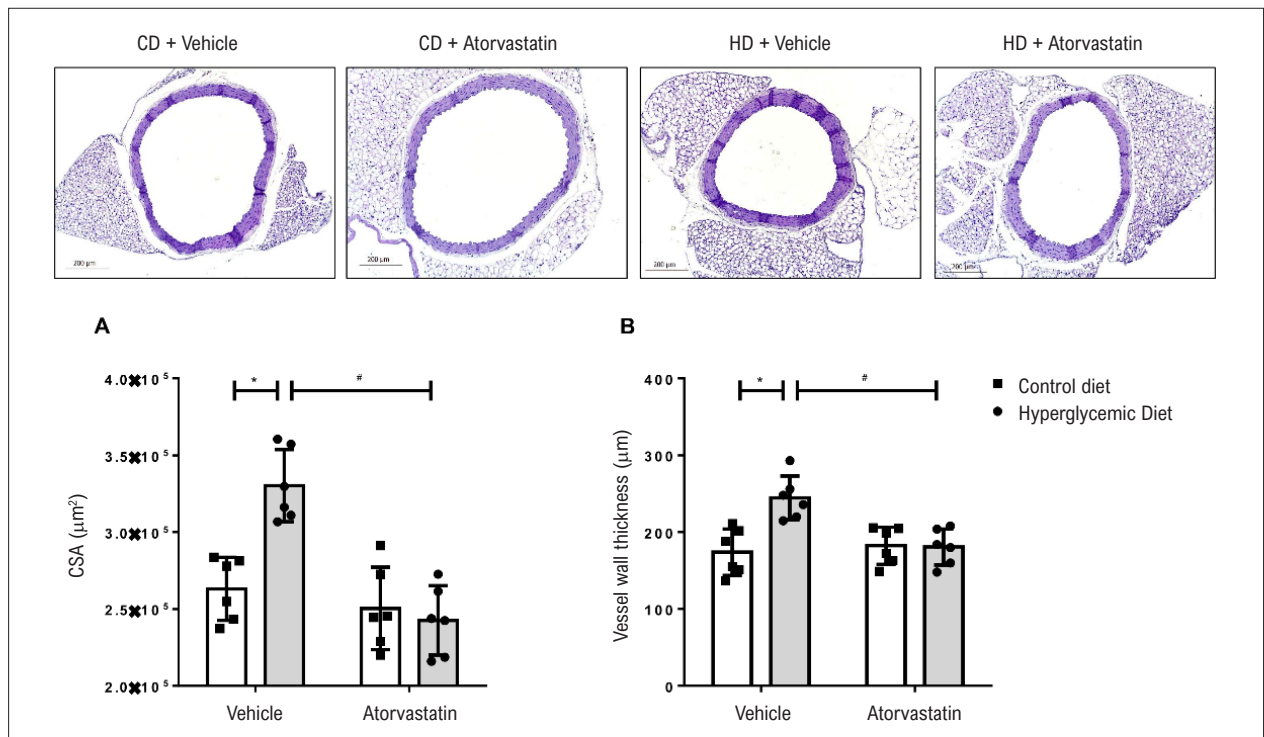


Figure 4 – Atorvastatin attenuates remodeling of vascular smooth muscle associated with metabolic syndrome induced by hyperglycemic diet. The figures show representatives images, size of CSA (A) and vessel wall thickness (B) of mice fed with a control diet or with a hyperglycemic diet for 18 weeks and treated with vehicle solution or atorvastatin (20 mg/kg for 4 weeks). Results expressed as mean $\pm$ SD. *, $p < 0.05$ vs. Control Diet_Vehicle; #, $p < 0.05$ vs. Hyperglycemic Diet_Vehicle (n=6 for each experimental group). CD: Control Diet, HD: Hyperglycemic Diet.

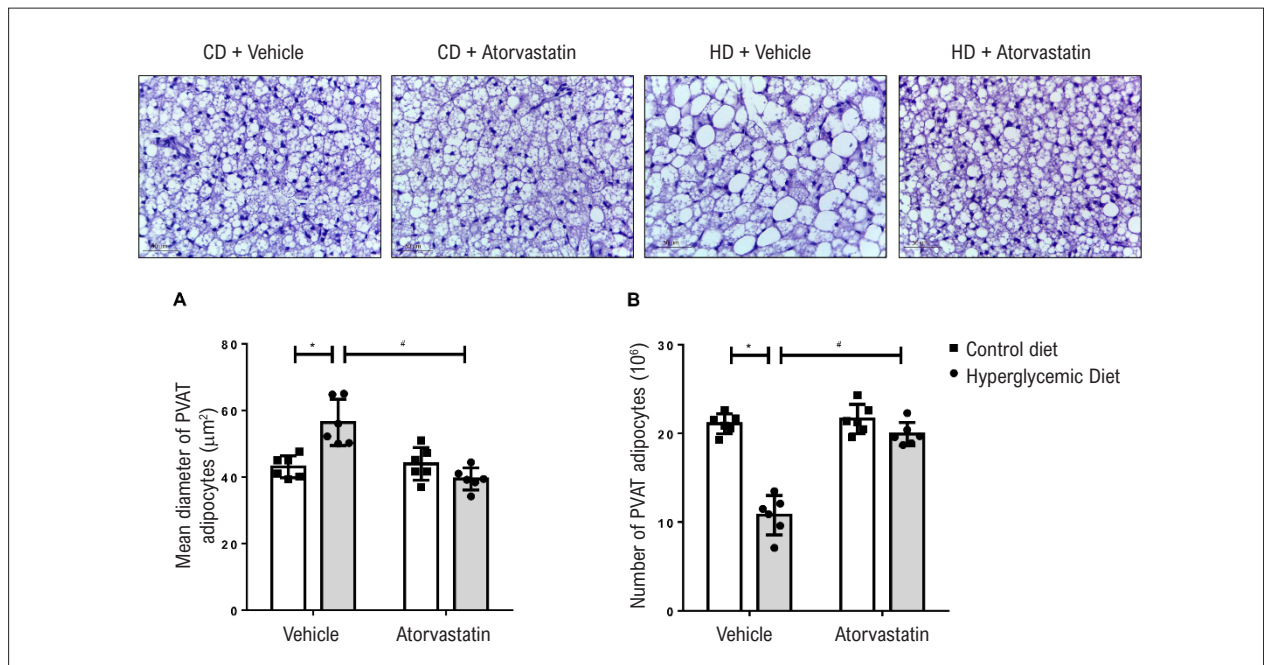


Figure 5 – Atorvastatin attenuates PVAT remodeling associated with metabolic syndrome induced by hyperglycemic diet. The figures show representative images (A) and size of PVAT adipocytes (B) of mice fed with a control diet or with a hyperglycemic diet for 18 weeks and treated with vehicle solution or atorvastatin (20 mg/kg for 4 weeks). Results expressed as mean $\pm$ SD. *, $p < 0.05$ vs. Control Diet_Vehicle; #, $p < 0.05$ vs. Hyperglycemic Diet_Vehicle (n=6 for each experimental group). CD: Control Diet, HD: Hyperglycemic Diet.

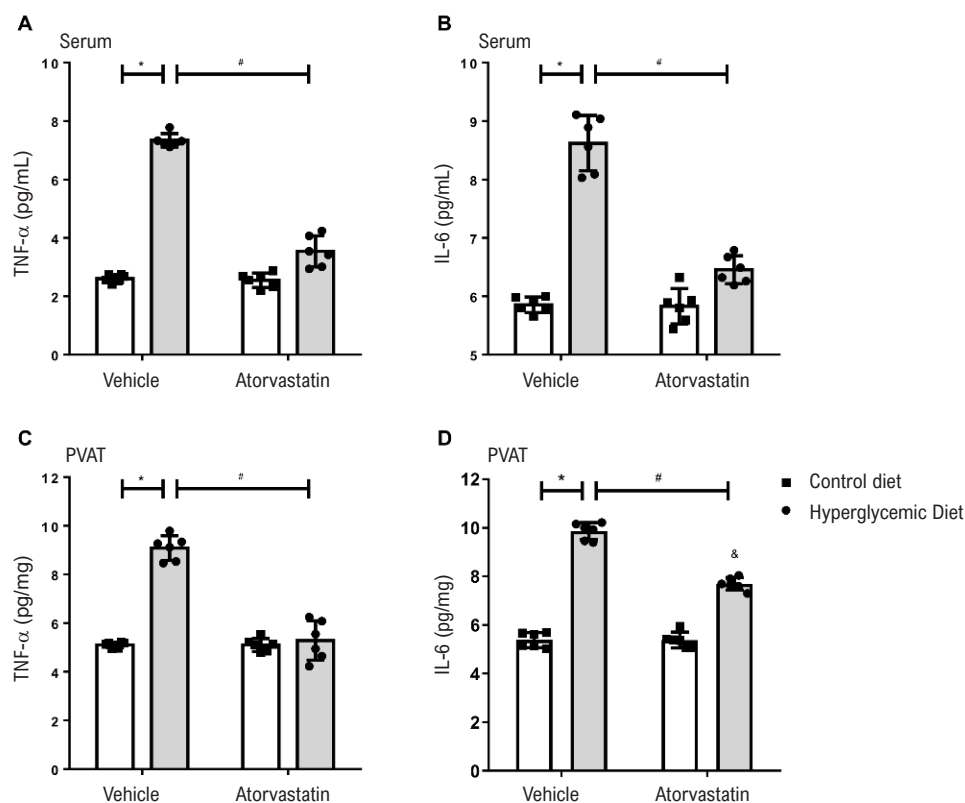


Figure 6 – Atorvastatin attenuates increased concentrations of pro-inflammatory cytokines associated with metabolic syndrome induced by hyperglycemic diet. The figures show the levels of TNF-α (A and C) and IL-6 (B and D) in serum and in PVAT, respectively, of mice fed with a control diet or with a hyperglycemic diet for 18 weeks and treated with vehicle solution or atorvastatin (20 mg/kg for 4 weeks). Results expressed as mean ± SD. *, $p < 0.05$ vs. Control Diet_Vehicle; &, $p < 0.05$ vs. Control Diet_Atorvastatin; #, $p < 0.05$ vs. Hyperglycemic Diet_Vehicle ($n = 6$ for each experimental group).

intolerance and insulin resistance, Suzuki et al.⁵¹ performed OGTT and insulin tolerance test (ITT) in groups treated and not treated with atorvastatin and showed that the treated group had reduced levels of glucose and insulin in OGTT and ITT compared to the group that received the vehicle solution.^{50,51}

The mechanisms through which atorvastatin improves parameters related to glucose metabolism are not known yet. This improvement may be related to decreased gluconeogenesis.⁵¹ However, it is possible to suggest that reduced glucose intolerance may be related to reduced deposits of visceral fat and may also be related to reduced production of cytokines (TNF-α and IL-6), which are potential causes of metabolic disorders.

According to Mulvany (1999), vascular remodeling may be classified based on measures of CTA and wall thickness. Increased CTA and wall thickness is typical of hypertrophic remodeling.⁵² One of the causes of vascular remodeling is inflammation mediated by increased levels of pro-inflammatory cytokines. Studies on MS showed that PVAT hypertrophy results in migration, activation of immune cells and secretion of the above mentioned cytokines, leading to a low-intensity chronic inflammatory process.⁵³⁻⁵⁵

Changes in the structure and composition of PVAT reflect in vessel tunica media, because PVAT is physiologically constituted by adipocytes that act as regulators of the proliferation of vascular smooth muscle cells (VSMCs). The change to non-specialized adipocytes culminates in increased VSMC proliferation and smooth muscle hypertrophy. This hypertrophy has a major role in vascular diseases such as restenosis and arterial hypertension.⁵⁶

TNF-α and IL-6 are found in increased concentrations during chronic inflammation present in obesity, insulin resistance, and MS. Additionally, there is a clear relationship between increased levels of these cytokines and phenotypic changes in PVAT.^{57,58} Pro-inflammatory cytokines promote vascular remodeling and dysfunction, since increased concentrations of TNF-α promote neointimal hyperplasia and endothelial dysfunction. Similarly, increased concentration of IL-6 may induce macrophage infiltration into PVAT, contributing to development of aneurism and vascular remodeling associated with PVAT inflammation.^{59,60}

Hypercholesterolemia was induced from a hyperlipidemic diet in rabbits to investigate what changes this condition could develop in their pulmonary arteries. These arteries had increased VSMC proliferation, tunica media hypertrophy, and tunica intima hyperplasia. Furthermore, there were a large

infiltrate of inflammatory cells, e.g., macrophages, in lung tissue a higher concentration of serum IL-6 in the rabbits. These animals were treated with atorvastatin, which led to a reversal of hypercholesterolemia, vascular remodeling, and inflammatory processes in lung tissue.⁶¹ Similarly, atorvastatin inhibits aldosterone-induced vascular remodeling by decreasing pro-inflammatory cytokines.³¹

The main limitation of this study was the impossibility of establishing a direct causal relationship of pharmacological therapy with atorvastatin with improvements in metabolic profile and vascular remodeling. Based on the experimental design used in this study, we showed that atorvastatin reduces adiposity and improves lipid, glucose and inflammatory profiles. Literature has extensively shown that these facts are beneficial for vascular structure and function. Therefore, it is not clear yet whether attenuated vascular remodeling may be explained by direct actions of atorvastatin on vessels or by effects underlying the metabolism. We reinforce that, in multicompartmental organisms, isolated mechanisms do not justify the genesis of diseases, since it always involves a vast interaction between mechanisms and systems. Therefore, regardless whether atorvastatin has a direct or pleiotropic action, the final therapy has shown to be promising for the context of this study.

Conclusions

In short, this study shows that atorvastatin therapy attenuates the metabolic damages associated with MS

induced by hyperglycemic diet, in addition to attenuating remodeling of vascular smooth tissue and PVAT; these effects are associated with reduced levels of the pro-inflammatory cytokines TNF- α and IL-6.

Author Contributions

Conception and design of the research, Statistical analysis, Writing of the manuscript and Critical revision of the manuscript for intellectual content: Carvalho KFS, Costa RM; Acquisition of data: Carvalho KFS, Ferreira AAM, Barbosa NC, Alves JV; Analysis and interpretation of the data: Carvalho KFS, Ferreira AAM, Barbosa NC, Alves JV, Costa RM; Obtaining financing: Costa RM.

Potential Conflict of Interest

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

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Study Association

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

References

- Ribeiro ALP, Duncan BB, Brant LCC, Lotufo PA, Mill JG, Barreto SM. Cardiovascular health in Brazil. *Circulation*. 2016; 133(4):422-33.
- Lotufo PA. Cardiovascular and cancer mortality in Brazil from 1990 to 2017. *Sao Paulo Med J*. 2019; 137(2):107-111.
- Punthakee Z, Goldenberg R, Katz P. Definition, classification and diagnosis of diabetes, prediabetes and metabolic syndrome. *Can J Diabetes*. 2018; 42(1):S10-S15.
- Lam DW, LeRoith D. Metabolic Syndrome. [Updated 2019 Feb 11]. In: Feingold KR, Anawalt B, Boyce A, et al., editors. *Endotext*. South Dartmouth (MA): MDText.com, Inc.; 2000.
- Silva MA, Cau SB, Lopes RA, Manzato CP, Neves KB, Bruder-Nascimento T, et al. Mineralocorticoid receptor blockade prevents vascular remodeling in a rodent model of type 2 diabetes mellitus. *Clin Sci*. 2015; 129(7):533-45.
- Costa RM, Silva JF, Alves JV, Dias TB, Rassi DM, Garcia LV, et al. Increased O-GlcNAcylation of endothelial nitric oxide synthase compromises the anti-contractile properties of perivascular adipose tissue in metabolic syndrome. *Front Physiol*. 2018; 9(eCollection 2018):341.
- Tran V, Silva TM, Sobey CG, Lim K, Drummond GR, Vinh A, et al. The vascular consequences of metabolic syndrome: rodent models, endothelial dysfunction, and current therapies. *Front Pharmacol*. 2020; 11(eCollection 2020):148.
- Virdis A. Endothelial dysfunction in obesity: role of inflammation. *High Blood Press Cardiovasc Prev*. 2016; 23(2):83-85.
- Xia N, Li H. The role of perivascular adipose tissue in obesity-induced vascular dysfunction. *Br J Pharmacol*. 2017; 174(20):3425-42.
- Costa RM, Neves KB, Tostes RC, Lobato NS. Perivascular adipose tissue as a relevant fat depot for cardiovascular risk in obesity. *Front Physiol*. 2018; 9(eCollection 2018):253.
- Victorio JA, da Costa RM, Tostes RC, Davel AP. Modulation of vascular function by perivascular adipose tissue: sex differences. *Curr Pharm Des*. 2020; 26(1):1-12.
- Nosalski R, Guzik TJ. Perivascular adipose tissue inflammation in vascular disease. *Br J Pharmacol*. 2017; 174(20):3496-513.
- Chatterjee TK, Stoll LL, Denning GM, Harrelson A, Blomkalns AL, Idelman G, et al. Proinflammatory phenotype of perivascular adipocytes: influence of high-fat feeding. *Circ Res*. 2009; 104(4):541-9.
- Costa RM, Fais RS, Dechandt CRP, Louzada-Junior P, Alberici LC, Lobato NS, et al. Increased mitochondrial ROS generation mediates the loss of the anti-contractile effects of perivascular adipose tissue in high-fat diet obese mice. *Br J Pharmacol*. 2017; 174(20):3527-41.
- Anzai T. Inflammatory mechanisms of cardiovascular remodeling. *Circ J*. 2018; 82(3):629-35.
- Ilatovskaya DV, Halade GV, DeLeon-Pennell KY. Adaptive immunity-driven inflammation and cardiovascular disease. *Am J Physiol Heart Circ Physiol*. 2019; 317(6):H1254-H1257.
- Aroor AR, Jia G, Sowers JR. Cellular mechanisms underlying obesity-induced arterial stiffness. *Am J Physiol Regul Integr Comp Physiol*. 2018; 314(3):R387-R398.
- Saladini F, Palatini P. Arterial distensibility, physical activity, and the metabolic syndrome. *Curr Hypertens Rep*. 2018; 20(5):39.
- Wang X, Khalil RA. Matrix metalloproteinases, vascular remodeling, and vascular disease. *Adv Pharmacol*. 2018; 81(1):241-330.
- Lee D, Sui X, Church TS, Lavie CJ, Jackson AS, Blair SN. Changes in fitness and fatness on the development of cardiovascular disease risk factors: hypertension, metabolic syndrome, and hypercholesterolemia. *J Am Coll Cardiol*. 2012; 59(7):665-72.

21. Stokes KY, Calahan L, Russell JM, Gurwara S, Granger DN. Role of platelets in hypercholesterolemia-induced leukocyte recruitment and arteriolar dysfunction. *Microcirculation*. 2006; 13(5):377-88.
22. Stokes KY, Calahan L, Hamric CM, Russell JM, Granger DN. CD40/CD40L contributes to hypercholesterolemia-induced microvascular inflammation. *Am J Physiol Heart Circ Physiol*. 2009; 296(3):H689-H697.
23. Xu Y, Arai H, Murayama T, Kita T, Yokode M. Hypercholesterolemia contributes to the development of atherosclerosis and vascular remodeling by recruiting bone marrow-derived cells in cuff-induced vascular injury. *Biochem Biophys Res Commun*. 2007; 363(3):782-7.
24. Lewis GF, Rader DJ. New insights into the regulation of HDL metabolism and reverse cholesterol transport. *Circ Res*. 2005; 96(12):1221-32.
25. Karlson BW, Palmer MK, Nicholls SJ, Lundman P, Barter PJ. Doses of rosuvastatin, atorvastatin and simvastatin that induce equal reductions in LDL-C and non-HDL-C: results from the VOYAGER meta-analysis. *Eur J Prev Cardiol*. 2016; 23(7):744-7.
26. Wang CY, Liu PY, Liao JK. Pleiotropic effects of statin therapy: molecular mechanisms and clinical results. *Trends Mol Med*. 2008; 14(1):37-44.
27. Brooks SD, DeVallance E, d'Audiffret AC, Frisbee SJ, Tabone LE, Shrader CD, et al. Metabolic syndrome impairs reactivity and wall mechanics of cerebral resistance arteries in obese Zucker rats. *Am J Physiol Heart Circ Physiol*. 2015; 309(11):H1846-H1859.
28. Izidoro-Toledo TC, Guimaraes DA, Belo VA, Gerlach RF, Tanus-Santos JE. Effects of statins on matrix metalloproteinases and their endogenous inhibitors in human endothelial cells. *Naunyn-Schmiedeberg Arch Pharmacol*. 2011; 383(6):547-54.
29. Luan Z, Chase AJ, Newby AC. Statins Inhibit Secretion of metalloproteinases -1, -2, -3, and -9 From Vascular Smooth Muscle Cells and Macrophages. *Arterioscler Thromb Vasc Biol*. 2003; 23(5):769-75.
30. Rupérez M, Rodrigues-Díez R, Blanco-Colio LM, Sánchez-López E, Rodríguez-Vita J, Esteban V, et al. HMG-CoA Reductase Inhibitors Decrease Angiotensin II-induced Vascular Fibrosis: Role of RhoA/ROCK and MAPK Pathways. *Hypertension*. 2007; 50(2):377-83.
31. Bruder-Nascimento T, Callera GE, Montezano AC, Chantemele EB, Tostes RC, Touyz RM. Atorvastatin inhibits pro-inflammatory actions of aldosterone in vascular smooth muscle cells by reducing oxidative stress. *Life Sci*. 2019; 221(1):29-34.
32. Liping Z, Xiufang L, Tao Y, Baomin Z, Houshuai T. Efficacy comparison of rosuvastatin and atorvastatin in the treatment of atherosclerosis and drug safety analysis. *Pak J Pharm Sci*. 2018; 31(5(Special)):2203-8.
33. Kumar B, Shah MAA, Kumar R, Kumar J, Memon A. Comparison of atorvastatin and rosuvastatin in reduction of inflammatory biomarkers in patients with acute coronary syndrome. *Cureus*. 2019; 11(6):e4898.
34. Yamada Y, Takeuchi S, Yoneda M, Ito S, Sano Y, Nagasawa K, et al. Atorvastatin reduces cardiac and adipose tissue inflammation in rats with metabolic syndrome. *Int J Cardiol*. 2017; 240(1):332-8.
35. Taylor BA, Phillips SJ. Detection of obesity QTLs on mouse chromosomes 1 and 7 by selective DNA pooling. *Genomics*. 1996; 34(3):389-98.
36. Fernandes SAT, Natali AJ, da Matta SLP, Teodoro BG, Franco FSC, Laterza MC, et al. Effect of hyperlipidic diet and aerobic training on atherosclerosis in apoE^{-/-} mice. *Rev Bras Med Esporte*. 2013; 19(6):436-41.
37. Costa RM, Neves KB, Mestriner FL, Louzada-Junior P, Bruder-Nascimento T, Tostes RC. TNF- α induces vascular insulin resistance via positive modulation of PTEN and decreased Akt/eNOS/NO signaling in high fat diet-fed mice. *Cardiovasc Diabetol*. 2016; 15(1):119.
38. Parlee SD, Lentz SI, Mori H, MacDougald OA. Quantifying size and number of adipocytes in adipose tissue. *Methods Enzymol*. 2014; 537(1):93-122.
39. Silva JF, Correa IC, Diniz TF, Lima PM, Santos RL, Cortes SF, et al. Obesity, inflammation, and exercise training: relative contribution of iNOS and eNOS in the modulation of vascular function in the mouse aorta. *Front Physiol*. 2016; 7(eCollection 2016):386.
40. Leopoldo AS, Lima-Leopoldo AP, Nascimento AF, Luvizotto RAM, Sugizaki MM, Campos DHS, et al. Classification of different degrees of adiposity in sedentary rats. *Braz J Med Biol Res*. 2016; 49(4):e5028.
41. Rezende R, Santos C, Dubow C, Vargas SC, Pohl HH, Paiva DN. Effects of physical exercise on insulin resistance to obese individuals. *Cinergis*. 2016; 17(3):245-9.
42. Mullugeta Y, Chawla R, Kebede T, Worku Y. Dyslipidemia associated with poor glycemic control in type 2 diabetes mellitus and the protective effect of metformin supplementation. *Indian J Clin Biochem*. 2012; 27(4):363-9.
43. Fonseca VA, Lovre D. Diabetes-related dyslipidemia and cardiovascular events. *Am J Med Sci*. 2017; 354(2):103-4.
44. Silva JM. The efficacy of Atorvastatin in correcting the lipid profile - An open evaluation study. *Medicina Interna*. 2002; 9(2):68-75.
45. Parhofer KG, Barrett PH, Schwandt P. Atorvastatin improves postprandial lipoprotein metabolism in normolipidemic subjects. *J Clin Endocrinol Metab*. 2000; 85(11):4224-30.
46. Kissebah AH, Vydellingum N, Murray R, Evans DJ, Hartz AJ, Kalkhoff RK, et al. Relation of body fat distribution to metabolic complications of obesity. *J Clin Endocrinol Metab*. 1982; 54(2):254-60.
47. Taylor AE, Ebrahim S, Ben-Shlomo Y, Martin RM, Whincup PH, Yarnell JW, et al. Comparison of the associations of body mass index and measures of central adiposity and fat mass with coronary heart disease, diabetes, and all-cause mortality: a study using data from 4 UK cohorts. *Am J Clin Nutr*. 2010; 91(3):547-56.
48. Carvalho MHC, Colaço AL, Fortes ZB. Cytokines, endothelial dysfunction, and insulin resistance. *Arq Bras Endocrinol Metab*. 2006; 50(2):304-12.
49. Karczewski J, Sledzinska E, Baturo A, Jonczyk I, Maleszko A, Samborski P, et al. Obesity and Inflammation. *Eur Cytokine Netw*. 2018; 29(3):83-94.
50. Suzuki M, Kakuta H, Takahashi A, Shimano H, Tadalida K, Yokoo T, et al. Effects of atorvastatin on glucose metabolism and insulin resistance in kk/ay mice. *J Atheroscler Thromb*. 2005; 12(2):77-84.
51. Huptas S, Geiss HC, Otto C, Parhofer KG. Effect of atorvastatin (10 mg/day) on glucose metabolism in patients with the metabolic syndrome. *Am J Cardiol*. 2006; 98(1):66-9.
52. Mulvany MJ. Vascular remodelling of resistance vessels: can we define this? *Cardiovasc Res*. 1999; 41(1):9-13.
53. Galic S, Oakhill JS, Steinberg GR. Adipose tissue as an endocrine organ. *Mol Cell Endocrinol*. 2010; 316(2):129-39.
54. Heber D. An integrative view of obesity. *Am J Clin Nutr*. 2010; 91(1):280S-283S.
55. Marginean CO, Melit LE, Hutanu A, Ghiga DV, Sasaran MO. The adipokines and inflammatory status in the era of pediatric obesity. *Cytokine*. 2020; 126(1):154925.
56. Miao CY, Li ZY. The Role of Perivascular Adipose Tissue in Vascular Smooth Muscle Cell Growth. *Br J Pharmacol*. 2012; 165(3):643-58.
57. Matsuzawa Y. Adipocytokines and metabolic syndrome. *Semin Vasc Med*. 2005; 5(1):34-9.
58. Takaoka M, Suzuki H, Shioda S, Sekikawa K, Saito Y, Nagai R, et al. Endovascular injury induces rapid phenotypic changes in perivascular adipose tissue. *Arterioscler Thromb Vasc Biol*. 2010; 30(8):1576-82.
59. Blomkalns AL, Gavrila D, Thomas M, Neltner BS, Blanco VM, Benjamin SB, et al. CD14 directs adventitial macrophage precursor recruitment: role in early abdominal aortic aneurysm formation. *J Am Heart Assoc*. 2013; 2(1):e000065.
60. Ozen G, Daci A, Norel X, Topal G. Human perivascular adipose tissue dysfunction as a cause of vascular disease: focus on vascular tone and wall remodeling. *Eur J Pharmacol*. 2015; 766(1):16-24.
61. Duan S, Zhang Y, Wu S, Jiang L, Zhang J, Gan Y, et al. Atorvastatin attenuates inflammatory infiltration and vascular remodeling in lung of hypercholesterolemia rabbits. *Exp Lung Res*. 2010; 36(10):573-92.



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Anti-Inflammatory Effects of Atorvastatin Therapy in Metabolic Syndrome

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Short Editorial related to the article: Atorvastatin Attenuates Vascular Remodeling in Mice with Metabolic Syndrome

Metabolic Syndrome (MS) is a condition characterized by abdominal obesity accompanied by high fasting glucose levels, insulin resistance, arterial hypertension, and dyslipidemia.¹ It configures a critical risk factor for developing other clinical conditions, primarily type 2 diabetes mellitus (DM2) and cardiovascular diseases.^{1,2} Also, MS has been associated with endothelial dysfunction, characterized by changes in arterial vascular architecture, especially in the endothelium and capillary basement membrane, causing microvascular complications. Endothelial basement membrane remodeling commonly includes erosion and vascular thrombosis processes in individuals with MS.²

Endothelial dysfunction pathogenesis is a multifactorial event and may include chronic inflammation resulting from leukocytes activation and increased production of reactive oxygen species, which are commonly associated with MS.³ The pro-inflammatory phenotype related to MS makes the vasculature highly vulnerable to tumor necrosis factor- α (TNF- α), C-reactive protein, interleukin-6 (IL-6), and interleukin-8 (IL-8)-induced inflammatory processes.^{4,5} High levels of these pro-inflammatory markers are commonly associated with MS.⁵⁻⁷ Likewise, low-density lipoproteins (LDL) oxidation resulting from lipid peroxidation has immunogenic and pro-inflammatory effects, based on the recruitment and accumulation of pro-inflammatory cells.⁵ These effects may sustain endothelial dysfunction that is associated with smooth muscle cell proliferation and perivascular adipose tissue hypertrophy, events commonly observed during the endothelial remodeling process.⁸

Classically, ectopic fat deposition around visceral vessels and organs has contributed to low-grade chronic inflammatory conditions and insulin resistance onset, which is also common in obesity.^{9,10} In this aspect, perivascular adipose tissue has an essential paracrine function sustained by substantial protein activation and vascular morphological

changes; these mechanisms contribute to the endothelial dysfunction during MS.^{8,11} Consequently, clarifying the potential efficiency of therapeutic interventions is essential to manage MS conditions. In this context, hydroxymethyl glutaryl coenzyme A reductase inhibitors (HMG-CoA), also called statins, are commonly used to treat atherosclerotic cardiovascular disease, and have proved efficacy in normalizing serum cholesterol levels.¹² Indeed, atorvastatin is currently one of the most used statins in the clinical context as it has a long plasma half-life and presents significant tolerability and safety.¹³

In the current edition of the Arquivos Brasileiros de Cardiologia, Carvalho et al.¹⁴ documented beneficial effects of atorvastatin intervention on nutritional, metabolic and vascular aspects in an experimental model of hyperglycemic diet-induced metabolic syndrome. As expected, hyperglycemic diet-induced MS was accompanied by several disorders, as increased body mass and adiposity, high levels of total cholesterol, low (LDL) and very low (VLDL) densities hypertriglyceridemia, hyperglycemia, and reduced high-density lipoprotein (HDL) levels. Moreover, the dietary intervention promoted inflammatory effects, sustained by an increase in systemic and tissue levels of TNF- α and IL-6, perivascular adipose tissue hypertrophy and vascular changes.¹⁴ In response to atorvastatin, findings included a reduction in body mass and adiposity measures and decreased LDL, VLDL, triglycerides, as well as increased HDL levels. In the morphological context, atorvastatin reduced the transverse sectional area and the thickness of the vessel's media layer and reduced the size and number of perivascular adipocytes. Another substantial atorvastatin effect included the reduction of TNF- α and IL-6 levels into MS, suggesting that these cytokines modulate the endothelial remodeling process.¹⁵

Therefore, the results of this study show that atorvastatin interventions may be effective as a medical intervention for preventive strategy and treatment of vascular conditions associated with MS. However, further studies are needed to elucidate potential mechanisms involved with metabolic and cardiovascular disorders in MS.

Keywords

Metabolic Syndrome; Obesity, Abdominal; Diabetes Mellitus; Hypertension; Endothelium/etiology; Inflammation; Atorvastatin/drug therapy.

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References

1. Lima TR, Silva DAS, Giehl MWC, D'Orsi E, González-Chica DA. Clusters of Cardiometabolic Risk Factors and Their Association with Atherosclerosis and Chronic Inflammation among Adults and Elderly in Florianópolis, Southern Brazil. *Arq Bras Cardiol.* 2021; 117(1):39-48. doi: 10.36660/abc.20200230.
2. Tran V, De Silva TM, Sobey CG, Lim K, Drummond GR, Vinh A, Jelinic M. The Vascular Consequences of Metabolic Syndrome: Rodent Models, Endothelial Dysfunction, and Current Therapies. *Front Pharmacol.* 2020;11:148. doi: 10.3389/fphar.2020.00148.
3. Varghese JF, Patel R, Yadav UCS. Novel Insights in the Metabolic Syndrome-induced Oxidative Stress and Inflammation-mediated Atherosclerosis. *Curr Cardiol Rev.* 2018; 14(1):4-14. doi: 10.2174/1573403X13666171009112250.
4. Faria AP, Ritter AMV, Gasparetti CS, Corrêa NB, Brunelli V, Almeida A, et al. A Proposed Inflammatory Score of Circulating Cytokines/Adipokines Associated with Resistant Hypertension, but Dependent on Obesity Parameters. *Arq Bras Cardiol.* 2019;112(4):383-9. doi: 10.5935/abc.20190032.
5. Francisco G, Hernández C, Simó R. Serum markers of vascular inflammation in dyslipemia. *Clin Chim Acta.* 2006;369(1):1-16. doi: 10.1016/j.cca.2005.12.027.
6. Sharafi SM, Mahdavi M, Riahi R, Kheirollahi M, Kelishadi R. Meta-Analysis on the Association of C-Reactive Protein Polymorphisms with Metabolic Syndrome. *Glob Med Genet.* 2020;7(1):8-13. doi: 10.1055/s-0040-1710548.
7. Jarecki P, Herman WA, Losy J, Lacka K. The Comparison of Predictive Value Among Chemerin, IL-18 and Hormonal Parameters in Assessing the Risk of Metabolic Syndrome in Men. *Am J Mens Health.* 2021;15(4):15579883211034984. doi: 10.1177/1557988321103498.
8. Xia N, Li H. The role of perivascular adipose tissue in obesity-induced vascular dysfunction. *Br J Pharmacol.* 2017; 174(20):3425-42. doi: 10.1111/bph.13650.
9. Martins F, Campos DH, Pagan LU, Martinez PF, Okoshi K, Okoshi MP, et al. High-fat Diet Promotes Cardiac Remodeling in an Experimental Model of Obesity. *Arq Bras Cardiol.* 2015;105(5):479-86. doi: 10.5935/abc.20150095.
10. Oliveira-Junior SA, Muzili N, Carvalho MR, Ota CE, Moraes CS, Vieira LFC, et al. AT1 Receptor Blockade Improves Myocardial Functional Performance in Obesity. *Arq Bras Cardiol.* 2020;115(1):17-28. doi: 10.36660/abc.20190131.
11. Margaritis M, Antonopoulos AS, Digby J, Lee R, Reilly S, Coutinho P, et al. Interactions between vascular wall and perivascular adipose tissue reveal novel roles for adiponectin in the regulation of endothelial nitric oxide synthase function in human vessels. *Circulation.* 2013; 127(22):2209-21. doi: 10.1161/CIRCULATIONAHA.112.001133.
12. Toth PP, Banach M. Statins: Then and Now. *Methodist Debakey Cardiovasc J.* 2019;15(1):23-31. doi: 10.14797/mdcj-15-1-23.
13. Moon J, Yoo S, Koh G, Min KW, Shin HH. Efficacy and Safety of High-Dose Atorvastatin in Moderate-to-High Cardiovascular Risk Postmenopausal Korean Women with Dyslipidemia. *J Lipid Atheroscler.* 2020;9(1):162-71. doi: 10.12997/jla.2020.9.1.162.
14. Carvalho KFS, Ferreira AAM, Barbosa NC, Alves JV, Costa RM. Atorvastatin Attenuates Vascular Remodeling in Mice with Metabolic Syndrome. *Arq Bras Cardiol.* 2021; 117(4):737-747.
15. Chu T, Huang M, Zhao Z, Ling F, Cao J, Ge J. Atorvastatin Reduces Accumulation of Vascular Smooth Muscle Cells to Inhibit Intimal Hyperplasia via p38 MAPK Pathway Inhibition in a Rat Model of Vein Graft. *Arq Bras Cardiol.* 2020;115(4):630-6. doi: 10.36660/abc.20190231.



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Update on the Treatment of Pulmonary Arterial Hypertension

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Abstract

In the last decades, important advances have been made in the treatment of pulmonary arterial hypertension (PAH), a severe, progressive, incurable, and potentially fatal disease. For an adequate therapy, correct hemodynamic diagnosis and etiology classification are fundamental. Many etiologies – rheumatic disease, portal hypertension, congenital heart diseases, schistosomiasis – require specific measures, in addition to drug therapy for PAH. The specific therapy for PAH is based on medications that act on three pathophysiological pathways – prostacyclin, endothelin, and nitric oxide pathways. These drugs have multiple presentations (oral, intravenous, subcutaneous, and inhaled) and have changed the history of PAH. This review presents an overview of drug therapy strategies and different forms and peculiarities of PAH.

Introduction

Pulmonary arterial hypertension (PAH) is a clinical condition that leads to remodeling and obliteration of the pulmonary vascular bed, ultimately resulting in increased vascular resistance.¹ This causes an increase in systemic pressure and right ventricular overload, which progresses to a gradual ventricular failure, which is the main cause of the symptoms associated with the disease.²

PAH is a rare and severe condition that affects 2-5 million patients per million adults per year,³ with a median survival of 2.8 years in the absence of specific treatment.⁴ However, since the 90's, a number of medications with multiple presentations (oral, intravenous, subcutaneous and inhaled) have been developed and drastically changed the PAH course and the quality of life of these patients.⁶

Data from the French Pulmonary Hypertension Network registry showed that, after introduction of specific therapy,

patients' survival increased to 82.9% in one year and 58.2% in three years, corresponding to an estimated improvement of at least 15% as compared with the predicted survival in case of no access to pharmacological treatment.⁷ The type of these medications and their strategy use, as well as the different forms of PAH are the focus of this review.

Definitions

Pulmonary hypertension (PH) is defined as an increase of mean pulmonary arterial pressure (MPAP) greater than 20 mmHg.⁸ Although a threshold of 25 mmHg had been classically used in PH definition,⁹ evidence from recent studies has supported that lower levels are already associated with a worse prognosis.¹⁰ A concomitant pulmonary artery occlusion pressure (PAOP) equal to or lower than 15 mmHg characterizes the pre-capillary PH; in this situation, vascular disease is predominantly in the arterial territory. A PAOP higher than 15 mmHg determines the presence of post-capillary PH, suggesting changes in the left heart chamber (Figure 1). Based on this definition, it seems clear that right cardiac catheterization is fundamental for an adequate characterization of PH.¹¹

It is worth pointing out that, while current criteria for PAH definition include pulmonary vascular resistance (PVR) values greater than 3.0 W, recent data have indicated that PVR values greater than 2.2 W already have an impact on patients' survival and a response to medical treatment.¹² Thus, it is possible that future definitions of PAH will include PVR values greater than 2.2 W in addition to the criterion for MPAP greater than 20 mmHg.

Classification

Based on hemodynamic definitions, and also considering pathophysiological, clinical and therapeutic features of different etiologies of PH, the cases of this disease can be classified into five groups.^{8,13} Group I, patients with predominant pulmonary arterial disease, in the absence of pulmonary or thromboembolic disease (focus of this revision); group II, patients with PH caused by left heart disease and elevation in hydrostatic pressure from the left atrium.¹⁴ Group III includes patients with PH associated with chronic pulmonary disease, caused by loss of pulmonary vascular bed and hypoxic vasoconstriction.¹⁵ Group IV includes patients with pulmonary hypertension due to chronic pulmonary embolism, and has a distinct clinical management, beyond the scope of this text. Recommendations for the diagnosis

Keywords

Pulmonary Arterial Hypertension; Pulmonary Hypertension; Diagnosis; Therapeutics.

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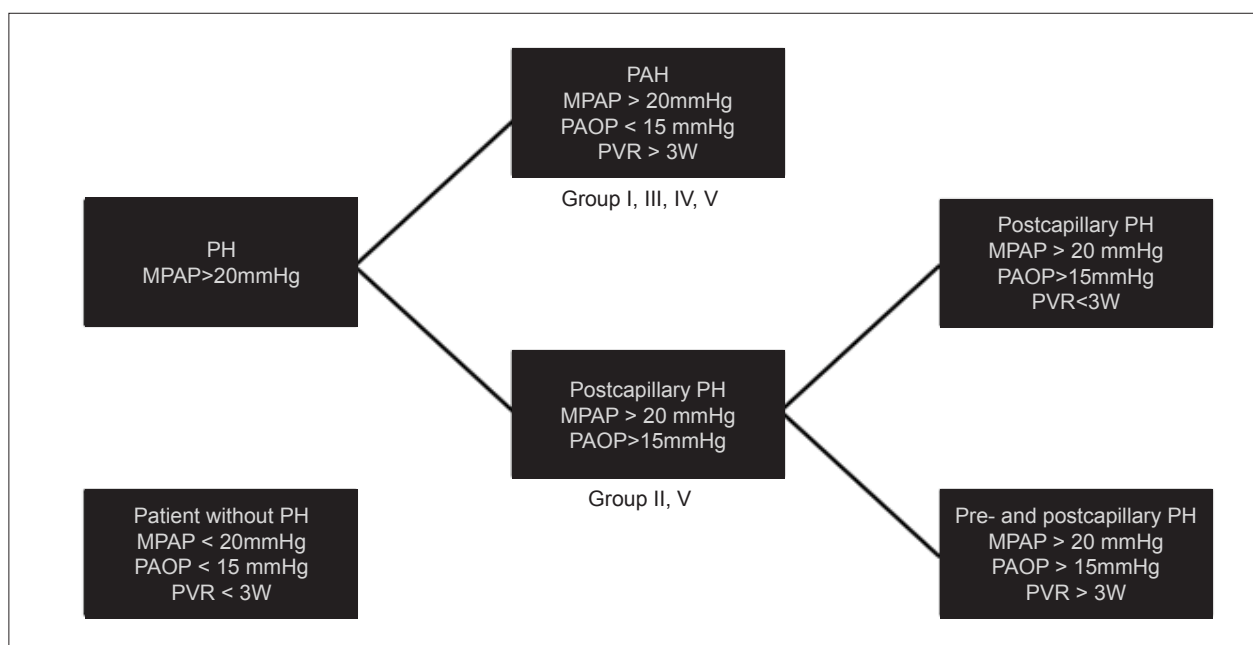


Figure 1 – Definitions of hemodynamic changes of pulmonary vascular system and its correlation with pulmonary hypertension classification groups. PH: pulmonary hypertension; PAH: pulmonary arterial hypertension; MPAP: mean pulmonary arterial pressure; PAOP: pulmonary artery occlusion pressure; PVR: pulmonary vascular resistance; W: Woods, mmHg: millimeter of mercury.

and treatment of patients with pulmonary hypertension due to chronic pulmonary embolism can be found in other publications.¹⁶ Group V includes patients with rarer diseases, involving multiple mechanisms.⁸ The different etiologies of PH and their classifications are described in Table 1. Of note, although out of the scope of this review, the diagnostic process for a correct classification of PH cases is extensive and comprehensive, allowing the provision of appropriate treatment strategies to the predominant pathophysiological mechanisms of pulmonary vascular pressure elevation.¹⁷

Treatment of PAH

General measures

After the diagnosis of PAH is confirmed, general measures aiming at minimizing the consequences of the disease should be implemented. In this context, three important measures should be considered: to prevent pregnancy (which is associated with a worsening of hemodynamic status due to cardiac output increase, leading to elevated maternal-fetal mortality),¹⁸ immunization against influenza and pneumococcal disease,⁹ and psychosocial support to PAH patients.¹⁹ Other measures include the use of diuretics, supplemental oxygen, and avoidance of strenuous exercise. Supervised physical exercises, as part of a rehabilitation program, may be recommended²⁰ after introduction of specific pharmacological therapy.

Studies in the 80s²¹ suggested a beneficial effect of anticoagulation based on the occurrence of *in situ* thrombosis reported in studies on lung biopsies in PAH patients. However,

subsequent data²² have indicated a beneficial effect of anticoagulation only in patients with idiopathic PAH, heritable PAH or PAH associated with the use of anorectic drugs. Since then, indication for anticoagulation has been made based on a case-by-case risk and benefit analysis.²³

Vasoreactivity testing

For patients with idiopathic, heritable, or drug-induced PAH, vasoreactivity test should be performed during diagnostic right heart catheterization. Inhaled nitric oxide (NO) at a dose of 10-20 ppm for 10 minutes is recognized as the gold-standard method to assess pulmonary vasoreactivity in patients with PAH. A positive vasoreactivity test is a fall of at least 10 mmHg in MPAP, fall to an absolute MPAP less than 40 mmHg, and unchanged cardiac output.² Vasoreactivity testing aims to identify a subgroup of patients in whom the increase in vascular tone is the main mechanism of the genesis of PAH, rather than vascular remodeling.²⁴

Patients with PAH that show a positive response to the vasoreactivity test should receive treatment with calcium channel blocker (CCB), preferably long-acting CCB at the highest tolerable dose.²⁵ Administration of 10 mg amlodipine once a day, 30 mg nifedipine twice a day, and 60 mg diltiazem three times a day has been recommended. Patients who do not show improvements in functional class (to I/II) or in hemodynamic function should receive specific medications for PAH. Although nearly 12.6% of patients diagnosed with idiopathic PAH show an acute response to vasodilation, half of these patients do not show good clinical response to CCB at one year of follow-up.²⁶ Patients who have not undergone vasoreactivity test should not be treated with CCB.²³

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Table 1 – Classification of pulmonary hypertension etiologies by groups (modified from reference 5)

1. Pulmonary arterial hypertension (PAH)
1.1 Idiopathic PAH
1.2 Heritable PAH
1.3 Drug- or toxin-induced PAH
1.4 PAH associated with:
• 1.4.1 Connective tissue disease
• 1.4.2 HIV infection
• 1.4.3 Portal hypertension
• 1.4.4 Congenital heart diseases
• 1.4.5 Schistosomiasis
1.5 Calcium channel blocker responders
1.6 Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis
1.7 Persistent pulmonary hypertension of the newborn
2. Pulmonary hypertension (PH) due to left heart disease
2.1 Heart failure with preserved ejection fraction
2.2 Heart failure with reduced ejection fraction
2.3 Valvular heart disease
2.4 Congenital or acquired heart diseases leading to post-capillary pulmonary hypertension
3. Pulmonary hypertension due to pulmonary disease and/or hypoxia
3.1 Obstructive lung disease
3.2 Restrictive lung disease
3.3 Other lung diseases with mixed obstructive/restrictive pattern
3.4 Hypoxia without structural lung disease
3.5 Developmental lung diseases
4. Pulmonary hypertension due to pulmonary artery obstruction
4.1 Pulmonary hypertension due to chronic pulmonary thromboembolism
4.2 Other pulmonary artery obstructions
5. Pulmonary hypertension with multifactorial and/or unknown mechanisms
5.1 Hematological diseases: chronic hemolytic anemia, myeloproliferative disorders
5.2 Systemic and metabolic diseases: pulmonary Langerhans cell histiocytosis, Gaucher's disease, glycogen storage disease, neurofibromatosis and sarcoidosis
5.3 Others: fibrosing mediastinitis, chronic renal failure, with or without hemodialysis
5.4 Complex congenital heart diseases

PH: pulmonary hypertension; PAH: pulmonary arterial hypertension; HIV: human immunodeficiency virus.

Specific treatment

Treatment pathways

The main anatomical and physiological feature in PAH is pulmonary vascular remodeling, with development of intimal and medial thickening.²⁷ Vasoconstriction also plays a role in the development of the disease, because of the increase of vascular tone and proliferation of smooth muscle cells (SMC) in arterioles.²⁵ Three pathophysiological pathways related to molecular mechanisms involved in these histological findings

have been identified and been used as pharmacological targets for the treatment of PAH – the prostacyclin (PGI_2), pathway, the endothelin pathway, and the NO pathway.²⁸

The prostacyclin pathway

PGI_2 , a derivative of arachidonic acids, acts on transmembrane receptors of multiple tissues involved in many biological activities.²⁹ In the pulmonary circulation, by stimulation of the IP receptor, PGI_2 induces relaxation of SMC in pulmonary arterioles leading to vasodilation,

and inhibits their proliferation by stimulation of cyclic AMP synthesis.³⁰ On the other hand, another molecule of the PGI₂ pathway, the thromboxane A₂ (TXA₂), counterbalances the PGI₂ effects, causing vasoconstriction and increase of platelet aggregation. In PAH, the levels of PGI₂ and the enzymatic activity of prostacyclin synthase are reduced, and the balance is shifted towards TXA₂.³¹ Therefore, one of the strategies for the treatment of PAH is the direct action on IP receptor, by administration of prostacyclin (epoprostenol)³² or of a structural analog of TXA₂ (e.g. treprostinil, beraprost and iloprost).^{33,34} Other drugs with different structures can also act on the IP receptor, like the selexipag.³⁵

The endothelin pathway

Endothelin-1 (ET-1) is the most potent natural vasoconstrictor of the biological systems.³⁶ ET-1 levels are elevated in both pulmonary vascular endothelium and in the blood of patients with PAH.³⁷ ET-1 exerts its physiological effect via two receptors, endothelin A receptor (ETA) and endothelin B receptor (ETB). Bosentan³⁸ and macitentan³⁹ are two endothelin receptor antagonists that non-selectively block ETA and ETB, and ambrisentan⁴⁰ exhibits a higher affinity for ETA. These three drugs have been shown to be effective in the treatment of PAH.

The nitric oxide pathway

NO is a potent endogenous vasodilator that acts in the SMC by stimulation of guanylyl cyclase (GC) and synthesis of cyclic GMP.⁴¹ Patients with PAH have reduced low levels of serum and tissue NO.⁴² The phosphodiesterase type 5 (PDE-5) is an enzyme responsible for degradation of cyclic GMP. Inhibition of PDE-5 leads to an increase in cyclic GMP levels and consequent relaxation of SMC and vasodilatation.⁴³ Sildenafil, tadalafil and vardenafil are the PDE-5 inhibitors currently available.

Targeting another part of the NO pathway, riociguat, a GC stimulant, potentializes GC activity independently from NO.⁴⁴ GC, stimulated by riociguat, potentializes the conversion of GTP into cyclic GMP and promotes vasodilation. Riociguat can be used for treatment of both PAH⁴⁵ and chronic thromboembolic pulmonary hypertension.⁴⁶ The drugs commercially available for the treatment of PAH in Brazil are listed in Table 2.

Strategies of treatment

Over recent years, there has been a marked change in the use strategies of different drugs available, with trends towards earlier treatment and combination of different drug pathways/classes.

The combination of drugs is based on the potential synergy between these drugs acting simultaneously in different pathophysiological pathways. As compared with monotherapy, the addition of a second drug (sequential combined therapy) has shown to be beneficial for different combinations of drugs.^{35,39,47} These findings were corroborated by a meta-analysis of 14 studies on sequential combined therapy, showing a reduction in clinical worsening compared with monotherapy.⁴⁸

In a different approach, a large clinical trial evaluated the use of ambrisentan plus tadalafil since the diagnosis of PAH.⁴⁷ This drug combination caused a 50% reduction in the combined endpoint of clinical worsening when compared with the use of any of the other drugs alone, with no significant differences in side effects.

Although there are no studies directly comparing initial versus sequential combination therapies, evidence has suggested that initial combined therapy is well tolerated and beneficial even in patients classified as low risk.⁴⁷ Thus, the current recommendation is to consider combined oral therapy since diagnosis as detailed in Figure 2.

However, a minority of patients could still benefit from monotherapy strategy. Patients with portal hypertension, HIV,

Table 2 – Authorized drugs for the treatment of pulmonary arterial hypertension, available in Brazil

Drugs	Posology	Administration route	Common side effects	Pathway	Reference
Iloprost	2,5-5 mcg 6-9x day	Inhaled	Cough Local irritation	PGI ₂	34
Selexipag	200-1600 mcg 2x day	Oral	Headache Diarrhea	PGI ₂	35
Ambrisentan	5-10 mg 1 x day	Oral	Anemia Edema	ET1	40
Bosentan	62,5-125 mg 2x day	Oral	Anemia Hepatotoxicity	ET1	38
Macitentan	10 mg 1x day	Oral	Anemia Hepatotoxicity Edema	ET1	39
Sildenafil	20-80 mg 3x day	Oral	Headache	NO	43
Riociguat	0,5-2,5 mg 3x day	Oral	Headache Hypotension	NO	45

PGI₂: prostacyclin; ET1: endothelin-1; NO: nitric oxide.

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complex congenital heart disease, veno-occlusive disease, idiopathic PAH, and those with high likelihood of left heart failure and preserved ejection fraction can begin treatment with one drug class. Besides, long-term clinically stable patients in monotherapy may not need combination therapy.²³

The potential of combination of three drugs since diagnosis has also been evaluated. A French retrospective study evaluated the efficacy of a triple combination therapy (epoprostenol, bosentan and sildenafil) in the initial treatment of severe PAH, and showed an improvement in NYHA functional class, exercise performance, and hemodynamic parameters. The study also showed longer survival of patients under triple therapy compared with that expected by the French historical registry, suggesting a long-term benefit of this approach.⁴⁹

Nevertheless, for less severe patients, there is no evidence supporting the efficacy of initial triple therapy. A recent study evaluated the efficacy and safety of initial triple oral therapy with selexipag, macitentan and tadalafil versus initial double oral therapy with macitentan and tadalafil in 247 newly diagnosed PAH patients.⁵⁰ No difference was found in terms of improvement of PVR, six-minute walk distance and N-terminal pro-brain natriuretic peptide (NT-proBNP) levels. Also, adverse effects were more common in the initial triple therapy group.

Triple combination therapy for the treatment of PAH patients seems efficient. The addition of selexipag as a third agent in patients receiving endothelin receptor antagonist and PDE-5 inhibitor was associated with less hospitalizations and events of disease progression.⁵¹ The beneficial effects

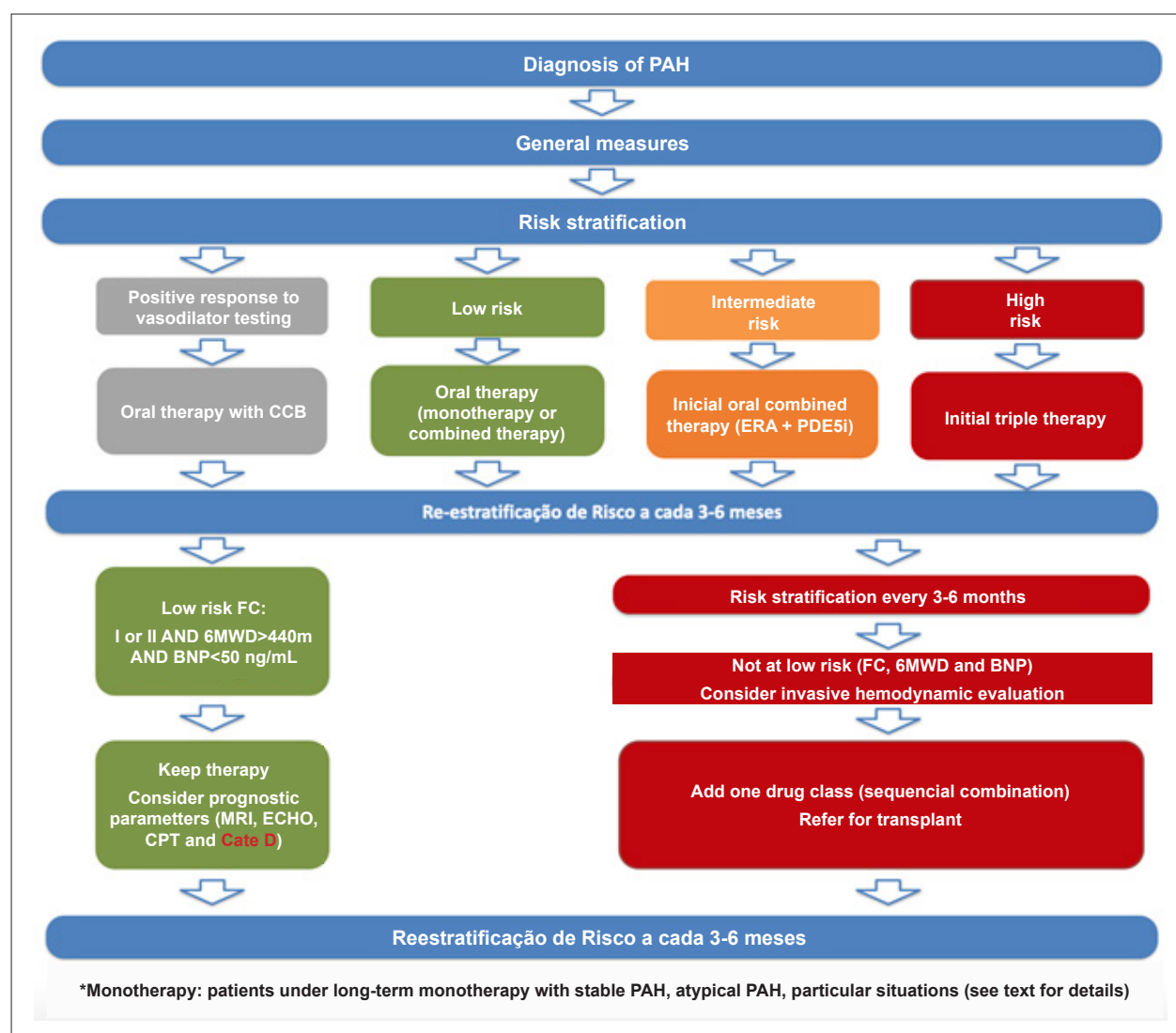


Figure 2 – Treatment algorithm and risk stratification in the follow-up of pulmonary arterial hypertension proposed by a work group on pulmonary circulation (Heart Institute [INCOR], University of Sao Paulo). CCB: calcium-channel blockers; FC: functional class; 6MWD: six-minute walk distance; BNP: brain natriuretic peptide; MRI: magnetic resonance imaging; ECHO: echocardiography; CPT: cardiopulmonary test; ERA: endothelin receptor antagonists; PDE5i: phosphodiesterase type 5 (PDE-5).

were more pronounced in patients with World Health Organization functional class II.

Another potential strategy is the substitution of drugs targeting the same biochemical pathway. However, although promising, this strategy still lacks robust scientific evidence and should not be performed routinely.⁵²

Risk stratification and clinical follow-up

Assessing the risk of progression of PAH is essential to guide treatment. Strategies for mortality risk stratification evaluating the combination of multiple markers (Table 3), both at diagnosis and during treatment, have shown effective in predicting the clinical course of the disease.⁵³⁻⁵⁵

There are several methods to assess the risk of progression of PAH. One of them is to assign a score (from 1 to 3) to each variable, according to the range risk group (low, intermediate, or high, respectively). The overall risk is estimated by dividing the sum of all points by the number of variables. The nearest whole number classifies the risk as low (1), intermediate (2) or high (3) risk.⁵⁵ A simpler approach aims to identify only patients at low risk, by using the combination of the following parameters: brain natriuretic peptide (BNP) levels < 50 pg/mL, six-minute walk distance > 440m and functional class of II.⁵³ A third approach, derived from the REVEAL (Registry to Evaluate Early and Long-Term PAH Disease Management Registry) risk score calculator, includes up to 12 variables and has been recently updated.⁵⁶

Although a more comprehensive approach can be superior to a more simplified evaluation, the low availability of the different tests limits their application.

Thus, risk stratification, here suggested, is based on what is considered the minimum requirements for an adequate clinical management of patients with PAH, by a combination of functional class, six-minute walk test and BNP for identification of patients at “low risk” and “not low risk” (Figure 2). According to their availability, tests like magnetic resonance, echocardiography and cardiopulmonary stress test should be encouraged due to their potential adjuvant role.^{23,57} The main objective of PAH treatment is to achieve or maintain a low risk of disease progression using the strategies and risk stratification above discussed.

Particularities of different types of PAH

PAH associated with connective tissue disease

PAH is a known complication of connective tissue disease (CTD). The main CTDs associated with PAH are systemic sclerosis (SS), systemic erythematosus lupus (SEL), and mixed CTD (MCTD), and in a lesser degree, dermatomyositis, and Sjögren syndrome.⁵⁸ In Brazil, PAH associated with CTD represents nearly 25%⁵⁹ of PAH cases. The primary disease associated with PAH is SS in western countries, and SEL in Asian,⁶⁰⁻⁶² and the prevalence of PAH in SS and SEL patients is around 10%,⁶³ and 4%, respectively.⁶⁴

The presence of antiphospholipid, anti-RNP and anti-Ro antibodies is predictive of PAH in SEL patients.⁶⁵ In patients with SS, the presence of long-term disease, telangiectasias, anti-centromere antibody positivity and reduction in the diffusing capacity for carbon monoxide (DLCO) are the main factors related to PAH.⁶⁶

Table 3 – Prognostic factors in pulmonary arterial hypertension (adapted from reference 8)

Prognostic determinants	One-year mortality (estimated)		
	Low risk < 5%	Intermediate risk 5-10%	High risk > 10%
Clinical signs of right ventricular failure	Absent	Absent	Present
Progression of symptoms	None	Slow	Fast
Syncope	None	Occasionally*	Repeatedly **
WHO FC	I, II	III	IV
6M-WD	> 440 m	165-440 m	< 165 m
Cardiopulmonary exercise test	Peak VO ₂ > 15 mL/min/Kg (>65% predicted) VE/VCO ₂ slope < 36	Peak VO ₂ 11–15 mL/min/Kg (35–65% predicted) VE/VCO ₂ slope 36–44.9	Peak VO ₂ < 11mL/min/Kg (<35% predicted) VE/VCO ₂ ≥ 45
NT-proBNP plasma levels	BNP < 50 ng/l NT-proBNP < 300 ng/mL	BNP 50–300 ng/l NT-proBNP 300–1,400 ng/L	BNP > 300 ng/L NT-proBNP > 1,400 ng/L
Imaging tests (ECHO, chest magnetic resonance)	Right atrial area < 18 cm ² Absence of pericardial effusion	Right atrial area 18–26 cm ² Absent or minimal pericardial effusion	Right atrial area > 26 cm ² Presence of pericardial effusion
Hemodynamic parameters	Right atrial pressure < 8 mmHg CI ≥ 2.5 L/min/m ² ScvO ₂ > 65%	Right atrial pressure 8–14 mmHg CI 2.0–2.4 L/min/m ² ScvO ₂ 60–65%	Right atrial pressure > 14 mmHg CI < 2.0 L/min/m ² ScvO ₂ < 60%

* Occasional syncope during brisk or heavy exercise, or occasional orthostatic syncope in an otherwise stable patient; ** Repeated episodes of syncope, even with little or regular physical activity. ECHO: echocardiogram; peakVO₂: oxygen consumption at peak exercise; VE: ventilatory equivalents; VCO₂: volume of exhaled CO₂; BNP: brain natriuretic peptide; NT-proBNP: N-terminal pro-brain natriuretic peptide; CI: cardiac index, ScvO₂: Central venous oxygen saturation; WHO: World Health Organization; 6M-WD: six-minute walk distance.

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SS is characterized by an association between vasculopathy and tissue fibrosis.⁶⁷ Clinically, SS is marked by a high prevalence of interstitial pulmonary disease (up to 50% of patients),⁶⁸ and cardiac involvement (50-80% of patients), frequently leading to diastolic dysfunction.⁶⁹ Therefore, in these patients, PH may be a result of either a pulmonary vascular disease alone or a combination of different pathophysiological mechanisms related to PH in groups II and III.⁶⁸ Besides, these patients are at increased risk of pulmonary thromboembolism and associated veno-occlusive disease, which may even worsens patients' prognosis.⁶⁸ It is imperative to determine the preponderant mechanism to guide treatment of these patients.

In SS patients, annual screening for PH is recommended, even in asymptomatic patients.⁷⁰ Screening models including risk factors, DLCO and BNP seem to be more sensitive than echocardiography alone.⁷¹ In SEL, due to the low prevalence of PH, the screening for this condition is not recommended as a routine practice, and echocardiography should be performed only for symptomatic patients (Table 4).

In case of clinical suspicion, the diagnostic flow is the same, aiming at differentiating the diagnosis of PAH (group I) from other forms of PH. Vasoreactivity testing is not applied for patients with DTC, as at least 1% of them have a sustained response.

For patients with inflammatory diseases, such as SEL and DMTC-PAH, immunosuppression is an alternative approach before specific therapy is initiated. In patients with functional class I and II, it is recommended to start treatment with cyclophosphamide (CCP) and glucocorticoid (GCT), whereas in those with functional class III and IV, a combination of CCP, GCT with specific therapy is recommended, due to a lower

chance of response to immunosuppression, with reassessment after six months of CCP (5).^{58,72} In patients with SS, there is no evidence of improvement with immunosuppression.⁷³

PAH associated with HIV

The association between human immunodeficiency virus (HIV) and PAH was first described in 1987.⁷⁴ Today, the estimated prevalence of PAH in HIV patients is 0.5%,⁷⁵ and HIV infection is an important etiology of PAH in referral centers. In a Brazilian registry, 4.5% of PAH patients had HIV diagnosed.⁵⁹

The pathophysiological mechanisms involved in the association between HIV and PAH are not fully understood. From a histological point of view, concentric laminar intimal fibrosis, medial hypertrophy, and plexiform lesions were found in up to 78% of patients, which resembles the changes observed in patients with PAH.⁷⁶

The presence of PAH worsens the prognosis of HIV patients. CD4 counts lower than 200 cells/ μ L and a cardiac output lower than 2.8 L/min per m² are independent predictors of survival.⁷⁷ Then, antiretroviral therapy (ART) is recommended for all patients with HIV, regardless of CD4 count, viral load,⁷⁸ or concomitant PAH.

With respect to the NO pathway, there are no controlled studies with sildenafil evaluating therapy response in patients with HIV and PAH. Positive results regarding exercise performance, functional class, and hemodynamic parameters were obtained from case studies.⁷⁹ Caution is advised because of the interaction with ART, particularly with protease inhibitors.⁸⁰ Also, there are no studies with riociguat, despite

Table 4 - Risk factors and screening for pulmonary hypertension in patients with connective tissue disease

	Risk factors	Screening
SS	Long term disease Telangiectasias Anti-centromere Reduced DLCO or FVC/DLCO>1.6	-Annually in asymptomatic patients Echocardiogram $\pm$ biomarkers/ PFT or DETECT algorithm BNP/NTproBNP and PFT $\pm$ ECHO
LES	Serositis Antibodies: Antiphospholipid, RNP and Ro	In symptomatic patients only

SS: systemic sclerosis; SEL: systemic erythematosus lupus; PFT: pulmonary function test; DLCO: diffusing capacity for carbon monoxide; forced vital capacity (FVC); BNP: brain natriuretic peptide; NT-proBNP: N-terminal pro-brain natriuretic peptide.

Table 5 - Treatment of pulmonary arterial hypertension associated with connective tissue

	Immunosuppression (IS)	Specific therapy
SS	Not recommended	According to risk stratification
SEL functional class I/II	CCP and GCT for six months	If PH continues after IS
SEL functional class III/IV	CCP and GCT plus specific therapy	Associated with IS, according to risk stratification
MCTD functional class I/II	CCP and GCT for six months	If PH continues after IS
MCTD functional class III/IV	CCP and GCT plus specific therapy	Associated with IS, according to risk stratification

IS: immunosuppression; SS: systemic sclerosis; SEL: systemic erythematosus lupus; MCTD: mixed connective tissue disease; CCP: cyclophosphamide; GCT: glucocorticoid; PH: pulmonary hypertension.

recent publication showing good safety and tolerability of riociguat and ART combination regimens.⁸¹

Among the endothelin receptor antagonists, bosentan was evaluated for the treatment of 59 HIV patients with PAH in a prospective study.⁸² There was an improvement in six-minute walk distance, symptoms and hemodynamic status. In pivotal studies on ambrisentan⁴⁰ and macitentan,³⁹ 17 and 10 HIV patients with PAH were included, respectively, and no interactions with ART were observed.⁷⁸

Small case series evaluated prostanoids for treatment of HIV-PAH patients. Treatment with epoprostenol resulted in improvement of hemodynamics,⁸³ and iloprost improved functional lass and six-minute walk test in four patients.⁸⁴ In a pivotal trial, selexipag was administered to 10 HIV patients.³⁵ In a study evaluating potential interactions between ART and selexipag, no interaction was detected, and adaptations of the selexipag dose were not required in a study with healthy subjects treated with a single dose of 400 µg selexipag in combination with multiple doses of lopinavir/ritonavir (400/100 mg) twice daily.⁸⁵

Portopulmonary hypertension

Portopulmonary hypertension (PPH) refers to a form of PAH that is associated with portal hypertension. Portal hypertension leads to the formation of portosystemic shunts and increased pulmonary blood flow, which results in endothelial remodeling and dysfunction, with elevations in ET-1 production and pulmonary vascular pressure.⁸⁶

It is estimated that 10.6% of PAH patients have PPH,⁸⁷ and in a review⁸⁸ of 1,205 consecutive liver transplant patients, the incidence of pulmonary hypertension 8.5% of liver transplant candidates. PPH is not associated with the etiology of portal hypertension nor with the severity of lung disease.⁸⁹

Clinical presentation of PPH is similar to other forms of PAH, and the most common symptom in PPH patients is dyspnea. In PAH, the presence of ascites may be indicative of PPH.⁹⁰ For diagnosis of this condition, right catheterization can be made to confirm PAH, as described before, and portal hypertension can be confirmed by a hepatic venous pressure gradient greater than 4 mmHg.⁹¹

The treatment of PPH was evaluated by small studies, that demonstrated beneficial effects of three classes of drugs. Hepatotoxicity of endothelin receptor antagonists may not be a major problem in continuously monitored patients.⁹² The largest study conducted with PPH patients showed hemodynamic improvements after 12 weeks of macitentan, with no hepatic side effects.⁹³ Some well-established drugs for the treatment of portal hypertension, including beta-blockers, should not be administered in PPH, due to worsening of hemodynamic status and exercise capacity.⁹⁴

It is worth pointing out the role of PPH in liver transplant candidates. PPH is a marker of a worse prognosis in the perioperative period, and MPAP values lower than 35 mmHg indicated a lower risk of death in liver transplant recipients.⁹¹ Therefore, a screening echocardiogram to detect PAH is mandatory for patients in the liver transplant waiting list and for patients with portal hypertension presenting with (even mild) dyspnea.⁹⁵

Schistosomiasis

Schistosomiasis (Sch) is an endemic parasitic disease in Brazil, associated with poverty and poor sanitation. It is caused by trematode worms of the genus *Schistosoma*, and its transmission has been documented in more than 70 countries. Although the hepatosplenic form is the most common manifestation of chronic Sch,⁹⁶ one of the most severe and limiting manifestations of the disease are related to impairment of the pulmonary circulation in the presence of PAH (Sch-PAH).

Nearly 5% of patients with the hepatosplenic form of Sch have PAH.^{96,97} Thus, considering the high prevalence of schistosomiasis worldwide, Sch-PAH is potentially one of the most prevalent PAH, especially in developing countries.⁹⁷ A recent registry showed that Sch-PAH can represent about 20% of the incident cases of PAH.⁵⁹

The diagnosis of Sch-PAH requires invasive confirmation of PAH (see "definition" session) and confirmation of hepatosplenic Sch, with presence of ultrasound changes compatible with the disease (e.g., periportal fibrosis) plus one of the following epidemiological factors: 1) patients from endemic areas; OR 2) previous treatment for Sch; OR 3) detection of *Schistosoma* eggs in stool samples or rectal biopsies.⁹⁸

Although Sch-PAH usually have a better clinical course than idiopathic PAH, even in the absence of specific therapy, it does not mean that the disease poses no risk. Sch-PAH mortality can reach 15% in three years.⁹⁹ Cases of PAH with pronounced dilatation of pulmonary arteries should suggest Sch-PAH, especially in areas where Sch is highly prevalent.¹⁰⁰

Treatment of Sch-PAH is similar to the other forms of PAH. Cases series have demonstrated clinical and hemodynamic benefits,¹⁰¹ in addition to longer survival with specific therapy.⁹⁷ Thus, also for Sch-PAH, it is recommended to follow the therapeutic algorithm as proposed in Figure 2. Anticoagulation should be avoided due to the risk of upper gastrointestinal bleeding. All patients should receive at least one cycle of anti-parasite treatment, since it is not known whether the persistence of infection can contribute to progression of pulmonary vascular dysfunction.⁹⁷

Congenital heart disease

PAH is a relatively common condition in patients with congenital heart diseases (CHDs), affecting 5-10% of this group.¹⁰² CHDs can cause pulmonary hyperflow, inducing endothelial remodeling and consequent PVR, which is histologically indistinguishable from other forms of PAH. Thus, most cases of CHD-PAH are classified as group I. In this group, when PVR exceeds the systemic vascular resistance, the direction of the shunt reverses, which characterizes the Eisenmenger syndrome.¹⁰³ Patients with this syndrome have severe hypoxemia, and hematological changes (erythrocytosis and low platelet count). Also, these patients may have hemoptysis, stroke, brain abscess in addition to a higher incidence of sudden death.⁹

The treatment of CHD-PAH should follow the guidelines previously established for other forms of group I. Therapeutic phlebotomy can be considered for Eisenmenger syndrome

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patients who present hyperviscosity symptoms (usually hematocrit levels above 65%).⁹ As in other forms of PAH, anticoagulation is controversial in Eisenmenger syndrome,¹⁰⁴ and should be weighed case by case. Likewise, the benefit of supplemental oxygen in patients with Eisenmenger syndrome and hypoxemia is questionable,¹⁰⁵ and indication should be tailored to the patient's needs.

With respect to the specific therapy for CHD-PAH, the only validated drug treatment was bosentan, which improved the six-minute walk test and decreased PVR after 16 weeks of treatment in functional class III patients.¹⁰⁶ Smaller series have shown beneficial effects with PDE-5 inhibitors and prostanoids.⁹

Some CHDs, including patent ductus arteriosus, sinus venosus atrial septal defect, or anomalous pulmonary venous drainage can be unnoticed in PAH patients, who would be considered as idiopathic PAH. However, in the context of PAH, the diagnosis of a CHD in the context may indicate the need for surgical repair of the defect, according to PCR at diagnosis¹⁰⁷ and the clinical course. This evaluation should be performed in centers with expertise in this condition for a proper referral (or not) for surgery. The mere possibility of correction reinforces the necessity of actively investigating the presence of CHD. In patients undergoing diagnostic evaluation, this can include echocardiography with microbubbles for examination of intracardiac and extracardiac shunts.

In addition, some complex, rarer CHDs, are classified as group V, i.e., of uncertain or multifactorial mechanisms.⁸ In these cases, due to the absence of prospective studies, the pharmacological or surgical approach (including heart-lung transplantation) should be individually performed.

Special situations

Pulmonary hypertension and pregnancy

Physiological changes in pregnancy, including increase in blood volume and cardiac output,^{108,109} are generally not well tolerated in PAH patients. Thus, pregnancy is associated with high morbidity and mortality rates, varying from 30 to 56%.¹⁸

Thus, because of the high lethality of PAH in pregnancy, it is recommended the use of two contraceptive methods, although there is no consensus on the best method. Barrier methods are considered safe, although their efficacy is directly related to a correct use.¹⁰⁸ Hormonal methods of birth control, as those containing progestin only, are effective; combination with estrogen should be avoided due to the increased risk in thromboembolic events.¹⁰⁹ Intrauterine devices may be used, but vasovagal reactions may occur at their insertion.¹¹⁰

When pregnancy is confirmed, the patient should be informed about potential risks. In extreme cases, therapeutic interruption of gestation may be considered,¹⁰⁹ preferably before 22 weeks of gestational age.¹¹¹ In a recent European registry of PH and pregnancy,¹¹² therapeutic abortion was performed in 4% of cases, whereas perinatal mortality in idiopathic PAH was performed in 43% of the cases. Although there is no consensus about the safest birthing method, cesarean section at 32-36 weeks' gestation, without general anesthesia, has been the preferable method.^{111,113} Preeclampsia

or eclampsia, preterm birth, fetal death, postpartum bleeding were the most common complications in pregnant women with PH.¹¹⁴

Specific therapy should be adapted to pregnant women with PAH who do not accept pregnancy termination and insist on continuing with their pregnancy. Case series have demonstrated the efficacy of sildenafil and prostacyclin analogues in pregnancy.^{18,113,115} However, endothelin receptor antagonists should be avoided due to their potential teratogenic effect.¹¹⁶

Angina and PAH

Angina is reported by 15.8¹¹⁷-29.0%⁹ of patients with PAH and may result by an imbalance between myocardial oxygen supply and demand in the right ventricle, with no change in the flow of epicardial coronary arteries. The increase in ventricular wall tension leads to a decrease in the coronary flow reserve, which, associated with greater ventricular work and oxygen consumption, and myocardial hypertrophy, results in ischemia. However, another consequence of PAH is vascular remodeling, with increased pulmonary artery diameter.

Dilated pulmonary artery may induce inferior displacement of the left main coronary artery (LMCA), which become in close contact with the left aortic sinus (Figure 3). This compression may cause LMCA stenosis.¹¹⁸ A prevalence of up to 40% of LMCA occlusion caused by external compression has been described in PAH patients with angina.¹¹⁷ The main predictor of LMCA compression was a pulmonary artery diameter > 40 mm, followed by a pulmonary artery to ascending aorta diameter ratio ≥ 1.5 .¹¹⁷

The prognostic impact of LMCA compression is still uncertain. Therapeutic management of this condition is similar to that performed in LMCA lesion caused by atherosclerosis: myocardial revascularization, with the percutaneous approach being the safest and most attractive modality for these patients.¹¹⁹ Data from an Italian study demonstrated good results with this approach. In a mean follow-up of 4.5 years of 53 patients who underwent angioplasty, 19 patients (37.3%) died, with no case of infarction or stent thrombosis, and five patients required a new angioplasty.¹²⁰

LMCA compression should be considered in all patients with PH and angina, with initial investigation by computed tomography angiography. Patients with a high clinical probability of extrinsic compression of the LMCA (e.g., patients with large pulmonary artery aneurysm and angina), referred for right catheterization, should be submitted to coronary cineangiography, even without coronary computed tomography angiography. With the increase in survival of PAH patients, atherosclerotic comorbidity should also be considered, with control of traditional cardiovascular risk factors.

Supraventricular arrhythmias and PAH

Cardiac arrhythmias are frequent in PAH patients, notably supraventricular tachycardias, caused by either by increased automation or re-entry. Retrospective studies have reported an annual incidence of sustained supraventricular

tachycardia between 2.8%¹²¹ and 3.5%.¹²² However, these numbers underestimate the real incidence, due to the lack of prospective studies with a strategic search and strategy of continuous monitoring or of accessible demand. These arrhythmias are caused by right ventricular pressure overload, cardiac remodeling, and increased adrenergic tone, associated with PH. Also, hypokalemia and hypomagnesemia caused by chronic treatment with diuretic may also be a cause of arrhythmias.

The most common sustained arrhythmias are atrial fibrillation and atrial flutter, followed by atrioventricular-nodal reentrant tachycardia and sustained atrial tachycardia. Most patients have worsening of functional class, and persistence of arrhythmia leads to higher mortality.¹²¹ The treatment of arrhythmias is focused on restoring cardiac rhythm by using drugs of modest inotropic effect (e.g., amiodarone), programmed electrical cardioversion, and in some cases, electrophysiological study and ablation (which should be early considered in atrial flutter). In preparation for cardioversion, or in cases of recurrence or cardioversion failure, monitoring of ventricular response is essential to guarantee cardiac output, and tailor the therapy according to the right ventricular functional reserve. Patients with important right ventricular dysfunction caused by pulmonary hypertension have poor tolerance to betablockers, and even the use of calcium channel blockers may result in clinical decompensation. In these situations, digoxin and amiodarone may be convenient. It is worth pointing out that all patients with PH and atrial fibrillation should receive anticoagulant therapy, due to the high risk of systemic and cerebral thromboembolism.

Conclusion

In the last decades, important advances have been made in the treatment of PAH, a severe, progressive, incurable, and potentially fatal disease. For an adequate therapy, correct hemodynamic diagnosis and etiology

classification are fundamental. Many etiologies – rheumatic disease, portal hypertension, CHDs, Sch – require specific measures, in addition to drug therapy for PAH. The specific therapy for PAH is based on medications that act on three pathophysiological pathways – prostacyclin, endothelin, and NO pathways. Today, it is recommended that initial treatment begins with a combination of two oral therapies and increases if patient does not achieve the desired therapeutic target, which was established based on the stratification of cardiovascular death risk.

Cardiovascular complications of PAH (LCMA compression, supraventricular arrhythmias) are common and should be promptly identified and treated, as they affect the quality of life and probably the prognosis of patients with PAH.

Author Contributions

Conception and design of the research: Fernandes CJ, Calderaro D; Acquisition of data and Writing of the manuscript: Fernandes CJ, Calderaro D, Assad APL, Salibe-Filho W, Kato-Morinaga LT, Hoette S, Piloto B, Castro MA, Lisboa RP, Silva TAF, Martins MA, Alves-Jr JL, Jardim C, Terra-Filho M, Souza R; Critical revision of the manuscript for intellectual content: Fernandes CJ, Souza R.

Potential Conflict of Interest

Dr. Caio J. Fernandes - lecture fees and advisory board from Bayer and Janssen. Dra. Daniela Calderaro - palestras e conselho consultivo da Bayer. Dra. Ana Paula Luppino Assad - conselho consultivo da Janssen. Dr. Jose L. Alves-Jr - lecture fees and advisory board from Janssen. Dr. Carlos Jardim - lecture fees and advisory board from Janssen and lecture fees from Bayer. Dr. Mario Terra-Filho - lecture fees and advisory board from Bayer. Dr. Rogerio de Souza - lecture fees and advisory board from Bayer, GSK and Janssen.

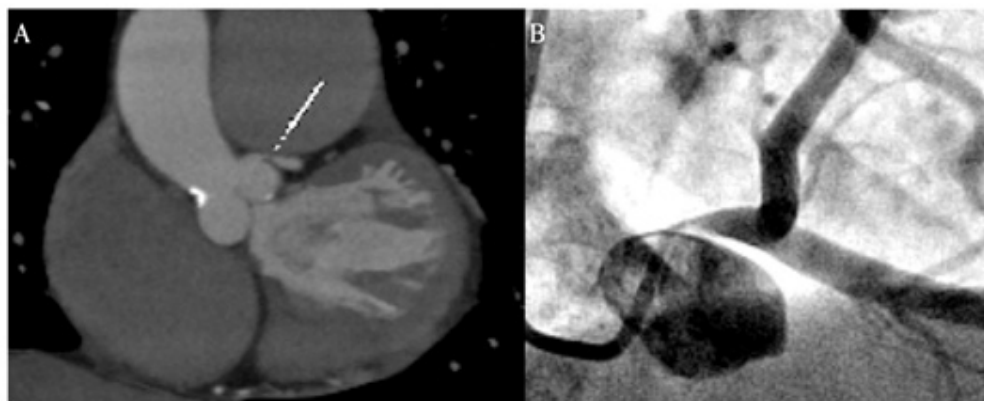


Figure 3 – A) Computed tomography angiography showing inferior displacement of the left main coronary artery caused by an aneurysm of the pulmonary artery and left coronary ostial stenosis. B) coronary cineangiography of the same patient, showing occlusion of the left main coronary artery ostium.

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References

- Humbert M. Pulmonary Arterial Hypertension and Chronic Thromboembolic Pulmonary Hypertension: Pathophysiology. *Eur Respir Rev*. 2010;19(115):59-63. doi: 10.1183/09059180.00007309.
- Alves JL Jr, Oleas FG, Souza R. Pulmonary Hypertension: Definition, Classification, and Diagnosis. *Semin Respir Crit Care Med*. 2017;38(5):561570. doi: 10.1055/s-0037-1606577.
- Hoeper MM, Humbert M, Souza R, Idrees M, Kawut SM, Sliwa-Hahnle K, et al. A global View of Pulmonary Hypertension. *Lancet Respir Med*. 2016;4(4):306-22. doi: 10.1016/S2213-2600(15)00543-3.
- D'Alonzo GE, Barst RJ, Ayres SM, Bergofsky EH, Brundage BH, Detre KM, et al. Survival in Patients with Primary Pulmonary Hypertension. Results from a National Prospective Registry. *Ann Intern Med*. 1991;115(5):343-9. doi: 10.7326/0003-4819-115-5-343.
- Jardim C, Fernandes CJ, Souza R. Goal-Oriented Treatment of Pulmonary Arterial Hypertension. *Curr Opin Pulm Med*. 2014;20(5):409-13. doi: 10.1097/MCP.0000000000000086.
- Fernandes CJ, Martins BC, Jardim CV, Ciconelli RM, Morinaga LK, Breda AP, et al. Quality of Life as a Prognostic Marker in Pulmonary Arterial Hypertension. *Health Qual Life Outcomes*. 2014;12(1):130. doi: 10.1186/s12955-014-0130-3.
- O'Callaghan DS, Humbert M. A Critical Analysis of Survival in Pulmonary Arterial Hypertension. *Eur Respir Rev*. 2012;21(125):218-22. doi: 10.1183/09059180.00003512.
- Simonneau G, Montani D, Celermajer DS, Denton CP, Gatzoulis MA, Krowka M, et al. Haemodynamic Definitions and Updated Clinical Classification of Pulmonary Hypertension. *Eur Respir J*. 2019;53(1):1801913. doi: 10.1183/13993003.01913-2018.
- Galiè N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, et al. 2015 ESC/ERS Guidelines for the Diagnosis and Treatment of Pulmonary Hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *Eur Respir J*. 2015;46(4):903-75. doi: 10.1183/13993003.01032-2015.
- Maron BA, Hess E, Maddox TM, Opatowsky AR, Tedford RJ, Lahm T, et al. Association of Borderline Pulmonary Hypertension with Mortality and Hospitalization in a Large Patient Cohort: Insights from the Veterans Affairs Clinical Assessment, Reporting, and Tracking Program. *Circulation*. 2016;133(13):1240-8. doi: 10.1161/CIRCULATIONAHA.115.020207.
- Cavillanes F, Alves JL Jr, Fernandes C, Prada LFL, Jardim CV, Morinaga LT, et al. Left Ventricular Dysfunction in Patients with Suspected Pulmonary Arterial Hypertension. *J Bras Pneumol*. 2014;40(6):609-16. doi: 10.1590/S1806-37132014000600004.
- Maron BA, Brittain EL, Hess E, Waldo SW, Barón AE, Huang S, et al. Pulmonary Vascular Resistance and Clinical Outcomes in Patients with Pulmonary Hypertension: A Retrospective Cohort Study. *Lancet Respir Med*. 2020;8(9):873-84. doi: 10.1016/S2213-2600(20)30317-9.
- Simonneau G, Montani D, Celermajer DS, Denton CP, Gatzoulis MA, Krowka M, et al. Haemodynamic Definitions and Updated Clinical Classification of Pulmonary Hypertension. *Eur Respir J*. 2019;53(1):1801913. doi: 10.1183/13993003.01913-2018.
- Calderaro D, Alves JL Jr, Fernandes CJ, Souza R. Pulmonary Hypertension in General Cardiology Practice. *Arq Bras Cardiol*. 2019;113(3):419-28. doi: 10.5935/abc.20190188.
- Nathan SD, Barbera JA, Gaine SP, Harari S, Martinez FJ, Olschewski H, et al. Pulmonary Hypertension in Chronic Lung Disease and Hypoxia. *Eur Respir J*. 2019;53(1):1801914. doi: 10.1183/13993003.01914-2018.
- Fernandes CJCS, Ota-Arakaki JS, Campos FTA, Corrêa RA, Gazzana MB, Jardim CVP, et al. Brazilian Thoracic Society Recommendations for the Diagnosis and Treatment of Chronic Thromboembolic Pulmonary Hypertension. *J Bras Pneumol*. 2020;46(4): e20200204. doi: 10.36416/1806-3756/e20200204.
- Frost A, Badesch D, Gibbs JSR, Gopalan D, Khanna D, Manes A, et al. Diagnosis of Pulmonary Hypertension. *Eur Respir J*. 2019;53(1):1801904. doi: 10.1183/13993003.01904-2018.
- Jais X, Olsson KM, Barbera JA, Blanco I, Torbicki A, Peacock A, et al. Pregnancy Outcomes in Pulmonary Arterial Hypertension in the Modern Management Era. *Eur Respir J*. 2012;40(4):881-5. doi: 10.1183/09031936.00141211.
- Guillemin L, Armstrong I, Aldrighetti R, Howard LS, Ryfienius H, Fischer A, et al. Understanding the Impact of Pulmonary Arterial Hypertension on Patients' and Carers' Lives. *Eur Respir Rev*. 2013;22(130):535-42. doi: 10.1183/09059180.00005713.
- Mereles D, Ehlken N, Kreuscher S, Ghofrani S, Hoeper MM, Halank M, et al. Exercise and Respiratory Training Improve Exercise Capacity and Quality of Life in Patients with Severe Chronic Pulmonary Hypertension. *Circulation*. 2006;114(14):1482-9. doi: 10.1161/CIRCULATIONAHA.106.618397.
- Fuster V, Steele PM, Edwards WD, Gersh BJ, McGoon MD, Frye RL. Primary Pulmonary Hypertension: Natural History and the Importance of Thrombosis. *Circulation*. 1984;70(4):580-7. doi: 10.1161/01.cir.70.4.580.
- Olsson KM, Delcroix M, Ghofrani HA, Tiede H, Huscher D, Speich R, et al. Anticoagulation and Survival in Pulmonary Arterial Hypertension: Results from the Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension (COMPERA). *Circulation*. 2014;129(1):57-65. doi: 10.1161/CIRCULATIONAHA.113.004526.
- Galiè N, Channick RN, Frantz RP, Grünig E, Jing ZC, Moiseeva O, et al. Risk Stratification and Medical Therapy of Pulmonary Arterial Hypertension. *Eur Respir J*. 2019;53(1):1801889. doi: 10.1183/13993003.01889-2018.
- Langen D, Orfanos SE, Giovannazzo M, Schlesinger RD, Hirsch AM, Blenkhorn F, et al. Acute Vasodilator Responsiveness and Microvascular Recruitment in Idiopathic Pulmonary Arterial Hypertension. *Ann Intern Med*. 2015;162(2):154-6. doi: 10.7326/M14-1402.
- Rich S, Kaufmann E, Levy PS. The Effect of High Doses of Calcium-Channel Blockers on Survival in Primary Pulmonary Hypertension. *N Engl J Med*. 1992;327(2):76-81. doi: 10.1056/NEJM199207093270203.
- Sitbon O, Humbert M, Jais X, Ios V, Hamid AM, Provencher S, et al. Long-term Response to Calcium Channel Blockers in Idiopathic Pulmonary Arterial Hypertension. *Circulation*. 2005;111(23):3105-11. doi: 10.1161/CIRCULATIONAHA.104.488486.
- Stacher E, Graham BB, Hunt JM, Gandjeva A, Groshong SD, McLaughlin VV, et al. Modern Age Pathology of Pulmonary Arterial Hypertension. *Am J Respir Crit Care Med*. 2012;186(3):261-72. doi: 10.1164/rccm.201201-0164OC.
- Humbert M, Sitbon O, Simonneau G. Treatment of Pulmonary Arterial Hypertension. *N Engl J Med*. 2004;351(14): 1425-36. doi: 10.1056/NEJMra040291.
- Mitchell JA, Ahmetaj-Shala B, Kirkby NS, Wright WR, Mackenzie LS, Reed DM, et al. Role of Prostacyclin in Pulmonary Hypertension. *Glob Cardiol Sci Pract*. 2014;2014(4):382-93. doi: 10.5339/gcsp.2014.53.

30. Tuder RM, Cool CD, Geraci MW, Wang J, Abman SH, Wright L, et al. Prostacyclin Synthase Expression is Decreased in Lungs from Patients with Severe Pulmonary Hypertension. *Am J Respir Crit Care Med*. 1999;159(6):1925-32. doi: 10.1164/ajrccm.159.6.9804054.
31. Christman BW, McPherson CD, Newman JH, King GA, Bernard GR, Groves BM, et al. An Imbalance Between the Excretion of Thromboxane and Prostacyclin Metabolites in Pulmonary Hypertension. *N Engl J Med*. 1992;327(2):70-5. doi: 10.1056/NEJM199207093270202.
32. Barst RJ, Rubin LJ, Long WA, McGoon MD, Rich S, Badesch DB, et al. A Comparison of Continuous Intravenous Epoprostenol (prostacyclin) with Conventional Therapy for Primary Pulmonary Hypertension. *N Engl J Med*. 1996;334(5):296-301. doi: 10.1056/NEJM199602013340504.
33. Galie N, Manes A, Branzi A. Prostanoids for Pulmonary Arterial Hypertension. *Am J Respir Med*. 2003;2(2):123-37. doi: 10.1007/BF03256644.
34. Olschewski H, Simonneau G, Galie N, Higenbottam T, Naeije R, Rubin LJ, et al. Inhaled Iloprost for Severe Pulmonary Hypertension. *N Engl J Med*. 2002;347(5):322-9. doi: 10.1056/NEJMoa020204.
35. Sitbon O, Channick R, Chin KM, Frey A, Gaine S, Galie N, et al. Selexipag for the Treatment of Pulmonary Arterial Hypertension. *N Engl J Med*. 2015;373(26):2522-33. doi: 10.1056/NEJMoa1503184.
36. Kawanabe Y, Nauli SM. Endothelin. *Cell Mol Life Sci*. 2011;68(2):195-203. doi: 10.1007/s00018-010-0518-0.
37. Chester AH, Yacoub MH. The Role of Endothelin-1 in Pulmonary Arterial Hypertension. *Glob Cardiol Sci Pract*. 2014;2014(2):62-78. doi: 10.5339/gcsp.2014.29.
38. Rubin LJ, Badesch DB, Barst RJ, Galie N, Black CM, Keogh A, et al. Bosentan Therapy for Pulmonary Arterial Hypertension. *N Engl J Med*. 2002;346(12):896-903. doi: 10.1056/NEJMoa012212.
39. Pulido T, Adzerikho I, Channick RN, Delcroix M, Galie N, Ghofrani HA, et al. Macitentan and Morbidity and Mortality in Pulmonary Arterial Hypertension. *N Engl J Med*. 2013;369(9):809-18. doi: 10.1056/NEJMoa1213917.
40. Galie N, Olschewski H, Oudiz RJ, Torres F, Frost A, Ghofrani HA, et al. Ambrisentan for the Treatment of Pulmonary Arterial Hypertension: Results of the Ambrisentan in Pulmonary Arterial Hypertension, Randomized, Double-blind, Placebo-controlled, Multicenter, Efficacy (ARIES) Study 1 and 2. *Circulation*. 2008;117(23):3010-9. doi: 10.1161/CIRCULATIONAHA.107.742510.
41. Chester AH, Yacoub MH, Moncada S. Nitric Oxide and Pulmonary Arterial Hypertension. *Glob Cardiol Sci Pract*. 2017;2017(2):14. doi: 10.21542/gcsp.2017.14.
42. Sim JY. Nitric Oxide and Pulmonary Hypertension. *Korean J Anesthesiol*. 2010;58(1):4-14. doi: 10.4097/kjae.2010.58.1.4.
43. Galie N, Ghofrani HA, Torbicki A, Barst RJ, Rubin LJ, Badesch D, et al. Sildenafil Citrate Therapy for Pulmonary Arterial Hypertension. *N Engl J Med*. 2005;353(20):2148-57. doi: 10.1056/NEJMoa050010.
44. Boutou AK, Pitsiou G. Treatment of Pulmonary Hypertension with Riociguat: A Review of Current Evidence and Future Perspectives. *Expert Opin Pharmacother*. 2020;21(10):1145-55. doi: 10.1080/14656566.2020.1727446.
45. Ghofrani HA, Galie N, Grimminger F, Grünig E, Humbert M, Jing ZC, et al. Riociguat for the Treatment of Pulmonary Arterial Hypertension. *N Engl J Med*. 2013;369(4):330-40. doi: 10.1056/NEJMoa1209655.
46. Ghofrani HA, D'Armini AM, Grimminger F, Hoeper MM, Jansa P, Kim NH, et al. Riociguat for the Treatment of Chronic Thromboembolic Pulmonary Hypertension. *N Engl J Med*. 2013;369(4):319-29. doi: 10.1056/NEJMoa1209657.
47. Galie N, Barberà JA, Frost AE, Ghofrani HA, Hoeper MM, McLaughlin VV, et al. Initial Use of Ambrisentan plus Tadalafil in Pulmonary Arterial Hypertension. *N Engl J Med*. 2015;373(9):834-44. doi: 10.1056/NEJMoa1413687.
48. Lajoie AC, Lauzière G, Lega JC, Lacasse Y, Martin S, Simard S, et al. Combination Therapy versus Monotherapy for Pulmonary Arterial Hypertension: A Meta-analysis. *Lancet Respir Med*. 2016;4(4):291-305. doi: 10.1016/S2213-2600(16)00027-8.
49. Sitbon O, Jaïs X, Savale L, Cottin V, Bergot E, Macari EA, et al. Upfront Triple Combination Therapy in Pulmonary Arterial Hypertension: A Pilot Study. *Eur Respir J*. 2014;43(6):1691-7. doi: 10.1183/09031936.00116313.
50. Chin KM, Sitbon O, Doelberg M, Gibbs JSSR, Hoeper MM, Martin N, et al. Efficacy and Safety of Initial Triple Oral Versus Initial Double Oral Combination Therapy in Patients With Newly Diagnosed Pulmonary Arterial Hypertension (PAH): Results of The Randomized Controlled Triton Study. *Am J Respir Crit Care Med*. 2020;201:A2928. doi: 10.1164/ajrccm-conference.2020.201.1_MeetingAbstracts.A2928.
51. Coghlan JG, Channick R, Chin K, Di Scala L, Galie N, Ghofrani HA, et al. Targeting the Prostacyclin Pathway with Selexipag in Patients with Pulmonary Arterial Hypertension Receiving Double Combination Therapy: Insights from the Randomized Controlled GRIPHON Study. *Am J Cardiovasc Drugs*. 2018;18(1):37-47. doi: 10.1007/s40256-017-0262-z.
52. Fernandes CJCS, Humbert M, Souza R. Challenging the Concept of Adding More Drugs in Pulmonary Arterial Hypertension. *Eur Respir J*. 2017;50(3):1701527. doi: 10.1183/13993003.01527-2017.
53. Boucly A, Weatherald J, Savale L, Jaïs X, Cottin V, Prevot G, et al. Risk Assessment, Prognosis and Guideline Implementation in Pulmonary Arterial Hypertension. *Eur Respir J*. 2017;50(2):1700889. doi: 10.1183/13993003.00889-2017.
54. Hoeper MM, Kramer T, Pan Z, Eichstaedt CA, Spiesshoefer J, Benjamin N, et al. Mortality in Pulmonary Arterial Hypertension: Prediction by the 2015 European Pulmonary Hypertension Guidelines Risk Stratification Model. *Eur Respir J*. 2017;50(2):1700740. doi: 10.1183/13993003.00740-2017.
55. Kylhammar D, Kjellström B, Hjalmarsson C, Jansson K, Nisell M, Söderberg S, et al. A Comprehensive Risk Stratification at Early Follow-up Determines Prognosis in Pulmonary Arterial Hypertension. *Eur Heart J*. 2018;39(47):4175-81. doi: 10.1093/eurheartj/ehx257.
56. Benza RL, Gomberg-Maitland M, Elliott CG, Farber HW, Foreman AJ, Frost AE, et al. Predicting Survival in Patients With Pulmonary Arterial Hypertension: The REVEAL Risk Score Calculator 2.0 and Comparison with ESC/ERS-Based Risk Assessment Strategies. *Chest*. 2019;156(2):323-37. doi: 10.1016/j.chest.2019.02.004.
57. Alves JL Jr, Souza R. Prognostic Relevance of Appropriate Renal Function Evaluation in Pulmonary Arterial Hypertension. *J Heart Lung Transplant*. 2018;37(6):692-3. doi: 10.1016/j.healun.2018.02.005.
58. Aithala R, Alex AG, Danda D. Pulmonary Hypertension in Connective Tissue Diseases: An Update. *Int J Rheum Dis*. 2017;20(1):5-24. doi: 10.1111/1756-185X.13001.
59. Alves JL Jr, Gavilanes F, Jardim C, Fernandes CJCS, Morinaga LTK, Dias B, et al. Pulmonary arterial hypertension in the southern hemisphere: results from a registry of incident Brazilian cases. *Chest*. 2015;147(2):495-501. doi: 10.1378/chest.14-1036.
60. Badesch DB, Raskob GE, Elliott CG, Krichman AM, Farber HW, Frost AE, et al. Pulmonary Arterial Hypertension: Baseline Characteristics from the REVEAL Registry. *Chest*. 2010;137(2):376-87. doi: 10.1378/chest.09-1140.
61. Assad APL, Oleas FG, Alves JL Jr, Fernandes CJCS, Sampaio-Barros PD, Souza R. Survival of Connective Tissue Disease Associated Pulmonary Arterial Hypertension. *Clin Exp Rheumatol*. 2018;36(4):186.
62. Hao YJ, Jiang X, Zhou W, Wang Y, Gao L, Wang Y, et al. Connective Tissue Disease-Associated Pulmonary Arterial Hypertension in Chinese Patients. *Eur Respir J*. 2014;44(4):963-72. doi: 10.1183/09031936.00182813.
63. Avouac J, Airò P, Meune C, Beretta L, Dieude P, Caramaschi P, et al. Prevalence of Pulmonary Hypertension in Systemic Sclerosis in European Caucasians and Metaanalysis of 5 Studies. *J Rheumatol*. 2010;37(11):2290-8. doi: 10.3899/jrheum.100245.

Review Article

64. Ruiz-Irasterza G, Garmendia M, Villar I, Egurbide MV, Aguirre C. Pulmonary Hypertension in Systemic Lupus Erythematosus: Prevalence, Predictors and Diagnostic Strategy. *Autoimmun Rev*. 2013;12(3):410-5. doi: 10.1016/j.autrev.2012.07.010.
65. Kim JS, Kim D, Joo YB, Won S, Lee J, Shin J, et al. Factors Associated With Development and Mortality of Pulmonary Hypertension in Systemic Lupus Erythematosus Patients. *Lupus*. 2018;27(11):1769-77. doi: 10.1177/0961203318788163.
66. Coghlan JG, Denton CP, Grünig E, Bonderman D, Distler O, Khanna D, et al. Evidence-Based Detection of Pulmonary Arterial Hypertension in Systemic Sclerosis: The DETECT study. *Ann Rheum Dis*. 2014;73(7):1340-9. doi: 10.1136/annrheumdis-2013-203301.
67. Denton CP, Wells AU, Coghlan JG. Major Lung Complications of Systemic Sclerosis. *Nat Rev Rheumatol*. 2018;14(9):511-27. doi: 10.1038/s41584-018-0062-0.
68. Launay D, Sobanski V, Hachulla E, Humbert M. Pulmonary Hypertension in Systemic Sclerosis: Different Phenotypes. *Eur Respir Rev*. 2017;26(145):170056. doi: 10.1183/16000617.0056-2017.
69. Desai CS, Lee DC, Shah SJ. Systemic Sclerosis and the Heart: Current Diagnosis and Management. *Curr Opin Rheumatol*. 2011;23(6):545-54. doi: 10.1097/BOR.0b013e32834b8975.
70. Kiely DG, Lawrie A, Humbert M. Screening Strategies for Pulmonary Arterial Hypertension. *Eur Heart J Suppl*. 2019;21(Suppl K):9-20. doi: 10.1093/eurheartj/suz204.
71. Hao Y, Thakkar V, Stevens W, Morrisroe K, Prior D, Rabusa C, et al. A Comparison of the Predictive Accuracy of Three Screening Models for Pulmonary Arterial Hypertension in Systemic Sclerosis. *Arthritis Res Ther*. 2015;17(1):7. doi: 10.1186/s13075-015-0517-5.
72. Jais X, Launay D, Yaici A, Le Pavec J, Tchérakian C, Sitbon O, et al. Immunosuppressive Therapy in Lupus- and Mixed Connective Tissue Disease-Associated Pulmonary Arterial Hypertension: A Retrospective Analysis of Twenty-three Cases. *Arthritis Rheum*. 2008;58(2):521-31. doi: 10.1002/art.23303.
73. Sanchez O, Sitbon O, Jais X, Simonneau G, Humbert M. Immunosuppressive Therapy in Connective Tissue diseases-Associated Pulmonary Arterial Hypertension. *Chest*. 2006;130(1):182-9. doi: 10.1378/chest.130.1.182.
74. Hachinski V, Oveisgharan S, Romney AK, Shankle WR. Optimizing the Hachinski Ischemic Scale. *Arch Neurol*. 2012;69(2):169-75. doi: 10.1001/archneurol.2011.1698.
75. Speich R, Jenni R, Opravil M, Pfab M, Russi EW. Primary Pulmonary Hypertension in HIV Infection. *Chest*. 1991;100(5):1268-71. doi: 10.1378/chest.100.5.1268.
76. Petitpretz P, Brenot F, Azarian R, Parent F, Rain B, Herve P, et al. Pulmonary Hypertension in Patients With Human Immunodeficiency Virus Infection. Comparison with Primary Pulmonary Hypertension. *Circulation*. 1994;89(6):2722-7. doi: 10.1161/01.cir.89.6.2722.
77. Degano B, Guillaume M, Savale L, Montani D, Jais X, Yaici A, et al. HIV-Associated Pulmonary Arterial Hypertension: Survival and Prognostic Factors in the Modern Therapeutic Era. *AIDS*. 2010;24(1):67-75. doi: 10.1097/QAD.0b013e328331c65e.
78. Jarrett H, Barnett C. HIV-associated Pulmonary Hypertension. *Curr Opin HIV AIDS*. 2017;12(6):566-71. doi: 10.1097/COH.0000000000000418.
79. Pergola V, Caruso C, Gnarini R, Fazio S, Ferraro S. Efficacy of Sildenafil in HIV-Related Pulmonary Arterial Hypertension. *J Cardiovasc Med*. 2015;16(Suppl 2):136-7. doi: 10.2459/JCM.0b013e3283388fb3.
80. Muirhead GJ, Wulff MB, Fielding A, Kleinermans D, Buss N. Pharmacokinetic Interactions Between Sildenafil and Saquinavir/Ritonavir. *Br J Clin Pharmacol*. 2000;50(2):99-107. doi: 10.1046/j.1365-2125.2000.00245.x.
81. DeJesus E, Saleh S, Cheng S, van der Mey D, Becker C, Frey R, et al. Pharmacokinetic Interaction of Riociguat and Antiretroviral Combination Regimens in HIV-1-Infected Adults. *Pulm Circ*. 2019;9(2):2045894019848644. doi: 10.1177/2045894019848644.
82. Degano B, Yaici A, Le Pavec J, Savale L, Jais X, Camara B, et al. Long-term Effects of Bosentan in Patients with HIV-Associated Pulmonary Arterial Hypertension. *Eur Respir J*. 2009;33(1):92-8. doi: 10.1183/09031936.00094808.
83. Aguilar RV, Farber HW. Epoprostenol (Prostacyclin) Therapy in HIV-Associated Pulmonary Hypertension. *Am J Respir Crit Care Med*. 2000;162(5):1846-50. doi: 10.1164/ajrccm.162.5.2004042.
84. Chinello P, Petrosillo N. Pharmacological Treatment of HIV-Associated Pulmonary Hypertension. *Expert Rev Clin Pharmacol*. 2016;9(5):715-25. doi: 10.1586/17512433.2016.1151785.
85. Kaufmann P, Niglis S, Bruderer S, Segrestaa J, Äänismaa P, Halabi A, et al. Effect of Lopinavir/Ritonavir on the Pharmacokinetics of Selexipag an Oral Prostacyclin Receptor Agonist and its Active Metabolite in Healthy Subjects. *Br J Clin Pharmacol*. 2015;80(4):670-7. doi: 10.1111/bcp.12650.
86. Porres-Aguilar M, Zuckerman MJ, Figueroa-Casas JB, Krowka MJ. Portopulmonary Hypertension: State of the Art. *Ann Hepatol*. 2008;7(4):321-30. doi: 10.1016/S1665-2681(19)31832-0.
87. Alves JL Jr, Gavilanes F, Jardim C, Fernandes CJDS, Morinaga LTK, Dias B, et al. Pulmonary arterial hypertension in the southern hemisphere: results from a registry of incident Brazilian cases. *Chest*. 2015;147(2):495-501. doi: 10.1378/chest.14-1036. (Citação repetida (vide nº 59). Verificar com os autores a possibilidade de incluir outra citação no lugar da 87 ou se será preciso renumerar todas as citações a partir deste ponto.)
88. Ramsay MA, Simpson BR, Nguyen AT, Ramsay KJ, East C, Klintmalm GB. Severe Pulmonary Hypertension in Liver Transplant Candidates. *Liver Transpl Surg*. 1997;3(5):494-500. doi: 10.1002/lt.500030503.
89. Le Pavec J, Souza R, Herve P, Lebrec D, Savale L, Tcherakian C, et al. Portopulmonary Hypertension: Survival and Prognostic Factors. *Am J Respir Crit Care Med*. 2008;178(6):637-43. doi: 10.1164/rccm.200804-613OC.
90. Elliott CG, Barst RJ, Seeger W, Porres-Aguilar M, Brown LM, Zamanian RT, et al. Worldwide Physician Education and Training in Pulmonary Hypertension: Pulmonary Vascular Disease: The Global Perspective. *Chest*. 2010;137(Suppl 6):85-94. doi: 10.1378/chest.09-2816.
91. Cosarderelioglu C, Cosar AM, Gurakar M, Pustavoitau A, Russell SD, Dagher NN, et al. Portopulmonary Hypertension and Liver Transplant: Recent Review of the Literature. *Exp Clin Transplant*. 2016;14(2):113-20. doi: 10.6002/ect.2015.0351.
92. Hoeper MM, Seyfarth HJ, Hoeffken G, Wirtz H, Spiekerkoetter E, Pletz MW, et al. Experience with Inhaled Iloprost and Bosentan in Portopulmonary Hypertension. *Eur Respir J*. 2007;30(6):1096-102. doi: 10.1183/09031936.00032407.
93. Raevens S, Fallon MB. PORTICO: First Randomized Controlled Trial of Vasomodulator Therapy in Portopulmonary Hypertension. *Hepatology*. 2020;71(5):1870-2. doi: 10.1002/hep.31166.
94. Provencher S, Herve P, Jais X, Lebrec D, Humbert M, Simonneau G, et al. Deleterious Effects of Beta-blockers on Exercise Capacity and Hemodynamics in Patients with Portopulmonary Hypertension. *Gastroenterology*. 2006;130(1):120-6. doi: 10.1053/j.gastro.2005.10.013.
95. Krowka MJ, Swanson KL, Frantz RP, McGoon MD, Wiesner RH. Portopulmonary Hypertension: Results From a 10-year Screening Algorithm. *Hepatology*. 2006;44(6):1502-10. doi: 10.1002/hep.21431.
96. Gavilanes F, Fernandes CJ, Souza R. Pulmonary Arterial Hypertension in Schistosomiasis. *Curr Opin Pulm Med*. 2016;22(5):408-14. doi: 10.1097/MCP.0000000000000300.
97. Fernandes CJC, Piloto B, Castro M, Oleas FG, Alves JL Jr, Prada LFL, et al. Survival of Patients with Schistosomiasis-Associated Pulmonary Arterial Hypertension in the Modern Management Era. *Eur Respir J*. 2018;51(6):1800307. doi: 10.1183/13993003.00307-2018.

98. Fernandes CJ, Jardim CV, Hovnanian A, Hoette S, Morinaga LK, Souza R. Schistosomiasis and Pulmonary Hypertension. *Expert Rev Respir Med*. 2011;5(5):675-81. doi: 10.1586/ers.11.58.
99. Fernandes CJCS, Dias BA, Jardim CVP, Hovnanian A, Hoette S, Morinaga LK, et al. The Role of Target Therapies in Schistosomiasis-Associated Pulmonary Arterial Hypertension. *Chest*. 2012;141(4):923-8. doi: 10.1378/chest.11-0483.
100. Hoette S, Figueiredo C, Dias B, Alves JL Jr, Gavilanes F, Prada LFL, et al. Pulmonary Artery Enlargement in Schistosomiasis Associated Pulmonary Arterial Hypertension. *BMC Pulm Med*. 2015;15:118. doi: 10.1186/s12890-015-0115-y.
101. Fernandes CJC, Jardim C, Souza R. The Global View. *Curr Opin Pulm Med*. 2019;25(5):391-7. doi: 10.1097/MCP.0000000000000603.
102. Engelfriet PM, Duffels MG, Möller T, Boersma E, Tijssen JG, Thaulow E, et al. Pulmonary Arterial Hypertension in Adults Born with a Heart Septal Defect: The Euro Heart Survey on Adult Congenital Heart Disease. *Heart*. 2007;93(6):682-7. doi: 10.1136/hrt.2006.098848.
103. Beghetti M, Galie N. Eisenmenger Syndrome a Clinical Perspective in a New Therapeutic Era of Pulmonary Arterial Hypertension. *J Am Coll Cardiol*. 2009;53(9):733-40. doi: 10.1016/j.jacc.2008.11.025.
104. Broberg CS, Ujita M, Prasad S, Li W, Rubens M, Bax BE, et al. Pulmonary Arterial Thrombosis in Eisenmenger Syndrome is Associated with Biventricular Dysfunction and Decreased Pulmonary flow Velocity. *J Am Coll Cardiol*. 2007;50(7):634-42. doi: 10.1016/j.jacc.2007.04.056.
105. Sandoval J, Aguirre JS, Pulido T, Martinez-Guerra ML, Santos E, Alvarado P, et al. Nocturnal Oxygen Therapy in Patients with the Eisenmenger Syndrome. *Am J Respir Crit Care Med*. 2001;164(9):1682-7. doi: 10.1164/ajrccm.164.9.2106076.
106. Galie N, Beghetti M, Gatzoulis MA, Granton J, Berger RM, Lauer A, et al. Bosentan Therapy in Patients with Eisenmenger Syndrome: A Multicenter, Double-blind, Randomized, Placebo-controlled Study. *Circulation*. 2006;114(1):48-54. doi: 10.1161/CIRCULATIONAHA.106.630715.
107. Rosenzweig EB, Abman SH, Adatia I, Beghetti M, Bonnet D, Haworth S, et al. Paediatric Pulmonary Arterial hypertension: Updates on Definition, Classification, Diagnostics and Management. *Eur Respir J*. 2019;53(1):1801916. doi: 10.1183/13993003.01916-2018.
108. Olsson KM, Jais X. Birth Control and Pregnancy Management in Pulmonary Hypertension. *Semin Respir Crit Care Med*. 2013;34(5):681-8. doi: 10.1055/s-0033-1355438.
109. Hemnes AR, Kiely DG, Cockrill BA, Safdar Z, Wilson VJ, Al Hazmi M, et al. Statement on Pregnancy in Pulmonary Hypertension from the Pulmonary Vascular Research Institute. *Pulm Circ*. 2015;5(3):435-65. doi: 10.1086/682230.
110. Thorne S, Nelson-Piercy C, MacGregor A, Gibbs S, Crowhurst J, Panay N, et al. Pregnancy and Contraception in Heart Disease and Pulmonary Arterial Hypertension. *J Fam Plann Reprod Health Care*. 2006;32(2):75-81. doi: 10.1783/147118906776276486.
111. Olsson KM, Channick R. Pregnancy in pulmonary arterial hypertension. *Eur Respir Rev*. 2016;25(142): 431-7. doi: 10.1183/16000617.0079-2016
112. Sliwa K, van Hagen IM, Budts W, Swan L, Sinagra G, Caruana M, et al. Pulmonary Hypertension and Pregnancy Outcomes: Data From the Registry of Pregnancy and Cardiac Disease (ROPAC) of the European Society of Cardiology. *Eur J Heart Fail*. 2016;18(9):1119-28. doi: 10.1002/ehf.594.
113. Duarte AG, Thomas S, Safdar Z, Torres F, Pacheco LD, Feldman J, et al. Management of Pulmonary Arterial Hypertension During Pregnancy: A Retrospective, Multicenter Experience. *Chest*. 2013;143(5):1330-1336. doi: 10.1378/chest.12-0528.
114. Thomas E, Yang J, Xu J, Lima FV, Stergiopoulos K. Pulmonary Hypertension and Pregnancy Outcomes: Insights From the National Inpatient Sample. *J Am Heart Assoc*. 2017;6(10):e006144. doi: 10.1161/JAHA.117.006144.
115. Terek D, Kayikcioglu M, Kultursay H, Ergenoglu M, Yalaz M, Musayev O, et al. Pulmonary Arterial Hypertension and Pregnancy. *J Res Med Sci*. 2013;18(1):73-6.
116. Madden BP. Pulmonary hypertension and pregnancy. *Int J Obstet Anesth*. 2009;18(2):156-64. doi: 10.1016/j.ijoa.2008.10.006.
117. Galie N, Saia F, Palazzini M, Manes A, Russo V, Reggiani MLB, et al. Left Main Coronary Artery Compression in Patients With Pulmonary Arterial Hypertension and Angina. *J Am Coll Cardiol*. 2017;69(23):2808-2817. doi: 10.1016/j.jacc.2017.03.597.
118. Kajita LJ, Martinez EE, Ambrose JA, Lemos PA, Esteves A, Gama MN, et al. Extrinsic Compression of the Left Main Coronary Artery by a Dilated Pulmonary Artery: Clinical, Angiographic, and Hemodynamic Determinants. *Catheter Cardiovasc Interv*. 2001;52(1):49-54. doi: 10.1002/1522-726x(200101)52:1<49::aid-ccd1012>3.0.co;2-0.
119. Fernandes CJ, Steigner ML, Piazza G, Goldhaber SZ. Collaborative Cardiology and Pulmonary Management of Pulmonary Hypertension. *Chest*. 2019;156(2):200-202. doi: 10.1016/j.chest.2019.04.099.
120. Saia F, Dall'Ara G, Marzocchi A, Dardi F, Palazzini M, Manes A, et al. Left Main Coronary Artery Extrinsic Compression in Patients With Pulmonary Arterial Hypertension: Technical Insights and Long-Term Clinical Outcomes After Stenting. *JACC Cardiovasc Interv*. 2019;12(3):319-21. doi: 10.1016/j.jcin.2018.08.002.
121. Tongers J, Schwerdtfeger B, Klein G, Kempf T, Schaefer A, Knapp JM, et al. Incidence and Clinical Relevance of Supraventricular Tachyarrhythmias in Pulmonary Hypertension. *Am Heart J*. 2007;153(1):127-32. doi: 10.1016/j.ahj.2006.09.008.
122. Drakopoulou M, Nashat H, Kempny A, Alonso-Gonzalez R, Swan L, Wort SJ, et al. Arrhythmias in Adult Patients With Congenital Heart Disease and Pulmonary Arterial Hypertension. *Heart*. 2018;104(23):1963-69. doi: 10.1136/heartjnl-2017-312881.

Review Article



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Impact of the COVID-19 Pandemic on Cardiac Implantable Electronic Devices Procedures in a Tertiary Referral Center

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Introduction

The COVID-19 pandemic has caused a change in the surgical practice of many medical specialties worldwide.¹⁻⁴ Medical societies have supported changes in cardiac pacing services routines and established new recommendations on the definition of case severity and urgency of surgical procedures.^{5,6}

The aim of the present study was to evaluate the impact of the measures implemented in surgical procedures performed for artificial cardiac pacing during the pandemic. We compared the number of patients operated, clinical profile of patients, characteristics of procedures, and the rate of confirmed COVID-19 cases in the peak of the pandemic, and compared them with the period immediately before the pandemic.

Methods

This was a prospective study, approved by the ethics committee Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (Plataforma Brasil: 26587419.7.0000.0068).

A total of 557 patients undergoing first implantation or reimplantation of cardiac implantable electrical devices (CIEDs) were evaluated. Specific data related to COVID-19 were included for analysis.

On March 21, 2020, the Instituto do Coração do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (InCor-HCFMUSP) board established specific measures to be adopted for the fight against the COVID-19 pandemic – isolation of patients with COVID-19, postponement of elective surgeries, and prioritization of urgent life-saving procedures and those performed to prevent hemodynamic disturbances. For this purpose, surgeries were classified into

urgent or elective ones (Table 1), according to international recommendations.^{5,6}

The study patients were hospitalized after admission to the emergency department, by referral from other health care settings, or after analysis of the surgery waiting list. All surgeries were performed following routine surgical procedures. All patients were followed-up for 30 days after hospital discharge.

According to the time of surgery, patients were grouped into: Group 1 – before the pandemic (01 January – 20 March); Group 2 – peak of the pandemic (21 March – 31 July). Data were collected and organized using the REDCap software.⁷

The univariate analysis was used for comparison of surgical data during and before the pandemic, and significance level was set at 5%. Comparisons of means between the two periods were made using the Student's t-test or the Mann Whitney test when assumption of data normality was not met. The chi-square test or the Fisher's exact test was used to test the homogeneity of proportions.

Results

Among the 557 patients, there was a similar distribution of men and women. Most patients were white (86.5%), and mean age was 64.5 ± 20.4 years. During the pandemic, there was a significant increase in the prevalence of patients with structural heart disease ($p=0.016$), arterial hypertension ($p=0.047$), atrial fibrillation ($p=0.047$), heart valve disease ($p=0.048$) and neoplasms ($p=0.011$) (Table 2).

On average, 2.3 patients were operated per day during the peak of the pandemic, versus 3.2 patients/day in the period prior to the pandemic, representing a 27% reduction in the number of patients treated (Figure 1). Also, during the pandemic, the type of procedures shifted to a predominance of reoperations ($p=0.070$) and increase in the rate of use of single-chamber pacemakers ($p=0.007$) (Table 1).

In addition, during the pandemic peak, the length of hospital stay was shorter ($p=0.001$), with no difference in the rates of postoperative complications, readmissions, and mortality between the study groups (Table 3).

Fifteen patients (2.7%) had a confirmed diagnosis of COVID-19. Two of them (0.4%) had been operated before the pandemic and were still hospitalized at the time of the study. Thirteen patients were operated during the pandemic; 6 (1.1%) had a confirmed diagnosis of COVID-19 during hospitalization, and 7 (1.3%) during the 30-day follow-up.

Keywords

Defibrillators Implantable; Pacemaker, Artificial; Cardiac Pacing, Artificial; Pandemic; COVID-19; Hospitalization; Contamination; Quality of Health Care.

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Table 1 – Classification of surgical procedures for implantation of cardiac electronic devices during the COVID-19 pandemic

Urgent procedures	Elective procedures
First implantation	First implantation
PM for irreversible advanced atrioventricular block Sinus node dysfunction with severe symptoms or long pauses	PM for non-advanced stable atrioventricular block Mild symptomatic sinus node disease
ICD for secondary prevention	ICD for primary prevention
CRT for severe refractory heart failure	CRT in stable patients
Pulse generator replacement	Pulse generator replacement
PM or ICD with minimum remaining battery life	PM or ICD with more than 6 weeks of remaining battery life
Lead replacement	CIED upgrade
Lead revision for malfunction in a PM dependent patient or ICD patient receiving inappropriate therapy	Upgrade for ICD only in case of secondary prevention Upgrade for CRT only in case of severe refractory heart failure
Lead extraction	Lead extraction
Treatment of CIED-related infection	Non-infected leads except when there is a need for obtaining venous access for lead replacement

ICD: implantable cardioverter defibrillator; CIEDs: cardiac implantable electrical devices; PM: pacemaker; CRT: cardiac resynchronization therapy.

All-cause mortality occurred in 18 (3.2%) patients, with no significant difference between the groups (Table 3). Of the 15 patients with COVID-19, seven died, and COVID-19 was the primary cause in all of them. The other deaths were caused mainly by cardiovascular diseases (n=7; 1.3%), followed by infection unrelated to CIEDs (n=2; 0.4%), surgical complications (n=1; 0.2%) and advanced cancer (n=1; 0.2%).

Discussion

The present study showed that changes in health care routines allowed a safe and effective management of patients with indications for cardiac pacing surgical procedures during the COVID-19 pandemic. However, these changes caused a reduction in the number of patients undergoing CIED implantation for the first time and in the complexity of the CIEDs used, and a relative increase in replacements of pulse generator due to battery depletion.

Despite the greater severity of patients seen during the pandemic, there was a significant reduction in the length of hospital stay, due to a reduction in both preoperative and postoperative periods. On the other hand, no significant differences were found in the types of CIED-related complications, need for surgical reinterventions or rehospitalization rate within 30 days after discharge between the two periods analyzed or as compared with the historical profile of the institution.⁸

Unfortunately, the measures adopted could not prevent patients from being infected with the new coronavirus, which was observed in 2.7% of the study patients. Supply shortages impacting COVID-19 testing, as reported previously,⁹ as well as the non-detection of patients already infected with SARS-CoV-2 at admission may have contributed to the under-notification of cases. At least two patients who had been operated before the pandemic, with prolonged hospital stay, had COVID-19. Among those operated during the pandemic, six patients had manifestations of COVID-19 during

hospitalization. In the other seven, diagnosis of COVID-19 was made during the 30-day period after discharge, and thus we cannot know whether the patient was infected during the pandemic or after hospital discharge.

Although not statistically significant, overall mortality of patients operated during the pandemic was higher as compared with those operated before the pandemic and influenced by the death of seven patients (out of 15) who developed COVID-19 during the pandemic. The high rate of comorbidities in the COVID-19 patients was determinant for the unfavorable outcome of this group.

Now, post-pandemic recommendations for a safe return to general activities are being discussed.¹⁰ The experience here reported may serve as a basis for actions that should be taken during a possible new pandemic peak.

Limitations

This study was conducted in a referral center for artificial cardiac pacing procedures, and the possibility that our results may have been influenced by the expertise of the surgery team and specialized facilities cannot be ruled out. Also, during the study period, adaptations in health care services and greater knowledge of the management of COVID-19 occurred over the epidemiological weeks. So far, it has not been possible to measure the impact of postponement or cancellation of elective surgeries, or of the fact that patients have avoided going to the hospital because of the fear of getting infected with the new coronavirus.

Conclusions

The present study showed that the health care measures adopted to face the COVID-19 pandemic had an impact on the number and the types of surgeries performed. Although these changes allowed safe surgical procedures during the pandemic, they did not prevent patients from contracting COVID-19 and the negative impact of this disease on

Table 2 – Clinical and surgical data of the study patients

Clinical and surgical data	Total (N= 557)	Group 1 Before the pandemic (N= 253)	Group 2 Pandemic peak (N= 304)	p
Male sex, n (%)	281 (50.4)	135 (53.4)	146 (48.0)	0.210
Age (years)	64.5 ± 20.4	65.6 ± 19.7	63.6 ± 20.9	0.248
Functional class (NYHA), n (%)				
I – II	453 (81.6)	212 (83.8)	241 (79.8)	0.378
III - IV	102 (18.4)	41 (16.2)	61 (20.2)	
Structural heart disease, n (%)				
Conduction or rhythm disturbance	204 (36.6)	109 (43.1)	95 (31.3)	0.016
Ischemic heart disease	101 (18.2)	48 (19.0)	53 (17.4)	
Non-ischemic heart disease	252 (45.2)	96 (37.9)	156 (51.3)	
Comorbidities, n (%)				
Arterial hypertension	360 (64.9)	153 (60.5)	207 (68.5)	0.047
Diabetes mellitus	151 (27.2)	66 (26.1)	85 (28.2)	0.587
Atrial fibrillation	143 (25.8)	55 (21.7)	88 (29.1)	0.047
Heart valve disease	96 (17.3)	35 (13.8)	61 (20.2)	0.048
Chronic renal failure	59 (10.6)	25 (9.9)	34 (11.3)	0.600
Current or recent treatment for cancer	15 (2.7)	2 (0.8)	13 (4.3)	0.011
Procedures performed, n (%)				
First implantations	269 (48.3)	138 (54.6)	131 (43.1)	0.007
Reoperations	288 (51.7)	115 (45.4)	173 (56.9)	
Indication – First implants, n (%)				
Symptomatic bradyarrhythmia	202 (75.1)	107 (77.5)	95 (72.5)	0.533
Prophylaxis of sudden cardiac death	30 (11.2)	15 (10.9)	15 (11.5)	
Cardiac resynchronization	37 (13.8)	16 (11.6)	21 (16.0)	
Indication - Reoperations, n (%)				
Natural depletion of pulse generator	192 (66.7)	72 (62.6)	120 (69.4)	0.204
Lead malfunction	44 (15.3)	16 (13.9)	28 (16.2)	
CIED upgrade	25 (8.7)	11 (9.6)	14 (8.1)	
CIED infection	10 (3.5)	5 (4.3)	5 (2.9)	
Others	17 (5.9)	11 (9.6)	6 (3.5)	
Type of CIED, n (%)				
Ventricular pacemaker	76 (13.6)	21 (8.3)	55 (18.1)	0.007
Atrioventricular pacemaker	322 (57.8)	155 (61.3)	167 (54.9)	
Ventricular ICD	23 (4.1)	8 (3.2)	15 (4.9)	
Atrioventricular ICD	49 (8.8)	28 (11.1)	21 (6.9)	
Cardiac resynchronization therapy	82 (14.7)	37 (14.6)	45 (14.8)	
CIED removal	5 (0.9)	4 (1.6)	1 (0.3)	

CIED: cardiac implantable electronic device; ICD: implantable cardioverter defibrillator.

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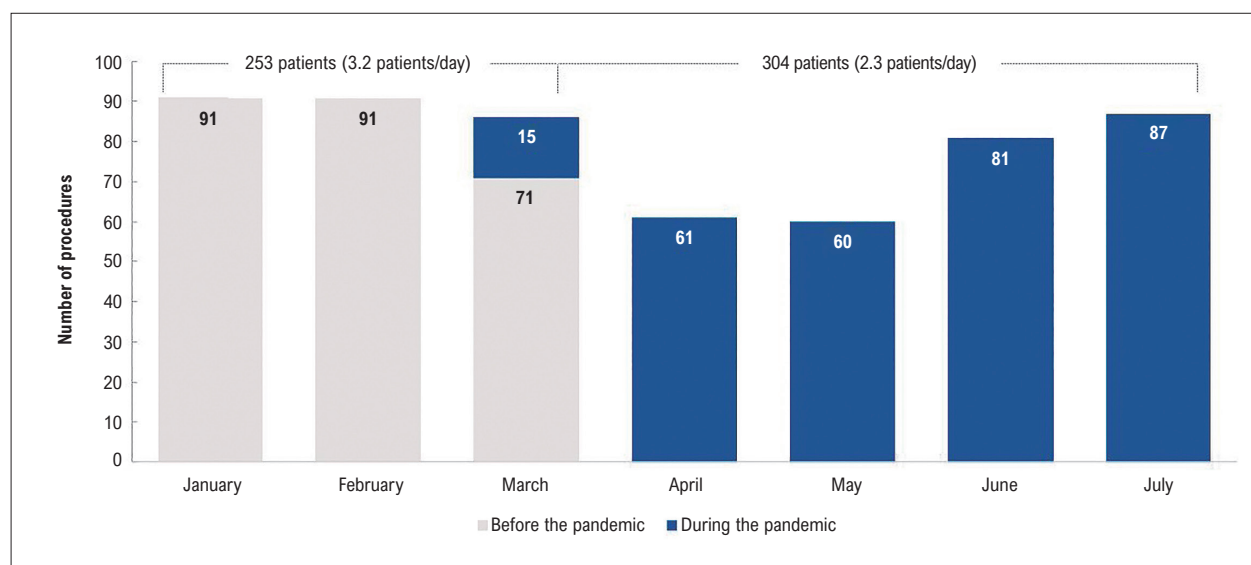


Figure 1 – Number of patients undergoing surgical procedures before and during the peak of the COVID-19 pandemic.

Table 3 – Post-operative outcomes in patients undergoing implantation of cardiac implantable electrical devices before the COVID-19 and during the peak of the pandemic

Outcomes	Total (N= 557)	Group 1 Before the pandemic (N= 253)	Group 2 Pandemic peak (N= 304)	p
Time interval between hospital admission and surgical procedure (days)	5.4 ± 12.3	7.7 ± 15.3	3.5 ± 8.7	<0.001
Time interval between surgical procedure and hospital discharge (days)	2.9 ± 7.3	3.5 ± 9.1	2.4 ± 5.4	<0.001
Length of hospital stay (days)	8.3± 16.6	11.2 ± 20.7	5.9 ± 11.8	<0.001
In-hospital death, n (%)	11 (2.0)	4 (1.6)	7 (2.3)	0.542
Thirty-day mortality, n (%)	7 (1.3)	2 (0.8)	5 (1.6)	0.367
Thirty-day rehospitalization, n (%)	16 (2.9)	9 (3.6)	7 (2.3)	0.377
Reoperation related to the CIED, n (%)	21 (3.8)	10 (4.0)	11 (3.6)	0.837
Confirmed diagnosis of COVID-19, n (%)	15 (2.7)	2 (0.8)	13 (4.3)	0.011

CIED: cardiac implantable electrical device.

the course of patients known to be at high risk due to cardiovascular diseases and underlying comorbidities.

Author Contributions

Conception and design of the research, Analysis and interpretation of the data, Obtaining financing and Writing of the manuscript: Costa R, Silva KR; Acquisition of data: Saucedo SCM, Silva LA, Crevelari ES, Nascimento WTJ, Silveira TG, Fiorelli A; Critical revision of the manuscript for intellectual content: Costa R, Silva KR, Saucedo SCM, Silva LA, Crevelari ES, Nascimento WTJ, Silveira TG, Fiorelli A, Martinelli Filho M, Jatene FB.

Potential Conflict of Interest

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

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Study Association

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

References

1. Melo CML, Silva GAS, Melo ARS, Freitas AC. COVID-19 pandemic outbreak: the Brazilian reality from the first case to the collapse of health services. *An. Acad. Bras. Ciênc.* 2020;92(4):e20200709. <https://doi.org/10.1590/0001-3765202020200799>.
2. Lv M, Luo X, Estill J, Liu Y, Ren M, Wang J, et al. On Behalf of the COVID-Evidence and Recommendations Working Group. Coronavirus disease (COVID-19): a scoping review. *Euro Surveill.* 2020 Apr;25(15):2000125.
3. Mouawad NJ, Woo K, Malgor RD, Wohlauser MV, Johnson AP, Cuff RF, et al. The impact of the COVID-19 pandemic on vascular surgery practice in the United States. *J Vasc Surg.* 2021 mar;73(3):772-779.e4.
4. COVIDSurg Collaborative. Global guidance for surgical care during the COVID-19 pandemic. *Br J Surg.* 2020 Aug;107(9):1097-103.
5. Lakkireddy DR, Chung MK, Gopinathannair R, Patton KK, Gluckman TJ, Turagam M, et al. Guidance for cardiac electrophysiology during the COVID-19 pandemic from the Heart Rhythm Society COVID-19 Task Force; Electrophysiology Section of the American College of Cardiology; and the Electrocardiography and Arrhythmias Committee of the Council on Clinical Cardiology, American Heart Association. *Heart Rhythm.* 2020;17(9):e233-e241.
6. Saenz LC, Miranda A, Speranza R, Texeira RA, Rojel U, Enriquez A, et al. Recommendations for the organization of electrophysiology and cardiac pacing services during the COVID-19 pandemic: Latin American Heart Rhythm Society (LAHRS) in collaboration with: Colombian College Of Electrophysiology, Argentinian Society of Cardiac Electrophysiology (SADEC), Brazilian Society Of Cardiac Arrhythmias (SOBRAC), Mexican Society Of Cardiac Electrophysiology (SOMECC). *J Interv Card Electrophysiol.* 2020;59(2):307-13.
7. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research Electronic Data Capture (REDCap) - A metadata-driven methodology and workflow process for providing translational research informatics support. *Journal of biomedical informatics.* 2009;42(2):377-81.
8. Silva KR, Albertini CMM, Crevelari ES, Carvalho EJ, Fiorelli AI, Martinelli Filho M, et al. Complications after Surgical Procedure in Patients with Cardiac Implantable Electronic Devices: Results of a Prospective Registry. *Arq Bras Cardiol.* 2016;107(3):245-56.
9. Silva LV, Harb MPAA, Santos AMTB, Teixeira CAM, Gomes VHM, Cardoso EHS, et al. Mortality Underreporting in Brazil: Analysis of Data From Government Internet Portals. *J Med Internet Res.* 2020;22(8):e21413.
10. Lakkireddy DR, Chung MK, Deering TF, Gopinathannair R, Albert CM, Epstein LM, et al. Guidance for Rebooting Electrophysiology Through the COVID-19 Pandemic from the Heart Rhythm Society and the American Heart Association Electrocardiography and Arrhythmias Committee of the Council on Clinical Cardiology. *Heart Rhythm.* 2020;17(9):e242-e254.



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Chagas Cardiomyopathy in the Brazilian Amazon Region: Low Prevalence or Underdiagnosis?

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Introduction

Chagas disease (CD) was discovered in 1909 by the Brazilian physician Carlos Chagas, who described the etiological agent – a flagellated protozoan named *Trypanosoma cruzi* (*T. cruzi*) – its morphological features and transmission and life cycle, as well as clinical manifestations of the disease.¹ Although triatomine insects are the primary transmission vectors of CD, the oral route through contaminated food has been considered the main transmission path in the Brazilian Amazon.

The disease presents two clinical phases: an acute infection, mostly symptomatic with high parasitemia, and a chronic infection divided into asymptomatic indeterminate form or symptomatic (digestive or cardiac) form.²

Chronic Chagas cardiomyopathy (CCM) is characterized by a dilated cardiomyopathy due to the long-term inflammation and is the main cause of death of patients with nonischemic cardiomyopathy in Latin America.^{3,4} The World Health Organization estimates eight million infections worldwide, and about 232 thousand people with CCM in Brazil.² In the Brazilian Amazon region, little has been published about chronic CD and CCM; the first report of chronic cases was made in 1977,⁵ and the first case of CCM reported in 2003.⁶ Xavier et al.⁷ and Ferreira et al.⁸ have also reported new cases of chronic CD and CCM. In ten years, no new report has updated the epidemiological features of CCM in the region.

The diagnosis of chronic CD is made by two different serological tests: enzyme-linked immunosorbent assay (ELISA), indirect immunofluorescence (IIF). Parasitological test, molecular biology test, and western blotting are used as complementary methods. Molecular biology techniques have been widely used to genotype the *T. cruzi* strain circulating in the area.^{2,9}

Keywords

Chagas Disease; Heart Failure; Chagas cardiomyopathy. Chagas Cardiomyopathy.

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Therefore, this study aimed to evaluate the prevalence of CD in patients with dilated cardiomyopathy of unknown etiology in the Brazilian Amazon region to try to answer the questions: is CCM being underdiagnosed? Or rather, is there a low prevalence of this disease in our region?

Methods

Study sites

This was a cross-sectional study conducted at Francisca Mendes University Hospital (Cardiology Unit) and Dr. Heitor Vieira Dourado Tropical Medicine Foundation (Infectious Diseases/Chagas Disease Unit), two specialized tertiary care centers in the state of Amazonas, Brazil.

Study Population

Participants were recruited from July, 2017 to July, 2018 and were eligible for inclusion if: 1) were aged ≥ 18 years, 2) had a cardiac profile of idiopathic dilated cardiomyopathy, and any other cause of cardiomyopathy had been already excluded, 3) had abnormal echocardiogram (reduced left-ventricular ejection fraction [LVEF] and/or segmental alterations), and/or electrocardiogram (bundle branch block, atrial ventricular block, or arrhythmias).

The following epidemiological risk factors were also considered: 1) being from the Brazilian Amazon; 2) coming from rural areas; 3) having the habit of entering the forest; and 4) consuming palm tree fruits and/or meat of wild mammals.

Patients with any evidence of ischemic or congenital cardiomyopathy or valve disease were not eligible for inclusion. Also, participants that reported a previous trip to another Brazilian region or foreign country were excluded from the study.

Data and blood sample collection

All patients who met the inclusion criteria were invited to participate in the study, and those who agreed to participate signed the informed consent form. Participants were first evaluated using a clinical and an epidemiological questionnaire. Then, blood samples were collected, centrifuged, separated, and stored at -20°C .

Serological tests

The diagnosis of CD was performed by ELISA (Chagatest ELISA recombinante v. 4.0, Wiener Laboratorios, Argentina)

and IIF (Imuno-CON Chagas, WAMA Diagnostica, Brazil), following the manufacturers' instructions.

For indeterminate results, the TESA (trypomastigote excreted-secreted antigen)-blot test was performed. The TESA fractions were obtained from the supernatant of MK2 cells infected with *T. cruzi* Y strain, following the protocol as previously described.¹⁰

T. cruzi molecular detection and characterization

DNA extraction was done using peripheral blood and following the protocol of the commercial kit PureLink™ Genomic DNA Mini (Invitrogen, Life Technologies, California, USA). This method was performed as a complementary test for sera with indeterminate serological test results, in order to increase diagnostic accuracy.¹¹

Samples were subjected to mitochondrial DNA typing by analysis of polymorphisms in the cytochrome oxidase subunit II (COII) genes.¹² The amplified PCR products were purified by using the Wizard SV Gel and PCR Clean-up System kit (Promega) and sequencing performed with ABI 3130 DNA sequencer (Applied Biosystems).

We followed the BigDye Terminator v3.1 Cycle Sequencing Kit protocol (Applied Biosystems) and sequences from standard strains: TcI (Silvio X10 cl1), TcII (Esmeraldo cl3), TcIII (M6241 cl6), TcIV (CANIII cl1), TcV (Mn cl2), and TcVI (CL Brener). Evolutionary analysis was conducted in MEGA X.¹³

Ethical Considerations

This study was approved by the Research Ethics Committee of Tropical Medicine Foundation Dr. Heitor Vieira Dourado (Manaus, AM, Brazil) (approval number 69904017.9.0000.0005-2.191.571/28, July 2017), in agreement with the Resolution 466/12 of the Brazilian National Health Council and ethical guidelines of the 1975 Declaration of Helsinki.

Data presentation and analysis

Clinical and epidemiological data were organized using Microsoft Excel 2016 and a descriptive analysis was done using Stata/MP 13.0. Categorical variables were described as frequencies and proportions (%), and continuous variables as means and standard deviations (SD).

Results

Prevalence of Chagas disease

Fifty-three patients were included, and eight of them were excluded: one died before blood collection, two mentioned having lived elsewhere, and five did not show up for blood sample collection. Demographic and clinical characteristics of the 45 patients are described in Table 1.

In 45 suitable samples, two serological tests were performed, ELISA and IIF. One was reactive in the ELISA but not reactive in the IIF, and 13 were reactive in IIF. In these 14 (31%) samples, TESA-blot confirmatory test was performed,

and all came up with negative results. Thus, none of the suspected CCM was confirmed by serological methods.

T. cruzi molecular detection and characterization

The samples that had at least one positive serological reaction were subjected to molecular analysis; two were positive and genotyped as TcIII/IV (Figure 1). Clinical and laboratory data of these two patients are summarized in Table 2.

Discussion

Prevalence of Chagas disease

For a long time, it was believed that CD did not exist in the Brazilian Amazon. However, this has changed over the years as many cases of acute and chronic CD have been reported.

According to the Brazilian Consensus, the diagnosis of CD should be confirmed by the combination of two serological methods. Previous studies in the state of Amazonas¹⁴ have reported a low prevalence and low morbidity of Chagas disease, and discussed the probable low efficacy of commercially available serological tests for the strain circulating, considering that these tests are made with different strains.¹¹

Eight cases of CCM have been reported until now,⁶⁻⁸ and four of these patients (50%) showed apical aneurysms, an expected frequency according to studies with patients from endemic areas.¹⁵ Ferreira et al.⁸ studied patients with left ventricular systolic dysfunction of unknown etiology, and found a prevalence of CCM of 8.1%.

In our study, the two DNA-positive patients had no apical aneurysm and one of these patients had normal ECG findings. A normal ECG is uncommon (5%) according to previous studies on Chagas heart disease, but it is possible even in the presence of a clinical heart disease or echocardiogram dysfunction.^{16,17} It is worth pointing out, however, that the presence of *T. cruzi* DNA may not be sufficient to confirm CCM, and we cannot exclude a possible coincidence in the identification of the parasite genotype in the patient with severe ventricular dysfunction, without apical aneurysm or serological diagnosis, and with a normal ECG. The second patient with positive DNA had right bundle branch block and left anterior fascicular block (typical findings of CCM) on ECG. In this patient the presence of *T. cruzi* DNA and typical ECG changes makes the diagnosis of CCM very possible even without of serological diagnosis.

Even though our study did not identify new cases of CCM, as initially proposed, these results raise some questions: Is chronic Chagas disease, and consequently, CCM still underdiagnosed in the Brazilian Amazon region? Have the serological methods available been losing efficiency in relation to the circulating strains of the parasite in this region?

T. cruzi molecular detection and characterization

Despite the fact that molecular techniques have not been used for diagnosis of CD due to possible false-positive results, the method was included in this study based on previous studies supporting its specificity in chronic infections and its role as a complementary method where inconclusive

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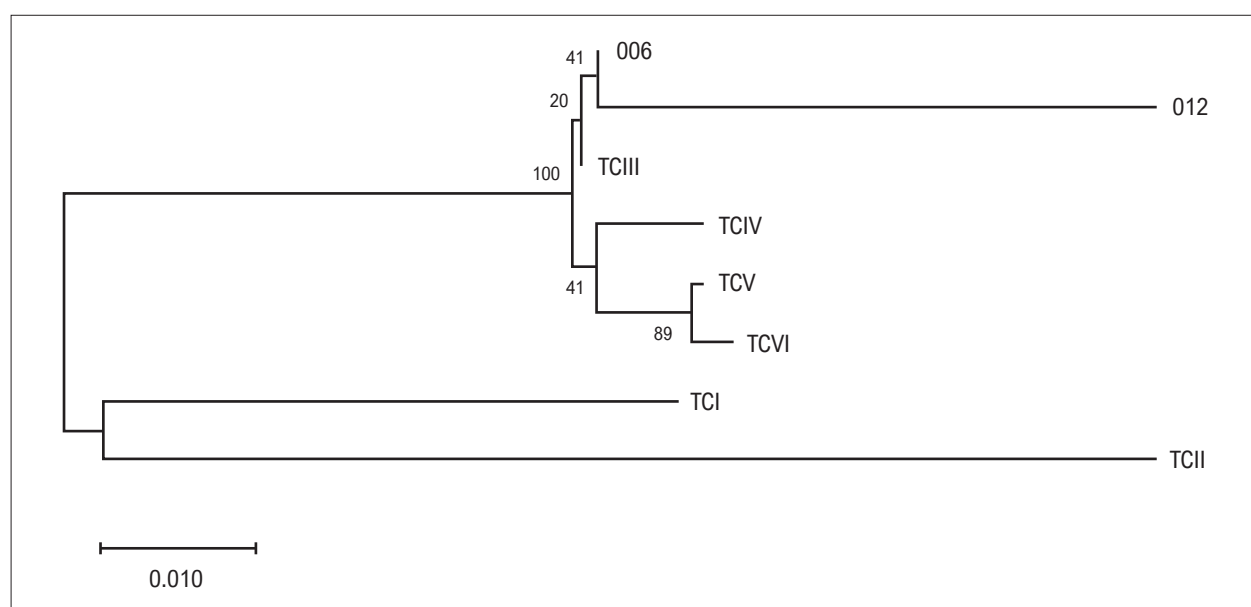


Figure 1 – Phylogenetic position of *Trypanosoma cruzi* in samples 006 and 012 based on the cytochrome oxidase subunit II gene sequences.

serological techniques persist.¹⁸ We identified the parasite's DNA in two samples and genotyped as TcIII/TcIV.

This is the first time that TcIII/TcIV strain of *T. cruzi* is found in a chronic phase of the disease. This fact may be related to the presence of TcIII in the vectors and reservoirs, and TcIV in the acute phase of CD, as previously reported in the region.^{11,19} Other studies have shown a satisfactory reactivity to serological and TESA-blot test in endemic regions in Brazil and Panamá.⁹ Nevertheless, due to the Amazon region still having a particular epidemiology, all available resources were used in this study in order to reach a satisfactory result for the patient, including a qualitative reactive PCR.²⁰

Study limitations

The small sample size in this work limited our ability to demonstrate the real scenario of CMM in our region. Similarly, we have seen a low reactivity of commercially available serological kits and a moderate cross-reactivity with other endemic diseases.

Conclusions

A low prevalence of CCM was observed in this group of study participants. In two of 45 samples (4%) *T. cruzi* DNA fragments were detected following strict protocols. However, it is important to remember that most sera from patients from this location have low serological reactivity and moderate cross-reactivity with other diseases, which makes diagnosis difficult. Therefore, it is very important to continue epidemiological and clinical research to determine the real situation of CCM in the Amazon region.

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Author Contributions

Conception and design of the research: Ortiz JV, Barbosa-Ferreira JMB; Acquisition of data: Ortiz JV, Couceiro KN, Sousa DRT, Barbosa-Ferreira JMB; Analysis and interpretation of the data: Ortiz JV, Couceiro KN, Doria SS, Sousa DRT, Silveira HMC, Kesper Junior K, Barbosa-Ferreira JMB; Obtaining financing: Barbosa-Ferreira JMB; Writing of the manuscript: Ortiz JV, Kesper Junior K; Critical revision of the manuscript for intellectual content: Couceiro KN, Silveira HMC, Guerra MGVB, Guerra JAO, Barbosa-Ferreira JMB.

Potential Conflict of Interest

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Study Association

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Table 1 – Demographic and clinical characteristics of all suspected cases of Chagas cardiomyopathy

Variable	Total (n=45)
Age (y)	59.3 ± 12.3
Gender	
Male	35 (77.8%)
Female	10 (22.2%)
Area	
Rural	34 (75.6%)
Urban	11 (24.4%)
Origin	
Acre	4 (9.0%)
Amazonas	32 (71.1%)
Maranhão	1 (2.2%)
Pará	6 (13.3%)
Roraima	2 (4.4%)
Susceptibility factors	
Agriculture/extractivism/fishing	27 (60.0%)
Game meat consumption	32 (71.1%)
Açaí fruit consumption	30 (66.7%)
Habit to enter the forest	30 (66.7%)
Electrocardiogram	
Right bundle branch block	2 (4.4%)
Left bundle branch block	4 (8.9%)
Left anterior fascicular block	2 (4.4%)
Atrial fibrillation	3 (6.7%)
Ventricular repolarization	21 (46.7%)
Normal	13 (28.9%)
Transthoracic echocardiogram	
LVEF (%)	30.3 ± 10.7
Left ventricular diastolic diameter (mm)	64.6 ± 9.1
Localized akinesia	7 (15.6%)
Anterior septal wall	3 (42.8%)
Inferior lateral wall	2 (28.6%)
Inferior septal wall	1 (14.3%)
Inferior wall	1 (14.3%)
Diffuse hypokinesia	11 (24.4%)
Comorbidities	
Diabetes mellitus	9 (20.0%)
Hypertension	22 (49.0%)

Data expressed as mean ± SD and percentages; LVEF: left ventricular ejection fraction.

References

1. Chagas C. Nova Tripanozomíaze Humana: Estudos sobre a Morfologia e o Ciclo Evolutivo do *Schizotrypanum* *Cruzi* n. gen., n. sp., Agente Etiológico de Nova Entidade Morbida do Homem. *Mem Inst Oswaldo Cruz*. 1909;1(2):159-218. doi: 10.1590/S0074-02761909000200008.
2. World Health Organization. Integrating Neglected Tropical Diseases into Global Health and Development: Fourth WHO Report on Neglected Tropical Diseases. Geneva: World Health Organization; 2017.
3. Vieira JL, Távora FRF, Sobral MGV, Vasconcelos GG, Almeida GPL, Fernandes JR, et al. Chagas Cardiomyopathy in Latin America Review. *Curr Cardiol Rep*. 2019;21(2):8. doi: 10.1007/s11886-019-1095-y.
4. Bestetti RB, Muccillo G. Clinical Course of Chagas' Heart Disease: A Comparison with Dilated Cardiomyopathy. *Int J Cardiol*. 1997;60(2):187-93. doi: 10.1016/S0167-5273(97)00083-1.
5. Ferraroni J, Melo JN, Camargo M. Moléstia de Chagas na Amazônia: Ocorrência de Seis Casos Suspeitos, Autóctones, Sorologicamente Positivos. *Acta Amaz*. 1977;7(3):438-40.
6. Albajar PV, Laredo SV, Terrazas MB, Coura JR. Dilated Cardiomyopathy in Patients With Chronic Chagasic Infection: Report of Two Fatal Autochthonous Cases From Rio Negro, State of Amazonas, Brazil. *Rev Soc Bras Med Trop*. 2003;36(3):401-7.
7. Xavier SS, Sousa AS, Viñas PA, Junqueira AC, Bóia MN, Coura JR. Chronic Chagasic Cardiopathy in the Rio Negro, Amazon State. Report of Three New Autochthonous Cases Confirmed by Serology, Clinical Examination, Chest X-rays, Electro and Echocardiography. *Rev Soc Bras Med Trop*. 2006;39(2):211-6. doi: 10.1590/S0037-86822006000200015.
8. Ferreira JM, Guerra JA, Magalhães BM, Coelho LI, Maciel MG, Barbosa M. Chronic Chagasic Cardiopathy in Amazon Region: An Etiology to Remember. *Arq Bras Cardiol*. 2009;93(6):93-109. doi: 10.1590/S0066-782X2009001200028.
9. Caballero EZ, Correa R, Nascimento MS, Villarreal A, Llanes A, Kesper N Jr. High Sensitivity and Reproducibility of in-house ELISAs Using Different Genotypes of *Trypanosoma* *Cruzi*. *Parasite Immunol*. 2019;41(7):e12627. doi: 10.1111/pim.12627.
10. Umezawa ES, Nascimento MS, Kesper N Jr, Coura JR, Borges-Pereira J, Junqueira AC, et al. Immunoblot Assay Using Excreted-Secreted Antigens of *Trypanosoma* *Cruzi* in Serodiagnosis of Congenital, Acute, and Chronic Chagas' Disease. *J Clin Microbiol*. 1996;34(9):2143-7. doi: 10.1128/jcm.34.9.2143-2147.1996.
11. Barbosa M, Ferreira JM, Arcanjo AR, Santana RA, Magalhães LK, Magalhães LK, 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. doi: 10.1590/0037-8682-0258-2013.
12. Freitas JM, Augusto-Pinto L, Pimenta JR, Bastos-Rodrigues L, Gonçalves VF, Teixeira SM, et al. Ancestral Genomes, Sex, and the Population Structure of *Trypanosoma* *Cruzi*. *PLoS Pathog*. 2006;2(3):24. doi: 10.1371/journal.ppat.0020024.
13. Kumar S, Stecher G, Li M, Knyaz C, Tamura K. MEGA X: Molecular Evolutionary Genetics Analysis Across Computing Platforms. *Mol Biol Evol*. 2018;35(6):1547-9. doi: 10.1093/molbev/msy096.
14. Coura JR, Junqueira AC, Ferreira JMB. Surveillance of Seroepidemiology and Morbidity of Chagas Disease in the Negro River, Brazilian Amazon. *Mem Inst Oswaldo Cruz*. 2018;113(1):17-23. doi: 10.1590/0074-02760170169.
15. Prata A. Clinical and Epidemiological Aspects of Chagas Disease. *Lancet Infect Dis*. 2001;1(2):92-100. doi: 10.1016/S1473-3099(01)00065-2.
16. Rosenbaum MB, Alvarez AJ. The Electrocardiogram in Chronic Chagasic Myocarditis. *Am Heart J*. 1955;50(4):492-527. doi: 10.1016/0002-8703(55)90296-9.
17. Fernandez AB, Nunes MC, Clark EH, Samuels A, Menacho S, Gomez J, et al. Electrocardiographic and Echocardiographic Abnormalities in Chagas Disease: Findings in Residents of Rural Bolivian Communities Hyperendemic for Chagas Disease. *Glob Heart*. 2015;10(3):159-66. doi: 10.1016/j.gheart.2015.07.004.
18. Hernández C, Cucunubá Z, Flórez C, Olivera M, Valencia C, Zambrano P, et al. Molecular Diagnosis of Chagas Disease in Colombia: Parasitic Loads and Discrete Typing Units in Patients from Acute and Chronic Phases. *PLoS Negl Trop Dis*. 2016;10(9):e0004997. doi: 10.1371/journal.pntd.0004997.
19. Santana RA, Magalhães LK, Magalhães LK, 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;7:267. doi: 10.1186/1756-3305-7-267.
20. Schijman AG. Molecular Diagnosis of *Trypanosoma* *Cruzi*. *Acta Trop*. 2018;184:59-66. doi: 10.1016/j.actatropica.2018.02.019.



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Infective Endocarditis in the Elderly: Distinct Characteristics

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Introduction

Infectious endocarditis (IE) is a serious disease with a mean in-hospital mortality of 20%.¹⁻³ It has shown an increasing incidence, and the rise in its prevalence among the elderly population deserves to be highlighted.⁴⁻⁹ In elderly patients with IE, there are differences regarding the clinical presentation, complications, presence of comorbidities, therapeutic approach and mortality.^{4,10-13} IE guidelines do not specifically address the elderly population and it is not clear to what extent they can be appropriately used in these patients.^{2,14,15} The elderly population has clearly benefited from medical progress, with diagnostic-therapeutic techniques that influence the increase in life expectancy and less invasive procedures.¹⁰ One example is the transcatheter aortic valve implantation in the management of aortic valve diseases.¹⁵ However, these procedures, together with the increasing implantation of cardiovascular electronic devices (CED) contribute to infections such as IE. Comorbidities are found in more than half of the elderly, with the consequent need for long-term care from health professionals, which increases the probability of acquiring IE.^{3,16} The diagnosis of IE in the elderly is often delayed or forgotten.³ Manifestations may be nonspecific, attributed to aging and other conditions. Fever may be absent, with the presence of mental confusion only.¹⁷ IE can present with complications similar to those of other conditions, such as heart failure (HF), cerebrovascular accident (CVA) or systemic embolism attributable to atrial fibrillation.^{3,16} In Brazil, despite a growing elderly population, to date there is no published article about IE in this group. The aim of our study was to describe the elderly group in our adult IE cohort and compare them with non-elderly individuals, highlighting the differences between the groups.

Methods

The study site is a tertiary, public, high-complexity cardiology hospital with on-site cardiac surgery. This is a retrospective study of elderly patients, as defined by the Statute

of the Elderly of Brazil,¹⁸ identified in the cohort of adult patients with definitive IE, according to the modified Duke criteria, conducted from January 2006 to December 2019. The study variables were included in the previously described data collection form (case report form).⁴ The statistical analysis was performed using the Jamovi software, version 1.2.2. Data were expressed as frequencies, means $\pm$ standard deviation of the mean, median and interquartile range. For the bivariate analysis, Chi-square and Fisher's exact tests were used. The Shapiro-Wilk test was used to verify the normality of the distribution. The unpaired Student's *t* test and the Mann-Whitney test were used to compare numerical variables between the groups of interest. A value of $p < 0.05$ was considered statistically significant.

Results

Elderly patients accounted for 97 of 370 (26.2%) cases of IE in the period. The mean age was 68.8 ± 6.3 years; the male gender corresponded to 73 cases (75.2%). The presentation was acute, i.e., signs and symptoms were observed in less than one month of evolution, in 60% (57/95) of the cases and subacute in 40% (38/95). The disease was community acquired in 49 (50.5%), nosocomial in 37 (38.1%) and related to non-nosocomial health care in 11 (11.3%). The most prevalent microorganisms were *enterococci* 18 (25.7%). Of the 12 isolated *S. aureus* cases, 10 (83.3%) were MRSA and of these, 6 were hospital and 4 community-acquired cases. Blood cultures were negative in 27.8% (Figure 1). Transesophageal echocardiography was positive in 88/96 (91.6%), and transthoracic echocardiography in 75/96 (78.1%). The most common findings were aortic regurgitation in 37/96 (38.5%) and mitral regurgitation in 43/96 (44.7%); aortic vegetation in 40/96 (41.6%), mitral in 36/96 (37.5%), tricuspid in 9/96 (9.3%), and in CED in 11/96 (11.4%). The most frequent comorbidities were arterial hypertension, heart failure (HF) and coronary artery disease (Figure 2); previous heart surgery (HS) was reported in 50/97 (51.5%). There was predisposition of the native valve in 36/92 (39.1%), prosthetic valve in 45/97 (46.4%) and previous IE in 10/97 (10.7%). The complications were HF due to aortic or mitral regurgitation 57/97 (58.7%), abscess 24/97 (24.7%), prosthetic paravalvular dehiscence 7/45 (15.5%), and valve perforation in 25/97 (25.7%). Splenic embolic phenomena occurred in 28/97 (28.8%) and cerebral in 18/97 (18.5%).

Of the 80 (82.4%) elderly with surgical indication, 59 (73.7%) were submitted to surgery. Hospital mortality was 38 (39.1%); 22/59 (37%) died among those who were submitted to surgery and 16/38 (42%) among those who were not.

A comparative analysis was performed using data from 359 adult patients with IE from January 2006 to September 2019 (Table 1). A total of 266 patients were aged < 60 years, while 93

Keywords

Endocarditis; Aged; Comorbidity; Mortality; Thoracic Surgery.

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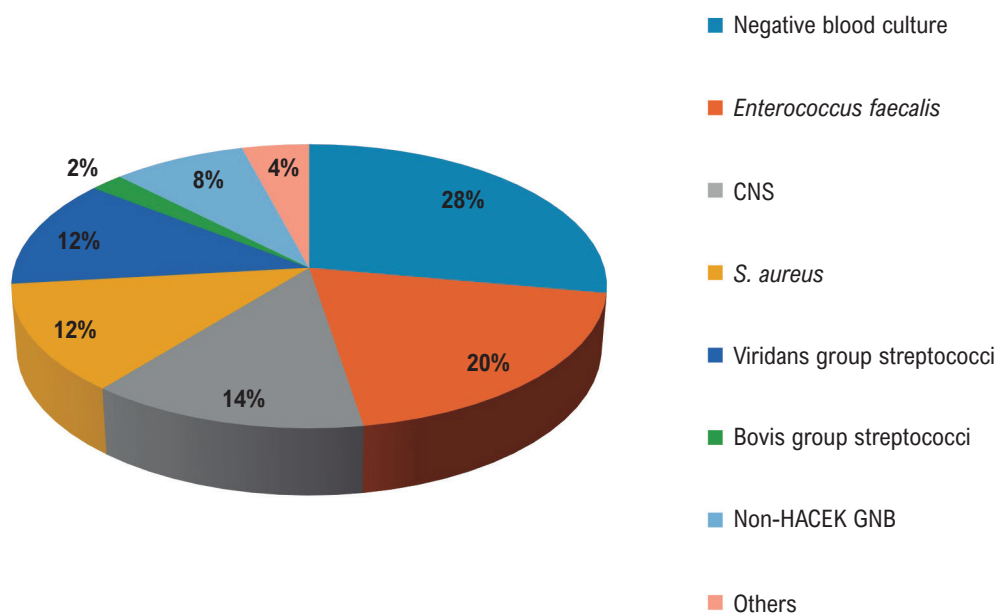


Figure 1 – Agents identified in blood cultures of 97 cases of IE in the elderly, 2006-2019. Others: 1 *Granulicatella*, 1 *Trichosporon beigeli*, 1 *Bartonella henselae*, 1 *Listeria monocytogenes*. CNS: coagulase-negative staphylococci; GNB: Gram negative bacilli; HACEK: *Haemophilus* spp, *Aggregatibacter* spp, *Cardiobacterium hominis*, *Eikenella corrodens*, *Kingella kingae*.

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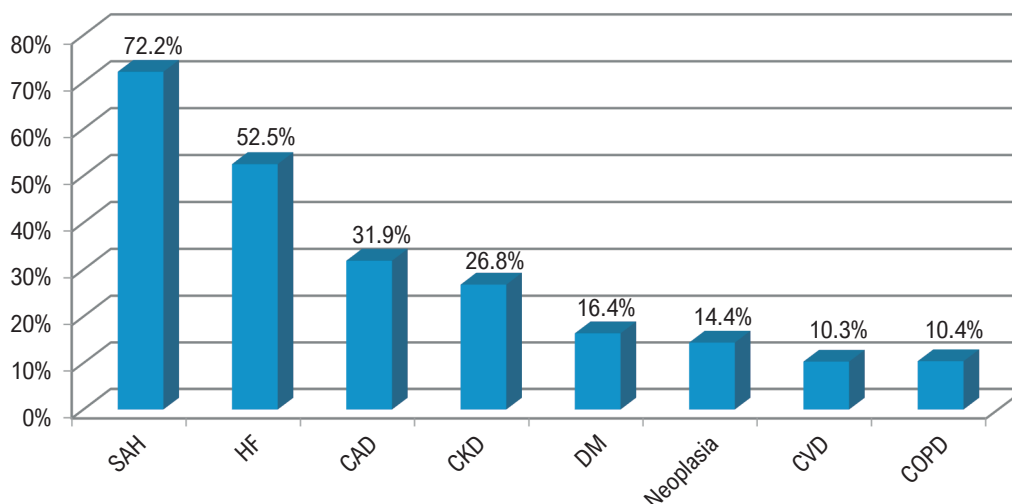


Figure 2 – Most frequent comorbidities in 97 elderly people with IE, 2006-2019. SAH: Systemic Arterial Hypertension; HF: Heart Failure; CAD: Coronary Artery Disease; CKD: Chronic Kidney Disease; DM: Diabetes Mellitus; CVD: Cerebrovascular Disease; COPD: Chronic Obstructive Pulmonary Disease.

(25.9%) patients were aged ≥ 60 years. The proportion of men among the elderly was higher, as well as the acute evolution and in-hospital IE.

Regarding clinical features, elderly patients had less often presented with fever, new regurgitant murmur, embolic events, including central nervous system events, and splenomegaly.

As for the etiology, the elderly had *enterococci* more frequently, *streptococci* from the *Viridans* group less frequently, and similar frequency of *S. aureus*. Elderly individuals had a greater need for mechanical ventilation and inotropic agent use before the surgery. There was no difference regarding acute kidney injury, conduction disorders, recurrent embolization and abscesses. There was no

Table 1 – Comparison of clinical-laboratory characteristics and outcomes between elderly and non-elderly individuals with IE, January 2006 to September 2019

Variable/proportion in percentage (%)	Elderly (n=93)	Non-elderly (n=266)	p-value
Male gender	72	60.2	p=0.04
Acute evolution	63.3	46.8	p=0.019
Hospital-acquired infection	39.8	24.5	p=0.005
Non-hospital healthcare setting acquired infection	10.8	7.2	p=0.285
Fever	88.2	94.7	p=0.034
New regurgitating murmur	48.8	60.4	p=0.064
Embolic events	35.2	56.9	p<0.001
Embolic events for CNS	17.2	29.1	p=0.025
Splenomegaly	10.5	26.5	p=0.002
Enterococci	20.4	7.5	p<0.001
Viridans group streptococci	16	26	p=0.047
Staphylococcus aureus	12.9	10.5	p=0.531
Rheumatic valve disease	20.2	37.7	0.002
Congenital cardiopathy	1.1	18	<0.001
Valve prosthesis*	25.7	11.8	0.006
SAH	72.9	39.2	<0.001
DM	16.1	10.2	0.123
Dyslipidemia	35.0	14.8	<0.001
Atrial fibrillation	26.1	13.2	0.004
Previous HF	53.3	35.7	0.003
COPD	10.9	2.7	0.002
CAD	31.5	6.1	<0.001
CVD	10.8	4.9	0.047
PM	20.4	8.3	0.002
CKD	27.5	17.7	0.044
Hemodialysis	7.5	7.1	0.902
Neoplasia	12.9	3.9	0.002
Previous HS	52.7	32.2	<0.001
PCI	10.9	3.4	0.006
CABG	16.2	2.3	<0.001
ASA use	24.4	5.9	<0.001
Warfarin use	24.4	18.1	0.222
Surgical indication for IE	81.7	88.7	p=0.085
Mechanical ventilation**	30.3	18	p=0.015
Inotropic use**	33.7	21.8	p=0.028
In-hospital death	43.0	18.1	<0.001

CNS: central nervous system; SAH: systemic arterial hypertension; DM: diabetes mellitus; HF: heart failure; COPD: chronic obstructive pulmonary disease; CAD: coronary artery disease; CVD: cerebrovascular disease; PM: pacemaker; CKD: chronic kidney disease; HS: heart surgery; PCI: percutaneous coronary interventions; CABG: coronary artery bypass graft; ASA: acetylsalicylic acid; *valve prosthesis with more than 1 year of insertion; ** in the preoperative period of valve replacement for IE.

difference regarding the proportion of surgical indications between the elderly and non-elderly (NE). Elderly individuals had surgical indication in 81.7% of the cases and 66.3% were submitted to surgery; in comparison, of the 88.7% of NE patients for whom surgery was indicated, 84% were operated. The indication was heart failure failure secondary to acute mitral or aortic regurgitation in 56.5% of the elderly vs. 63.4% of NE (p=0.243). Other surgical indications were myocardial/paravalvular abscess in 21.5% of elderly vs. 20% of NE (p=0.757); prosthesis dehiscence (6.5% vs. 4.3%, respectively, p=0.409) and persistent bacteremia in 9%

vs. 4% of NE (p=0.062). Mortality was more than twice as high in elderly patients (Table 1).

Discussion

Our study is an unprecedented one in Brazil, as it focuses on IE in the elderly. More than a quarter of the patients with IE in our cohort of adults were elderly, and studies from developed countries have shown an increase in the proportion of elderly individuals among IE cases.⁴⁻⁹ A lower frequency of fever, new regurgitant

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murmur and embolic complications was identified among the elderly, which was found in other publications,^{4,12} with the latter being related to the use of antiplatelet and/or anticoagulant agents. This situation may indicate protection against embolization with the use of these drugs, but more scientific evidence is required to prove this hypothesis. In our study, elderly individuals used significantly more aspirin, but not warfarin, when compared to NE.

Comorbidities were more prevalent among the elderly, as expected; this is similar to a multicenter study with a large number of patients, with the frequencies in the elderly and non-elderly, of DM being 22.9% vs. 11.9% ($p < 0.001$); of genitourinary cancer, being 4.7%, respectively, vs. 0.6% ($p < 0.001$) and 3.2% vs. 0.8% of gastrointestinal tract cancer ($p < 0.001$).⁴ Previous invasive procedures were also more frequent among the elderly in our study, as it was in this same publication (56.2% vs. 38.5%, $p < 0.001$).⁴ It has been confirmed that the elderly population continues to be more exposed to diagnostic/therapeutic procedures, with a greater predisposition to IE due to bacteremic events that occurred in these scenarios and the presence of synthetic material/devices.

A higher frequency of in-hospital IE was observed, which represented 39.8% among our elderly patients; a similar proportion has been observed in the literature, in which hospital-acquired disease represents 10.2 to 37% of IE cases in the elderly.^{6,11,12,19} Table 2 lists the IE studies carried out in the elderly that are considered to be the most relevant ones.

The most prevalent microorganisms observed in our series were *enterococci* (25.7%), *streptococci* from the *Viridans* group (17.1%) and *S. aureus* (17.1%). Although oral *streptococci* have been previously responsible for most cases of IE in the elderly, *staphylococci* have predominated in recent decades, especially *S. aureus*.^{8,9} *Enterococci* are also related to bacteremia caused by vascular access. This epidemiological trend is linked to the increased incidence of IE associated with healthcare.^{5,6,12} The frequency of IE caused by *streptococci* that colonize the digestive tract, such as *Streptococcus gallolyticus* and *enterococci*, is also higher due to the higher incidence of colon lesions in elderly patients;^{4,8,19} all 7 patients with IE caused by the *bovis* group had their GIT investigated, but not those with IE caused by *enterococci*.

In our referral center for heart surgery, valve replacement was indicated in more than 4/5 of the elderly, but more than 1/4 of them were not submitted to surgery. This fact has a multifactorial aspect, including older age, multiple comorbidities, frailty, high surgical risk, non-acceptance of surgery by the patient or their family, among others, as observed in a study on IE in octogenarians.⁶ In our study, the reasons why elderly individuals who had surgical indication were not submitted to the surgical procedure are mainly related to their critical preoperative status, as noted by the high frequency of mechanical ventilation and the use of inotropic agents in the preoperative period. It is noteworthy that events such as mycotic aneurysms and acute kidney injury were not more frequent among the elderly compared to the NE, and that CNS events were less frequent in the elderly. In some studies, older age is an independent predictor of in-hospital mortality,^{4,12} which negatively influences the decision to perform the procedure. However, in a study carried out recently in China, it was observed that the one-year survival among the elderly submitted to surgical procedures was greater than that of those who underwent drug therapy alone (95.8% vs. 68.6%, $p = 0.007$).¹¹ Moreover, even among octogenarians,⁶

those submitted to the surgical procedure showed better one-year (93.6%) and three-year (75.0%) survival, respectively. Mortality among the elderly in our study was 39.1%; in the literature, the mortality varies from 16% to 43.2%.^{4-6,11,12,17,19,20}

As conclusions, we observed that i) a significant proportion (one quarter) of IE occurred in the elderly, even in the public health system in Brazil ii) *enterococci* were the most frequent pathogens, and there was a high proportion of MRSA in the *staphylococcal* etiology, suggesting nosocomial acquisition or gastrointestinal/genitourinary focus, iii) the clinical picture is less exuberant in the elderly, with less fever, new murmur and embolic events and iii) mortality in the elderly was high, suggesting the contribution of age and comorbidities, and possibly a late diagnosis and not undergoing cardiac surgery.

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Author Contributions

Conception and design of the research and Writing of the manuscript: Lemos LHB, Lamas CC; Acquisition of data: Lemos LHB, Silva LR, Golebiovski W, Garrido RQ, Barbosa GF, Lamas CC; Analysis and interpretation of the data: Lemos LHB, Correa MG, Lamas CC; Statistical analysis: Correa MG; Obtaining financing: Lamas CC; Critical revision of the manuscript for intellectual content: Weksler C, Garrido RQ, Barbosa GF, Lamas CC.

Potential Conflict of Interest

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

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Study Association

This article is part of the graduation work by de Luiz Henrique Braga Lemos, from Unigranrio.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Instituto Nacional de Cardiologia under the protocol number 080/12.09.2005 and 171/2006. 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.

Table 2 – Aspects of endocarditis in the elderly in a literature review, 2000-2020

Author	Country	N of study	Period	Age/ Sex	Affected valves	More frequent microorganisms	Underlying conditions	Complications	% of Surgeries	Mortality
Durante-Mangoni, 2008 ⁴	Several	2,759	2000-2005.	1056 elderly (65 years and over) females: (35.8%)	MI (50%) Ao (41%) Tri (7%) Intracardiac devices (10%); prostheses (26%)	<i>S. aureus</i> (28.3%) (MRSA 35.8%), <i>bovis</i> group (8.3%), <i>Enterococci</i> (16.5%) CoNS (14%); <i>Viridans</i> group <i>streptococci</i> (14.2%)	CABG (63%) AS (28%) invasive procedure (56.2%) DM (22.9%) and GUT (4.7%) and GIT CA (3.2%)	CHF (33.1%); CVA (146%); systemic embolism (15.3%); Abscess (14%); persistent Bacteremia (9.2%)	38.9%	24.9%
Remadi, 2009 ¹⁷	France	348	1991 – 2006	75 elderly (75 years or older) M:47; F:28	Mi: 45.3%; Ao: 54.7%; MI-Ao: 16%; right-side IE: 16% valvar prosthesis (28%); Pacemaker (26.7%)	<i>Streptococci</i> (37.4%), <i>staphylococci</i> (36%), CoNS (27.8%) in patients submitted to surgery.	DM 2 (25.3%); CKD (17.3%); Neoplasia (26.7%);	CHF (28%); embolism 18.7%; CNS major event 9.3%; Intracerebral Hemorrhage 1.3% Abscesses 18.7%	29.3%	Overall: 16% Surgical: 9%;
Lopez, 2010 ¹⁸	Spain	600 Left-side IE cases	1996-2008	Q3 (64-72 years): 152 and Q4 (>72 years): 148.	Nosocomial: 33%-37%; Prosthesis: 47%-42%; Early prosthesis: 36%-39%; Mi (nat): 51%-61% Mi (mech): 54%-35% Ao (nat): 49%-39% Ao (mech): 35%-21% Ao (bio): 12%-33%	CoNS: 22%-18%. <i>S. aureus</i> : 14%-14% MRSA: 18%-33% <i>Enterococci</i> : 12%-13%; <i>Viridans</i> group: 12%-12% <i>bovis</i> group: 5%-7%.	Rheumatics: 11%-8% Prostheses 45- 48%; Degeneration 12%-21%; DM: 28%- 29% CA: 11%-13% IV Catheter: 6%-12% Previous H. surgery: 14%- 12%.	CHF : 59-64% ; CVA: 18- 23% ; AKI: 40- 46%; Persistent Bacteremia: 32- 37%; Embolism: 24- 28%; Sepsis: 14%- 16%; Perivalvar abscess: 25- 26%.	54%-40%	Overall: 37%-36%; Urg. S: 44%-39%; Elec S.: 28%-34%. D. Treatment: 40%-36%
Ramirez-Duque 2011 ¹²	Spain	961 Left IE cases	1984 –2008	65 years or older: 356 M: 63.3%	Nosocomial: 21.1%; native valve: 74.5%; Late prosthesis: 13.2%; Early prosthesis: 12.4% Ao: 50%; Mi: 37%; Mi-Ao: 11.4%;	<i>Viridans</i> group: 16.9%; <i>S. aureus</i> : 17.4%; MRSA 12.9%; CoNS: 17.1%; <i>Enterococci</i> : 16.3%; <i>bovis</i> group: 5.3%; GNB: 4.2%.	80%.	CVA: 26.6%; Embolism: 29.2%; AKI: 39.6%; sepsis 16.5%; Intracardiac Complications: 27.8%; CHF: 28.9%	36%	Overall: 43.2%
Bassetti, 2014 ⁶	Italy	436	2004 –2011	Group B: 65-74 years: 145 F: 30% Group C: 75 years or older: 137 F: 38.6%	Vegetation: 77.2%-78.1%	<i>Enterococci</i> : 11.7%-27%; <i>Streptococci</i> spp.: 33.1%-22.6%; <i>Viridans</i> group: 15.2%-7.3%; <i>bovis</i> group: 12.4%-11.2%; <i>S. aureus</i> : 14.5%-19.7%; CoNS: 11%-13.1%.	Valve disease: 47.6%-40.2%; Prosthesis: 40%-40.2% CHF: 30.3%-47.7%; CKD: 22.1%-29.2% DM2: 30.3%-23.4% CA: 23.5%-25.6% rheumatic carditis: 7.6%-2.9%	Embolism: 22.1%-13.9% Focal neurological sign: 11%-9.5%; Abscess: 15.9%-14.6%	37.9%-22.6%	Overall: 19.3%-22.6%.

Research Letter

continuation

Oliver, 2017 ⁶	France	454	2008–2013	G2: 65–80 years: 173 M: 71.7% G3: age > 80 years: 51 M: 64.7% Hosp.: 19.9%–23.5%; Post-op.: 11%–11.8%; Native valve: 57.8%–58.8%; Ao: G2: 42% Mi: G3: 43.1%; Prosthetic valve: 42.2%–41.2%; Acute IE: 57.1%–68.8%; IE > 3 months: 14.3%–6.3%; Most common sites of entry (G3): GIT: 33.3%, GUT: 7.8%, skin (23.6%); Enterococci: 15.6%–21.6%; <i>bovis</i> group: 16.2%–17.7%; <i>viridans</i> group: 17.9%–15.7%; CoNS: 9.3%–5.9%; MSSA: 12.7%–11.8%; MRSA: 2.9%–2% Previous IE: 11%–11.8%; DM2: 19.1%–25.5%; SAH: 49.1%–58.8%; CAD: 17.8%–17%; CVA: 9.3%–7.8%; CKD: 14.5%–27.5%; CA: 24.3%–29.4% Embolism in ATB: G3: 21.6%; AKI: G3: 51%; Spondylitis: 12.6%–23.5%; Abscess: 26.5%–29.4% In-hospital: 13.3%–15.7%; One-year: 19.7%–37.3%; Surgical: G3: 6.3%
Wu, 2019 ¹¹	China	405	2007–2016	Native: 83.1%; Mitral: 25.4%; Ao: 30.5%; Valves to the right: 6.8%; Prostheses: 13.6%; Pacemaker: 3.4%; Community: 79.7%; Nosocomial: 10.2% Streptococci: 22%; Viridans group: 5.1%; Staphylococci: 18.5%; S. aureus: 3.4%; CoNS: 15.3%; Enterococci: 1.7% Rheumatics: 18.6%; Previous Heart Surgery: 23.7%; Degenerative: 10.2%; COPD: 3.4%; CA: 3.4%; HD: 6.8%; SAH: 42.4%; DM: 16.9%; Bad oral hygiene: 49.2% CHF: 62.7%; Embolism: 39%; AKI: 30.5%; CVA: 23.7%; Arrhythmia: 39%; AF: 33.9%; Abscess: 13.6%; Indication: 96.6%; Surgery: 40.7%; In-hospital: 20.3%
Chun-Yu Lin, 2020 ²⁰	Taiwan	179 left IE cases	2005–2015	Ao: 50% Exchange for: bio Ao: 100%; mech Ao: 0% Mi: 36.8 Streptococci: 28.9%; Viridans group: 13.2%; Enterococci: 10.5%; S. aureus: 7.9% Exchange for: bio Mi: 100%; mech Mi: 0% MV: 23.7%; Inotropic drugs: 10.5%; Embolism: 23.7%; AKI: 5.3%; AF: 13.2%; CHF: 18.4%; Abscess: 2.6% All patients underwent surgery, as the study evaluates patients undergoing it In-hospital: 26.3%

F: female; M: male; Mi: mitral; Ao: aortic; Tri: tricuspid; MRSA: methicillin-resistant Staphylococcus aureus; CoNS: Coagulase Negative Staphylococci; CABG: coronary artery bypass graft; AS: aortic stenosis; DM: diabetes mellitus; CA: cancer; GIT: gastrointestinal tract; CHF: congestive heart failure; CVA: cerebrovascular accident; IE: infective endocarditis; CKD: chronic kidney disease; CNS: central nervous system; (mech): mechanical; (nat): native; (bio): biological; AKI: acute kidney injury; Urg. S: urgent surgery; Elec. S: elective surgery; D. Treatment: Drug Treatment; GNB: Gram-Negative Bacilli; Valv. P: Valve procedure; Hosp.: Hospital; Post-op.: Post-operative; GUT: genitourinary tract; SAH: systemic arterial hypertension; CAD: coronary artery disease; COPD: chronic obstructive pulmonary disease; MV: mechanical ventilation; AF: atrial fibrillation.

References

1. Instituto Brasileiro de Geografia e Estatísticas. Estatísticas Sociais. Projeção da população 2018: número de habitantes do país deve parar de crescer em 2047 [Internet]. Rio de Janeiro: Agência de Notícias IBGE; c2021 [cited 2021 Aug 31]. Available from: <https://agenciadenoticias.ibge.gov.br/agencia-sala-de-imprensa/2013-agencia-de-noticias/releases/21837-projecao-da-populacao-2018-numero-de-habitantes-do-pais-deve-parar-de-crescer-em-2047>.
2. Baddour LM, Wilson WR, Bayer AS, Fowler VG Jr, Tleyjeh IM, Rybak MJ, et al. Infective Endocarditis in Adults: Diagnosis, Antimicrobial Therapy, and Management of Complications: A Scientific Statement for Healthcare Professionals from the American Heart Association. *Circulation*. 2015;132(15):1435-86. doi: 10.1161/CIR.0000000000000296.
3. Ursi MP, Durante-Mangoni E, Rajani R, Hancock J, Chambers JB, Prendergast B. Infective Endocarditis in the Elderly: Diagnostic and Treatment Options. *Drugs Aging*. 2019;36(2):115-24. doi: 10.1007/s40266-018-0614-7.
4. Durante-Mangoni E, Bradley S, Selton-Suty C, Tripodi MF, Basic B, Bouza E, et al. Current Features of Infective Endocarditis in Elderly Patients: Results of the International Collaboration on Endocarditis Prospective Cohort Study. *Arch Intern Med*. 2008;168(19):2095-103. doi: 10.1001/archinte.168.19.2095.
5. Bassetti M, Venturini S, Crapis M, Ansal di F, Orsi A, Della Mattia A, et al. Infective Endocarditis in Elderly: An Italian Prospective Multi-Center Observational Study. *Int J Cardiol*. 2014;177(2):636-8. doi: 10.1016/j.ijcard.2014.09.184.
6. Oliver L, Lavoute C, Giorgi R, Salaun E, Hubert S, Casalta JP, et al. Infective Endocarditis in Octogenarians. *Heart*. 2017;103(20):1602-9. doi: 10.1136/heartjnl-2016-310853.
7. Dhawan VK. Infective Endocarditis in Elderly Patients. *Clin Infect Dis*. 2002;34(6):806-12. doi: 10.1086/339045.
8. Selton-Suty C, Célard M, Le Moing V, Doco-Lecompte T, Chirouze C, lung B, et al. Preeminence of *Staphylococcus Aureus* in Infective Endocarditis: A 1-year Population-Based Survey. *Clin Infect Dis*. 2012;54(9):1230-9. doi: 10.1093/cid/cis199.
9. Slipczuk L, Codolosa JN, Davila CD, Romero-Corral A, Yun J, Pressman GS, et al. Infective Endocarditis Epidemiology Over Five Decades: A Systematic Review. *PLoS One*. 2013;8(12):e82665. doi: 10.1371/journal.pone.0082665.
10. Faulkner CM, Cox HL, Williamson JC. Unique Aspects of Antimicrobial Use in Older Adults. *Clin Infect Dis*. 2005;40(7):997-1004. doi: 10.1086/428125.
11. Wu Z, Chen Y, Xiao T, Niu T, Shi Q, Xiao Y. The Clinical Features and Prognosis of Infective Endocarditis in the Elderly from 2007 to 2016 in a Tertiary Hospital in China. *BMC Infect Dis*. 2019;19(1):937. doi: 10.1186/s12879-019-4546-6.
12. Ramírez-Duque N, García-Cabrera E, Ivanova-Georgieva R, Nouredine M, Lomas JM, Hidalgo-Tenorio C, et al. Surgical Treatment for Infective Endocarditis in Elderly Patients. *J Infect*. 2011;63(2):131-8. doi: 10.1016/j.jinf.2011.05.021.
13. Baddour LM, Epstein AE, Erickson CC, Knight BP, Levison ME, Lockhart PB, et al. Update on Cardiovascular Implantable Electronic Device Infections and their Management: A Scientific Statement from the American Heart Association. *Circulation*. 2010;121(3):458-77. doi: 10.1161/CIRCULATIONAHA.109.192665.
14. Gould FK, Denning DW, Elliott TS, Fowleraker J, Perry JD, Prendergast BD, et al. Guidelines for the Diagnosis and Antibiotic Treatment of Endocarditis in Adults: A Report of the Working Party of the British Society for Antimicrobial Chemotherapy. *J Antimicrob Chemother*. 2012;67(2):269-89. doi: 10.1093/jac/dkr450.
15. Habib G, Lancellotti P, Antunes MJ, Bongiorni MG, Casalta JP, Del Zotti F, et al. 2015 ESC Guidelines for the Management of Infective Endocarditis: The Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). *Eur Heart J*. 2015;36(44):3075-128. doi: 10.1093/eurheartj/ehv319.
16. Forestier E, Fraisse T, Roubaud-Baudron C, Selton-Suty C, Pagani L. Managing Infective Endocarditis in the Elderly: New Issues for an Old Disease. *Clin Interv Aging*. 2016;11:1199-206. doi: 10.2147/CIA.S101902.
17. Remadi JP, Nadji G, Goissen T, Zomvuama NA, Sorel C, Tribouilloy C. Infective Endocarditis in Elderly Patients: Clinical Characteristics and Outcome. *Eur J Cardiothorac Surg*. 2009;35(1):123-9. doi: 10.1016/j.ejcts.2008.08.033.
18. Brasil. Secretaria Especial dos Direitos Humanos. Estatuto do Idoso: Lei Federal nº 10.741. Brasília, DF (Oct 1 2003).
19. López J, Revilla A, Vilacosta I, Sevilla T, Villacorta E, Sarriá C, et al. Age-Dependent Profile of Left-Sided Infective Endocarditis: A 3-Center Experience. *Circulation*. 2010;121(7):892-7. doi: 10.1161/CIRCULATIONAHA.109.877365.
20. Lin CY, Lu CH, Lee HA, See LC, Wu MY, Han Y, et al. Elderly Versus Non-Elderly Patients Undergoing Surgery for Left-Sided Native Valve Infective Endocarditis: A 10-year Institutional Experience. *Sci Rep*. 2020;10(1):2690. doi: 10.1038/s41598-020-59657-1.



Update of the Brazilian Guideline for Familial Hypercholesterolemia – 2021

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Note: These updates are for information purposes and should not replace the clinical judgment of a physician, who must ultimately determine the appropriate treatment for each patient.

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Update of the Brazilian Guideline for Familial Hypercholesterolemia – 2021

The report below lists declarations of interest as reported to the SBC by the experts during the period of the development of these statement, 2020/2021.

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Update

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Definition of Grades of Recommendation and Levels of Evidence

Classes (grades) of recommendation:

Class I – Conditions for which there is conclusive evidence or, if not, a consensus that the procedure is safe and useful/effective.

Class II – Conditions for which there is conflicting evidence and/or divergence of opinions on the safety and usefulness/efficacy of the procedure.

Class IIA – Evidence or opinion in favor of the procedure. The majority agrees.

Class IIB – Safety and usefulness/efficacy are less well established, and there is no predominance of opinions in favor of the procedure.

Class III – Conditions for which there is evidence and/or a consensus that the procedure is not useful/effective, and in some cases may be harmful.

Levels of evidence:

Level A – Data obtained from several large randomized studies showing concurring results and/or a robust meta-analysis of randomized controlled trials.

Level B – Data obtained from a less robust meta-analysis, a single randomized study, or from nonrandomized (observational) studies.

Level C – Data obtained from consensual expert opinions.

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Introduction

Familial hypercholesterolemia (FH) is a common genetic cause of premature coronary artery disease (CAD), especially myocardial infarction, related to lifetime exposure to high concentrations of low-density lipoprotein cholesterol (LDL-C). It is a severe form of genetic dyslipidemia in which approximately 85% of men and 50% of women may experience a coronary event before 65 years of age if not properly treated.

FH is considered a public health problem because of the high prevalence (approximately 1:200-300 in the general population) and the association with early CAD. Reduced life expectancy was also observed in several families. In addition, nearly 200,000 people die each year worldwide from early heart attacks due to the disease, which could be prevented with appropriate treatments. If not treated, men and women with heterozygous FH will develop CAD before the ages of 55 and 60 years, respectively. Homozygotes, in turn, commonly develop CAD very early in life and, if not treated, may die before the age of 20. However, once the diagnosis is made and the treatment is initiated, the natural history of atherosclerotic disease can be changed.

A key step is early diagnosis, which allows early initiation of lipid-lowering medication and may change the natural history of the disease. Diagnosis should be supported by guidelines and algorithms. Identifying more severe cases and promoting integrated care are strategies to minimize the impact of FH on cardiovascular disease (CVD) outcomes. Diagnostic approaches, nutritional measures, and potent drugs, such as high-intensity statins, combined medications, and new lipid-lowering agents, can modify the natural history of the disease in patients.

Another important aspect is the recognition that FH is an autosomal codominant genetic condition, and thus cascade screening of patients' family members is imperative. This is

a cost-effective measure that allows early detection and the initiation of therapies aimed at delaying or preventing the onset of atherosclerotic disease. Special attention is given to children and adolescents, pregnant women, and patients with severe FH in different sections of this guideline.

The Department of Atherosclerosis of the Brazilian Society of Cardiology and Brazil's leading experts met with the purpose of gathering the best available data and presenting them clearly and objectively to improve clinical practice in Brazil. This guideline can now be used to prevent and treat premature cardiovascular atherosclerotic disease, thus reassuring the families affected by this condition.

Yours sincerely,

Prof. Maria Cristina de Oliveira Izar, MD, PhD

1. Natural History of Familial Hypercholesterolemia

1.1. Definition

FH is a genetic disease with an autosomal codominant mode of inheritance that affects lipoprotein metabolism. It is characterized by highly elevated levels of LDL-C and specific clinical signs, such as tendon xanthomata, corneal arcus, and atherosclerotic cardiovascular disease (ASCVD) before the age of 45 years.^{1,2}

The disease was first described by the pathologist Francis Harbitz in the mid-18th century, when he reported cases of sudden death in patients with xanthomas. In 1938, Müller³ described FH as a clinical entity. He identified that the combination of hypercholesterolemia, xanthomas, and CAD manifestations was a common finding in some families, inherited as a dominant trait. Approximately 50 years later, Brown and Goldstein⁴⁻⁶ elucidated the complex pathway of endogenous cholesterol synthesis and identified a defect in the internalization of receptor-bound low-density lipoprotein (LDL) by studying patients and cell cultures. In 1983, the LDL receptor gene was cloned and mapped on the short arm of chromosome 19⁷, being named the LDL receptor (*LDLR*) gene in 1989.⁸

The estimated historical prevalence of FH was 1:500 people with the heterozygous form and 1:1,000,000 people with the homozygous form.^{9,10} Khachadurian¹⁰ was the first to discriminate one presentation from the other. However, recent studies based on clinical and molecular criteria suggest that the prevalence of FH is actually higher: 1:200-300 in those with heterozygous FH (HeFH) and 1:160,000-300,000 in those with homozygous FH (HoFH).^{11,12}

LDL-C plasma concentrations are, in general, 2 to 3 times higher in people with HeFH than in those without the disease, and those with HeFH are more likely to develop premature ASCVD in the second or third decades of life. People with HoFH, in turn, have LDL-C concentrations approximately 6 to 8 times higher and develop ASCVD very early in life, often dying by the age of 20 years if the disease is not treated.^{9,13}

The clinical phenotype of FH is usually caused by defects in the *LDLR* gene, which encodes the LDLR,^{5,10} with more than

2,251 mutations described to date.¹⁴ Point mutations, or single base-pair substitutions (single nucleotide polymorphism, SNP), account for over 84% of mutations, and major rearrangements occur in 16% of all mutations described in the *LDLR* gene.

The clinical phenotype of FH may also be secondary to defects in the apolipoprotein-B (*APOB*) gene, which encodes apolipoprotein B-100 (Apo B-100)¹⁵ – when defective, it has lower affinity for the LDLR. It may also occur in case of accelerated LDLR catabolism due to gain-of-function mutations in the proprotein convertase subtilisin/kexin type 9 (*PCSK9*) gene, which encodes NARC-1,¹⁶ a protein involved in LDLR catabolism.

In most cases, FH is caused by mutations in genes encoding proteins involved in LDLR uptake and catabolism. The *LDLR*, *APOB*, and *PCSK9* genes are linked to the development of FH, causing defective homeostasis of LDL particles and, consequently, elevated plasma concentrations of LDL-C. Thus, patients with a molecular diagnosis of FH frequently have pathogenic variants in the *LDLR* gene,¹⁷ while mutations in the *APOB* and *PCSK9* genes account for a lower proportion of cases of FH in its autosomal codominant form.¹⁸ Autosomal recessive FH (ARH), conversely, is rare and occurs when pathogenic mutations are inherited in both copies of the low-density lipoprotein adaptor protein 1 (*LDLRAP1*) gene, which encodes the LDLR adaptor protein.¹⁹ However, FH may also be caused by pathogenic mutations in unidentified genes or in several genes, known as polygenic FH.²⁰

The clinical phenotype is remarkably similar among the most common forms of FH; however, *APOB* gene defects are more common among some European populations (1:300-700 in Central Europe), while *PCSK9* gene mutations do not have an established frequency (generally ~1%). FH has high penetrance and,²⁰⁻²² therefore, most carriers of FH-causing mutations have the clinical phenotype. Because of its autosomal codominant mode of inheritance, half of the first-degree relatives of a person with FH will carry the genetic defect and show high LDL-C levels at birth and over the lifespan. Men and women are equally affected.^{9,22}

In heterozygotes, only half of the LDLRs are functional, while in homozygotes, due to a defect in the *LDLR*, both receptors have loss of function or null function.²³ Genetic diagnosis is important because patients are often unaware of clinical/laboratory criteria, which makes diagnostic confirmation more difficult.

According to a recent statement,²³ FH comprises multiple clinical phenotypes because of different underlying molecular etiologies and additional genetic factors. LDL-C levels, number of mutations, and additional protective or pathogenic factors determine the risk of CAD; therefore, people at risk due to family history and those with the FH phenotype should be genotyped. The test results indicate three categories of individuals:

1. Genotype-positive, phenotype-negative
2. Genotype-positive, phenotype-positive
3. Genotype-negative, phenotype-positive

In some cases, alternative molecular etiologies should be explored,²³ such as mutations in the *APOE* gene or in the *LIPA*

gene, which encodes lysosomal acid lipase, as well as the polygenic form. Carriers of pathogenic mutations are at higher risk of CAD in any LDL-C level when compared to noncarriers. Those with causative mutations and LDL-C levels > 190 mg/dL have a 3-fold higher risk of CAD compared with noncarriers with the same LDL-C levels. This is probably due to lifetime exposure to very high levels of LDL-C.²⁴

FH is considered a public health problem because of the high prevalence of early coronary heart disease and reduced life expectancy observed in several families. If the disease is not properly treated, approximately 85% of men and 50% of women may experience a coronary event before the age of 65 years. Studies have shown that approximately 200,000 people die each year worldwide from early heart attacks due to FH, which could be prevented with appropriate treatments.²⁰

1.2. Epidemiology of Atherosclerotic Cardiovascular Disease

ASCVD and its complications are a serious public health problem in Brazil and worldwide. According to data from the Information Technology Department of the Brazilian Unified Health System (DATASUS), CVDs are the leading cause of death in the country, accounting for approximately 27.65% of all deaths.²⁵ Regarding the specific mortality rate for circulatory system diseases, ischemic heart diseases account for 32% of deaths.²⁵ According to Ribeiro et al.,²⁶ the Brazilian public health system funded 940,323 hospitalizations for CVD in 2012. From 2008 to 2012, the rates of hospitalization for congestive heart failure and hypertension decreased, whereas the rates of hospitalization for angioplasty and acute myocardial infarction (AMI) increased.²⁶

Ischemic heart diseases and stroke are, respectively, the first and second leading causes of death worldwide, accounting for more than 15.2 million deaths. These conditions have remained the global leading causes of death for the past 15 years.²⁷ A study conducted in the United States (US) from 1989 to 1998 found that 51% of women and 41% of men with sudden cardiac death died out of hospital. Acute coronary syndrome (ACS) accounted for 27% of these deaths.²⁸

Most deaths from AMI occur in the first hours of manifestations. Forty to 65% of cases occur in the first hour, while approximately 80% occur in the first 24 hours.²⁹ Among survivors, 19% on average progress to heart failure, which is a major cause of hospitalization and morbidity.^{30,31}

Although known cardiovascular risk factors are responsible for most cases of ASCVD and its complications,³²⁻³⁶ some clinical conditions increase the risk of ASCVD and accelerate its onset, such as FH.³⁷⁻⁴⁰

1.3. Epidemiological Aspects of Familial Hypercholesterolemia Worldwide and In Brazil

The estimated historical prevalence of FH in the general population is 1:500.²² However, according to the Copenhagen General Population Study, the estimated current prevalence of FH is 1:223 by clinical criteria³⁷ and 1:217 by genetic testing.³⁸ A Danish government report concluded that, with a prevalence of 1:200-250, only 11 to 13% of HeFH carriers would be identified (failure to diagnose is particularly significant in children).

The estimated prevalence of HoFH was 1:1,000,000. However, current data suggest that HoFH affects 1:300,000 people, although the number can be higher (1:160,000) when there is a founder effect. This means that HoFH may be more prevalent in some populations, such as South Africans (1:100,000), Lebanese (1:170,000), French Canadians (1:270,000), and Finns, because of consanguineous marriage.^{13,14}

Therefore, according to the Danish study, an HeFH prevalence of 1:220 translates into an allele frequency of 1:440, with an assumed HoFH frequency of 1:193,600. Based on these estimates, the predicted number of cases of HoFH in Denmark is approximately 28. However, the fact is that very few cases are diagnosed^{38,39} and, in most countries, the condition remains underdiagnosed (less than 1% in Brazil).¹⁴ The estimated number of people with FH worldwide is over 34,000,000.^{9,14} However, less than 10% are diagnosed, and less than 25% receive lipid-lowering medication.³⁸ If the same prevalence is assumed in Brazil, approximately 1,033 cases of HoFH are estimated in the country.

There are no objective data on the prevalence of FH in Brazil. Based on clinical and laboratory data and family history of the adult population of participating institutions in the ELSA-Brazil study and according to the Dutch Lipid Clinic Network (DLCN) criteria, the estimated prevalence of FH is 1:263, which corresponds to 766,000 people living with FH in Brazil.⁴¹ The prevalence varies according to gender (0.38% in women and 0.30% in men), race (0.25% in White people, 0.47% in multiethnic people, and 0.67% in Black people), and age (0.10% in 35-45 years, 0.42% in 46-55 years, 0.60% in 56-65 years, and 0.26% in 66-75 years).⁴¹ Data from a recent meta-analysis showed that the global prevalence of FH in the general population is 1:311, being 18-fold higher among those with ASCVD.⁴² Another meta-analysis showed a higher prevalence of FH among those with ischemic heart disease (10-fold), premature ischemic heart disease (20-fold), and severe hypercholesterolemia (23-fold).⁴³

1.4. Impact of Familial Hypercholesterolemia on Atherosclerotic Cardiovascular Disease

FH is a common genetic cause of premature coronary disease, especially AMI and angina pectoris, related to lifetime exposure to elevated LDL-C concentrations.^{44,45} If not treated, men and women with HeFH and total cholesterol levels between 310 and 580 mg/dL will develop CAD before the ages of 55 and 60 years, respectively. Homozygotes with total cholesterol levels between 460 and 1,160 mg/dL usually develop CAD very early in life and, if not treated, may die before the age of 20 years. However, when the diagnosis is made and the treatment is initiated, the natural history of atherosclerotic disease can be changed.⁴⁶

Although there are no data on the risks of ASCVD or the rates of lipid-lowering treatment in FH, the prevalence of CAD among those with a probable or definite diagnosis of FH (according to DLCN criteria) in a large sample of the general population in Copenhagen, Denmark, was 33%,³⁷ of which only 48% received statins. Those with probable or definite FH who did not receive statins had a 13-fold increase in the

risk of CAD (95% confidence interval [CI] 10- to 17-fold). Similar results were found in other FH cohorts.⁴⁷

Conversely, FH patients receiving statins had a 10-fold higher risk of ASCVD (95% CI 8- to 14-fold), which suggests that the statin treatment was insufficient to lower lipid levels or was introduced late in life, when atherosclerosis was already severe. Similar treatment data were reported in other studies.⁴⁸⁻⁵⁰

The risk of premature ASCVD in FH is very high, and 5 to 10% of coronary events occur before the age of 50 years.^{47,51} If not treated, young patients with FH have a 90-fold increase in the risk of death.^{47,51} FH also accounts for a significant number of hospitalizations and loss of productivity due to the high incidence of ASCVD.⁴⁷

Therefore, a key step is early diagnosis, which allows early initiation of lipid-lowering medication and may change the natural history of the disease. Diagnosis should be supported by guidelines⁵²⁻⁵⁴ and algorithms.⁵⁵ In addition, identifying more severe cases^{56,57} and promoting integrated care⁵⁸ are strategies to minimize the impact of FH on CVD outcomes.

2. Lipid Metabolism in Familial Hypercholesterolemia

The amount of circulating cholesterol depends, on the one hand, on the balance between hepatic synthesis and intestinal absorption and, on the other hand, on excretion, especially via biliary tract. When this process is unbalanced, as is the case with FH, cholesterol levels can increase significantly and form deposits such as xanthomas and early atherosclerosis²². Body cholesterol input and output are regulated by a feedback system in which increased cholesterol absorption from diet leads to reduced hepatic synthesis. Unlike dietary fats, which are almost completely absorbed by the intestine, cholesterol is only partially absorbed. When the amount of cholesterol from diet increases, absorption decreases proportionally. In men, cholesterol is mostly transported by LDLs. These particles are produced by metabolism of very low-density lipoproteins (VLDLs), which are rich in triglycerides but also provide, especially as remnants (intermediate-density lipoproteins, IDLs), cholesterol for the formation of atheromatous plaques. In addition, when LDLs are delipidated in triglyceride content, they originate smaller and denser LDLs, which are very atherogenic. LDLs are removed from circulation and transported into cells by cell membrane receptors that recognize Apo B-100, the only protein found in LDL. Remnants and IDL are also removed by these receptors, but much faster than LDL. This happens because these particles, in addition to Apo B-100, also have apolipoprotein E (Apo E) on their surface, which has higher affinity for receptors than Apo B-100.

In FH, genetic defects also affect the LDLR, leading to decreased lipoprotein endocytosis.⁵⁹ Receptor-mediated LDL endocytosis and defects causing impaired receptor function and hypercholesterolemia were described by Brown and Goldstein in the 1970s. The several hundred polymorphisms in the receptor gene can affect the structure of the receptor that binds to Apo B-100 in LDL particle, other protein domains, and the recirculation of receptors that are normally recycled

back to the cell membrane after endocytosis. However, only some *LDLR* gene polymorphisms are associated with the FH phenotype. Apo B defects and those related to gain-of-function of PCSK9, participating in LDLR catabolism, account for approximately 5% and < 1% of cases, respectively.²

A much rarer possibility is a homozygous defect in the *LDLRAP1*, since this type of defect is recessive. However, according to estimates, between 5 and 30% of patients with the FH phenotype do not have an identified causative gene, which suggests that there were mutations in unidentified genes or by combination (polygenic mutations). Thus, FH results from the inability to efficiently remove cholesterol from LDLs, causing elevated plasma concentrations and deposits in vessels and tissues.⁵⁹

In general, FH is genetically transmitted by one of the parents, with an autosomal codominant monogenic inheritance pattern, which most frequently characterizes the heterozygous form of the disease. The estimated prevalence of HeFH is 1:200-250 in Europe and approximately 1:250 in Brazil. However, a concomitant increase in Lp(a) or a concomitant defect in triglyceride metabolism is not uncommon, indicating even more severe dyslipidemia.

The occurrence of xanthomas during childhood or adolescence together with very high LDL-C levels (> 500 mg/dL), premature atherosclerotic disease, and aortic valve stenosis are suggestive of HoFH, which is much more severe and difficult to treat.¹³ In this case, most patients' parents have HeFH, usually due to mutations in the *LDLR* gene, but mutations may also occur in other genes (*APOB* or *PCSK9*). There may also be a combination of polymorphisms from different genes (*LDLR*, *APOB*, *PCSK9*, or *LDLRAP-1*). In the homozygous form, concomitantly low levels of high-density lipoprotein cholesterol (HDL-C) are also frequent, possibly due to accelerated removal of apolipoprotein A1 (Apo A-I) or a defect in cholesterol efflux. Homozygous manifestations should also be suspected in case of less markedly elevated LDL-C levels (> 300 mg/dL) occurring together with xanthomas before 10 years of age.¹³

3. Clinical Diagnosis of Familial Hypercholesterolemia

The clinical and laboratory criteria for the diagnosis of FH are arbitrary and based on the following:

- Clinical signs of extravascular cholesterol deposits
- Elevated plasma LDL-C or total cholesterol levels
- Family history of hypercholesterolemia and/or premature atherosclerotic disease
- Identification of mutations and genetic polymorphisms favoring the development of FH.

Some criteria have been proposed to standardize and formalize the diagnosis of FH, such as the US MEDPED criteria from the US Make Early Diagnosis to Prevent Early Deaths Program,⁶⁰ the Dutch MEDPED criteria from the DLCN (see Table 1),⁶¹ and the Simon Broome Register Group criteria.⁶² The Dutch MEDPED criteria are used in Brazil.

The Dutch MEDPED criteria are simple and recommended for diagnostic suspicion of FH and for decision-making regarding treatment initiation (see below). An algorithm based on the Dutch MEDPED criteria can be used to improve diagnostic accuracy, although validation for the Brazilian population is not yet available.

3.1. Medical History

Given the high prevalence of FH in the general population and its great impact on CVD and mortality rates, medical history should include information about family history of hypercholesterolemia, use of lipid-lowering medication, and premature atherosclerotic disease, including the age of onset. Patients with a family history of FH and/or premature atherosclerotic disease are more likely to have FH.

3.2. Physical Examination

The investigation for clinical signs of FH (xanthomas, xanthelasmas, and corneal arcus) should be part of routine physical examination and can be complemented by additional tests, such as tendon ultrasound, in specific cases. The clinical signs are not overly sensitive but can be highly specific; thus, although FH diagnosis does not depend on clinical signs, their presence strongly suggests this etiology.

Tendon xanthomas (Figure 1) are most commonly found in the Achilles tendon and in the extensor tendons of the fingers but may also be found in the patellar and triceps tendons. They should be assessed by both visual inspection and palpation. These xanthomas are almost pathognomonic for FH but occur in less than 50% of cases.⁶³ Intertriginous planar xanthomas may also occur, especially in HoFH (Figure 2).

Yellow-orange tuberos xanthomas (Figures 3 and 4) and eyelid xanthelasmas are not specific to FH and should be carefully assessed when found in patients aged 20 to 25 years. The presence of partial or total corneal arcus suggests FH when found in patients under 45 years of age (Figure 5). HoFH carriers may also have systolic ejection murmur due to stenosis in the aortic valve and supra-aortic region.

3.3. Screening and Lipid Levels

The collection of blood samples to measure LDL-C and total cholesterol levels for FH screening is extremely important to diagnose as many cases as possible and, consequently, reduce the impact of the disease on cardiovascular morbidity and mortality in the general population. The screening process can be based on two methods: universal screening and cascade screening.^{23,52}

3.3.1. Universal Screening

All those aged 10 years or over should undergo lipid profile testing.⁵² Plasma lipid measurement should also be considered in children aged 2 years or over in the following cases:⁵²

1. When there is a family history of premature atherosclerotic disease (men aged < 55 years or women aged < 65 years) and/or dyslipidemia.

Update

Table 1 – Diagnostic criteria for heterozygous familial hypercholesterolemia according to the Dutch Lipid Clinic Network (Dutch MEDPED criteria)⁶¹

Parameter	Score
Family history	
First-degree relative with premature coronary and vascular disease (men aged <55 years, women aged <60 years) OR Adult relative with total cholesterol >290 mg/dL*	1
First-degree relative with tendon xanthomas and/or corneal arcus OR First-degree relative aged <16 years with total cholesterol >260 mg/dL*	2
Clinical history	
Patient with premature CAD (men aged <55 years, women aged <60 years)	2
Patient with premature cerebral or peripheral vascular disease (men aged <55 years, women aged <60 years)	1
Physical examination	
Tendon xanthomas	6
Corneal arcus <45 years of age	4
LDL cholesterol levels (mg/dL)	
≥330	8
250 to 329	5
190 to 249	3
155 to 189	1
DNA analysis	
Presence of functional mutation in the LDL receptor gene, Apo B-100, or PCSK9*	8
FH diagnosis	
Definite if	>8
Probable if	6 to 8
Possible if	3 to 5

* Adapted from the Dutch Lipid Clinic Network with one criterion from the Simon Broome Register Group.⁶² CAD: coronary artery disease; DNA: deoxyribonucleic acid; FH: familial hypercholesterolemia; LDL: low-density lipoprotein.



Figure 1 – Tendon xanthoma in the Achilles tendon.

2. When the child has xanthomas or corneal arcus, risk factors (hypertension, diabetes mellitus, obesity), or atherosclerotic disease.

The recommended frequency for plasma lipid measurement is still open to debate. In general, if the lipid profile is normal, but other criteria suggest FH, such as family history of early atherosclerotic disease or significant hypercholesterolemia, the test can be repeated after 1 year. In the absence of these factors, the test can be repeated within 5 years. Data such as age, presence of other risk factors for atherosclerosis, degree of control of risk factors, lifestyle habits, and occasional use of medications that may affect lipid metabolism can be considered to individualize the frequency of lipid measurements.

A positive FH diagnosis should always be suspected in adults (≥ 20 years) with LDL-C levels ≥ 190 mg/dL. In the general population, people aged ≥ 30 years with LDL-C ≥ 250 mg/dL, those aged 20-29 years with LDL-C ≥ 220 mg/dL, and those aged < 20 years with LDL-C ≥ 190 mg/dL are 80% more likely to have FH.⁶¹ FH is also more likely to occur in patients with LDL-C ≥ 190 mg/dL whose families are characterized by a bimodal distribution of LDL-C, in which some members have typically low levels (LDL-C < 130 mg/dL), while others (those with FH) have typically high levels (≥ 190 mg/dL).⁶²

Before the diagnosis of FH is made, however, secondary causes of hypercholesterolemia, including hypothyroidism and nephrotic syndrome, should be ruled out. Importantly, the presence of hypertriglyceridemia does not exclude the diagnosis of FH.

Since 2017, total cholesterol levels ≥ 310 mg/dL in adults and ≥ 230 mg/dL in children and adolescents have been considered suggestive of FH by laboratory reports in Brazil.⁶⁴

Finally, it should be noted that lipid profile measurement is subject to a series of variations related to the method and procedures used as well as to patient-specific factors, such

as lifestyle, use of medications, and associated diseases. Therefore, diagnostic accuracy can be increased by laboratory analysis of new samples ideally collected at least 1 week after the first collection.

3.3.2. Cascade Screening

Cascade screening consists of measuring the lipid profiles of all first-degree relatives (father, mother, and siblings) of patients diagnosed with FH. The chances of identifying other FH carriers from an index case are 50% in first-degree relatives, 25% in second-degree relatives, and 12.5% in third-degree relatives.⁶³ As new cases are identified, additional relatives are recommended for screening. Cascade screening is considered the most cost-effective method for identifying FH carriers.

3.3.2.1. Cascade Genetic Screening

Genetic screening is cost-effective and can be used in all FH patients and their first-degree relatives. The most cost-effective cascade screening method is the one that uses genetic information from people who have been identified with an FH-causing mutation.⁶³

3.3.2.2. Reverse Cascade Screening

Reverse cascade screening consists of reversely testing first-, second-, and third-degree relatives of a child who has been identified as an index case. Children with FH are often the first to be diagnosed by a pediatrician, and their parents are unaware if they are also FH carriers. Therefore, it is an opportunity to identify and treat asymptomatic parents who have never used any medication for the disease.²³

3.3.2.3. Opportunistic Diagnosis

Opportunistic diagnosis occurs when the lipid profile is measured at the time of immunization. Although this is not a

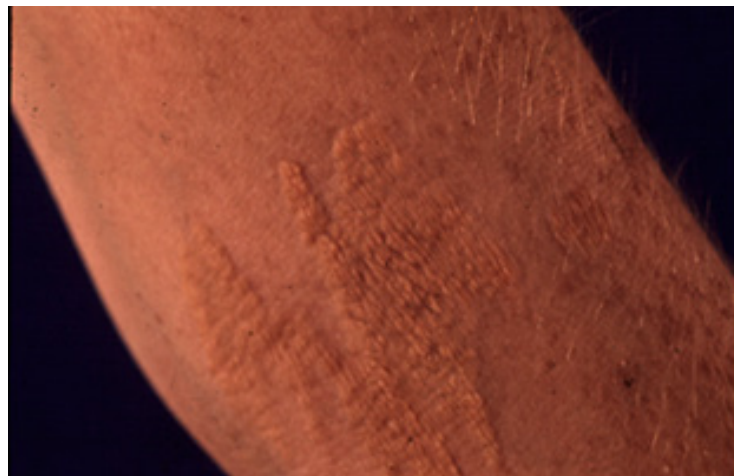


Figure 2 – Planar xanthoma.



Figure 3 (A e B) – Tuberous xanthomas on the knees.

common practice in Brazil, the method is an opportunity for early diagnosis of asymptomatic children.^{23,59}

3.3.3. Homozygous Familial Hypercholesterolemia

The estimated historical prevalence of HoFH in the general population worldwide (1:1,000,000) is very low. However, higher prevalence rates are currently recorded in the general population, ranging from 1:160,000 to

1:300,000.^{13,52} The diagnostic criteria for HoFH are shown in Chart 1.

3.4. Recommendations

1. Clinical signs of FH and family history of early atherosclerotic disease and/or dyslipidemia should be investigated in all patients (grade of recommendation: I; level of evidence: C).



Figure 4 – Tuberous xanthomas on the hands.

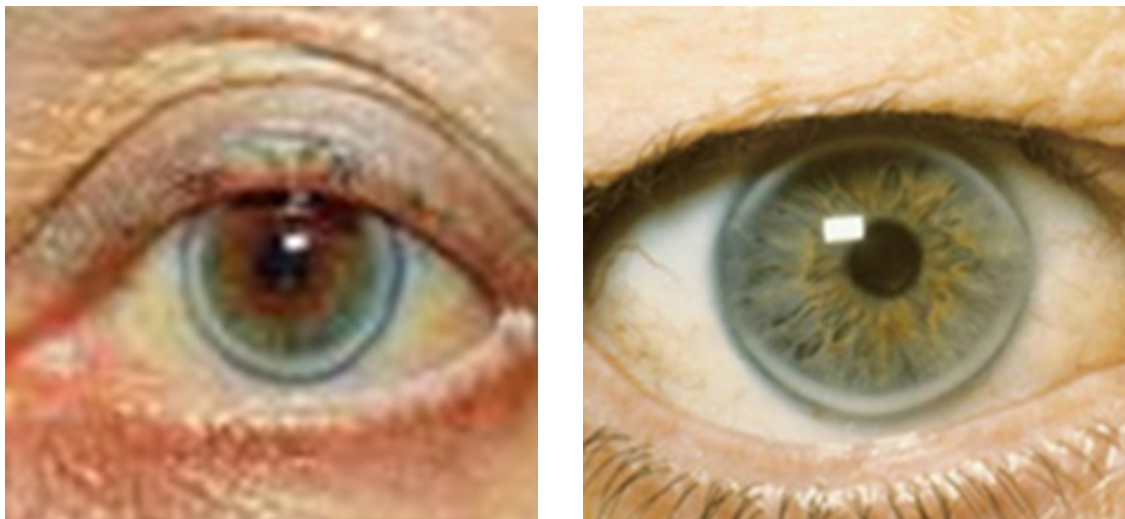


Figure 5 – Corneal arcus.

Chart 1 – Diagnostic criteria for homozygous familial hypercholesterolemia (HoFH).

1. Genetic confirmation of two mutant alleles at the *LDLR*, *APOB*, and *PCSK9* genes or at the *LDLRAP1* gene locus OR

2. Untreated LDL-C > 500 mg/dL or treated LDL-C > 300 mg/dL together with:
either cutaneous or tendon xanthomas before the age of 10 years OR elevated LDL-C levels consistent with heterozygous FH in both parents*

* Except for autosomal recessive hypercholesterolemia. FH: familial hypercholesterolemia; LDL-C: low-density lipoprotein cholesterol. The LDL-C levels are only suggestive of homozygous FH, but lower levels should be considered for the diagnosis of compound or double heterozygotes in the presence of additional criteria.

2. The lipid profile of all patients over 10 years of age should be measured (grade of recommendation: I; level of evidence: C).

3. Lipid profile measurement should be considered in those aged 2 years or over in the presence of risk factors, clinical signs of FH, and atherosclerotic disease, as well as in the case of a family history of premature atherosclerotic disease and/or dyslipidemia (grade of recommendation: I; level of evidence: C).

4. The lipid profile of all first-degree relatives of patients diagnosed with FH should be measured (grade of recommendation: I; level of evidence: C).

4. Genetic Testing for Familial Hypercholesterolemia

FH is an autosomal codominant disease. It is primarily caused by loss-of-function mutations in the *LDLR* and *APOB* and, less frequently, by gain-of-function mutations in *PCSK9*, which is responsible for LDLR degradation.

4.1. LDLR, APOB, PCSK9, and Removal of Circulating LDL

The LDLR is located on the surface of hepatocytes and cells from other organs, binding to LDL via Apo B, which leads to LDLR uptake by a mechanism of internalization and endocytosis of the LDL/Apo B/LDLR complex. This process is mediated by LDLRAP1 present in the clathrin-coated pits. After internalization, the LDL particle separates from the LDLR in the endosome, and the LDLR will either undergo lysosomal degradation facilitated by PCSK9 or be transferred back to the cell surface. Cholesterol is then released into the cell for metabolism or elimination. Alternatively, the LDLR can be degraded by exogenous PCSK9 binding to the LDLR on the cell surface, where it is internalized and processed for lysosomal degradation.¹⁶ When the LDLRs have any genetic mutation affecting their structure or function, the level of LDL removal from the plasma decreases and, consequently, the plasma LDL-C level increases inversely to the number of functional receptors.⁶⁵

4.2. Autosomal Dominant Inheritance

FH is classically caused by pathogenic mutations in the *LDLR*, *APOB*, and *PCSK9* genes. The *LDLR*-coding gene (*LDLR*), located on chromosome 19, consists of approximately 45,000 DNA base pairs and is formed by 18 exons and 17 introns. The *LDLR* is a protein composed of 839 amino acids, including a 21-amino-acid signal peptide with several functional domains.

The analysis of the mutations identified in the *LDLR* gene demonstrates that there are no mutation hot spots in the gene.^{66,67} Nonetheless, mutations in exon 4, which is responsible for binding LDLR via Apo B, seem to correlate with more severe phenotypes.⁶⁶⁻⁷⁰ Interestingly, de novo mutations in the *LDLR* gene seem to be rare.⁷¹ Production is finely regulated by a sophisticated feedback mechanism controlling the transcription of the *LDLR* gene in response to variations in intracellular sterol content and cellular cholesterol demand.⁷²

There are approximately 2,900 genetic variants associated with FH,⁷³ and approximately 85 to 90% occur in the *LDLR* gene. FH is most commonly attributed to mutations in the *LDLR* gene (including missense, nonsense, insertions, and deletions), resulting in partial-to-total functional reductions in LDLR ability to remove LDL from circulation. Depending on the impact of the mutation on the resulting protein, the patient may express little or no LDLR (receptor-negative) or LDLR isoforms with reduced affinity for LDL on the surface of hepatocytes (receptor-defective).^{70,74-77}

Heterozygotes inherit an allele with a pathogenic variant from one parent and a normal allele from the other. Since two functional alleles are needed to maintain a normal plasma LDL-C level, the absence of a functional allele may cause a 2-fold increase from normal LDL levels during childhood.⁷² Homozygotes inherit two alleles with pathogenic variants; consequently, the LDLR function is very reduced, and patients develop very severe hypercholesterolemia (400 to 1,000 mg/dL).⁷²

There are five main classes of *LDLR* gene mutations:^{70,76}

- Class I (null mutations): these mutations affect the promoter or coding regions of the gene, leading to the complete absence of LDLR synthesis or in the synthesis of a nonfunctional receptor.
- Class II: these mutations are caused by defects in post-translational processing or failure to transport LDLR from the endoplasmic reticulum to the Golgi complex, leading to lower LDLR expression on the cell surface.
- Class III: LDL does not bind correctly to the LDLR on the cell surface because of a defect in the ligand-binding domain or in the epidermal growth factor (EGF) precursor homologous domain of the LDLR.
- Class IV: the LDLR binds normally to LDL, but the latter is not efficiently internalized by the mechanism of endocytosis via clathrin-coated pits.
- Class V: the LDLR is not recycled back to the cell surface.

The *APOB* gene spans 42 kilobases (kb), consists of 29 exons and 28 introns, and yields two protein isoforms: a small one, named Apo B-48, and a large one, named Apo B-100. Apo B-48 is produced in the intestine and found in chylomicrons and their remnants, while Apo B-100 is produced in the liver and found in several lipoproteins, such as VLDL, IDL, LDL, and lipoprotein(a) (Lp(a)). Hypercholesterolemia due to a mutation in the *APOB* gene results in a clinical phenotype of FH similar to that caused by mutations in other genes and was classically referred to as familial defective Apo B-100 (FDB).¹⁵ However, it is worth noting that FDB is currently considered a type of FH, and its distinction is made only from an academic perspective.

Contrasting with the findings regarding the *LDLR* gene, only 353 variants have been identified in the *APOB* gene,⁸⁰ and most of them are in exon 26.⁷⁸⁻⁸⁰ The most common mutation in the *APOB* gene is the Arg3500Gln substitution, which causes disruption of the protein structure. The variant accounts for 5 to 10% of FH cases in northern European populations but is rare in other populations.^{79,80}

Another condition that may cause the FH phenotype is increased PCSK9 activity, also known as FH3, in which gain-of-function mutations lead to further LDLR degradation.^{16,80,81}

This is the least common cause of FH, accounting for 1 to 3% of clinically diagnosed cases.^{80,81} The *PCSK9* gene spans 25 kb, consists of 12 exons, and yields a 692-amino acid protein.

4.3. Autosomal Recessive Hypercholesterolemia

In addition to the previously described genes, mutations in *LDLRAP1* have also been considered to cause the HoFH phenotype. Unlike classic FH, these disorders have an autosomal recessive mode of inheritance. In ARH, reduced *LDLRAP1* expression hinders LDLR binding to clathrin-coated pits on the cell surface,^{82,83} which thus reduces or prevents the internalization of the LDL/LDLR complex in the hepatocytes. The *LDLRAP1* gene spans 25 kb, consists of 9 exons, and yields a 308-amino acid protein. Only patients with homozygous or compound heterozygous gene mutations are affected; simple heterozygotes are only carriers, as they usually do not have hypercholesterolemia. However, cases of ARH carriers with LDL-C levels higher than other noncarrier family members have been described in the literature.⁸⁴

4.4. Other Candidate Genes

In addition to the previously mentioned genes, there are other candidate FH-causing genes: *APOE*, *IDOL* (*MYLIP*), *HCHOLA4*, *STAP1*, and *LIPA*.⁸⁵

Rare forms of ARH (also known as FH phenocopies) include sitosterolemia and phytosterolemia, which occur due to mutations in two adjacent and oppositely oriented genes (*ABCG5* and *ABCG8*). These genes encode ATP-binding cassette transporter proteins, sterolin-1 and sterolin-2,⁸⁶ which are involved in the elimination of plant sterols, which cannot be used by human cells, and in cholesterol 7- α hydroxylase (*CYP7A1*) deficiency. *CYP7A1* is an enzyme involved in the first step in bile acid synthesis, and its deficiency results in increased intrahepatic cholesterol and reduced LDLR expression on the surface of the hepatocyte. *CYP7A1* deficiency is the least

common autosomal recessive disorder possibly causing severe hypercholesterolemia.⁸⁷

4.5. Phenotype Variability in Familial Hypercholesterolemia

Current studies show that FH encompasses a spectrum of clinical phenotypes partly based on the range of pathogenic variants. Therefore, people with more than one variant in the same gene and in different alleles (compound heterozygotes in *trans*, usually in the *LDLR* gene) may have a phenotype similar to that of a true homozygote (same variant in two alleles).^{23,88} Table 2 shows the variability in the distribution of pre-treatment LDL-C levels for different FH genotypes.²³

Importantly, normal LDL-C levels have been described in patients with pathogenic variants in families with FH, and a pathogenic variant is not always identified in people with the phenotype. Thus, the presence of a phenotype compatible with FH without an identified pathogenic variant in the classical *LDLR*, *APOB*, and *PCSK9* genes may be linked to polygenic inheritance. Talmud et al.⁸⁹ described sets of 12 polymorphisms in different genes in hypercholesterolemic patients without an identified causative mutation.⁸⁹ According to the authors, in the absence of classical monogenic causes, polygenic inheritance could explain up to 88% of cases of general hypercholesterolemia and approximately 20% of those with the FH phenotype.⁹⁰

4.6. Rationale for Cascade Screening

Cascade genetic screening has been used as a tool to identify new FH patients. Depending on the inclusion criteria and the sensitivity of the methods used for FH screening, pathogenic variants correlated to the disease can be identified in 30 to 80% of patients.^{91,92} The technique consists of sequencing variants in first-degree relatives of those diagnosed with FH.⁹³ In screening rounds, first-degree relatives identified with the condition become index cases, and their respective relatives are screened successively (Figure 6).

Table 2 – Variability in familial hypercholesterolemia phenotype in descending order of LDL-C concentrations

LDL-C levels	Possible genotypes
400 to 1,000 mg/dL	Homozygous pathogenic variants
	Null homozygous for <i>LDLR</i>
	True homozygous for <i>LDLR</i>
	Compound heterozygous for <i>LDLR</i>
	Heterozygous pathogenic variants
130 to 450 mg/dL	Null <i>LDLR</i>
	Defective <i>LDLR</i>
	Gain-of-function <i>PCSK9</i>
	<i>APOB</i>
	Polygenic forms (multiple LDL-C-raising SNPs)
130 to 200 mg/dL	High lipoprotein(a)
	Common hypercholesterolemia

Adapted from Sturm et al.²³ *APOB*: apolipoprotein B; *LDL-C*: low-density lipoprotein cholesterol; *LDLR*: LDL receptor; *PCSK9*: proprotein convertase subtilisin/kexin type 9; *SNP*: single nucleotide polymorphism.

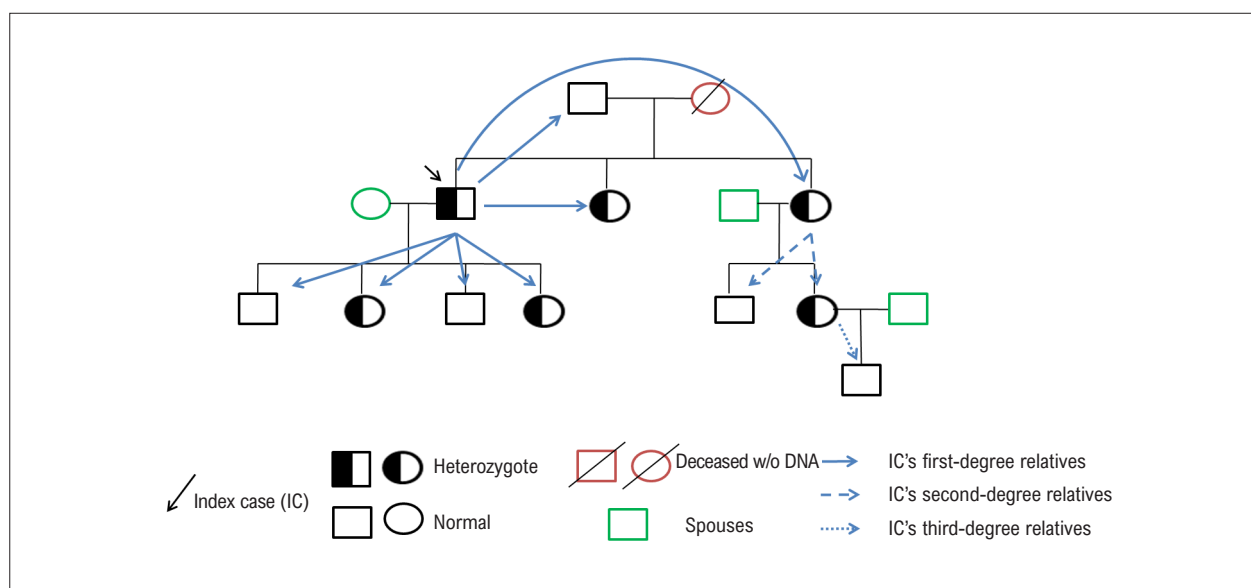


Figure 6 – Example of cascade genetic screening.

Cascade genetic screening is the most cost-effective strategy for identifying FH carriers.⁹³⁻⁹⁵ Marks et al.⁹³ analyzed the cost-effectiveness of the strategy and determined an incremental cost per life-years gained (LYG) of £3,300. It was the most cost-effective program in Denmark, with a cost per LYG of US\$8,700.00, which demonstrates a lower cost estimate than the expenditures on secondary prevention of non-FH carriers.⁹⁶

Studies have shown that very few FH carriers are diagnosed. In general, according to estimates, approximately 20% of patients are diagnosed, and less than 10% receive appropriate treatment.¹⁰ In view of that, cascade screening increases the number of diagnoses and decreases the age at diagnosis, thereby providing a greater chance of early treatment and reduction in global cardiovascular risk for patients.

Genetic testing is not usually necessary for the diagnosis or clinical treatment of an index case, but it can be useful when diagnosis is uncertain or when family members need to be assessed. The cascade screening method has been used in several countries, including Spain,⁹⁶ England, Netherlands,⁹⁷ Portugal,⁹⁸ and more recently in Brazil,⁹⁹ as a highly cost-effective tool for identifying new FH carriers.

A genetics consortium study²⁴ identified the presence of a FH-causing pathogenic variant in 2% of severe cases (LDL-C > 190 mg/dL detected in approximately 7% of the study population). Participants with the FH-causing monogenic variant had a 22-fold higher risk of cardiovascular events compared with normolipidemic participants without genetic mutations and a 4-fold higher risk compared with hypercholesterolemic participants without mutations.²⁴ The increase was mainly due to the exposure of FH patients to high cholesterol levels from birth, unlike polygenic hypercholesterolemia, which may manifest later in life. These data strongly suggest that the presence of a FH-causing pathogenic genetic variant has prognostic implications.

The identification of a causative mutation may provide additional motivation for some patients to initiate appropriate treatment, and genetic testing is the gold standard for a definite diagnosis of FH. It can be particularly useful in cases of family members with a misdiagnosis or with LDL-C level as the only indicator of the disease. Genetic testing may also be important to identify a causative mutation in families with a strong suspicion or recent diagnosis of FH. Furthermore, once a mutation is identified, the test provides a simple and definite answer for the diagnosis of FH, becoming an indisputable tool for identifying the disease as a family trait.²³

However, genetic testing has limitations. Among hypercholesterolemic patients with a possible FH diagnosis, the rate of identification of a causative mutation by genetic testing is 50% or less, while the rate of identification in patients with a definite FH diagnosis according to clinical criteria may be as high as 86%.^{23,100} Therefore, a negative genetic test does not exclude FH diagnosis. Also, people with elevated LDL-C levels remain at high cardiovascular risk and should be treated according to established guidelines regardless of genetic test results.

4.7. Methods for Genetic Diagnosis

Defects in the genes causing the FH phenotype – *LDLR*, *APOB*, *PCSK9*, or *LDLRAP1*, in addition to the rarer ones previously mentioned – cannot be clinically detected, thus genetic testing is required for confirmation. Thus, because of gene variability and the large number of possible mutations, the method of genetic diagnosis should include the sequencing of the coding region of all genes possibly linked to the etiology of the disease.¹⁰¹

To achieve large-scale sequencing, so that a group of genes can be sequenced (targeted gene panels), next-generation sequencing (NGS) should be used. In this technique, a panel is designed with all the genes to be sequenced, which are

placed on a chip. A broader approach is exome sequencing, which allows the determination of the coding region sequence of virtually every gene in the genome in question. However, although this approach provides extensive coverage of the genome, many genes may not be perfectly sequenced. Therefore, in specific cases of monogenetic diseases, such as FH, targeted gene panels are a more cost-effective alternative in addition to being more accurate.

NGS technology has many advantages over Sanger sequencing, which is considered the gold-standard sequencing method. Some of these advantages include the promptness of sequencing results, the amount of material required for the reaction, the cost of per-base sequencing, the amount of output data, and the accuracy of sequencing results. Briefly, for genetic testing, peripheral blood is collected in a tube containing ethylenediaminetetraacetic acid (EDTA), and the genomic DNA of leukocytes is extracted. The first step in preparing the material consists of generating a library of DNA fragments flanked by specific adaptors. The regions of interest of the genes under study are amplified by large-scale polymerase chain reaction in multiplex reactions, with hundreds of pairs of oligonucleotides in the same reaction tube. From these reactions, libraries with barcodes are created to identify each patient analyzed. The generated fragments are clonally amplified on beads by polymerase chain reaction, and the beads are then placed on a chip and inserted in the NGS device. Once generated, the data are transferred to a platform, in which the readings are mapped to the human genome (hg19/GRCh37) and the variants are interpreted.

Approximately 10% of genetic variants in the *LDLR* gene are not point mutations,⁹⁹ but rather large deletions or duplications of *LDLR* exons. Therefore, if no variants are identified by NGS,

the multiplex ligation-dependent probe amplification¹⁰² (MLPA) (MCR-Holland) technique should be used to identify probable deletions or duplications.

Cascade screening is cost-effective and should be used in all patients and first-degree relatives of those diagnosed with FH. The most cost-effective method is the one that uses genetic information from people with an identified FH-causing mutation. Clinical/biochemical screening should be performed even when genetic testing is not feasible.¹⁰³⁻¹⁰⁵

The benefits and limitations of cascade genetic testing are summarized in Chart 2, adapted from Sturm et al.²³

4.8. Recommendation

1. Laboratory screening: All patients with suspected FH (index case) should have their first-degree relatives tested for hypercholesterolemia. If the result is positive, other family members (second- and third-degree relatives) should undergo cascade screening. Grade of recommendation: I; level of evidence: A.

2. Genetic screening: Genetic testing should be provided for the index case; if positive, first-degree relatives should be tested. If their test results are also positive, other family members (second- and third-degree relatives) should undergo cascade screening. Grade of recommendation: II; level of evidence: A.

5. Cardiovascular Risk Stratification

5.1. Epidemiology of Cardiovascular Risk in Familial Hypercholesterolemia

The association between HeFH and CAD is well established,^{51,105} as the absence of lipid-lowering therapy

Chart 2 – Benefits and limitations of cascade genetic testing.²³

Benefits
1. Provides a definite diagnosis for FH. 2. Provides prognostic information and the ability to perform refined risk stratification because the detection of a pathogenic variant indicates higher cardiovascular risk. 3. Positive genetic test results have been shown to improve initiation of lipid-lowering therapy, adherence to therapy, and reductions in LDL-C levels. 4. Early detection provides the opportunity for earlier treatment and lifestyle changes. 5. When the genetic test result of a proband is positive, this leads to cascade genetic testing in at-risk family members, with high sensitivity and specificity. 6. May exclude FH in at-risk family members who did not inherit the pathogenic variant(s). 7. Genetic testing provides discrimination at the molecular level between HeFH, compound HeFH, double HeFH, HoFH, ARH, and those without an identifiable pathogenic variant but with the FH phenotype. The recurrence risks to relatives and the implications for family planning differ between these scenarios. 8. Genetic testing allows the potential identification of FH “phenocopies” that may require specific therapies and have inheritance patterns different from those of FH. 9. May provide additional motivation for patients to properly adhere to prescribed medications. 10. Provides an explanation for failure of diet and exercise management to control elevated lipid levels. 11. Provides a helpful explanation for a family history of premature heart disease and difficult-to-treat LDL-C levels.
Limitations
1. FH genetic testing is not completely sensitive or specific. 2. Not all patients with a clinical diagnosis of FH will have an identifiable pathogenic variant (or variants). 3. Some patients will have a variant of uncertain significance identified, which may be reclassified as pathogenic or benign over time as more information is obtained.
Cost
1. Patients may want to undergo genetic testing, but the cost may be a limiting factor.

Adapted from Sturm et al.²³

implies a cumulative risk of fatal CAD of approximately 50% in men and 33% in women of up to 60 years of age.⁵¹ A study conducted by the Simon Broome Register group from 1980 to 1995 identified a 125-fold increase in the relative risk of a fatal cardiovascular event in women with FH aged 20 to 39 years (annual mortality: 0.17%), despite treatment, compared with the general population of England and Wales. Men with FH aged 20 to 39 years had a 48-fold increase in relative risk (annual mortality: 0.46%).⁴

More recent studies confirmed the increased risk of CAD among people with FH (LDL-C $\geq$ 190 mg/dL) of either monogenic or polygenic causes. Khera et al.²⁴ found an increased risk of cardiovascular events among participants with LDL-C levels $\geq$ 190 mg/dL, even in those without an identified FH mutation, compared with those with normal cholesterol levels.²⁴ Of 1,386 participants with LDL-C $\geq$ 190 mg/dL (6.7% of the total), only 24 (1.7%) had a detected mutation. Those with LDL-C levels $\geq$ 190 mg/dL and no mutation had a 6-fold higher risk of CAD compared with the control group (LDL-C $<$ 130 mg/dL and no mutation), while those with LDL-C levels $\geq$ 190 mg/dL and some mutation had a 22-fold higher risk.²⁴

Another recent study identified that, among patients with clinically diagnosed FH, the presence of a monogenic cause for the disease was associated with a significantly increased cardiovascular risk (adjusted hazard ratio [HR] 1.96; 95% CI 1.24 to 3.12; $p = 0.004$), while there was no difference in cardiovascular risk between patients with polygenic hypercholesterolemia and those without an identified genetic cause. However, the presence of a polygenic score in participants with monogenic FH further increased their cardiovascular risk (adjusted HR 3.06; 95% CI 1.56 to 5.99; $p = 0.001$).¹⁰⁶

Despite the increased risk of CAD observed in FH patients, statin treatment is associated with a significant reduction in the risk of cardiovascular events. Versmissen et al.⁴⁶ showed that patients treated with statins had a 76% reduction (HR 0.24; 95% CI 0.18 to 0.30; $p < 0.001$) in the risk of coronary events compared with “untreated” patients (ie, those with delayed initiation of treatment). However, although lipid-lowering therapy significantly decreases the chances of cardiovascular events, recent studies have shown a residual risk of events. In a study of 821 FH patients (median age: 47.4; 35.3 to 58.3) treated with lipid-lowering therapy for 9.5 years (5.1 to 14.2), 102 (12%) patients developed CVD. Patients more likely to develop CVD had a previous history of cardiovascular events, a family history of premature CVD, and hypertension, in addition to higher on-treatment LDL-C, lower on-treatment HDL-C, and higher smoking rates than patients without cardiovascular events.¹⁰⁷

The CASCADE FH registry evaluated cardiovascular outcomes in FH patients in the US. In a cohort of 1,900 people whose mean age was 56 ± 15 years, with a mean follow-up of 20 ± 11 years and a prevalence of previous atherosclerotic CVD of 37%, only 48% participants achieved LDL-C $<$ 100 mg/dL and 22% achieved LDL-C $<$ 70 mg/dL, despite the use of lipid-lowering therapy in 92.8%. A total of 107 atherosclerotic events occurred in 69 (3.6%) participants during follow-up, corresponding to an annual incidence of events of 2.2/100 patient-years.¹⁰⁸ Thus, FH carriers are at increased risk of

atherosclerotic events even if on lipid-lowering treatment. The risk varies according to LDL-C control and the presence of several other factors, which indicates the importance of stratifying FH patients.

5.1.1. Recommendations for Risk Stratification in Familial Hypercholesterolemia

Cardiovascular risk in FH is increased. However, although increased, it varies according to the presence of several risk factors. Therefore, risk stratification is recommended in FH patients (grade of recommendation: I; level of evidence: B)

5.2. Role of Risk Factors in Familial Hypercholesterolemia

Classical risk factors for CAD in FH are of great importance in the stratification of this population. For example, as is the case with the general population, cardiovascular risk among FH patients is higher in men than in women, as demonstrated in different studies. In a Dutch cohort study conducted by Jansen et al.,¹⁰⁹ the risk of a cardiovascular event was almost 3 times higher in men than in women (relative risk [RR] 2.82; 95% CI 2.37 to 3.36).¹⁰⁹ A recent meta-analysis of 27 studies including 41,831 participants quantified the association between several risk factors and CVD in people with FH. The risk for men with CVD was almost 2 times higher (odds ratio [OR] 1.95; 95% CI 1.68 to 2.23).¹¹⁰ In this meta-analysis as well as in other studies, smoking was strongly associated with the development of CAD in patients with FH, with a risk approximately 1.7 to 1.8 times higher than in nonsmokers.¹⁰⁹⁻¹¹¹

Diabetes mellitus is an important cardiovascular risk factor in the general population. A meta-analysis of 12 prospective studies conducted by the Emerging Risk Factors Collaboration found that FH was associated with a 2-fold increase in CVD risk regardless of other risk factors.¹¹² As expected, diabetic FH patients are also at increased risk compared with nondiabetic FH patients. A meta-analysis conducted by Akiyamen et al.¹¹⁰ found that diabetes (OR 1.95; 95% CI 1.33 to 2.57) and hypertension (OR 2.11; 95% CI 1.64 to 2.58) increased the CVD risk in FH patients by 2 times. Smoking, hypertension, and diabetes accounted for more than 1/4 of cardiovascular risk in those with FH.¹¹⁰

In addition to traditional risk factors, other factors increase the risk of events in FH patients, such as a family history of CVD, which has been shown to be associated with a higher risk of CVD in those with FH. Akiyamen et al.¹¹⁰ found that participants with a family history of CVD had an almost 2-fold higher CVD risk (OR 1.83; 95% CI 1.58 to 2.07).

Some previous studies failed to demonstrate an association between LDL-C and CVD in FH, although high LDL-C is the main feature of this condition. However, there are several explanations for this. For example, a comparison between participants with high LDL-C levels and those with similarly elevated LDL-C levels may not be effective in showing the effects of LDL-C differences, especially when the comparison involves a small number of participants. Furthermore, patients with higher LDL-C levels are generally treated more aggressively, which introduces a confounding factor in the analyses. However, in the recent meta-analysis conducted by Akiyamen et al.,¹¹⁰ meta-regression analyses showed that

higher levels of untreated LDL-C and total cholesterol were associated with a higher risk of CVD (51% increase in CVD risk for every 1 mmol/L increase in cholesterol). Low levels of HDL-C (< 1 mmol/L) were also associated with increased cardiovascular risk in FH patients, unlike serum triglycerides and apolipoproteins A-I and B.

5.2.1. Recommendation on the Role of Risk Factors in FH

Several factors play an important role in the cardiovascular risk of patients with FH and should be actively investigated in this population (grade of recommendation: I; level of evidence: A).

5.3. Role of Other Factors in Cardiovascular Risk in Familial Hypercholesterolemia: Lipoprotein(a), Achilles Tendon Xanthoma, and C-Reactive Protein

Lp(a) is a lipoprotein composed of an LDL-like particle whose Apo B is covalently linked to an apolipoprotein(a).

According to evidence gathered over several years, high Lp(a) is an independent cardiovascular risk factor in the general population, with causal implication.¹¹²⁻¹¹⁴ In FH patients, the condition is also considered an additional risk factor, which is an extremely relevant observation in this group given the potential for high Lp(a) levels in this population.

5.3.1. Recommendation

Lp(a) measurement should be considered in those with FH (grade of recommendation: IIa; level of evidence: B).

Achilles tendon xanthoma is a peculiar sign of FH and is included in the diagnostic criteria. Approximately 30 to 50% of patients genetically diagnosed with HeFH have tendinous xanthoma. Civeira et al.¹¹⁵ showed that FH carriers with xanthomas had a higher prevalence of premature CVD compared with those without xanthomas (36.7% vs 13.8%, $p = 0.001$).¹¹⁵ A meta-analysis conducted by Oosterveer et al.¹¹⁶ of patients with genetically confirmed FH identified a 3-fold higher risk of CVD among those with tendinous xanthoma.¹¹⁶

A more recent Brazilian study also evaluated the association of Achilles tendon xanthomas with the presence and burden of subclinical atherosclerosis in HeFH patients. Participants with xanthomas (21%) had higher concentrations of LDL-C and Lp(a), as well as a higher calcium score. Furthermore, the association of xanthoma with calcium score remained positive and independent after adjustments for age, sex, smoking, hypertension, previous statin use, HDL-C, LDL-C, and Lp(a).¹¹⁷

Despite the positive association between xanthomas and CVD found in previous studies, the recent meta-analysis conducted by Akioyamen et al.¹¹⁰ did not report tendon xanthomas as risk factors in FH.

Other recommendations include the following:

1. Achilles tendon xanthoma seems to be associated with a higher cardiovascular risk in FH. Because xanthomas are often investigated only during physical examination, this should be encouraged (grade of recommendation: IIa; level of evidence: B).

2. The association between C-reactive protein and CVD in FH is based on small studies of subclinical atherosclerosis with controversial results.^{118,119}

3. There is no evidence to support routine C-reactive protein measurement in FH (grade of recommendation: IIB; level of evidence: C).

5.4. Cardiovascular Risk Stratification in Familial Hypercholesterolemia: Use of Clinical Scores for Risk Stratification

Conventional risk stratification with widely used clinical scores, such as the Framingham score, the Framingham Global score, the American Heart Association/American College of Cardiology (AHA/ACC) score, and others, was not designed for patients with FH.²² Indeed, a person with long-term exposure to high cholesterol levels over time (cholesterol-years score) cannot be approached as being at possibly low cardiovascular risk as in a traditional score.

Therefore, current studies on risk stratification in FH should include, if possible, a prospective design, molecular diagnosis, and the attenuating effects of previous statin therapy. In this context, Paquette et al.¹²⁰ developed the Montreal-FH-SCORE by evaluating 670 participants with a confirmed molecular diagnosis of FH and who had undergone statin treatment.¹²⁰ Being male, age, hypertension, and smoking independently associated with incidence of atherosclerotic CVD. More recently, the authors validated their risk equation in a different population of 718 patients with a molecular diagnosis of FH with good statistical discrimination;¹²¹ however, these studies are considered limited by their retrospective design and relatively small incidence of events.

Using the prospective Spanish Familial Hypercholesterolemia Registry (SAFEHEART), Perez de Isla et al.¹²² developed a new equation by adding the following to the risk markers defined in the Montreal-FH-SCORE: previous atherosclerotic cardiovascular event, high body mass index (BMI) (> 30 kg/m²), high residual LDL-C concentrations (> 100 or > 160 mg/dL), and Lp(a) levels > 50 mg/dL.¹²² These parameters were found to be independently associated with first or recurrent atherosclerotic cardiovascular event. Indeed, the SAFEHEART score had a good discrimination index (0.85 overall and 0.81 in primary prevention), with an excellent calibration for both primary and secondary preventions. However, the score was limited by the relatively low incidence of events (5.6%), a possible confounding effect, by previous statin therapy, and by a relatively short follow-up. Finally, similar to the Montreal-FH-score, the SAFEHEART registry equation was limited by the lack of validation in other FH populations.¹²³

5.4.1. Recommendation

1. Montreal-FH-SCORE: grade of recommendation, IIb; level of evidence, B.

2. SAFEHEART score: grade of recommendation, IIa; level of evidence, B.

3. Framingham score or other clinical FH scores: grade of recommendation, III; level of evidence, B.

5.5. Coronary Artery Calcium Score

The coronary artery calcium (CAC) score is a tool for quantifying the total burden of coronary artery atherosclerotic plaque: the higher the CAC score, the greater the plaque burden in the patient. The most common method to assess the CAC score is using the Agatston score, which corresponds to the weighted sum of lesions with a density above 130 Hounsfield units (HU). Then, the calcium area is multiplied by a factor related to maximum plaque attenuation: factor 1 – if maximum attenuation < 200 HU; factor 2 – if maximum attenuation between 200 and 300 HU; factor 3 – if maximum attenuation between 300 and 400 HU; or factor 4 – if maximum attenuation $\geq$ 400 HU.¹²⁴

Several studies have demonstrated the association of high CAC scores with coronary events.^{125,126} A 2004 meta-analysis conducted by Pletcher et al.¹²⁷ shows a linear association between CAC and the risk of coronary events. Those with a CAC score > 400 Agatston units (AU) were at higher risk of cardiovascular events. The most relevant studies regarding the association of CAC with predicted CAD are the Multi-Ethnic Study of Atherosclerosis (MESA)¹²⁵ and the Heinz Nixdorf Recall Study (HNR),¹²⁶ which showed that CAC is an independent marker of death and myocardial infarction. Not only did the score add discriminative power but also improved risk reclassification for CAD compared with classical risk factors. In the MESA study, a prospective evaluation of 6,814 patients followed-up for a mean period of 3.8 years showed that coronary event risk rates were increased by 7.73 for those with a CAC score between 101 and 300 AU and by 9.67 for those with a CAC score $\geq$ 300 AU ($p < 0.001$) compared with those with no CAC score.¹²⁵ Also, a CAC score of zero is associated with low rates of coronary events even in the medium term (11 years).¹²⁸

No randomized studies have addressed the management of lipid profile guided by CAC, but observational studies have showed that those with higher CAC scores benefit the most from statin therapy.^{129,130} The 2017 Brazilian guideline for dyslipidemia recommends that primary prevention patients with high CAC scores (> 100 AU) be considered at high cardiovascular risk and be treated according to appropriate lipid goals.⁵² The 2018 AHA/ACC guideline goes further and proposes postponing statin treatment in primary prevention patients aged 40 to 75 years without diabetes mellitus, with LDL-C levels between 70 and 189 mg/dL, and with a CAC score of zero.⁵³

FH carriers have higher CAC scores than noncarriers matched for age and sex.¹¹⁸ Coronary artery calcification determinants in FH are the classical risk factors for atherosclerosis. Indeed, Martinez et al.¹¹⁸ showed that the LDL-C exposure burden corresponding to the LDL-C-years score (LDL-C multiplied by age), the Framingham score, and being male were associated with CAC. A French study also showed an association between CAC and cholesterol-years score (total cholesterol multiplied by age).¹³¹

Guidelines for the treatment of dyslipidemia consider FH patients as being at least at high cardiovascular risk for having high LDL-C since childhood.^{52,132} In this context, questions remain regarding the usefulness of the CAC

score for risk stratification in FH when dealing with a population at high cardiovascular risk. A MESA study subanalysis showed an association between CAC and CVD even when LDL-C is high (LDL-C > 190 mg/dL). Patients with a CAC score of zero had low rates of cardiovascular events (10-year risk: 3.7%, per-year risk: 0.4%) when compared with those with a CAC score > 0 (10-year risk: 20%; per-year risk: 2.0%). The factors associated with a CAC score of zero were: age < 65 years, being female, and absence of diabetes mellitus. The association of CAC with cardiovascular events was analyzed in a Brazilian cohort of patients with confirmed molecular diagnosis of FH and in primary prevention. The study showed an association between CAC and cardiovascular events in FH despite high-potency statin treatment.¹³³ The mean age was 45 years, and 15 cardiovascular events were reported. The annual rates of events per 1,000 patients for CAC scores of 0, 1 to 100, and > 100 were, respectively, 0; 26.4 (95% CI 12.9 to 51.8); and 44.1 (95% CI 26.0 to 104.1). Despite the small sample size ($n = 206$) and the relatively short follow-up (median time: 3.7 years), the study demonstrated that a CAC score of zero can also be used as a marker of good prognosis in the FH population.¹³³

Thus, the CAC score is an additional tool in the risk stratification of HeFH patients in primary prevention (grade of recommendation: IIb; level of evidence: B).

5.6. Coronary Computed Tomography Angiography

Compared to the CAC score, coronary computed tomography (CT) angiography has some advantages such as visualization of noncalcified plaques and estimation of the degree of luminal stenosis.¹³⁴ Conversely, the disadvantages include the need for intravenous contrast infusion, higher costs, and higher radiation doses.

The use of coronary CT angiography has clear benefits in symptomatic patients at low risk for CAD both in the emergency department and in the outpatient setting as it rules out the disease as the cause of symptoms.¹³⁵ However, the benefits of this method over the CAC score in the risk stratification of asymptomatic patients are controversial. For example, the COronary CT Angiography EvaluationN For Clinical Outcomes InteRnational Multicenter (CONFIRM) registry did not show any advantage for coronary CT angiography over the CAC score in asymptomatic individuals.¹³⁶ However, two CONFIRM substudies showed that coronary CT angiography could improve stratification compared with the CAC score in patients at higher risk, particularly older patients¹³⁷ and those with intermediate-level CAC.¹³⁸

Previous studies have shown that FH carriers have a greater atherosclerotic plaque burden in coronary CT angiography, which is represented by a greater number of patients with plaque, luminal stenosis, and plaque segments compared with normolipidemic controls.^{139,140} The condition is associated with a higher risk of cardiovascular outcomes in a noncarrier population.¹⁴¹ The question, then, is about the usefulness of coronary CT angiography in asymptomatic FH patients in primary prevention. A small Japanese study including 101 FH carriers showed that a tomographic score based on segments

with stenosis on coronary CT angiography was associated with major cardiac events.¹⁴² However, the study was not able to provide a definite answer because of its small sample size, retrospective design, and the fact that many events occurred soon after the examination, which could mean that several revascularization events were “caused” by the examination. The only randomized clinical trial assessing the influence of coronary CT angiography on clinical outcomes in asymptomatic patients was conducted in a diabetic population and showed no benefit.¹⁴³ Therefore, coronary CT angiography is not currently recommended for asymptomatic HeFH patients in primary prevention (grade of recommendation: III; level of evidence: B).

However, the usefulness of coronary CT angiography in HoFH should be analyzed from a different perspective, since the disease is associated with accelerated atherosclerosis, and cardiovascular events and supraaortic stenosis may be developed very early.¹³ There are studies with small sample sizes demonstrating that HoFH patients may have coronary atherosclerosis and atherosclerotic involvement of the aortic root detected by coronary CT angiography at an early age.^{144,145}

The examination can be performed even in asymptomatic HoFH patients at diagnosis for a better assessment of cardiovascular risk profile. It can be repeated at the clinician's discretion (grade of recommendation: IIa; level of evidence: B).

5.7. Carotid Intima-Media Thickness

Carotid intima-media thickness (IMT) is defined as the distance between the lumen-intima interface and the media-adventitia interface. It is related to cardiovascular risk factors, prevalence and incidence of CVD, and degree of atherosclerosis at different arterial sites. The progression of carotid IMT can be reversed or attenuated by interventions in risk factors, which is associated with a reduction in cardiovascular events.¹⁴⁶ These findings suggest that carotid IMT is a potential surrogate marker of atherosclerosis. Martinez et al. analyzed carotid IMT in FH patients¹¹⁸ and found increased measures in the FH group compared with the control group.

Carotid IMT was used as a surrogate marker of atherosclerosis in an FH population to assess the progression of atherosclerosis with lipid-lowering medication.^{147,148} Increased carotid IMT was found in children with FH compared with those without FH. Also, a previous study of people aged 8 to 18 years showed a trend toward regression of carotid IMT with pravastatin, whereas a trend toward progression was observed in the placebo group.¹⁴⁹ Rosuvastatin treatment was able to decelerate the progression of carotid IMT in FH children aged ≥ 6 years compared with unaffected children, with no between-group difference after 2 years of treatment.¹⁵⁰

However, the potential use of carotid IMT in clinical practice is hampered by the variability in the methods of measurement, including measurement site, influence of cardiac cycle (no standardization on whether it should be measured in systole or diastole in different studies), use of mean or maximum measurements, definition of abnormal carotid IMT, and other difficulties

in standardizing the method.¹⁵¹ Also, the MESA study compared risk reclassification between different biomarkers in intermediate-risk patients and found that carotid IMT had low reclassification power compared with CAC: net reclassification improvement (NRI) was 0.060 for carotid IMT and 0.406 for CAC, which demonstrates the superiority of the latter.¹⁵²

A carotid ultrasound can also indicate the presence of carotid plaques. The relative risk of carotid plaques varies widely, ranging from 1.16 to 6.71 in different studies, possibly because of different definitions: carotid IMT > 1.2 mm; carotid IMT > 1.0 mm with protrusion into the lumen; subjective analysis; focal thickening $> 50\%$ around the carotid IMT or > 1.5 mm; and others. Furthermore, considering only the presence or absence of carotid plaque may be too simplistic given the diversity of plaque phenotypes (calcified, noncalcified, focal, etc.).¹⁵³ Therefore, the use of carotid Doppler ultrasound in asymptomatic FH patients for assessment of carotid IMT and carotid plaque can optimize cardiovascular risk stratification (grade of recommendation: IIb; level of evidence: B).

5.8. Investigation of Myocardial Ischemia

The investigation of myocardial ischemia with exercise testing is recommended for those who are planning to start high-intensity and/or competitive sports activities. A previous study of 639 FH patients diagnosed by clinical criteria found that 9% of tests were positive for myocardial ischemia. The study also showed that exercise testing parameters such as decreased exercise capacity, delayed decrease in heart rate during the first minute of graded exercise, and increased peak pulse pressure were predictors of coronary events.¹⁵⁴ A different study of 194 FH patients detected a rate of 21% of positive exercise tests.¹⁵⁵

Although there are no randomized studies of exercise testing in FH, and the few existing ones use clinical diagnostic criteria, periodic performance of exercise testing may be useful for asymptomatic HeFH patients who wish to start recreational or competitive physical activity, as well as for those with additional risk factors for coronary heart disease or delayed initiation of lipid-lowering treatment. The test can be repeated every 3 to 5 years (grade of recommendation: IIb; level of evidence: C). Additional risk factors or markers in patients with FH may be considered according to Table 3.

5.9. How to Perform Cardiovascular Risk Stratification of Patients with Familial Hypercholesterolemia in Clinical Practice

As previously discussed, patients with FH are at high risk of cardiovascular events in primary prevention compared with those without FH. However, the presence of classical risk factors for CAD further increases the risk, which contributes to risk heterogeneity. Even in the context of secondary prevention, there is evidence that the risk of recurrence after an index cardiovascular event in patients with FH is at least 2-fold higher than in non-FH patients.¹⁵⁶

Santos et al.⁵⁶ defined FH carriers according to the presence of the following **additional risk factors**: age

Table 3 – Risk factors/markers of cardiovascular risk in familial hypercholesterolemia.

Risk factor/marker	Grade of recommendation	Level of evidence
Diabetes mellitus	I	B
Hypertension	I	B
Smoking	I	B
Family history of premature CAD in first-degree relatives (men aged < 55 years and women aged < 60 years)	I	B
Initiation of lipid-lowering treatment after 40 years of age	IIa	B
HDL-C < 40 mg/dL	I	B
Lipoprotein(a) > 50 mg/dL (or > 125 nmol/L)	IIa	B
Achilles tendon xanthoma	IIb	B
Calcium score > 100 AU or > 75th percentile	IIa	B
Presence of atherosclerotic plaque with obstruction > 50% at any arterial site	IIa	C

CAD: coronary artery disease; HDL-C: high-density lipoprotein cholesterol.

> 40 years and no treatment; smoking; being male; Lp(a) > 50 mg/dL (> 125 nmol/L); HDL-C < 40 mg/dL; hypertension; diabetes mellitus; family history of premature CVD in first-degree relatives (men aged < 55 years and women aged < 60 years); chronic kidney disease (glomerular filtration rate [GFR] < 60 mL/min); and BMI > 30 kg/m². All these **additional risk factors** characterize higher risk situations.

Based on the presence of significant manifest or subclinical atherosclerotic disease, **additional risk factors**, and very high LDL-C levels, FH patients can be classified into the following three risk categories.¹³²

5.9.1. Very High-Risk

- Patients with clinically manifest ASCVD, defined as previous myocardial infarction, angina pectoris, previous myocardial revascularization, stroke or transient ischemic attack, and intermittent claudication.

- Patients with advanced subclinical atherosclerotic disease diagnosed by CAC score > 100 AU or 75th percentile for age and sex, or coronary CT angiography showing coronary obstructions > 50% or presence of nonobstructive plaques in more than one vessel.

5.9.2. High-Risk

- In primary prevention of HeFH, those with LDL-C > 400 mg/dL, even with no **additional risk factors**.

- In primary prevention of HeFH, those with **additional risk factors**.

Note: If LDL-C > 310 mg/dL with one high-risk feature; if LDL-C > 190 mg/dL with two high-risk features (**additional risk factors**).

5.9.3. Intermediate-Risk

- In primary prevention of HeFH, those with no **additional risk factors**.

6. Nutritional Recommendations

Following a healthy eating pattern is crucial for the treatment of FH because a poor diet may increase the established cardiovascular risk in FH patients.¹⁵⁷ The latest guideline for dietary treatment of FH, developed jointly by the American College of Cardiology (ACC), the American Heart Association (AHA), and other US societies,⁵³ is based on a previous guideline published by the societies in 2013.¹⁵⁸ The document recommends following healthy eating patterns with adequate energy intake, removing *trans* fatty acids, adjusting the intake of saturated fatty acids (SFAs), and encouraging an adequate consumption of monounsaturated fatty acids (MUFAs) and polyunsaturated fatty acids (PUFAs).¹⁵⁸ How these fatty acids act on plasma cholesterol has been exhaustively evaluated in several experimental, clinical, and epidemiological studies.^{158,159} Many results were controversial because of differences between the studies regarding duration, sample size, and type of nutrient used for comparison purposes.¹³² Also, different fatty acids are obtained from different food sources, such as meat, milk, oils, or processed foods, and may thus induce different effects on plasma lipids.¹⁶⁰

In recent years, the type of food has been more highly valued than the type of nutrient alone. Thus, eating patterns such as the Mediterranean diet^{161,162} and the DASH diet,¹⁶³ which are based on the consumption of grains, fruits, vegetables, lean meats, dairy products with reduced fat content, and oleaginous fruits (walnuts and chestnuts), were included in the recommendations of major international guidelines. Also, moderate use of vegetable oils rich in PUFAs (omega-3 and omega-6 acids) and MUFAs (omega-9 acids) is indicated for food preparation.⁵³ This recommendation is based on two important studies. The recent Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) study showed that plasma and tissue concentrations of omega-6 fatty acid biomarkers were associated with decreased cardiovascular events.¹⁶⁴ Similar results were observed with plasma concentrations of omega-3 and omega-6 fatty acid biomarkers, which were associated with decreased cardiovascular risk.¹⁶⁵

The guideline developed jointly by the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS)¹³² reinforces the previously mentioned recommendations and warns that foods such as palm oil, coconut oil, bacon, cookies, high-fat bakery products, and full-fat dairy products should be consumed only occasionally and in minimal amounts by FH patients.⁵³

6.1. Dietary Cholesterol

In recent years, the AHA guidelines^{53,158} and the Dietary Guidelines for Americans (2015-2020)¹⁶⁶ removed an upper limit for cholesterol intake because of limited evidence relating it to atherosclerosis¹⁶⁷ and CAD.¹⁶⁸ Nevertheless, the Dietary Guidelines for Americans suggest that considering dietary cholesterol when adopting healthy eating patterns is important, which is consistent with the Institute of Medicine recommendations¹⁶⁹ about the benefits of low cholesterol intake.

The hypercholesterolemic action of dietary cholesterol is lower than that of saturated fats, which is why dietary guidelines have emphasized the importance of reducing the consumption of saturated fatty acids. Thus, reducing the intake of saturated fats from animal sources ensures that cholesterol levels are lower, since both are found in the same foods. In general, the balance between cholesterol intake and endogenous cholesterol synthesis is responsible for cholesterol homeostasis;¹⁷⁰ however, increased intake may significantly contribute to high plasma concentrations of LDL-C,¹⁷¹ a response that is subject to great interpersonal variability and dependent on metabolic and genetic factors.^{170,172,173}

Indeed, the 2018 AHA/ACC guideline on the management of blood cholesterol, which is based on a document first published in 2014, found no evidence to determine whether reducing dietary cholesterol also lowers LDL-C.¹⁵⁸

Observational studies and meta-analyses evaluating the influence of dietary cholesterol on the risk of developing type 2 diabetes, CAD, and stroke are inconclusive^{168,171,173-177} or show no association with CVD and mortality.¹⁷⁸ However, a study evaluating the databases of Atherosclerosis Risk in Communities (ARIC), Coronary Artery Risk Development in Young Adults (CARDIA), Framingham Heart Study (FHS), Framingham Offspring Study (FOS), Jackson Heart Study (JHS), and MESA studies showed that increased cholesterol intake is dose-dependently related to increased CVD and overall mortality,¹⁷⁹ possibly because of the impact on LDL-C concentrations.¹⁸⁰

Eggs, despite being a source of cholesterol, are also highly nutritious and have an excellent profile of high biological value proteins, vitamins, and minerals, in addition to being affordable. Given such nutritional qualities, eggs should be included in the diet as long as they are part of a healthy eating pattern.

An increase in mortality and cardiovascular events due to a higher consumption of total cholesterol and from egg is independent of the quality of the diet. Therefore, moderate consumption of eggs and other sources of cholesterol is recommended,¹⁷⁹ especially among those

with higher plasma lipid concentrations and those who are hyperresponsive to cholesterol intake.

6.2. Action of Fatty Acids on Cholesterolemia

6.2.1. Saturated Fatty Acids

Fatty acids are classified as SFAs, MUFAs, PUFAs, or *trans* fatty acids, and each category has a different influence on plasma concentrations of total cholesterol and LDL-C. Among the main SFAs found in foods, we have the lauric acid (12:0), myristic acid (14:0), palmitic acid (16:0), and stearic acid (18:0), but only palmitic acid is abundant in nature. Coconut oil is an exuberant source of lauric and myristic acids; meat has a high content of palmitic acid; and milk is rich in stearic and myristic acids. Foods from plant sources, such as palm oil and cocoa, also have high contents of palmitic and stearic fatty acids, respectively.^{181,182} Pentadecylic (15:0) and margaric (17:0) fatty acids are found in small amounts in dairy products, and their plasma concentration is a marker of consumption.^{183,184} Foods also provide longer-chain fatty acids such as arachidic acid (20:0), behenic acid (22:0), and lignoceric acid (24:0), which are found in oleaginous fruits such as peanuts and macadamia nuts.^{185,186}

Several clinical and epidemiological studies have shown that cardiovascular risk increases with a higher consumption of SFAs¹⁸⁶⁻¹⁸⁸ because they induce greater plasma concentrations of total cholesterol and LDL-C.¹⁵⁹ Several mechanisms have been proposed to explain this action, including: (a) SFAs have straight carbon chains and are closely packed in the core of lipoproteins, which allows the accommodation of a greater amount of cholesterol;¹⁸⁹ (b) in association with cholesterol, SFAs reduce LDLR activity, protein, and mRNA levels,¹⁹⁰⁻¹⁹² a change that decreases the metabolism of LDL particles.^{193,194}

The World Health Organization (WHO) published a systematic review of clinical studies (mean SFA intake: 9.8%) and showed that isocaloric replacement of SFAs with PUFAs or MUFAs reduced plasma concentrations of total cholesterol and LDL-C.¹⁵⁹ Furthermore, replacement of carbohydrates with palmitic, myristic, or lauric acids was also found to induce an increase in those lipid parameters, an effect that was not observed with stearic acid. This reinforces the idea that SFAs behave differently with regard to their effect on plasma lipids. Stearic acid does not elevate plasma cholesterol because it is rapidly converted to oleic acid by the action of the liver enzyme stearoyl-CoA desaturase-1 (SCD1).¹⁹⁵

The Prospective Urban Rural Epidemiology (PURE)¹⁹⁶ study evaluated the diets of 135,000 people in 18 countries and showed that higher fat consumption (35% of energy) is related to lower mortality compared with lower fat consumption (10% of energy). It is worth noting that this amount of fat is within the recommended range (25 to 35% of total energy intake, TEI) reported in recent decades, and that median consumption ranged from 2.8 to 13.2% of energy. That study showed that increased SFA consumption was associated with higher LDL-C.¹⁹⁶

A 2015 Cochrane Library systematic review evaluating data from randomized clinical trials (59,000 participants in total) showed that decreased consumption of saturated fat from the usual diet reduced cardiovascular events by 17%.¹⁹⁷

Also, the results showed that cardiovascular events reduce by 27% when SFAs are replaced with PUFAs.

While some SFAs are related to greater cardiovascular risk, others are inversely associated, such as pentadecylic (15:0) and margaric (17:0) acids,¹⁸³ as well as those with a very long chain, such as lignoceric, behenic, and arachidic acids.¹⁸⁵

Thus, consumption of up to 10% of energy for SFAs is recommended, with a 7% limit for those with hypercholesterolemia, according to 2019 ESC/EAS^{132,158} and ACC/AHA guidelines.

6.2.2. Unsaturated Fats

Oleic acid (18:1) is the main MUFA, found in olive oil, canola oil, oilseeds, and oleaginous fruits. Omega-6 PUFAs consist of linoleic acid (18:2), found in corn, sunflower, soybean, and canola oils, and arachidonic acid (20:4), found in eggs, fish oil, and meat.¹⁹⁸ Omega-3 fatty acids can be from both plant and animal sources; α -linolenic acid (18:3) is found in linseed, canola, and soybean oils, and eicosapentaenoic acid (20:5) and docosahexaenoic acid (20:6) are found in very cold water fish.

Contrasting with saturated fats, MUFAs and PUFAs do not elevate plasma concentrations of cholesterol and LDL-C, a benefit that seems to be greater with PUFAs, since MUFAs have a neutral action on cholesterolemia.¹⁵⁸

6.2.3. Omega-3 Fatty Acids

Several clinical studies have shown that supplementation with pharmacological doses (2 to 4 g) of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) per day can decrease plasma concentrations of triglycerides by up to 25 to 30%, in addition to slightly increasing those of HDL-C (1 to 3%). It can also elevate LDL-C concentrations by up to 5 to 10%, with little or no difference in serum total cholesterol.¹⁹⁹⁻²⁰²

However, in the case of formulations containing only purified omega-3 fatty acids, LDL-C increase may not occur, as demonstrated in the Japan EPA Lipid Intervention Study (JELIS).^{203,204} Research on the effect of omega-3 fatty acids on FH patients remains incipient, and supplementation seems to be able to influence the progression of atherosclerosis in high-risk patients, but this requires further investigation.²⁰⁵⁻²⁰⁷

6.2.4. Trans Fatty Acids

The consumption of *trans* fatty acids present in processed foods increases cardiovascular risk because it induces an atherogenic lipid profile by elevating plasma LDL-C concentrations, decreasing Apo B catabolism,²⁰⁸ reducing HDL-C, and inducing increased Apo A-I catabolism.²⁰⁹ Also, *trans* fatty acids increase the severity of atherosclerotic lesions in CAD²⁰⁹ and induce endothelial dysfunction.²¹⁰

The results of controlled studies discussed in a meta-analysis showed that for every 1% energy replacement of *trans* fats with saturated, polyunsaturated, or monounsaturated fats, total cholesterol/HDL-C ratio reduced by 0.31, 0.54, and 0.67, respectively.²¹¹ The evaluation of prospective studies in another meta-analysis revealed that for every 2% energy

replacement of *trans* fats with other fatty acids, the risk of CAD decreases by 17%.²¹¹ Subsequently, a higher consumption of *trans* fat observed over a 10-year period in several countries was found to be associated with a 4% increase in deaths from coronary heart disease.²¹² A study evaluating diet-related mortality rate in 195 countries found a considerable number of cardiovascular deaths attributed to the consumption of *trans* fatty acids.²¹³ In addition to adverse effects on lipid metabolism, *trans* fat can induce a proinflammatory profile, which further intensifies its deleterious effects.²¹⁴ For all their adverse reactions, *trans* fatty acids used in processed foods should be excluded from diet.^{53,158,208,213,215}

6.2.5. Phytosterols

Phytosterols, phytostanols, and their esters are bioactive components present in plant foods, and their chemical structure is highly similar to that of cholesterol.²¹⁶ Their hypocholesterolemic effect is well documented in the scientific literature. After being incorporated to micelles, phytosterols are transported into the enterocyte via NPC1L1 transporter, and then most return to the intestinal lumen via ABCG5/ABCG8 transporters,²¹⁷ which keeps their plasma concentrations low. The mechanism for reducing plasma concentrations of total cholesterol and LDL-C is explained by the greater solubility of phytosterols in micelles, which displaces cholesterol and promotes its excretion. The mean consumption of phytosterol in the population is 100 to 400 mg/day, and a Brazilian study revealed that the mean consumption was 160 mg/day.²¹⁸ A daily supplementation of 2 g of phytosterols was shown to reduce plasma LDL-C concentrations by 8 to 10%.^{217,219} Despite the small lowering effect on cholesterolemia, the current ESC/EAS guideline⁵³ indicates that phytosterols may be beneficial for adults and children with moderately high cholesterol levels.²¹⁷ However, because responses to the use of phytosterols may vary, efficacy should be evaluated individually.²²⁰

Phytosterols can be administered in capsules containing 650 to 900 mg or spread (two tablespoons provide the recommended dose). Their use should be accompanied by healthy dietary and lifestyle habits to lead to the desired effects. Phytosterol consumption during the main meals seems to be the best option because of the mechanism of action of competition in the absorption of dietary cholesterol.²²¹

In FH patients, phytosterol can help achieve LDL-C goals when used in combination with statin/ezetimibe.²²² Meta-analysis data on the effect of phytosterols on children demonstrated reductions in total cholesterol (7 to 11%) and LDL-C (10 to 15%).²²³ According to the Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents, phytosterol supplementation (2 g/day) can be a good option for children and adolescents with FH who are not yet eligible for pharmacological treatment,²²⁴ since phytosterols are well tolerated and do not have significant adverse effects. In Brazil, phytosterols are approved for use in children aged 5 years or over; however, few studies have tested their use during pregnancy and lactation, and caution is recommended in such cases.²²⁵ Importantly, their use is contraindicated for patients with sitosterolemia.

6.2.6. Fiber

Dietary fiber intake seems to be associated with a significant reduction in total cholesterol because of mechanisms involving: 1) reduced cholesterol absorption induced by viscosity;²²⁶ 2) increased fecal excretion of cholesterol and bile acid;²²⁷ inducing increased activity of 7 α -hydroxylase,²²⁸ a key enzyme in the formation of bile acids from cholesterol;²²⁹ 3) reduced activity of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase;²³⁰ 4) reduced hepatic cholesterol content;²³¹ 5) altered composition of intestinal microbiota, leading to higher production of short-chain fatty acids and increased excretion of neutral steroids and bile acids;²³² or even a combination of the described mechanisms.

A meta-analysis of studies investigating the effect of soluble fiber (β -glucan) on plasma lipids found that an intake > 3 g/day led to a modest reduction in plasma concentrations of total cholesterol and LDL-C (11.6 and 9.6 mg/dL, respectively, relative to control), with no effect on HDL-C and triglycerides.²³³ A Cochrane Library systematic review²³⁴ evaluated the effects of fiber on primary prevention of CVD and found reduced total cholesterol and LDL-C levels (7.7 and 8.5 mg/dL, respectively) associated with increased fiber intake. However, the authors highlight that randomized, well-conducted, and long-term cohort studies are necessary to reliably determine the effect of fiber on cardiovascular health.²³⁴

In line with the current ESC/EAS guideline,⁵³ following a diet rich in fiber, especially soluble fiber, is recommended. This is found in vegetables, fruits, and whole grains, which should be part of a healthy eating pattern.

6.2.7. Soybean

The controversial results of studies evaluating the action of fat-free soy protein supplementation with or without isoflavones on plasma concentrations of total cholesterol and LDL-C can be partly attributed to the different methods used in the studies, the presence of other substances such as fiber and phospholipids, and the use of different concentrations of soy protein or isoflavones.^{235,236} Evidence suggests that soy protein is responsible for a modest reduction (~3%) in plasma cholesterol concentrations, and not isoflavone alone.²³⁷ Nevertheless, there is no evidence for the indication of isoflavone supplementation in the treatment of hypercholesterolemia. However, soy-based products have low concentrations of saturated fat and are rich in fiber, vitamins, minerals, and unsaturated fatty acids, thus they can be part of a healthy eating plan.

6.2.8. Chocolate

Cocoa beans are extracted from the cocoa tree (*Theobroma cacao* L.), which is native especially to South America and the west coast of Africa. Chocolate is obtained by mixing cocoa products (cocoa mass, cocoa powder, or cocoa butter) with additional ingredients such as sugar, milk, lecithin, nuts, and fruits. Thus, in addition to having a high energy density, chocolate is also rich in fat and sugar. Approximately 60% of cocoa fat consists of SFAs (stearic and palmitic acids), and approximately 30% is oleic acid.

Polyunsaturated fats are 3 to 5% of all fatty acids present in cocoa.²³⁸ High consumption of saturated fats has been shown to elevate plasma cholesterol concentrations; however, the results of two meta-analyses showed that cocoa-rich (dark) chocolate seems to have no hypercholesterolemic action,^{239,240} possibly because stearic acid, the main fatty acid in cocoa, is rapidly converted to oleic acid through the action of SCD1 in the liver.²⁴¹ However, it is worth noting that chocolate can be an important source of simple sugar and energy; therefore, it should be consumed in moderation, so that it does not contribute to weight gain. Also, chocolate is usually made from other sources of fat.

6.2.9. Tropical Oils

6.2.9.1. Coconut Oil

Coconut oil (*Coco nucifera*) consists primarily of saturated fat (82%), of which 42% is lauric acid, 16% is myristic acid, 9% is palmitic acid, and the rest is caprylic, capric, and stearic acids.²⁴² Coconut oil has a low concentration of unsaturated fats and lacks an essential fatty acid, α -linolenic acid (18:3).^{181,243} When compared with consumption of olive oil²⁴⁴ and safflower oil,²⁴⁵ coconut oil consumption increases plasma concentrations of total cholesterol and LDL-C. A study of normolipidemic men living in Sri Lanka showed that isocaloric replacement of coconut oil with soybean oil reduced plasma concentrations of total cholesterol, LDL-C, and triglycerides.²⁴⁶ Similar results were found in dyslipidemic adults after replacement of coconut oil with corn oil.²⁴⁷ Increased HDL-C concentrations with coconut oil consumption were accompanied by high LDL-C levels, which are a major cardiovascular risk factor.²⁴⁸

Furthermore, because it is rich in lauric acid,²⁴⁹ coconut oil can trigger inflammatory signaling pathways by activating receptors related to the innate immune response, named toll-like receptors (TLRs).²⁴⁹⁻²⁵¹ A study of macrophages found that lauric acid increased the expression of cyclooxygenase-2 (COX-2) by activating the NF- κ B/TLR 2 and 4 pathways.²⁵² Regarding oxidative capacity, no difference was found in energy metabolism and lipid oxidation when the acute effects of coconut oil and olive oil consumption were compared in overweight women.²⁵³

6.2.9.2. Palm Oil

Despite being a vegetable oil, palm oil is approximately 50% SFAs (45% palmitic acid and 5% stearic acid) and 50% unsaturated fats (40% oleic acid and 10% linoleic acid). Thus, greater palm oil intake, either added to food preparation or consumed in processed foods, increases the dietary concentrations of saturated fat. Consumption of palm oil, when compared with that of vegetable oils rich in unsaturated fat, increases plasma concentrations of total cholesterol and LDL-C.²⁵⁴ The results of a meta-analysis comparing palm oil to vegetable oils (eg, canola oil, soybean oil, and olive oil) showed that palm oil consumption elevated the concentrations of total cholesterol, LDL-C, and HDL-C, the latter modestly.²⁵⁵ This showed that, regarding

plasma lipids, palm oil is similar to animal fats, which are rich in saturated fat.^{255,256} Therefore, consumption should be kept within the recommended amount of saturated fat.

To date, in line with the ACC/AHA¹⁵⁸ and ESC/EAS⁵³ guidelines, the use of tropical oils to replace vegetable oils rich in unsaturated fatty acids is not indicated.

6.2.10. Dairy

Milk and its products are an important source of calcium and high biological value protein. However, whole milk consumption increases the intake of SFAs, especially myristic acid, which strongly correlates with increased plasma cholesterol concentration.¹⁵⁹ However, in the MESA study, dairy consumption was associated with reduced cardiovascular risk¹⁸³ but not with increased risk of stroke.²⁵⁷ More recently, the European Prospective Investigation into Cancer and Nutrition (EPIC) – Italy study, which included 45,009 participants followed-up for 14.9 years, showed that consumption of 160 mL to 200 mL of milk is related to lower all-cause mortality, but this benefit is lost with an intake greater than 200 mL.²⁵⁸ That study also demonstrated that skim milk consumption is related to lower cardiovascular mortality.

6.2.11. Butter

In a serving of butter (10 g), approximately 51.5% of fatty acids are saturated, with a predominance of palmitic (24%), stearic (10%), myristic (8%), and lauric (2%) acids. Monounsaturated fats are roughly 22% of all fatty acids in butter, while unsaturated fats are only 1.5%.²⁵⁹

A randomized study demonstrated that butter consumption increased plasma concentrations of total cholesterol, LDL-C, and Apo B compared with the consumption of the same amount of unsaturated fat.²⁶⁰ The MESA cohort study, which followed-up for 20 years approximately 6,800 nondiabetic participants with no prior CVD,¹⁸¹ found that highest consumption of butter (up to 5 g/day) was not associated with CVD. Another study showed similar results in older adults.²⁶¹ Butter consumption was also inversely associated with incidence of type 2 diabetes in a prospective cohort study.²⁶² A systematic review of high-level evidence cohort studies evaluated the effect of butter consumption and showed that a mean intake of 14 g/day was not associated with CVD risks.²⁶³

Butter should be consumed according to the recommendations for saturated fat, ie, less than 10% of TEI and even more reduced (less than 7%) for those with hypercholesterolemia (2019 EAS/ESC guideline).⁵³ Also, to avoid gain weight and obesity development, the calories in each product should be considered and consumption should be part of a healthy eating pattern, rich in fruits, vegetables, and whole grains.⁵³

6.3. Recommendations for Food Consumption to Control Familial Hypercholesterolemia

The recommendations for food consumption in patients with familial hypercholesterolemia are presented in Table 4.

7. Pharmacological Treatment of Heterozygous Familial Hypercholesterolemia

The treatment of patients with severe FH is a crucial topic. Because of the complications arising from disease progression and the early development of some of them, treatment should be initiated as soon as possible after diagnosis. The concept of cumulative cholesterol over a lifetime justifies this approach.

7.1. Therapeutic Goals for LDL-C

Some high-risk features must be considered: over 40 years of age without prior treatment, smoking, being male, Lp(a) greater than 50 mg/dL (> 125 nmol/L), HDL-C < 40 mg/dL, and percentile of coronary artery calcium (CAC) score calculated by the MESA criteria.

Thus, the proposed goals for treatment of LDL-C are the following: for high-risk FH, LDL-C > 400 mg/dL or LDL-C > 310 mg/dL with one previously described high-risk feature,* or LDL-C > 190 mg/dL with two high-risk features.^{56**} Thus, LDL-C should be reduced by at least 50%, with < 70 mg/dL being the ideal level.

Thus, cardiovascular risk and lipid goals are assessed according to presence of ASCVD, major risk factors, or baseline LDL-C levels, and are classified as follows.

7.1.1. Therapeutic Goals in Very High-Risk Patients

- In the case of clinically manifest atherosclerotic disease, defined as previous myocardial infarction, angina pectoris, previous coronary artery bypass graft, ischemic or transient stroke, or intermittent claudication, LDL-C should be reduced by at least 50%, with < 50 mg/dL being the ideal level.¹³²

- In the presence of advanced subclinical atherosclerotic disease diagnosed with a CAC score greater than 100 AU or 75th percentile for age and sex, or coronary CT angiography showing coronary obstructions > 50% or presence of nonobstructive plaques in more than one vessel, LDL-C should be reduced by at least 50%, with < 50 mg/dL being the ideal level.

7.1.2. Therapeutic Goals in High-Risk Patients

- In primary prevention of HeFH in patients with LDL-C > 400 mg/dL, even with no risk factors, LDL-C should be reduced by at least 50%, with < 70 mg/dL being the ideal level.

*In the case of advanced subclinical atherosclerotic disease diagnosed with a CAC score greater than 100 AU or 75th percentile for age and sex, or coronary CT angiography showing coronary obstructions greater than 50% or presence of nonobstructive plaques in more than one vessel, LDL-C should be reduced by at least 50%, with < 50 mg/dL being the ideal level.

**Additional risk factors in FH are the following:⁵⁶ age > 40 years and no treatment, smoking, being male, Lp(a) > 50 mg/dL, HDL-C < 40 mg/dL, hypertension, diabetes mellitus, family history of premature CAD in first-degree relatives (men aged < 55 years and women aged < 60 years), chronic kidney disease (GFR < 60 mL/min), and BMI > 30 kg/m².

Table 4 – Dietary recommendations for management of familial hypercholesterolemia.

Recommendation	Grade of recommendation	Level of evidence
Follow a healthy eating pattern: adjustment of energy intake, inclusion of grains, fruits, vegetables, lean meats, and dairy products with reduced fat content	I	A
Dietary cholesterol: < 300 mg/day	IIa	A
Saturated fatty acids: < 7% of TEI	I	A
Trans fatty acids: should be excluded from diet	III	A
Chocolate: if rich in cocoa, it is not related to increased cholesterol	I	B
Tropical oils: occasional consumption in minimal amounts	III	B
Eggs: moderate consumption, not exceeding daily cholesterol recommendations	IIa	A
Phytosterols: 2 g/day provides moderately reduced cholesterol (↓~10%)	I	A
Fiber: provides reduction of total and LDL-cholesterol (↓~5%)	I	A

• In primary prevention of HeFH in patients with additional risk factors,⁵⁶ LDL-C should be reduced by at least 50%, with < 70 mg/dL being the ideal level.¹³²

Note: If LDL-C > 310 mg/dL with one high-risk feature; if LDL-C > 190 mg/dL with two high-risk features.⁵⁶

7.1.3. Therapeutic Goals in Intermediate-Risk Patients

In primary prevention of HeFH in patients with no additional risk factors,¹ LDL-C should be reduced by at least 50%, with < 100 mg/dL being the ideal level. Periodic reassessment is required to monitor the onset of risk factors.

7.2. Pharmacological Treatment

7.2.1. Statins

Statins – hydroxymethylglutaryl-coenzyme A reductase inhibitors – are the first-choice drugs for the treatment of HeFH. Even in the absence of scientific evidence from studies evaluating the benefits of statins used exclusively in HeFH patients, the contribution of HeFH patients to the current understanding of LDL-C metabolism and their significant participation in large clinical trials are fully recognized²⁶⁴ (grade of recommendation: I; level of evidence: C).

The therapeutic goals recommended for HeFH patients, when classified as being at high and very high risk, are ≥ 50% reductions in LDL-C levels from baseline and achievement of the recommended goals according to stratified risk groups. In HeFH, high-intensity statins such as rosuvastatin and atorvastatin at maximum tolerated doses are the preferred options (grade of recommendation: I; level of evidence: A).⁵³

Relevant pharmacological properties of statins are the following: potent and reversible enzyme inhibition, selectivity in hepatocytes, low bioavailability to reduce systemic adverse effects, prolonged elimination half-life, and minimal or no hepatic metabolism to prevent drug-drug interactions. The mechanism of action is based on enzyme inhibition, which, by reducing the endogenous synthesis of intrahepatic cholesterol, stimulates the synthesis and

expression of LDL-C receptors, thus increasing the uptake of LDL in hepatocytes and reducing plasma concentrations.²²

Statin treatment has been shown to reduce coronary ischemic events, need for coronary artery bypass graft, stroke, and cardiovascular mortality in all subgroups, including those with manifest atherosclerosis, diabetes, or hypertension, older adults, and women, while also reducing total mortality in patients at high and very high cardiovascular risk (grade of recommendation: I; level of evidence: A). The benefits are attributed to reduced LDL-C levels and defined as a therapeutic class effect.⁵²

Statins are safe, and the most frequent adverse effect is myalgia with or without increased creatine kinase (CK). Rhabdomyolysis is the most severe and rarest adverse reaction, whose risk increases when statins are combined with fibrates. The frequency of adverse effects is proportional to the doses used.²⁶⁵

When efficacy is not sufficiently obtained with statin therapy alone, further LDL-C reductions may be attempted by adding adjuvant therapies.

7.2.2. Adjuvant Therapy to Statins

FH patients are at high cardiovascular risk, and high doses of potent statins remain the mainstay of treatment of dyslipidemia for reduction of risk in these patients.²⁶⁶⁻²⁶⁹ However, most FH patients will not achieve the goals, despite the use of maximum tolerated statin therapy. In a cross-sectional study of 1,249 patients with confirmed HeFH in the Netherlands, the country with highest rates of FH diagnosis, only 21% had LDL-C < 100 mg/dL, although 96% were on statins.²⁷⁰ Therefore, adding one or more lipid-lowering drugs other than statins will be frequently required to achieve the desired goals.²⁷¹

7.2.2.1. Ezetimibe

Ezetimibe selectively reduces the intestinal absorption of dietary and biliary cholesterol by acting on the Niemann-Pick C1-Like 1 (NPC1L1) transporter in the enterocyte. After oral administration, ezetimibe is rapidly absorbed (2 to 3 hours) and then undergoes glucuronidation in the liver. This

produces an active glucuronide located at the border of the enterocyte that returns to the enterohepatic circulation (20%). The glucuronide conjugate is hydrolyzed and absorbed and is equally effective in inhibiting sterol absorption. This enterohepatic recycling is responsible for a half-life of more than 22 hours, and the drug specifically inhibits the intestinal absorption of dietary and biliary cholesterol but does not affect the absorption of fat-soluble vitamins (A, D, E, K), fatty acids, or bile salts.

Reduced cholesterol influx from the intestine to the liver leads to a compensating increase in the expression of hepatic LDLRs and increased uptake of circulating LDL particles. The final LDL-C reduction obtained with ezetimibe 10 mg/day (single dose recommended), alone or combined with a statin, is 15 to 25%.²⁷² In a meta-analysis of five randomized clinical trials (5,039 patients) in which ezetimibe added to ongoing statin therapy was compared with placebo, the mean LDL-C reduction was 23.6%, with no increase in adverse effects.²⁷³ This potentiated lipid-lowering effect is also demonstrated in the population of HeFH patients.^{274,275} Although the concerning literature is obviously more limited, the lipid-lowering efficacy of ezetimibe has also been demonstrated in the HoFH population.²⁷⁶

The combined use of statin and ezetimibe was shown to be effective in reducing surrogate outcomes²⁷⁷ and ischemic events that were analyzed as a secondary outcome.²⁷⁸ However, the efficacy of the combination in reducing major cardiovascular events was demonstrated in the IMPROVE-IT study,²⁷⁹ which compared the ezetimibe-simvastatin combination with simvastatin alone in stable patients after an episode of ACS and with LDL-C within the recommended goals. The primary outcome was a composite of cardiovascular death, ACS (nonfatal AMI, unstable angina requiring hospitalization), and nonfatal stroke. Patients receiving ezetimibe plus statin had, after 1 year, a 24% reduction in LDL-C compared with those receiving statin alone. In a mean follow-up of 7 years, the relative risk reduction in the primary cardiovascular outcome, a composite of cardiovascular death, ACS (nonfatal AMI, unstable angina requiring hospitalization), and nonfatal stroke, was 6.4%. This risk reduction was proportional to the LDL-C reduction and was comparable to the risk reduction obtained for a reduction of the same magnitude with statin therapy.²⁸⁰ Therefore, ezetimibe should be used as an adjuvant therapy to high-intensity statins when the latter, at their maximum dose or at the maximum tolerated dose, are not sufficient to achieve the LDL-C goal (grade of recommendation: I; level of evidence: B).

7.2.2.2. PCSK9 Inhibitors

PCSK9 is a protease that regulates the activity of the LDLR and induces it for lysosomal degradation. Thus, by reducing the amount of LDLR on the surface of the hepatocyte and decreasing the activity of these receptors, PCSK9 increases the plasma concentration of LDL-C.²⁸¹ The use of monoclonal antibodies to prevent PCSK9 from binding to the LDLR is the most effective way of inhibiting the activity of this enzyme. These antibodies bind to the allosteric site of the LDLR and block PCSK9-LDLR binding. Consequently, they increase LDLR recirculation and reduce serum LDL-C levels. Published

meta-analyses report a consistent reduction of approximately 50% in serum LDL-C levels in different clinical settings with the antibodies, used alone or combined with the maximum tolerated therapy.²⁸²

Two antibodies are available on the Brazilian market, both consisting of a solution in a “pen” ready for injection, which does not allow fractionated doses: evolocumab 140 mg and alirocumab 75 and 150 mg. Both are used similarly, with a subcutaneous injection every two weeks (although evolocumab can also be administered at a dose of 420 mg once monthly). Both drugs were tested in an HeFH setting, in addition to the maximum tolerated statin therapy, combined or not with other lipid-lowering drugs, and showed a similar LDL-C reduction ranging from 50 to 60%.²⁸³⁻²⁸⁵ Three-hundred FH patients (106 with HoFH, including adolescents aged 14-18 years at inclusion) received evolocumab 420 mg every 4 weeks for a median time of 4.1 years. The LDL-C reduction from baseline to week 12 was 21.2% (-59.8 mg/dL) in patients with HoFH and 54.9% (-104.4 mg/dL) in those with severe HeFH. These results were sustained over time. Of 48 patients with HoFH receiving a dose up-titrated to 420 mg every two weeks, the LDL-C reduction improved from -19.6% at week 12 to -29.7% after 12 weeks of 420 mg every two weeks.²⁸⁵ Evolocumab was also tested in HoFH patients receiving 420 mg subcutaneously (SC) once monthly, with a mean LDL-C reduction of approximately 21%.²⁸⁶ For such reason, evolocumab is also approved for use in HoFH.

PCSK9 inhibitors have been shown to reduce cardiovascular outcomes in high cardiovascular risk populations with established clinical atherosclerotic disease. The FOURIER study²⁸⁷ evaluated 27,564 patients with established CVD (coronary heart disease, cerebrovascular disease, or peripheral artery disease) who, despite being on maximum tolerated therapy, failed to reach the LDL-C goal (< 70 mg/dL). After a median follow-up of 2.2 years, evolocumab was associated with a 15% reduction in the primary outcome, a composite of cardiovascular death, AMI, stroke, unstable angina requiring hospitalization, or need for coronary artery bypass graft. In the ODYSSEY Outcomes study,²⁸⁸ which included 18,924 patients with a recent ACS (1 to 12 months before inclusion in the study) and LDL-C $\geq$ 70 mg/dL despite being on maximum tolerated dose of statin therapy combined or not with other lipid-lowering drugs, alirocumab reduced the primary composite outcome of death from coronary heart disease, nonfatal AMI, fatal or nonfatal stroke, or unstable angina requiring hospitalization by 15%. The median duration of follow-up was 2.8 years.

Therefore, because of the lipid-lowering efficacy in FH patients and the reduced cardiovascular outcomes in high-risk populations, PCSK9 inhibitors are indicated for patients who, despite being on high-intensity statin therapy or maximum tolerated dose, preferably already combined with ezetimibe, failed to reach the LDL-C goal (grade of recommendation: I; level of evidence: A).

7.2.2.3. Cholestyramine

Cholestyramine is an anion exchange resin that binds to bile acids in the intestine and forms an insoluble complex

which is excreted in the feces. With increased excretion, the synthesis of bile acids increases in the hepatocyte at the expense of an elevation in cholesterol synthesis but mainly by an increased expression of LDLRs. This removes LDL-C from circulation, thus reducing plasma LDL-C levels.²⁸⁹ The lipid-lowering effect of cholestyramine may vary, reaching up to a 30% reduction in LDL-C at maximum doses.²⁹⁰ Cholestyramine is available as 4-g packets, and the initial dosage is 4 g daily, with a maximum of 24 g/day, although doses greater than 16 g are hardly tolerated.

The main adverse effects of cholestyramine refer to the digestive system (gastric fullness, nausea), since it may affect intestinal motility and cause constipation and meteorism. The drug reduces the absorption of fat-soluble vitamins (A, D, K, E) and folic acid, sometimes requiring vitamin supplementation. Cholestyramine should be taken 1 hour before or 3 hours after administration of other medications, so that their absorption is not reduced. Cholestyramine was shown to reduce cardiovascular outcomes when used prior to statin therapy. It also reduced the incidence of myocardial infarction by 19% in hypercholesterolemic men over a 7-year follow-up in the Lipid Research Clinics primary prevention study.²⁹¹

Cholestyramine can be used as an adjuvant therapy when high-intensity statin therapy, preferably already combined with ezetimibe and/or a PCSK9 inhibitor, is not sufficient to achieve the LDL-C goal (grade of recommendation: IIa; level of evidence: B). The drug may be especially useful in children under 8 years of age who are not yet eligible to receive statin therapy and in pregnant women.

8. Alternative Therapies for Treatment of Familial Hypercholesterolemia: Partial Ileal Bypass

Partial ileal bypass surgery was first performed for the treatment of hypercholesterolemia in the 1960s and provided a sustained LDL-C reduction for more than 20 years.²⁹² The procedure was evaluated in the Program on the Surgical Control of the Hyperlipidemias (POSCH) trial, which included 838 AMI survivors with a mean LDL-C of 179 mg/dL. Compared with the control group, the participants undergoing surgery showed a 38% reduction in LDL-C and a 35% decrease in the composite outcome of death from coronary heart disease or nonfatal AMI.²⁹³

In a small study of 11 patients with HeFH, partial ileal bypass surgery reduced LDL-C by approximately 20% after 2 years.²⁹⁴

The main adverse effect of this surgery is diarrhea (an average of more than three bowel movements per day after the procedure). Renal and biliary lithiasis is another reported adverse event.^{292,293}

With the introduction of statins in clinical practice in the 1980s-1990s and then of other lipid-lowering drugs, partial ileal bypass surgery was no longer used in the treatment of hypercholesterolemia. The role of this procedure in the management of FH and prevention of CVD under current pharmacological therapy is unknown.

It is worth noting that some contemporary bariatric surgery techniques leading to significant weight reductions, such as Roux-en-Y gastric bypass and biliopancreatic diversion, also provide LDL-C reductions.²⁹⁵

8.1. Recommendation

Although partial ileal bypass surgery has been shown to reduce LDL-C and cardiovascular events, this procedure is not routinely recommended for FH patients, given the existence of several other effective, noninvasive, and lower-risk treatment modalities (grade of recommendation: IIB; level of evidence: B).

8.2. Plasmapheresis and LDL apheresis

LDL apheresis (LDL-A) and plasmapheresis are two treatment options based on extracorporeal blood filtration. Both involve sessions lasting 2 to 3 hours weekly or fortnightly. The main difference between the two procedures is specificity. In plasmapheresis procedures, there is separation of the patient's plasma and blood cells, so that the blood cells are retained and mixed in a replacement fluid to return to the patient, while plasma together with proteins (including HDL-C) is discarded. Adverse effects include susceptibility to infections, nausea, hypertension, hypotension, and urticaria.²⁹⁶

In LDL-A procedures, in turn, plasma is not discarded; it passes through a precipitation filter for selective removal of LDL, VLDL, and Lp(a) cholesterol. The most frequent adverse effects include hypotension, anemia, nausea, flushing, headache, and venous access problems.²⁹⁷

There are several methods of apheresis, including dextran sulfate cellulose adsorption, heparin-induced extracorporeal LDL-C precipitation, immunoadsorption, and double filtration plasmapheresis. In a comparison of the available methods, only small differences were observed in their ability to reduce lipid levels. As a rule, these selective methods reduce plasma LDL-C levels by a mean of 50 to 70% after a single treatment.^{298,299} The time to return to baseline LDL-C levels ranges from 4 days to 3 to 4 weeks.

Because of its specificity, LDL-A is better tolerated than plasmapheresis; it has a lower rate of adverse effects (2% versus 12%, respectively) and is more effective in reducing LDL-C (60 to 65% versus 50%, respectively). However, LDL-A is less commonly available and costs twice as much.³⁰⁰

8.3. LDL Apheresis in Homozygous or Compound Heterozygous Children

The recommended criteria for indication of LDL-A or plasmapheresis following diet combined with optimized pharmacotherapy in homozygous or compound heterozygous children include the following:

- A reduction below 50% from baseline LDL-C or LDL-C levels kept above 360 mg/dL: these criteria are modifiable according to the clinical status of each patient, including but not limited to the progression of atherosclerotic disease. Retrospective and longitudinal follow-up studies demonstrate that LDL-A therapy in children led to a reduction and/or disappearance of cutaneous xanthomas, delayed progression of aortic and supra-aortic

valve stenosis, and regression of coronary lesions.³⁰¹⁻³⁰⁵ Diet and pharmacotherapy should be maintained concomitantly with apheresis procedures, since combined statin therapy reduces LDL-C by up to 70%. Statins also delay the rebound effect of increased LDL-C levels post apheresis.

- Age at initiation of LDL-A: cardiovascular prognosis depends on timing of treatment; the earlier the better. The age for initiation of LDL-A is 5 years or over, preferably before 8 years of age. In more severe cases, it can be initiated at an earlier age.³⁰³ After 10 years of age, LDL-A has not been shown to be as beneficial in follow-up and retrospective studies.³⁰³

- Monitoring the progression of atherosclerosis: the presence of progressive atherosclerosis is one of the criteria for choosing invasive treatments. Imaging tests, such as transthoracic echocardiogram to assess the presence and/or progression of aortic valve disease and aortic arch disease, carotid ultrasound to measure intima-media thickness and atheromatous plaques, and exercise tests should be done at treatment initiation and every 2 years during follow-up.^{303,304}

- Contraindications for apheresis: bleeding diathesis, resistance to adequate coagulation, and hypersensitivity to heparin.

- Adverse effects: iron deficiency anemia is the most frequent; hypotension and venous access problems are also reported but less frequently.

- Safety: it is a safe and tolerable procedure for children and adolescents in specialized centers.³⁰⁶

Many case studies and clinical evaluations have demonstrated that children who had undergone LDL-A for many years (up to 20 years) developed normally.³⁰⁶⁻³⁰⁸

8.4. LDL Apheresis in Adult Patients with HoFH or Severe HeFH

For patients with HoFH or severe HeFH, after 6 months with no adequate response³⁰⁹ to maximum drug therapy, which includes statins, ezetimibe, and PCSK9 inhibitors, or drug intolerance, LDL-A is indicated in the following situations:

1. Functional HoFH with LDL-C $\geq$ 300 mg/dL (or non-HDL-C $\geq$ 330 mg/dL).
2. Functional HeFH with LDL-C $\geq$ 300 mg/dL (or non-HDL-C $\geq$ 330 mg/dL) and one or no risk factors.
3. Functional HeFH with LDL-C $\geq$ 200 mg/dL (or non-HDL-C $\geq$ 230 mg/dL) and at least two risk factors or high Lp(a) ($\geq$ 50 mg/dL).
4. Functional HeFH with LDL-C $\geq$ 160 mg/dL (or non-HDL-C $\geq$ 190 mg/dL) and presence of clinical or subclinical CVD or risk factors such as diabetes and smoking.

Several clinical trials have confirmed the benefits of LDL-A in preventing and reducing the progression of atherosclerotic disease.³¹⁰⁻³¹⁷ Other beneficial effects have also been reported, such as improved endothelial function,³¹⁸ coronary artery vasodilation,³¹⁹ improved microvascular flow,³²⁰ and myocardial perfusion.³²¹ LDL-A is the only treatment that consistently reduces Lp(a) levels by more than 50%.^{322,323}

Although LDL-A is the most feasible treatment for some severe homozygous and heterozygous patients, the procedure is available in few centers worldwide because of its high cost.

8.5. Recommendation for Indication of LDL Apheresis in Adults with HoFH or Severe HeFH and Children with HoFH

Retrospective studies or long-term follow-up cohorts demonstrate that patients with severe HoFH or HeFH hardly achieve the recommended LDL-C goals, despite the maximum doses of optimized therapy combined with weekly or fortnightly LDL-A sessions. Studies demonstrated that, although reducing cholesterol was difficult, patients with lower LDL-C levels had higher survival rates and fewer cardiovascular events than those with higher levels. These benefits were independent of the type of treatment. Therefore, the degree of lipid lowering, as well as its early onset, independently determined clinical outcomes.³²⁴ Because LDL-A is the procedure that most reduces LDL-C levels, it is recommended for adults with HoFH or severe HeFH and children with HoFH (grade of recommendation: I; level of evidence: C).

8.6. Liver Transplantation

Liver transplantation can be an option for patients with FH refractory to pharmacological treatment³²⁵ and is especially indicated for patients with HoFH. However, patients and family members should always be included in the discussion so that the risks and benefits of the procedure are explained (grade of recommendation: IIB; level of evidence: C).

9. Treatment Algorithms for Familial Hypercholesterolemia in Adults

To facilitate the therapeutic approach to both heterozygous and homozygous FH in adults (> 18 years), with attention to cardiovascular risk, five treatment algorithms are shown in Figures 7-11.

Figure 7 shows a treatment flowchart for very high-risk HeFH, including goals and proposed therapeutic sequence to achieve these goals. Potent statins, ezetimibe, and PCSK9 inhibitors aimed at lowering LDL-C by > 50% and achieving LDL-C < 50 mg/dL are recommended for attaining goals gradually.

In Figure 8, there is a treatment flowchart for high-risk HeFH with proposed goals and therapeutic sequence to achieve these goals. Potent statins, ezetimibe, and PCSK9 inhibitors aimed at lowering LDL-C by > 50% and achieving LDL-C < 70 mg/dL are recommended for attaining goals gradually.

In Figure 9, a treatment flowchart for intermediate-risk HeFH is shown, including proposed goals and therapeutic sequence to achieve these goals. Potent statins, ezetimibe, and PCSK9 inhibitors aimed at lowering LDL-C by > 50% and achieving LDL-C < 100 mg/dL are recommended for attaining goals gradually.

Figure 10 shows a treatment flowchart for HoFH in secondary prevention, including therapeutic goals and proposed therapeutic sequence to attain these goals. The purpose is to achieve an LDL-C reduction > 50% and an LDL-C goal < 50 mg/dL. Potent statins and ezetimibe are recommended as first-line therapy, in addition to PCSK9 inhibitors, if an LDL-C reduction < 30% is sufficient to achieve goals and the patient does not carry LDLR-null

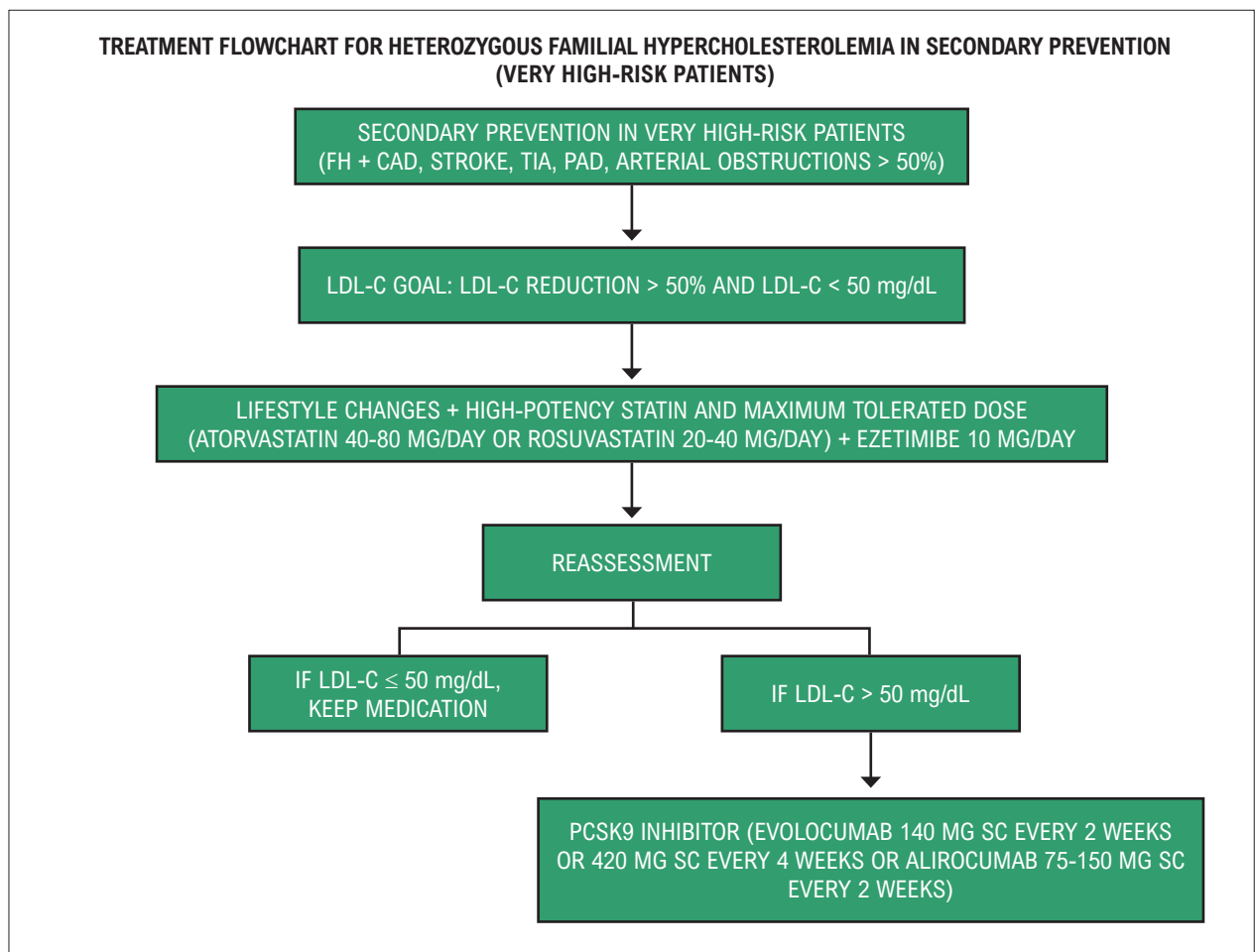


Figure 7 – Treatment flowchart for heterozygous familial hypercholesterolemia in secondary prevention (very high-risk patients).
CAD: coronary artery disease; FH: familial hypercholesterolemia; LDL-C: low-density lipoprotein cholesterol; PAD: peripheral artery disease;
SC: subcutaneously; TIA: transient ischemic attack.

mutations in both alleles; if LDL-C remains > 50 mg/dL or if the patient carries LDLR-null mutations in both alleles, additional therapies such as microsomal triglyceride transfer protein (MTP) inhibitor (lomitapide) may allow achieving goals with an additional 50% reduction in LDL-C. Other additional therapies such as apheresis and liver transplantation are included in the flowchart. Patients should always be referred to and followed-up by a specialist.

Figure 11 shows a treatment flowchart for HoFH in primary prevention, with therapeutic goals and a proposed therapeutic sequence to achieve these goals. The purpose is to achieve an LDL-C reduction > 50% and an LDL-C goal < 70 mg/dL. Potent statins and ezetimibe are recommended as first-line therapy, in addition to PCSK9 inhibitors, if an LDL-C reduction < 30% is sufficient to achieve goals and the patient does not carry LDLR-null mutations in both alleles; if LDL-C remains > 70 mg/dL or if the patient carries LDLR-null mutations in both alleles, additional therapies such as MTP inhibitor (lomitapide) may allow achieving goals with an additional 50% reduction in

LDL-C. Other additional therapies such as apheresis and liver transplantation are included in the flowchart. Patients should always be referred to and followed-up by a specialist.

10. Familial Hypercholesterolemia in Children

10.1. Screening

Suspecting that a child or adolescent has FH is extremely important because, according to estimates, one child is born with FH every minute worldwide. However, diagnosing the disorder in this group is a challenge in clinical practice.⁵⁹

Several factors contribute to underdiagnosis. Notably, there is a lack of knowledge regarding ideal age recommendations for laboratory screening as well as a clinical tendency to assess lipid profiles in overweight/obese or diabetic children (FH children are mostly healthy weight and generally do not have diabetes). Also, there are failures in the process of obtaining a detailed history during the first childcare visit, which should include a history of premature CVD or known high cholesterol levels in first-degree relatives.

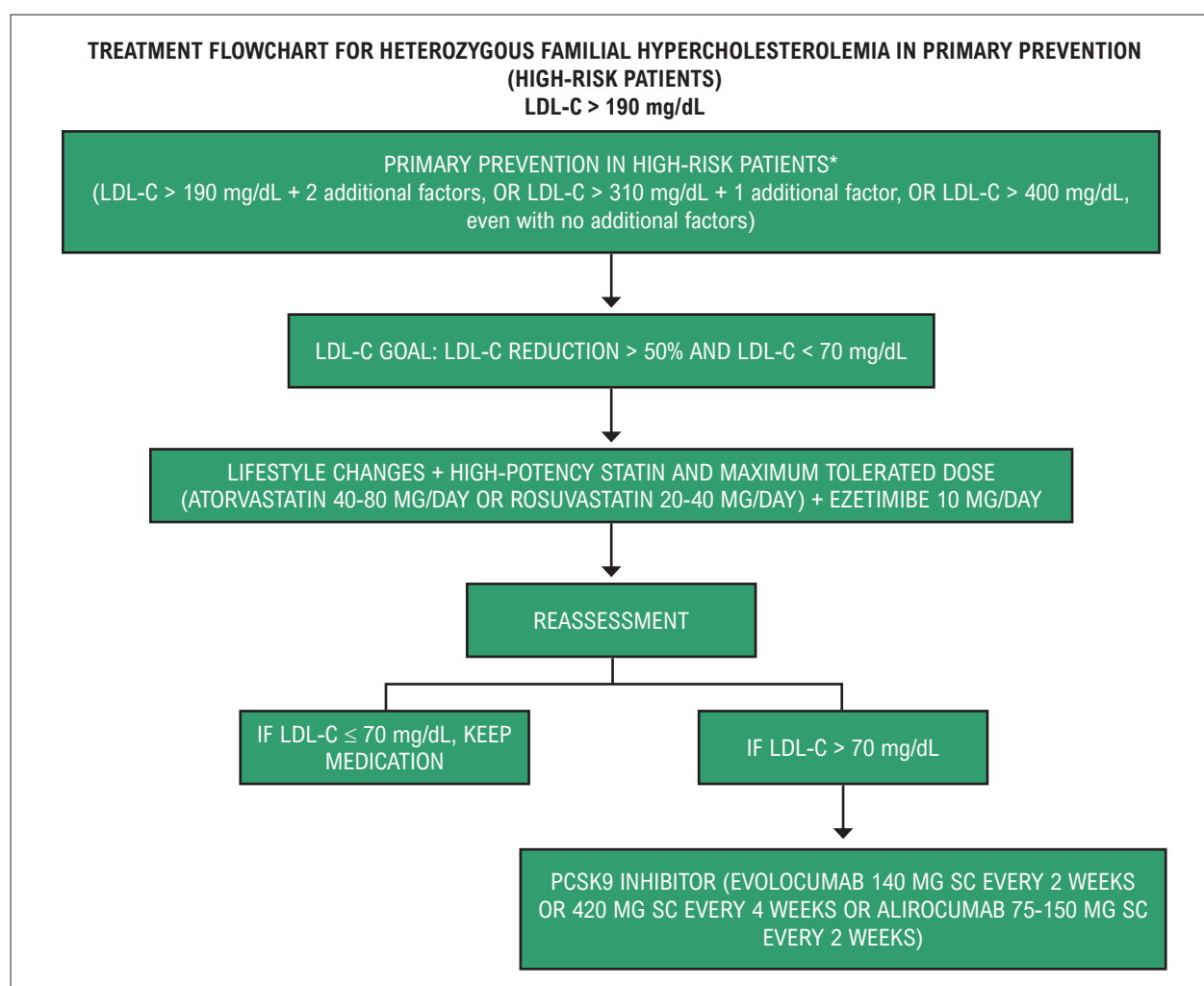


Figure 8 – Treatment flowchart for heterozygous familial hypercholesterolemia in primary prevention (high-risk patients). LDL-C: low-density lipoprotein cholesterol; SC: subcutaneously. *Additional risk factors in FH are the following:⁵⁶ age > 40 years and no treatment, smoking, being male, Lp(a) > 50 mg/dL, HDL-C < 40 mg/dL, hypertension, diabetes mellitus, family history of premature CAD in first-degree relatives (men aged < 55 years and women aged < 60 years), chronic kidney disease (GFR < 60 mL/min), and BMI > 30 kg/m².

Thus, HeFH in asymptomatic children is generally detected with a serum lipid profile test, when there is a close relative with a confirmed diagnosis of FH.⁵⁷ In this context, except for specific conditions in which early screening is recommended, laboratory screening for dyslipidemia, including FH, is universally recommended in children and adolescents aged 10 years or over (grade of recommendation: I; level of evidence: A).

A lipid profile test is the initial laboratory screening tool in this group, based on the analysis of total cholesterol and LDL-C levels. However, it should be noted that:

1. In universal screening, a lipid profile test does not require fasting because dietary status has no influence on concentrations of total cholesterol, LDL-C, and non-HDL-C.
2. An isolated measure of LDL-C is not sufficient for diagnosing dyslipidemia in children or adolescents. Studies demonstrate a wide variation in LDL-C when measurement is repeated after at least 2 weeks.³²⁶

10.2. Lipid Profile Levels for Suspected Familial Hypercholesterolemia

1. A laboratory screening algorithm for children or adolescents with FH is described in Figure 12 (grade of recommendation: I; level of evidence: A).

2. It should be noted that, if LDL-C levels are > 400 mg/dL, severe HeFH or HoFH should be suspected⁵⁹ (grade of recommendation: I; level of evidence: A).

10.3. Factors Related to Increased Cardiovascular Risk

FH patients are generally considered to be at high cardiovascular risk, and this risk may increase depending on the presence of additional factors.^{139,328,329} These include the following: reduced HDL-C levels, high triglyceride levels, high Lp(a) levels, and lifestyle factors such as smoking, atherogenic diet, and sedentary behavior.⁵⁶

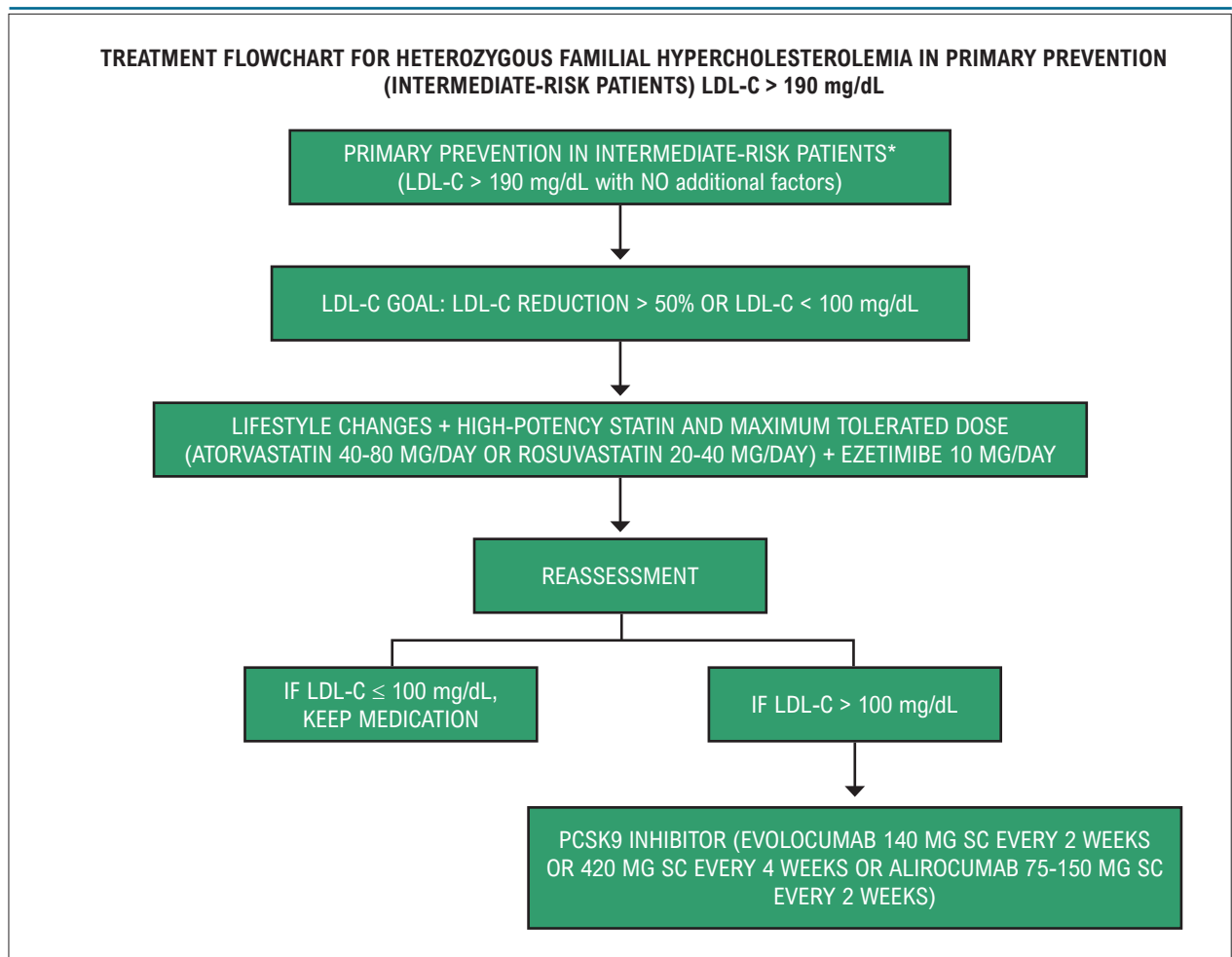


Figure 9 – Treatment flowchart for heterozygous familial hypercholesterolemia in primary prevention (intermediate-risk patients). LDL-C: low-density lipoprotein cholesterol; SC: subcutaneously.

*Additional risk factors in FH are the following:⁵⁶ age > 40 years and no treatment, smoking, being male, Lp(a) > 50 mg/dL, HDL-C < 40 mg/dL, hypertension, diabetes mellitus, family history of premature CAD in first-degree relatives (men aged < 55 years and women aged < 60 years), chronic kidney disease (GFR < 60 mL/min), and BMI > 30 kg/m².

Also, specific conditions related to premature CAD should be considered in the pediatric group, including type 1 and type 2 diabetes, chronic kidney disease, heart transplant, Kawasaki disease, chronic inflammatory disease, human immunodeficiency virus (HIV), nephrotic syndrome, and previous cancer treatment.²²⁴

10.3.1. Screening Tools for Diagnosis of Familial Hypercholesterolemia in Addition to Laboratory Lipid Profile

Given the severity of cases and the early development of cardiac lesions, there is a need to monitor complications, ideally at diagnosis, which usually happens after the age of 2 years. It consists of determining markers of accelerated progression of atherosclerosis, cardiac function, valvular and aortic root lesions.

Monitoring of atherosclerosis aims to determine the arterial structure and function periodically, which can be used for decision-making regarding drug management and LDL-C goals. IMT has been considered the ideal and easiest

method to conduct a structural assessment of the vessel wall in FH children, especially those over 8 years of age, based on internationally validated criteria for age³³⁰ (grade of recommendation: IIa; level of evidence: B). Recently, computerized axial tomography has been shown to be even more sensitive, but this procedure seems to be reserved for patients with HoFH¹⁴⁴ (grade of recommendation: IIa; level of evidence: C).

Several methods have been described to assess endothelial function in pediatric patients, including flow-mediated distensibility (with digital tonometry), post-occlusive reactive hyperemia, and pulse wave velocity. There is no consensus on which of them is more sensitive and specific, and use of the locally validated method is suggested^{331,332} (grade of recommendation: IIa; level of evidence: C).

Global longitudinal strain of the left ventricle seems to be decreased in children with severe dyslipidemias; for this reason, their ventricular function should be periodically assessed, initially with conventional echocardiography. Assessing cardiac valves

TREATMENT FLOWCHART FOR HOMOZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA IN SECONDARY PREVENTION (VERY HIGH-RISK PATIENTS) LDL-C > 500 mg/dL UNTREATED, OR > 300 mg/dL ON-TREATMENT*

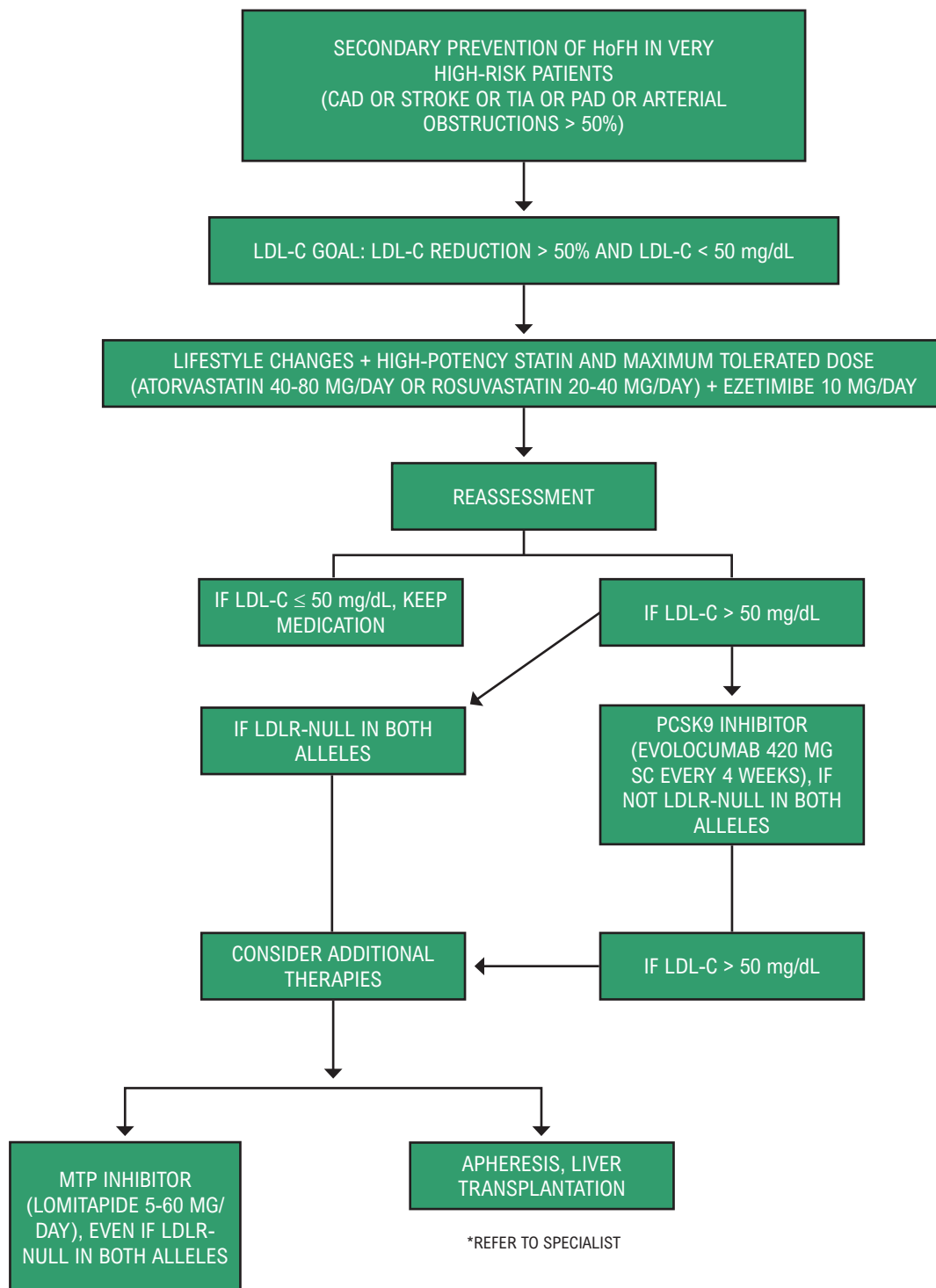


Figure 10 – Treatment flowchart for homozygous familial hypercholesterolemia in secondary prevention. CAD: coronary artery disease; HoFH: homozygous familial hypercholesterolemia; LDL-C: low-density lipoprotein cholesterol; MTP: microsomal triglyceride transfer protein; PAD: peripheral artery disease; SC: subcutaneously; TIA: transient ischemic attack.

TREATMENT FLOWCHART FOR HOMOZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA IN PRIMARY PREVENTION
LDL-C > 500 mg/dL UNTREATED, OR > 300 mg/dL ON-TREATMENT*

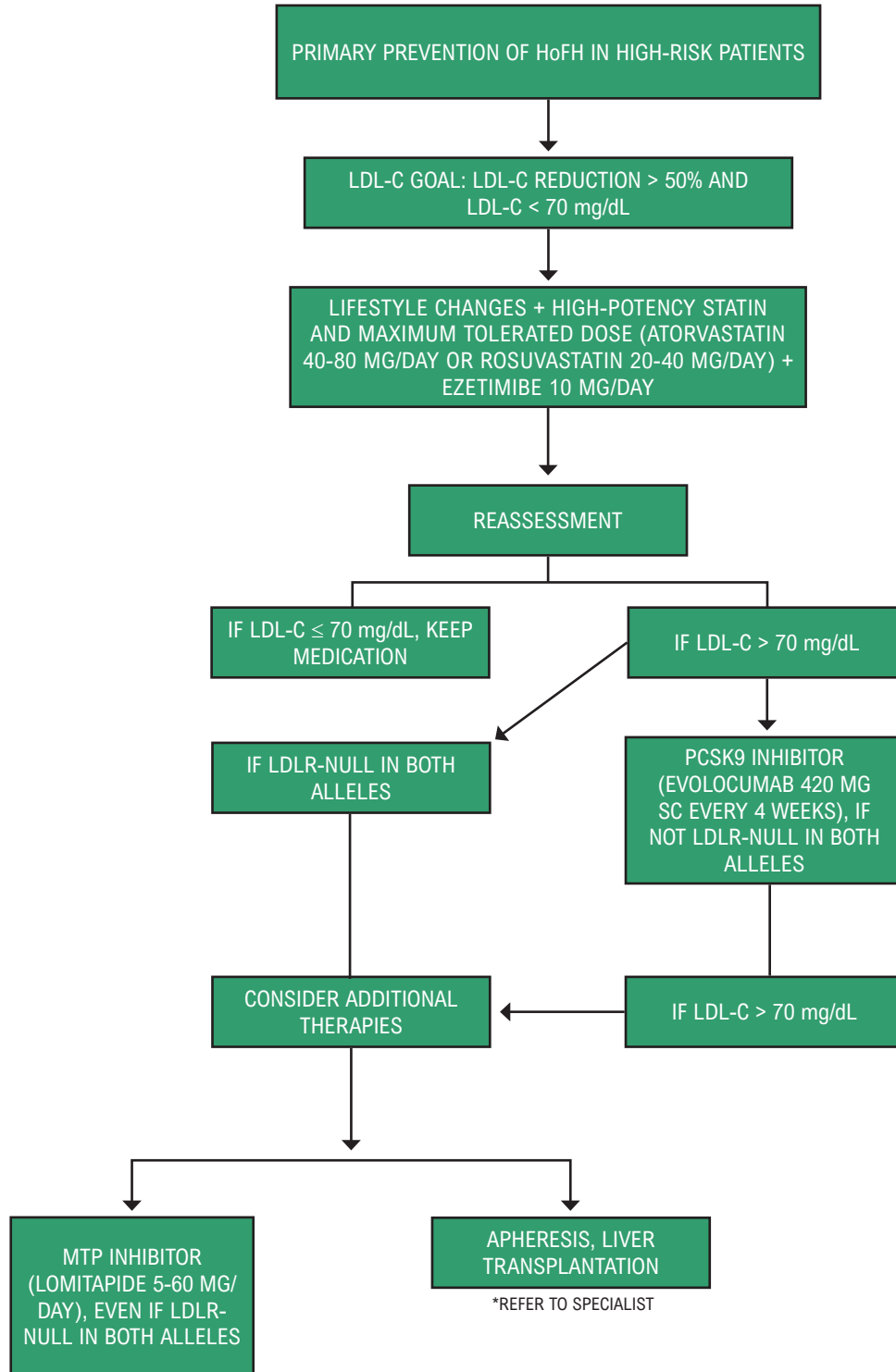


Figure 11 – Treatment flowchart for homozygous familial hypercholesterolemia in primary prevention. CAD: coronary artery disease; HoFH: homozygous familial hypercholesterolemia; LDL-C: low-density lipoprotein cholesterol; MTP: microsomal triglyceride transfer protein; PAD: peripheral artery disease; SC: subcutaneously; TIA: transient ischemic attack.

Update

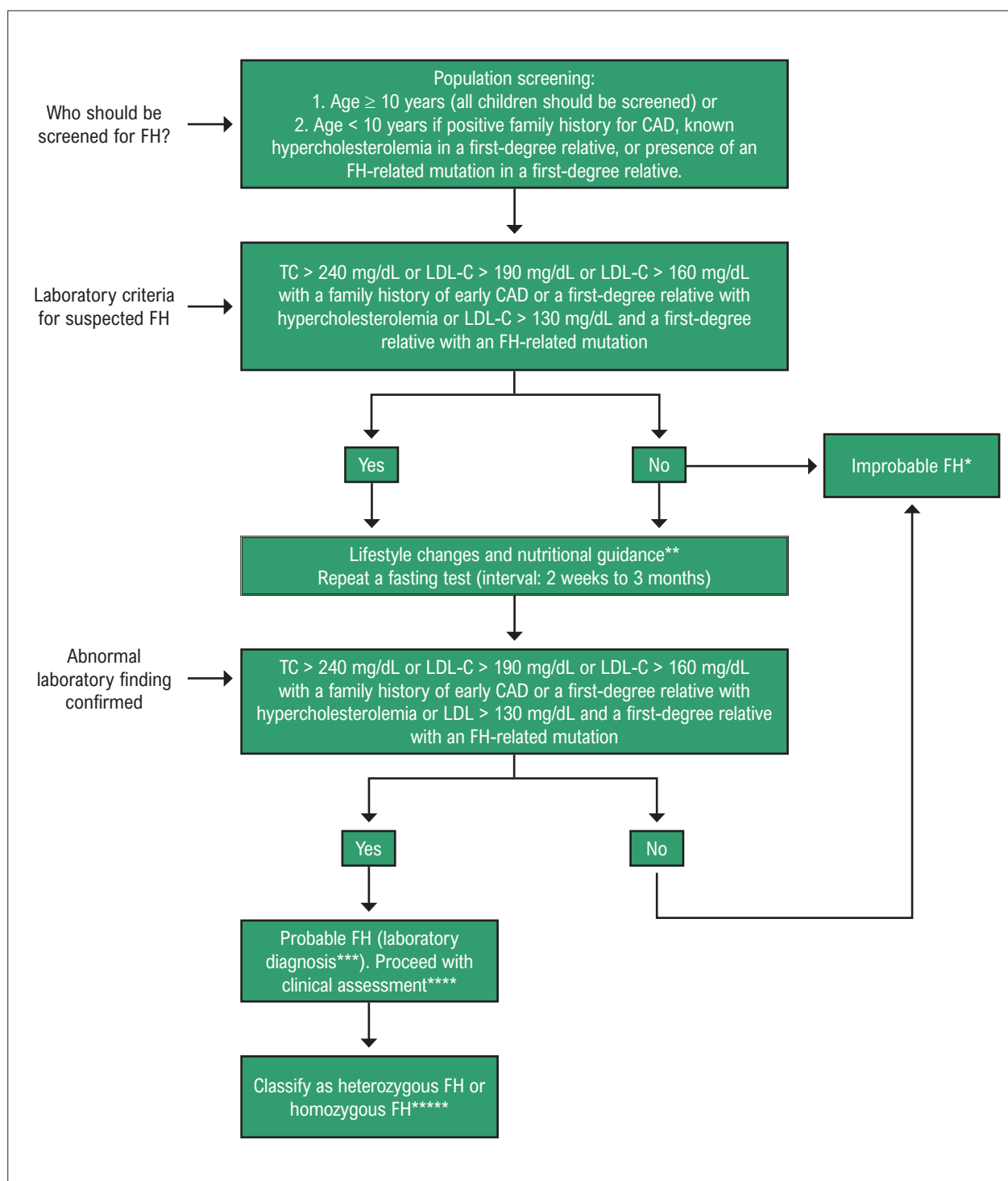


Figure 12 – Laboratory screening algorithm for familial hypercholesterolemia in children and adolescents. Adapted from Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents;²²⁴ Wiegman A, et al.³²⁷

CAD: coronary artery disease; FH: familial hypercholesterolemia; LDL-C: low-density lipoprotein cholesterol; TC: total cholesterol.

*Improbable FH: absence of laboratory criteria for FH does not mean that a different dyslipidemia is not present. Children or adolescents with lipid profile levels outside the reference range for their age group should undergo a clinical assessment. Secondary causes should be assessed in this age group: kidney or thyroid dysfunction, HIV, autoimmune diseases, diabetes, and obesity, among others.

**Lifestyle changes and nutritional guidance; see nonpharmacological therapy section.

***When available, genetic testing should be provided.

****Clinical assessment: clinical signs such as xanthomas, xanthelasma, corneal arcus, and thickened tendon should be assessed. Rule out non-FH clinical conditions that co-occur with hypercholesterolemia. Dutch scores should be used at this stage.

*****See peculiarities in the management of patients with HoFH section

and aortic root is also important to rule out the possibility of dysfunctions, dilations, or calcifications. Computerized axial tomography has been shown to be the most sensitive method³³³ (grade of recommendation: IIa; level of evidence: C).

10.4. Treatment

Indication, management, and goals to be achieved with the introduction of nonpharmacological and pharmacological treatments are described in Figure 13 (grade of recommendation: II; level of evidence: A).

10.4.1. Nonpharmacological Treatment

Lifestyle changes are a key step in the treatment of children with FH. Management of dyslipidemia should preferably be supported by an interdisciplinary team. Combating both active and passive smoking should be combined with close monitoring of hypertension and overweight or obesity in all patients, right from diagnosis.

10.4.1.1. Diet

Diet is known to have a partial effect on FH because of pathophysiological characteristics. Nonetheless, diet is

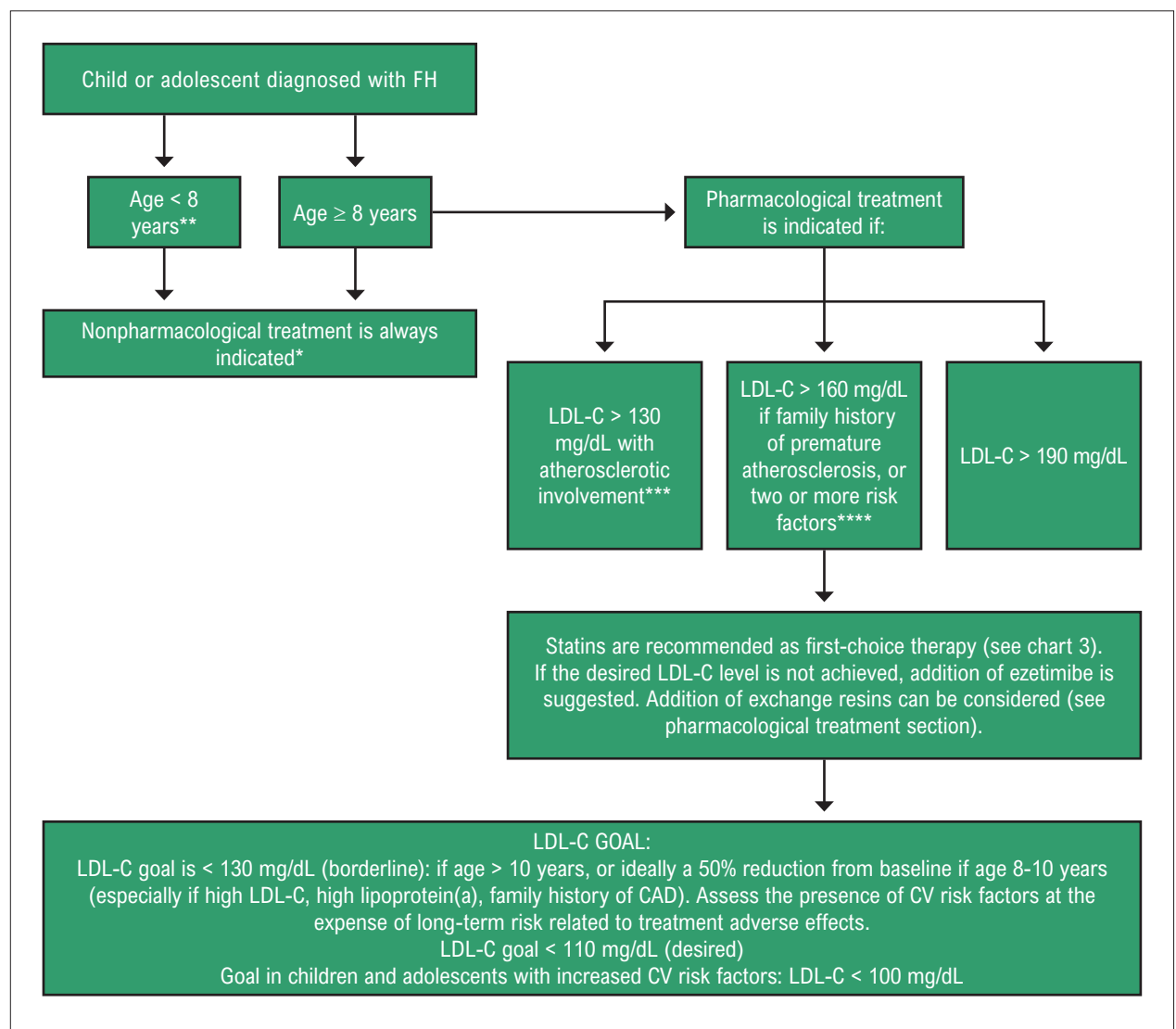


Figure 13 – Management algorithm for familial hypercholesterolemia in children and adolescents. Adapted from Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents;²²⁴ Wiegman A, et al.³²⁷

CAD: coronary artery disease; CV: cardiovascular; FH: familial hypercholesterolemia; LDL-C: low-density lipoprotein cholesterol.

*All children should undergo a nonpharmacological therapy. See nonpharmacological therapy section.

**In children under 8 years of age, the decision on drug therapy should be individualized, e.g. for cases of severe heterozygous or homozygous FH.

***If LDL-C > 130 mg/dL with no atherosclerotic involvement, choose nonpharmacological treatment.

****See factors related to increased cardiovascular risk section.

recommended at diagnosis because it has a significant effect on lipoproteins and apolipoproteins, and also there is evidence that diet decreases the inflammatory pattern of these patients: the higher the intake of PUFAs, the lower the inflammation, and the higher the intake of energy and cholesterol, the higher the inflammation.^{334,335}

As is the case with all children in the general population, intake of SFAs should be reduced and intake of MUFAs and PUFAs should be increased, mostly from plants (canola oil has the best results). Other recommendations are elimination of trans fatty acids, increased intake of fruits and vegetables (maximizing fiber consumption, but preferably from food sources), and restriction of intake of added sugar^{334,335} (grade of recommendation: IIa; level of evidence: B).

Even in children, initial dietary treatment should follow type I diet guidelines, with TEI calculations according to amounts of calories, macronutrients, and micronutrients required to allow adequate growth and development^{334,335} (grade of recommendation: I; level of evidence: B).

If the response to type I diet is inadequate, a type II diet is introduced, and management by a nutrition expert (a dietitian or a physician nutrition specialist) is strongly recommended, since the risk of malnutrition (lack of macronutrients or micronutrients, especially fat-soluble vitamins) is remarkably high, especially in younger patients on ezetimibe or anion exchange resins, who are at the highest risk³³⁶ (grade of recommendation: I; level of evidence: B).

10.4.1.2. Physical Activity

For children aged 6 to 17 years, vigorous-intensity aerobic activity for at least 60 minutes daily is recommended. Muscle-strengthening and bone-building activities at least three times weekly are also recommended (grade of recommendation: IIa; level of evidence: B).^{337,338}

Preschoolers should remain active throughout the day to have better conditions of growing and developing a repertoire of motor skills. Being active for at least 3 hours daily should be aimed (grade of recommendation: IIa; level of evidence: B).

Although there is no consensus on the level of physical activity required to control the impact of dyslipidemia on

children, active behavior is known to improve endothelial function and reduce IMT³³⁹ (grade of recommendation: IIa; level of evidence: B).

Patients with dyslipidemia, especially FH, may need a comprehensive, interdisciplinary cardiopulmonary and metabolic rehabilitation program. In children, initial supervised physical activity is safer because this type of approach is known to provide better control of cardiovascular risk factors and regression of subclinical atherosclerosis³⁴⁰ (grade of recommendation: IIa; level of evidence: A).

10.4.2. Pharmacological Treatment

Based on strict fulfillment of the criteria described below and after lifestyle changes, lipid-lowering therapy should be initiated at the age of 8 years. The treatment in children under 8 years of age may be indicated if the case is severe and after individual assessment. The aim is to reduce LDL-C by at least 50% and, if possible, achieve < 110 mg/dL (desired) or at least 130 mg/dL (borderline), in addition to reducing xanthomatosis and preventing the onset of CAD (grade of recommendation: I; level of evidence: A).

10.4.2.1. Statins

Statins significantly decrease total cholesterol, LDL-C, and Apo B, with no apparent significant occurrence of adverse effects related to sexual development and muscle or liver toxicity. The drugs can be used in children aged 8 years or over (in individual cases, they can be prescribed for those under 8 years of age).^{59,341,342} Statins can decrease LDL-C by approximately 30% and increase HDL-C by 5%³⁴³⁻³⁴⁸ (grade of recommendation: IIa; level of evidence: A).

Recent publications have shown that statins, in addition to reducing total cholesterol and LDL-C in children, improved endothelial function, decreased carotid IMT, and led to regression of xanthomas (grade of recommendation: IIa; level of evidence: B).³⁴⁹ The usual doses of lipid-lowering drugs for children and adolescents are described in Chart 3.

Doses higher than those described below can be used after individual risk assessment in children and adolescents. In this group, initial use of the lowest possible statin dose

Chart 3 – Doses of lipid-lowering drugs for children and adolescents

Drug	Doses (mg)
Lovastatin	10 to 40
Pravastatin	10 to 40
Simvastatin	10 to 40
Rosuvastatin	5 to 40
Atorvastatin	10 to 40
Cholestyramine*	4 to 16*
Ezetimibe	10

* In grams.

is suggested (grade of recommendation: IIa; level of evidence: C). When the LDL-C goal is not achieved with the maximum tolerated statin dose, ezetimibe is indicated as a second choice for combined treatment (grade of recommendation: I; level of evidence: B).

10.4.2.2. Cholesterol Absorption Inhibitors

Ezetimibe monotherapy lowers LDL-C levels by approximately 28% in children with HeFH. Monotherapy is recommended for those aged 5 years or over, while combined therapy with a statin is indicated for those over 8 years of age^{342,350} (grade of recommendation: IIb; level of evidence: C).

10.4.2.3. Bile Acid Sequestrants

Bile acid sequestrants can be used at any age. Sequestrants used as monotherapy lower LDL-C levels by approximately 10 to 15%. They can also be combined with statins or ezetimibe, but at different times of administration. Because of the risk of malnutrition related to fat-soluble vitamins, nutritional monitoring and supplementation according to objective deficiency criteria are recommended.³⁵¹ To improve palatability and increase children's tolerance, apple juice can be given together with the sequestrant (grade of recommendation: I; level of evidence: B).

10.4.2.4. Supplements

Supplementation with 1.2 to 1.5 g of phytosterols can lower total cholesterol and LDL-C levels in HeFH children by approximately 10%³⁵² (grade of recommendation: IIb; level of evidence: B). Importantly, omega-3 supplements, such as those found in fish oil products, are not recommended for FH children because they may increase LDL-C levels³²⁹ (grade of recommendation: III; level of evidence: B).

10.4.3. New Treatments

This group consists of medications such as lomitapide, mipomersen, and PCSK9 inhibitors (alirocumab and evolocumab). Evolocumab 420 mg SC every 4 weeks was studied in a pediatric population with HeFH (n = 170) aged 10 to 17 years, not controlled for standard treatment including statin and/or ezetimibe. Patients were randomly allocated to receive evolocumab (n = 104) or placebo (n = 53). Evolocumab reduced LDL-C at week 24 by 44.5%, with an absolute reduction of 77.5 mg/dL. There were reductions in other lipid variables.³⁵³ Alirocumab was evaluated in the Odyssey Kids dose-finding study,³⁵⁴ but the study data are yet to be completed.

Although some of these drugs have been approved for the adult population, their use in the pediatric population should be considered on a case-by-case basis⁵⁹ (grade of recommendation: IIa; level of evidence: C). To date, however, published long-term safety data are based on adult samples (age of 18 years or over), with limited evidence on children with FH.³⁵⁵⁻³⁵⁷

10.4.4. Particularities in the Management of Homozygous Familial Hypercholesterolemia

The subgroup representing the greatest management challenge and also with the greatest impact on treatment during childhood consists of children and adolescents with HoFH. Because they have a homozygous mutation in the *LDLR* gene or additional genetic defects, phenotypically characterized by very high LDL-C concentrations, intervention is needed at diagnosis, regardless of age, to prevent atherosclerotic manifestations, which sometimes appear in the first decade. Because of pathophysiological characteristics, anion exchange resins are often ineffective, especially in homozygous patients with *LDLR*-null mutations in both alleles.³⁵¹ Figure 14 shows the algorithm used to manage such children and adolescents³⁵⁸ (grade of recommendation: IIa; level of evidence: C). These patients should be referred to a lipid specialist.

In adolescents with severe, clinically manifest atherosclerosis, coronary artery bypass graft is indicated.^{359,360} In case of aortic disease due to severe dyslipidemia, pulmonary autograft (Ross-Konno procedure)³⁶¹ may be an interesting substitute in adolescents because of its durability (grade of recommendation: IIb; level of evidence: C).

10.5. Treatment Monitoring

Continuous use of single or combined drugs is recommended³⁶² (grade of recommendation: I; level of evidence: C). A large systematic review of randomized controlled trials evaluating the use of statins in children and adolescents demonstrated that the risk of adverse events in this group was similar to that in adults treated with statins, at least in the short term. The reviewed studies analyzed the effect of statin therapy on sexual development, growth, nutrition, and liver or kidney toxicity. In most parameters, there was no statistically significant difference between the treatment and placebo groups. No severe adverse events were reported. Elevations in liver transaminases and creatine phosphokinase (CPK), which are of particular concern in adults, did not differ in the study groups.³⁶²

Baseline assessment of CPK, transaminases (TGO, TGP), and HbA1C (for the risk of diabetes associated with statins) is recommended. Laboratory monitoring should be conducted every 4 to 8 weeks, until the measurements have stabilized, and then every 6 months^{59,329} (grade of recommendation: I; level of evidence: C). For patients with symptoms possibly related to statins, laboratory monitoring is recommended while symptoms are present, which can help the pediatrician decide whether there is indeed a relationship with the medication. Also, adolescents should be oriented about contraceptive methods because of the potential teratogenicity of statins³³¹ (grade of recommendation: I; level of evidence: C).

If laboratory abnormalities (transaminase levels > 3-fold higher; and/or CPK levels > 3- to 10-fold higher in asymptomatic patients; or CPK levels > 10-fold higher in asymptomatic patients) are detected, statin therapy should be discontinued, and a new test should be done after 2 weeks. With normal laboratory levels, statin therapy can be resumed with proper monitoring³³¹ (grade of recommendation: I; level of evidence: C).

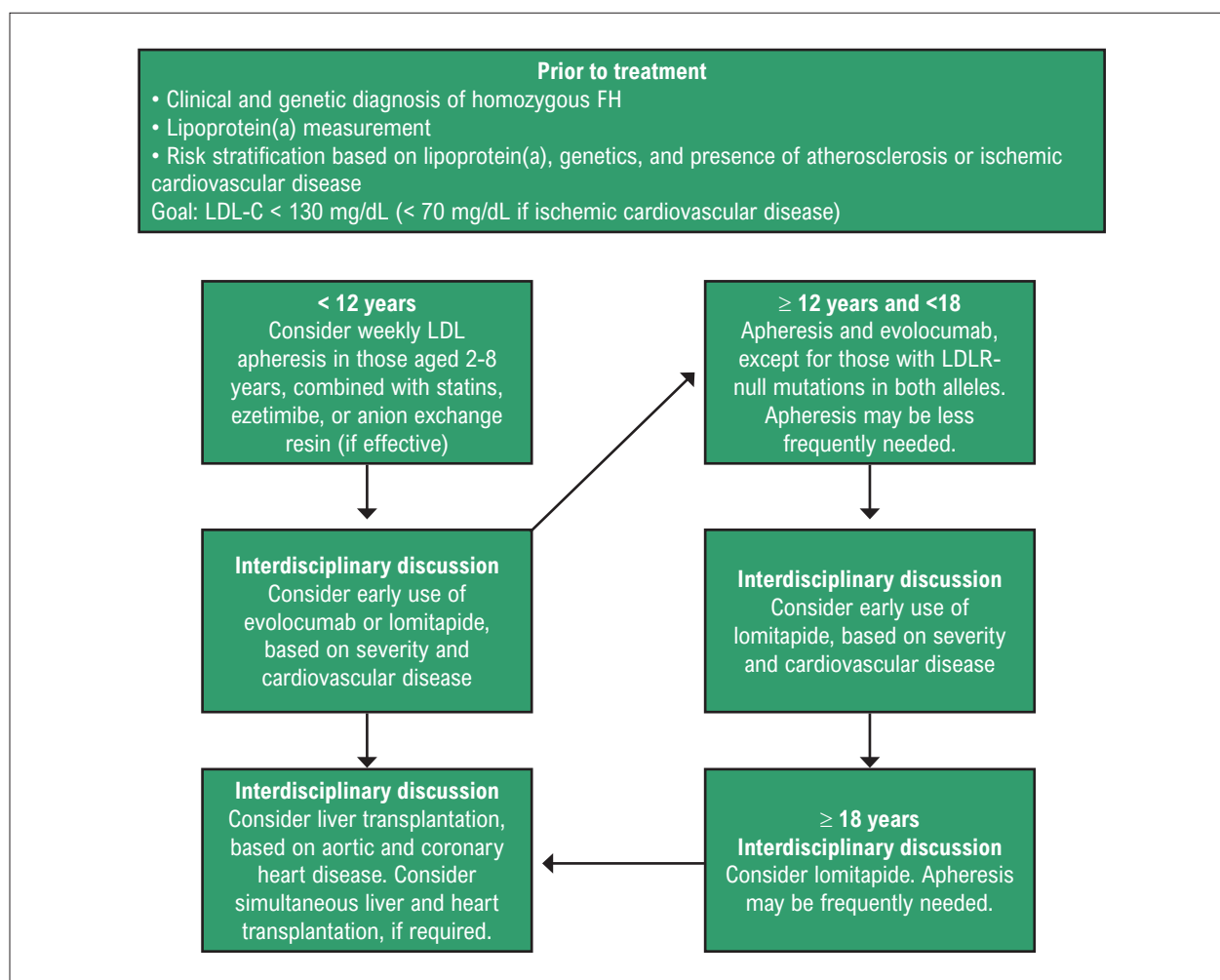


Figure 14 – Treatment algorithm for homozygous familial hypercholesterolemia in children and adolescents.³⁵⁸ FH: familial hypercholesterolemia.

10.6. Psychological Aspects

Pharmacological treatment does not seem to impact quality of life or anxiety in children with FH. Approximately 40% of children suffer because they have the condition, but lipid-lowering drugs provide greater safety in around 60%. Over 50% are on a diet, and 79% of parents suffer because their children have FH³⁶³ (grade of recommendation: IIb; level of evidence: B).

11. Treatment of Familial Hypercholesterolemia during Pregnancy

During pregnancy and lactation, the therapeutic options for FH are quite limited, since statins, ezetimibe, PCSK9 inhibitors, and nicotinic acid should not be prescribed in order to prevent the potential adverse fetal effects which have been associated with these agents (categories X, C, B, and C, respectively). This may be a cause for concern because plasma lipid levels are usually increased during pregnancy (increases of 25 to 50% in cholesterol and 150 to 300% in triglycerides), in addition to quite high baseline cholesterol concentrations due to FH.³⁶⁴

Other lipid-lowering medications, specifically resins, may be used when there is a clear need to maintain drug therapy because of their potential benefits. Resins, such as colestevam and cholestyramine, are category B agents in pregnancy and lactation and, therefore, can be considered for the treatment of FH in these situations, provided they are used under medical supervision.³⁶⁵ LDL-A is a treatment modality which can also be used in special cases, when the patient's cardiovascular risk, in the absence of treatment, is very high, such as in patients with HoFH or HeFH and severe atherosclerotic disease.³⁶⁶

Women with FH of childbearing potential who wish to become pregnant should receive pre-pregnancy counseling and discontinue statins, ezetimibe, and nicotinic acid for at least four weeks before stopping the contraceptive method. Importantly, oral contraceptives are generally not contraindicated for most women with FH³⁶⁷ and do not affect statin efficacy.³⁶⁸ Women at increased risk of cardiovascular events should discuss about contraceptive methods other than oral contraceptives.³⁶⁷

In the case of unplanned pregnancy, patients should discontinue lipid-lowering drugs immediately and search

for obstetric care. Few studies have evaluated women with FH who became pregnant while on statin therapy, with controversial results regarding the incidence of fetal malformations. In a case series reported by the Food and Drug Administration (FDA) in 2004, 52 selected cases of gestational exposure to statins were evaluated, and 20 consisted of structural birth defects, especially neurological and skeletal defects.³⁶⁹

The relative lack of safe and effective treatments to reduce plasma cholesterol levels in these pregnant patients is associated with concerns about adverse effects caused by hyperlipidemia itself. Indeed, some studies suggest that pregnant women with high cholesterol levels are at increased risk of preterm birth.^{370,371} A recent Norwegian study evaluating 2,319 births of 1,093 women with FH detected no differences in preterm births between women genetically diagnosed with FH and women in the general population.³⁶⁴ Concerning low birth weight, there also seems to be no significant difference between newborns of women with or without FH. The frequency of congenital malformations in newborns of women with FH does not seem to be higher compared with that of women in the general population (3.3 and 3.2%, respectively). Toleikyte et al.³⁶⁴ also found no differences in preterm birth, low birth weight, and malformations according to different types of genetic mutation.

Although most available studies do not demonstrate significant associations between adverse fetal events and FH, pregnant women with the disease should be monitored jointly by a lipid specialist and an obstetrician. Attention should be given to possible valve diseases, particularly aortic stenosis, and early coronary heart disease in these patients.³⁷² From an obstetric point of view, the investigation of uteroplacental vascular insufficiency is also important.^{373,374}

11.1. Conclusions

Lipid-lowering medications in pregnant women with FH including statins, ezetimibe, nicotinic acid, fibrates, and PCSK9 inhibitors are not recommended (grade of recommendation: III; level of evidence: B). Resins (grade of recommendation: IIB; level of evidence: B) and apheresis (grade of recommendation: IIB; level of evidence: B) can be used during pregnancy.

11.2. FDA Drug Classification for Possible Fetal Effects

- Category A: adequate, well-controlled studies have shown no risk to the fetus in the first trimester of pregnancy (and there is no evidence of risk in the following trimesters).
- Category B: animal studies have shown no risk to the fetus, and there are no adequate, well-controlled studies in pregnant women.
- Category C: animal studies have shown adverse effects on the fetus, but there are no adequate, well-controlled studies in pregnant women.
- Category D: there is evidence of risk to the fetus based on adverse reaction data from human studies or marketing or investigative experience. The benefits of using the drug in

pregnant women may outweigh the risks in some situations.

- Category X: studies in animals or humans have demonstrated fetal abnormalities, and/or there is evidence of fetal risk based on adverse effect data from marketing or investigative experience. The risks of using the drug in pregnant women clearly outweigh the potential benefits.

12. Lipid-lowering Therapies for Severe Forms of Familial Hypercholesterolemia

FH is a difficult-to-treat condition that causes cardiovascular events at an early age. There are two possible presentations: HeFH and HoFH.

The LDL-C goal recommended in guidelines is generally not achieved with conventional therapies, despite the maximum doses of high-potency statins, requiring then the introduction of adjuvant therapy. Conversely, a 50% reduction in LDL-C, another recommended goal, can be achieved with high-potency statins.⁹ Individualized goals for HeFH and HoFH according to the respective risk categories were discussed in sections 7 and 9.

Lipid-lowering drugs added to statins are generally required in the treatment of FH. Despite their adverse effects, they are used to reduce LDL-C and, especially, robust cardiovascular outcomes, such as fatal or nonfatal AMI, fatal or nonfatal stroke, and cardiovascular death. These drugs include:

- Anti-PCSK9 monoclonal antibodies.
- MTP inhibitor (lomitapide).
- Antisense oligonucleotide.

12.1. Anti-PCSK9 Monoclonal Antibodies in Familial Hypercholesterolemia

In classical Mendelian genetic studies, researchers found a region on chromosome 1 that was linked to the presence of FH, responsible for the transcription of the *PCSK9* gene, whose polymorphism transmits the autosomal codominant form of the disease.^{16,375} Subsequent mechanistic studies demonstrated that PCSK9 acts as a chaperone for the LDLR and that, once bound to the receptor, it blocks the conformational change required to prevent its degradation in the lysosome.³⁷⁶ Consequently, the LDLR, which can recirculate approximately 100 times, is degraded early, and this reduces LDL removal from the bloodstream. Consistently, PCSK9 gain-of-function mutations are associated with increased LDL-C and cardiovascular risk, while loss-of-function mutations are associated with reduced LDL-C and cardiovascular risk.^{377,378}

Monoclonal antibodies were developed to reduce the bioavailability of PCSK9, thus preventing it from binding to the LDLR. Evolocumab and alirocumab have been approved for clinical use. Both are fully human monoclonal antibodies administered SC. Evolocumab can be administered at a dose of 140 mg every two weeks or 420 mg once monthly. In both dosing regimens, evolocumab reduces LDL-C by approximately 60%, when administered alone or combined with other lipid-lowering drugs.^{377,379}

A similar reduction was observed in HeFH patients;^{283,284} however, the reduction achieved in HoFH patients was 38%.²⁸⁶ The degree of response will naturally depend on the type and number of mutations. In those with two defective (mutant) alleles (LDL uptake: 2 to 25%), the treatment can reduce LDL-C by up to 47%.²⁸⁶ In those with one defective allele and one negative allele, ie, with no LDLR production (LDL uptake < 2%), the maximum expected effect is 25%.²⁸⁶ Finally, in those with two negative alleles (no LDL uptake), no response is obtained with treatment.²⁸⁶ Data from the TESLA B study were expanded by an interim analysis of the TAUSSIG study, which included 106 patients with HoFH.³⁸⁰ In this open study, after 12 weeks of monthly use of evolocumab 420 mg, the mean reduction in LDL-C was 21% (standard deviation: 24%). Similar to the TESLA B study, response variability was partially dependent on the genetic defect causing the FH phenotype. Homozygotes with defects in the *APOB* or *LDLRAP1* genes (causing autosomal recessive hypercholesterolemia with a phenotype similar to that of HoFH) had mean reductions of 47 and 15%, respectively. Responses were sustained for up to 4 years of treatment, and the most frequent adverse events were symptoms of nasopharyngitis and common flu.

Therefore, evolocumab therapy should be attempted in HoFH patients, except in those homozygous for LDLR-null alleles. However, they will likely require additional therapies.

Alirocumab was tested at the doses of 75 mg and 150 mg every two weeks. The expected LDL-C reductions are 45 to 50% with the lowest dose and 60% with the highest dose.^{284,381,382} With the 300-mg monthly regimen, alirocumab reduces LDL-C by 55 to 60%.³⁸³ Similar to evolocumab, alirocumab reduces LDL-C in HeFH patients by approximately 40 to 60%.³⁸⁴ Equally consistent, LDL-C reductions in HoFH patients are genotype-dependent and range from 7 to 64%.³⁸⁵ Alirocumab is approved for use in HoFH by the FDA, and needs approval for use in the European Medicine Agencies (EMA) and Brazil (ANVISA).

Three randomized, double-blind, placebo-controlled cardiovascular trials evaluated the efficacy of PCSK9 inhibitor therapy for the risk of cardiovascular events. Although none of these trials targeted FH patients, their results can be extrapolated to this population. In the FOURIER trial, evolocumab was compared with placebo in 27,564 patients with clinically manifest atherosclerotic CVD and LDL-C ≥ 70 mg/dL despite optimized lipid-lowering therapy.³⁸⁶ From a baseline LDL-C level of 92 mg/dL, patients receiving evolocumab had a reduction to a mean level of 30 mg/dL, which was maintained over time (median follow-up: 2.2 years).²⁸⁷ Evolocumab therapy reduced the risk of the composite outcome of cardiovascular death, myocardial infarction, stroke, coronary revascularization, or unstable angina requiring hospitalization by 15% (HR 0.85; 95% CI 0.79 to 0.92). The main secondary outcome, a composite of cardiovascular death, myocardial infarction, or stroke, was reduced by 20% (HR 0.80; 95% CI 0.73 to 0.88).²⁸⁷ Similar to studies of statin therapy, clinical benefits progressively increased with time of treatment.²⁸⁷ In a neurocognitive substudy, 1,974 patients from the FOURIER study were evaluated before and after the intervention to assess safety

for cognitive function.³⁸⁷ No differences were observed in cognitive function between groups, and there was no association between LDL-C levels and cognitive changes.

In the SPIRE-1 and SPIRE-2 studies,³⁸⁸ bococizumab was administered to 27,438 patients with a previous cardiovascular event or a history of diabetes, chronic kidney disease, or peripheral vascular disease. The study was terminated prematurely after the investigators found that the effect of bococizumab was not sustained because of the development of neutralizing antibodies.³⁸⁹ The baseline LDL-C level was 109 mg/dL, and 85% of participants were receiving high-intensity statin therapy. Bococizumab lowered LDL-C by 59% at 14 weeks, but this effect reduced to 38% at 2 years.³⁸⁹ In the SPIRE-2 study, which had a longer follow-up, bococizumab reduced by 21% (HR 0.79; 95% CI 0.65 to 0.97; $p = 0.02$) the risk of the primary composite outcome of cardiovascular death, myocardial infarction, stroke, or coronary revascularization.³⁹⁰ A SPIRE substudy showed that the reduction in cardiovascular risk among participants with and without FH was not heterogeneous with the use of bococizumab.³⁹⁰

Finally, the ODYSSEY Outcomes study enrolled 18,924 patients 1 to 12 months after myocardial infarction or unstable angina for alirocumab treatment or placebo.³⁹¹ Alirocumab dose was up-titrated to provide an LDL-C level of 25 to 50 mg/dL, and the drug was discontinued if LDL-C level was persistently lower than 15 mg/dL. Alirocumab lowered LDL-C by 57% within 4 weeks, but this effect progressively reduced to 36% by the end of the study, presumably because of the drug titration regimen.²⁸⁸ The primary composite outcome of cardiovascular death, myocardial infarction, ischemic stroke, or unstable angina requiring hospitalization was reduced by 15% (HR 0.85; 95% CI 0.78 to 0.93; $p = 0.003$).²⁸⁸ A 15% reduction was observed (HR 0.85; 95% CI 0.73 to 0.98) in all-cause mortality with alirocumab treatment compared with placebo.²⁸⁸ However, as there was no significant reduction in two hierarchically important outcomes in this analysis, ie, death from cardiovascular causes and death from coronary heart disease, the results were found to be of exploratory value, not evidence.

12.2. Microsomal Triglyceride Transfer Protein Inhibitor (Lomitapide)

MTP is a lipid transfer protein found in the endoplasmic reticulum of hepatocytes and enterocytes which acts on the assembly of lipoproteins containing Apo B.³⁹²

Lomitapide is a small molecule that inhibits MTP, thus reducing the formation of chylomicrons in the intestine and VLDL in the liver. It is used in combination with statin therapy to reduce LDL-C concentrations, especially in FH patients.

Because VLDL is the metabolic precursor of LDL, plasma LDL concentrations are reduced.³⁹³ In the absence or dysfunction of MTP, similar to what occurs in recessive hypobetalipoproteinemia or abetalipoproteinemia, there is no production of VLDL and, consequently, of other lipoproteins containing Apo B, such as LDL, IDL, and Lp(a). Lomitapide is currently approved by the FDA and the European Medicines Agency (EMA) for use as an adjuvant

therapy in adults with HoFH; however, use in children has been documented.³⁹⁴ Recently, lomitapide was approved in Brazil in 2020 by the National Health Surveillance Agency (Agência Nacional de Vigilância Sanitária, ANVISA) for use in adults with HoFH.

Lomitapide is administered orally at an initial dose of 5 mg/day and may reach 60 mg/day. The dose should be individualized according to therapeutic goals and individual response and tolerance to treatment. A phase 3 study of HoFH patients treated at initial doses of 5 mg/day and up-titrated to 60 mg/day, combined with the current therapy, showed additional reductions of 50% in LDL-C and 49% in Apo B.³⁹⁵ Changes in HDL-C and Lp(a) concentrations have not been described with maintenance of lomitapide treatment after 78 weeks, except for slight variations in HDL-C.³⁹⁶

A phase 3 study consisting of 26 weeks of lomitapide treatment evaluated the achievement of European Atherosclerosis Society goals and the occurrence of major adverse cardiovascular events. The LDL-C goals < 100 mg/dL and < 70 mg/dL were achieved by 51% and 28% of participants, respectively, within 26 weeks.³⁹⁷ In the extension study of patients who remained on lomitapide after 176 weeks (N = 19), 74% achieved LDL-C < 100 mg/dL and 58% achieved LDL-C < 70 mg/dL in at least one measurement. The LDL-C level achieved with lomitapide treatment was 166 mg/dL. There were two cardiovascular events, ie, one cardiac death and one coronary artery bypass graft, equivalent to 1.7 events per 1,000 patient-months of treatment. These numbers are much lower than those observed in the cohorts of FH patients before the use of new therapies.³⁹⁸

A real-world study of 18 patients with HoFH undergoing adjuvant lomitapide treatment at a mean dose of 19 mg/day in a follow-up of 32.3 ± 29.7 months showed an LDL-C reduction of $68.2 \pm 24.8\%$. At the final visit, 60% of patients achieved LDL-C < 100 mg/dL and 46.6% achieved LDL-C < 70 mg/dL; 80% of patients no longer needed LDL-A because of their achievements. LDL-C reduction varied considerably (13-95%), regardless of genotype.³⁹² During follow-up, 53.3% of patients had adverse events, but none were severe. There was no increase in transaminases > 5 times the ULN, and no patient discontinued the medication because of adverse events. Five patients underwent liver ultrasound and fibroscan or nuclear magnetic resonance imaging with spectroscopy, and none had evidence of liver damage.³⁹⁹

Five-year registry data on HoFH patients receiving lomitapide (N = 187) were consistent for efficacy and safety in phase 3 studies, despite the use of a lower dose (10 mg vs 40 mg) in phase 3 studies. There were no new safety findings, and the incidence of adverse events, serious adverse events, and alanine aminotransferase elevations was lower than that in phase 3 studies, which is probably related to the lower dose used.⁴⁰⁰

The most common adverse effects involved the gastrointestinal tract, such as nausea, flatulence, and diarrhea. They can be minimized by reducing fat intake or by using drug titration.³⁹⁸ Increased transaminase levels have been described in some patients, but they are generally

reversible with drug reduction or discontinuation, or even transient with maintenance of treatment.

In most cases, concomitant elevation of bilirubin and alkaline phosphatase and onset of symptoms have not been described. However, the most concerning adverse effect of lomitapide, because of its mechanism of action, is hepatic steatosis, which is dose-dependent and attenuates with a reduction in daily dose. It can be detected especially by magnetic resonance imaging. Another relevant adverse effect is steatorrhea.³⁹⁷⁻⁴⁰¹

Studies using magnetic resonance imaging in HoFH patients have shown accumulation of liver fat. However, this may vary individually and is increased by alcohol consumption. The long-term effects of this accumulation of fat in the liver resulting from drug intervention could be deleterious and even cause liver cirrhosis.³⁹⁹

Because MTP inhibition leads to reductions not only in hepatic VLDL synthesis but also in intestinal chylomicron production, lomitapide could cause reduced absorption of essential fatty acids and fat-soluble vitamins, especially vitamin E, which is transported primarily by LDL. However, this finding has not been confirmed in FH patients after use of lomitapide.⁴⁰²

Furthermore, research has not shown any significant effect of lomitapide treatment on plasma levels of vitamins A and D.³⁹⁹ However, to prevent nutritional deficiencies, essential fatty acids and fat-soluble vitamins may be supplemented.

Because lomitapide is extensively metabolized by CYP3A4, caution is required for coadministration with CYP3A4 inhibitors (antifungals, diltiazem, verapamil, antibiotics such as ciprofloxacin, clarithromycin, and erythromycin, and protease inhibitors). The combined use of lomitapide 60 mg/day with simvastatin 40 mg/day increased the exposure to simvastatin by 1.7 times compared with simvastatin alone, increasing the risk of adverse effects from simvastatin.⁴⁰³ However, studies of other lipid-lowering drugs showed no significant interactions. Another possible adverse event caused by sudden discontinuation is elevation of LDL-C concentrations because of the rebound effect on VLDL secretion.

Lomitapide is contraindicated during pregnancy, and currently there is no evidence of safety. Undoubtedly, this issue should be addressed before indication for high-risk cases. Finally, the lipid-lowering efficacy of lomitapide was demonstrated in previous studies showing a dose-response effect on LDL-C, in which 10, 25, and 50 mg daily reduced LDL-C by 30, 55, and 70%, respectively.³⁹²

12.3. Antisense Oligonucleotide

12.3.1. Inhibitors of Apo B synthesis (antisense Apo B inhibition)

Antisense oligonucleotide technology can be used to block the synthesis of a particular protein target. Mipomersen is a second-generation antisense oligonucleotide that binds to the mRNA encoding Apo B-100, thus leading to its degradation by the action of RNase and reducing the production of Apo

B-100.⁴⁰⁴ Hence, mipomersen inhibits the hepatic synthesis of Apo B-100 and then reduces the plasma concentrations of VLDL, IDL, LDL, and Lp(a).⁴⁰⁵⁻⁴⁰⁷ A subcutaneous injection of 200 mg is administered once weekly.⁴⁰⁶

In clinical trials of patients with severe HoFH or HeFH, mipomersen reduced LDL-C by 25 and 28%, respectively. Adverse events include myalgia, fatigue, injection-site reactions, flu-like symptoms, and liver fat deposition (steatosis).

The high cost of this technology and its adverse effects prevented wider use; a possible therapeutic indication is for an extremely severe and rare condition of genetic dyslipidemia, such as HoFH.

Mipomersen was evaluated in a randomized phase 3 trial of HoFH patients. The mean LDL-C reduction was significantly greater in the mipomersen group (-24.7%; 95% CI 31.6 to 17.7%) than in the placebo group (-3.3%; 95% CI 12.1 to 5.5%; $p = 0.0003$). Injection-site reactions were the most common adverse effects (76% in the mipomersen group vs 24% in the placebo group).⁴⁰⁶

In 2013, the FDA approved mipomersen for the treatment of HoFH in adults, but data on children were lacking.⁴⁰⁸ However, marketing was discontinued in 2018.

Phase 3 studies showed that the efficacy of the drug varies considerably, with mean reductions of 25 to 37%, depending on the characteristics of the populations of interest (homozygous or heterozygous forms of FH, severe hypercholesterolemias, or patients at high cardiovascular risk).

12.4. Small Interfering RNA (siRNA)

Another method to inhibit the action of PCSK9 is to reduce its production in tissue. Small interfering RNAs (siRNAs) block the translation of messenger RNA.⁴⁰⁹ Inclisiran is a synthetic siRNA inhibiting hepatic PCSK9 synthesis. The drug was administered SC as first in class in the ORION program, which evaluated its efficacy and safety in reducing LDL-C. Phase 2 and phase 3 studies have shown LDL-C reductions of approximately 50% with an infrequent dose, one administration every six months, in patients with established atherosclerotic cardiovascular disease or at high cardiovascular risk, including FH patients. Ongoing phase 3 studies will provide evidence of long-term safety and efficacy in HoFH patients. Also, the ORION-4 study will evaluate the impact of inclisiran on cardiovascular events. Inclisiran efficacy was demonstrated in a phase 1 study and then confirmed in a phase 2 study, with a 52.6% reduction in LDL-C.⁴¹⁰ In the ORION-9 study, a phase 3 study of HeFH patients, inclisiran at a dose of 300 mg reduced LDL-C concentrations by 39.7% on day 510 (vs. 8.2% increase in the placebo group), and between days 90 and 540, there was a 38.1% reduction. The reductions were robust across all genotypes.⁴¹¹ The medication has not yet been approved for use.

12.5. Anti-ANGPTL3 Monoclonal Antibody

Another promising therapy, especially for refractory forms of FH and for HoFH, is based on angiopoietin-like 3 peptide (ANGPTL3) inhibition with evinacumab, an anti-ANGPTL3

monoclonal antibody. In HoFH patients, evinacumab reduced LDL-C by 47% when administered intravenously at a dose of 15 mg/kg body weight every 4 weeks.⁴¹² Evinacumab was effective in patients with *LDLR*-null mutations (43.4% reduction in LDL-C) and in those with other variants (49.1% reduction in LDL-C).

In severe and refractory forms of hypercholesterolemia, evinacumab was tested subcutaneously and intravenously at different doses and dosing intervals, leading to an LDL-C reduction greater than 50%.⁴¹³ Evinacumab has been recently approved for HoFH by the FDA.

12.6. Bempedoic Acid

Bempedoic acid is a small molecule that reduces LDL-C by inhibiting a key enzyme in the cholesterol biosynthesis pathway, named ATP citrate lyase, which acts upstream of 3-hydroxy-3-methylglutaryl-coenzyme A. Unlike statins, bempedoic acid has a specific action on the liver, not affecting skeletal muscles.⁴¹⁴ A randomized phase 3 study enrolled 779 patients with atherosclerotic cardiovascular disease, HeFH, or both, and with treated LDL-C > 70 mg/dL. Bempedoic acid reduced LDL-C by 15.1%, in addition to lowering non-HDL-C, total cholesterol, Apo B, and high-sensitivity C-reactive protein, compared with placebo.⁴¹⁵ In a study using a fixed-dose combination of bempedoic acid 180 mg and ezetimibe 10 mg in patients with hypercholesterolemia receiving the maximum tolerated statin dose and at high cardiovascular risk, a 36% reduction in LDL-C was obtained, superior to ezetimibe alone (-23.2%) and bempedoic acid alone (-17.2%).⁴¹⁶ The reduction obtained with bempedoic acid plus ezetimibe was similar between the groups receiving high- or moderate-intensity statin and those receiving no statins. Other lipids and high-sensitivity C-reactive protein also showed a greater reduction with the combined therapy.

This drug class is associated with modest elevations in uric acid level, explained by the competition between the drug metabolite and uric acid for the same renal transporters involved in the excretion of the compounds. Data on prolonged exposure safety and cardiovascular outcomes are being evaluated in a phase 3 study whose results are yet to be published. Bempedoic acid and its combination with ezetimibe received approval of the FDA for patients with HeFH and atherosclerotic cardiovascular disease (ASCVD).

13. Cost-Effectiveness of Screening and Treatment of Familial Hypercholesterolemia

13.1. Introduction

Health resources are currently insufficient to meet all the demands of society. Contemporary medicine is faced with an avalanche of therapies that have been proven to add clinical benefits to incorporated therapies but are usually associated with an incremental cost.

Traditionally, when different medical interventions are evaluated from both clinical and health policy perspectives, the purpose is to determine the efficacy and safety that

can be achieved under ideal conditions (randomized controlled trials). Effectiveness will show the real effect of the intervention when used in usual circumstances (real-world studies). Another concept is that of intervention efficiency, which considers not only the effectiveness of each intervention but also the resources needed for implementation.

This panorama has aroused the interest of different segments of the community in the search for solutions. Health economics is a field of interdisciplinary knowledge that can help physicians, managers, and health policy-makers in the difficult task of making decisions in a resource-limited setting.

13.2. Cost-of-Illness Study

To analyze the impact of a disease or a treatment in a specific setting (eg, a country, a health care system, a hospital), knowledge of the cost of illness is needed. This type of economic study is based on a descriptive method that, combined with prevalence, incidence, morbidity, and mortality data, helps measure the impact of a specific disease on society.

A cost-of-illness study is not categorized as an economic analysis because it does not compare interventions and does not assess health outcomes. The aim is to estimate the burden or impact of a disease to prioritize the allocation of resources in public health policies, guide research funds, and identify the most expensive diseases for the health budget, in addition to providing data for economic analyses.

13.3. Health Economic Analyses

Economic analyses compare different options competing for the allocation of limited resources intended for use in health care. All forms of economic analysis address the use of resources and the health benefits of therapeutic or preventive interventions or even health programs. The analyses compare alternatives and facilitate the process of making decisions for the appropriate use of health resources.

Cost-effectiveness analysis (CEA) is the most widely used type of health economic evaluation and measures the cost in monetary units divided by a nonmonetary unit, named natural unit, such as life years of survival or events prevented after a given health intervention.⁴¹⁷

A health intervention is said to be cost-effective if it produces a clinical benefit that justifies the cost. The determination of how much the additional effectiveness justifies the extra cost is based on social values and the availability of resources. WHO recommends using an amount corresponding to 1 to 3 times the gross domestic product (GDP) per capita of the country where the analysis was performed as a justifiable cost-effectiveness threshold for that context.⁴¹⁸ In Brazil, an explicit cost-effectiveness threshold was not determined for the Unified Health System (Sistema Único de Saúde, SUS) or the private health insurance system, ie, the amount from which an intervention is considered to be cost-effective was not defined. The definition of this amount is context-specific and depends on local wealth, characteristics of the health system, availability and ability to pay, as well as social preferences. Furthermore, this threshold

should always be used together with other value-adding criteria and has been discussed in recent years.

13.4. Costs of Familial Hypercholesterolemia

CVDs are the main causes of death and costs for the adult population in Brazil, and this impact will probably grow with increases in life expectancy. FH is an important risk factor for atherosclerotic disease and increases the risk of early events.

Siqueira et al.⁴¹⁹ estimated the costs of CVD in Brazil from a SUS perspective over 5 years, including direct costs of hospitalizations, outpatient care visits, and social security benefits, in addition to indirect costs of loss of income caused by CVD mortality. CVD accounted for 28% of all deaths in Brazil and reached 38% of deaths in the working-age population (18 to 65 years old). The estimated CVD costs were R\$37.1 billion in 2015, with a 17% increase in the years between 2010 and 2015. The estimated costs of premature death from CVD accounted for 61% of the total CVD cost; direct costs of hospitalizations and consultations were 22%, and costs of illness-related lost productivity were 15%. Estimated health expenditures in Brazil were 9.5% of GDP, and the estimated mean CVD cost was 0.7% of GDP.

Bahia et al.⁴²⁰ estimated the costs of hospitalizations for CAD attributable to FH in the Brazilian adult population from a SUS perspective between 2012 and 2014. With data from the international literature on the prevalence of FH and the relative risk of events, population attributable fractions were calculated and applied to hospitalization costs in all SUS health care units with the SIH-SUS database. In total, 245,981 hospitalizations were recorded over 1 year, and 7,249 (2.9%) to 12,915 (5.2%) were attributable to FH, according to the prevalence used. The total hospitalization cost was R\$985,919,299, of which R\$29,053,500 to R\$51,764,175 were attributable to FH and could be minimized if there was a proper control of this risk factor in the population with adequate treatment.

13.5. Cost-Effectiveness of Screening and Treatment of Familial Hypercholesterolemia

Less than 25% of people with FH are diagnosed, according to estimates, and most are incorrectly treated.⁴²¹ The clinical and economic implications of the low number of diagnoses are significant as an important share of the population with FH which was not treated early will develop atherosclerotic CVD. Thus, an important topic of discussion refers to the cost-effectiveness of population screening for FH for early diagnosis and treatment purposes. Rosso et al.⁴²² conducted a systematic review of economic analyses of genetic screening for FH (cost-effectiveness, cost-utility, cost-benefit, and cost-minimization analyses). Seven economic evaluations were conducted in Europe between 2002 and 2015 focusing on relatives of index patients with a genetic or clinical diagnosis of FH (cascade screening strategy), but this was not compared with a no-screening strategy. Only direct costs were analyzed in studies adopting a health care payer perspective, which means that estimates were conservative as they did not include indirect CVD costs (absenteeism, leaves, retirement, and early deaths).

In all contexts, cascade screening was cost-effective, except in a North American study that showed no evidence of economic benefit of genetic screening compared with the currently recommended management of dyslipidemias.⁴²³

The effectiveness and cost-effectiveness of statin treatment in FH patients has been clearly demonstrated in different secondary prevention contexts.^{424,425} For primary prevention, cost-effectiveness will depend on cardiovascular risk and age of the population, with results supporting a more aggressive treatment in those at higher risk.⁴²⁶ In Brazil, a cost-effectiveness analysis of three statin dosing regimens (low-, intermediate-, and high-intensity statins) was performed from a SUS perspective. Based on government procurement prices, the therapeutic regimen of intermediate-intensity statins (eg, atorvastatin 10 mg and simvastatin 40 mg) was found to be the most cost-effective and was suggested as the most attractive economic approach for SUS in both primary prevention (high CV risk population) and secondary prevention.⁴²⁷

New treatment approaches with PCSK-9 inhibitors require context-specific economic analyses as they are drugs that have shown additional efficacy in the treatment of high-risk patients with residual risk, but treatment costs are remarkably high. Cost-effectiveness of new therapies is important because the costs of health care services are increasing significantly, and accurate data on costs and potential benefits of different therapies are crucial for budget impact analyses.

In the US, three modeling studies demonstrated that PCSK9 inhibitor treatment in patients with established CVD exceeded generally accepted cost-effectiveness thresholds and could significantly increase health care costs.⁴²⁸⁻⁴³⁰ The mean annual treatment cost observed in the US models ranged from \$14,000 to 15,000, and the authors suggest that cost reduction should be greater than 50% per year for the therapy to be considered cost-effective for reducing cardiovascular events.

13.6. Final Considerations

The contribution of cost-of-illness studies and economic analyses consists of supporting physicians and managers in the decision-making process, when they analyze several aspects, including the costs (what, how much, to whom, at what cost) and the benefits, of the action being produced. This will rationally guide decision-making with the purpose of achieving the greatest collective benefit with the available resources.

Choices are frequently made between treatments that have different costs and effectiveness levels but used for the same clinical purpose. Therefore, the best evidence on the treatment of the illness in question should be obtained, and the benefits provided to the patient should be analyzed, with a preference for the intervention with the best cost-effectiveness ratio. In real-world clinical practice, where there is a lack of resources and inequality in health care access, the use of health economic studies can be of great help in decision-making.

References

- Burns FS. A contribution to the study of the etiology of xanthoma multiplex. *Arch Derm Syphilol*. 1920; 2(4):415-29.
- Ose L. An update on familial hypercholesterolaemia. *Ann Med*. 1999; 31(Suppl 1):13-8.
- Müller C. Xanthomata, hypercholesterolemia and angina pectoris. *Acta Med Scand Suppl*. 1938; 89:75-84.
- Brown MS, Goldstein JL. Analysis of a mutant strain of human fibroblasts with a defect in the internalization of receptor bound low density lipoprotein. *Cell*. 1976; 9(4 Pt 2):663-74.
- Brown MS, Goldstein JL. Receptor-mediated control of cholesterol metabolism. *Science*. 1976; 191(4223):150-4.
- Goldstein JL, Brown MS. Regulation of the mevalonate pathway. *Nature*. 1990; 343(6257):425-30.
- Russell DW, Yamamoto T, Schneider WJ et al. c-DNA cloning of the bovine low-density lipoprotein receptor: feedback regulation of a receptor mRNA. *Proc Natl Acad Sci USA*. 1983; 80(24):7501-5.
- Motulski AG. Genetic aspects of familial hypercholesterolemia and its diagnosis. *Arteriosclerosis*. 1989; 9(1 Suppl):13-7.
- Nordestgaard BC, Chapman MJ, Humphries SE et al. Familial hypercholesterolemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease: consensus statement of the European Atherosclerosis Society. *Eur Heart J*. 2013; 34(45):3478-90a.
- Khachadurian AK. The inheritance of essential familial hypercholesterolemia. *Am J Med*. 1964; 37:402-7.
- Sjouke B, Kusters DM, Kindt I et al. Homozygous autosomal dominant hypercholesterolemia in the Netherlands: prevalence, genotype-phenotype relationship, and clinical outcome. *Eur Heart J*. 2015; 36(9):560-5.
- Hobbs HH, Brown MS, Goldstein JL. Molecular genetics of the LDL receptor gene in familial hypercholesterolemia. *Hum Mutat*. 1992; 1(6):445-66.
- Cuchel M, Bruckert E, Ginsberg HN et al. Homozygous familial hypercholesterolemia: new insights and guidance for clinicians to improve detection and clinical management. A position paper from the Consensus Panel on Familial Hypercholesterolemia of the European Atherosclerosis Society. *Eur Heart J*. 2014; 35:2146-57.
- Stenson PD, Ball EV, Mort M et al. Human gene mutation database (HGMD): 2003 update. *Hum Mutat*. 2003; 21(6):577-81.
- Soria LF, Ludwig EH, Clarke HR et al. Association between a specific apolipoprotein B mutation and familial defective apo B 100. *Proc Natl Acad Sci USA*. 1989; 86(2):587-91.
- Abifadel M, Varret M, Rabès JP et al. Mutations in PCSK9 cause autosomal dominant hypercholesterolemia. *Nat Genet*. 2003; 34(2):154-6.
- Henderson R, O'Kane M, McGilligan V et al. The genetics and screening of familial hypercholesterolemia. *J Biomed Sci*. 2016; 23(1):39.
- Medeiros AM, Alves AC, Bourbon M. Mutational analysis of a cohort with clinical diagnosis of familial hypercholesterolemia: considerations for genetic diagnosis improvement. *Genet Med*. 2016; 18(4):316-24.
- Zuliani G, Arca M, Signore A et al. Characterization of a new form of inherited hypercholesterolemia: familial recessive hypercholesterolemia. *Arterioscler Thromb Vasc Biol*. 1999; 19(3):802-9.

20. Brænne I, Kleiweck M, Reiz B et al. Systematic analysis of variants related to familial hypercholesterolemia in families with premature myocardial infarction. *Eur J Hum Genet.* 2016; 24(2):191-7.
21. Abul-Husn NS, Manickam K, Jones LK et al. Genetic identification of familial hypercholesterolemia within a single U.S. health care system. *Science.* 2016; 354(6319):aqf7000.
22. Santos RD, Gagliardi AC, Xavier HT et al. First Brazilian guidelines for familial hypercholesterolemia. *Arq Bras Cardiol.* 2012; 99(2 Suppl 2):1-28.
23. Sturm AC, Knowles JW, Gidding SS et al. Convened by the Familial Hypercholesterolemia Foundation. Clinical Genetic Testing for Familial Hypercholesterolemia: JACC Scientific Expert Panel. *J Am Coll Cardiol.* 2018; 72(6):662-80.
24. Khera AV, Won HH, Peloso GM et al. Diagnostic yield and clinical utility of sequencing familial hypercholesterolemia genes in patients with severe hypercholesterolemia. *J Am Coll Cardiol.* 2016; 67(22):2578-89.
25. Brasil. Ministério da Saúde. Departamento de Informática do Sistema Único de Saúde (Datasus). Disponível em: <http://tabnet.datasus.gov.br/cgi/tabcgi.exe?sim/cnv/obt10uf.def>. Acesso em: 8 fev 2019.
26. Ribeiro AL, Duncan BB, Brant LC et al. Cardiovascular health in Brazil: trends and perspectives. *Circulation.* 2016; 133(4):422-33.
27. World Health Organization (WHO). The top 10 causes of death. Geneva; 2016.
28. Zheng ZJ, Croft JB, Giles WH et al. Sudden cardiac death in the United States, 1989 to 1998. *Circulation.* 2001; 104(18):2158-63.
29. Piegas LS, Timmerman A, Feitosa GS et al. V Diretriz da Sociedade Brasileira de Cardiologia sobre Tratamento do Infarto Agudo do Miocárdio com Supradesnível do Segmento ST. *Arq Bras Cardiol.* 2015; 105(2):1-105.
30. O'Gara PT, Kushner FG, Ascheim DD et al. 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-e140.
31. Benjamin EJ, Blaha MJ, Chiuve SE et al. Heart disease and stroke statistics - 2017 update: a report from the American Heart Association. *Circulation.* 2017; 135(10):e146-e603.
32. Kannel WB, Castelli WP, Gordon T et al. Serum cholesterol, lipoproteins, and the risk of coronary heart disease. The Framingham Study. *Ann Intern Med.* 1971; 74(1):1-12.
33. Assmann G, Schulte H. The Prospective Cardiovascular Münster (PROCAM) Study: prevalence of hyperlipidemia in persons with hypertension and/or diabetes mellitus and the relationship to coronary heart disease. *Am Heart J.* 1988; 116(6 Pt 2):1713-24.
34. Yusuf S, Hawken S, Ounpuu S et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (Interheart Study): case control study. *Lancet.* 2004; 364(9438):937-52.
35. Lanas F, Avezum A, Bautista LE et al. Risk factors for acute myocardial infarction in Latin America: the Interheart Latin American Study. *Circulation.* 2007; 115(9):1067-74.
36. O'Donnell MJ, Xavier D, Liu L et al. Risk factors for ischemic and intracerebral hemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study. *Lancet.* 2010; 376(9735):112-23.
37. Benn M, Watts GF, Tybjaerg-Hansen A et al. Familial hypercholesterolemia in the Danish general population: prevalence, coronary artery disease, and cholesterol-lowering medication. *J Clin Endocrinol Metab.* 2012; 97(11):3956-64.
38. Benn M, Watts GF, Tybjaerg-Hansen A et al. Mutations causative of familial hypercholesterolemia: screening of 98 individuals from the Copenhagen General Population Study estimated a prevalence of 1 in 217. *Eur Heart J.* 2016; 37(17):1384-94.
39. Vallejo-Vaz AJ, De Marco M, Stevens CAT et al. Overview of the current status of familial hypercholesterolemia care in over 60 countries - the EAS Familial Hypercholesterolemia Studies Collaboration (FHSC). *Atherosclerosis.* 2018; 277:234-55.
40. World Health Organization (WHO). Familial hypercholesterolemia (FH). Report of a second WHO consultation. Geneva; 1998.
41. Harada P, Miname MH, Bensenor IM et al. Familial hypercholesterolemia prevalence in an admixed racial society: Sex and race matter. The ELSA-Brazil. *Atherosclerosis.* 2018; 277:273-7.
42. Hu P, Dharmayat KI, Stevens CAT et al. Prevalence of familial hypercholesterolemia among the general population and patients with atherosclerotic cardiovascular disease: a systematic review and meta-analysis. *Circulation.* 2020; 141(22):1742-59.
43. Beheshti SO, Madsen CM, Varbo A, Nordestgaard BG. Worldwide Prevalence of Familial Hypercholesterolemia: Meta-Analyses of 11 Million Subjects. *J Am Coll Cardiol.* 2020; 75(20):2553-66.
44. Goldstein JK, Hobbs HH, Brown MS. Familial hypercholesterolemia. In: Scriver CR, Beaudet AL, Sly WS, Valle D (eds.). *The metabolic & molecular basis of inherited disease.* 8th ed. New York: McGraw-Hill; 2001. p. 2863-913.
45. Austin MA, Hutter CM, Zimmern RL et al. Genetic causes of monogenic heterozygous familial hypercholesterolemia: a HuGe prevalence review. *Am J Epidemiol.* 2004; 160(5):407-20.
46. Verschmissen J, Oosterveer DM, Yazdanpanah M et al. Efficacy of statins in familial hypercholesterolemia: a long-term cohort. *BMJ.* 2008; 337:a2423.
47. Neil A, Cooper J, Betteridge J et al. Reductions in all-cause, cancer, and coronary mortality in statin-treated patients with heterozygous familial hypercholesterolemia: a prospective registry study. *Eur Heart J.* 2008; 29(21):2625-33.
48. Mortality in treated heterozygous familial hypercholesterolemia: implications for clinical management. Scientific Steering Committee on behalf of the Simon Broome Register Group. *Atherosclerosis.* 1999; 142(1):105-12.
49. Huijgen R, Vissers MN, Defesche JC et al. Familial hypercholesterolemia: current treatment and advances in management. *Expert Rev Cardiovasc Ther.* 2008; 6(4):567-81.
50. de Ferranti SD, Rodday AM, Mendelson MM et al. Prevalence of familial hypercholesterolemia in the 1999 to 2012 United States National Health and Nutrition Examination Surveys (NHANES). *Circulation.* 2016; 133(11):1067-72.
51. Stone NJ, Levy RI, Fredrickson DS et al. Coronary artery disease in 116 kindred with familial type II hyperlipoproteinemia. *Circulation.* 1974; 49(3):476-88.
52. Faludi AA, Izar MCO, Saraiva JFK et al. Atualização da Diretriz Brasileira de Dislipidemias e Prevenção da Aterosclerose – 2017. *Arq Bras Cardiol.* 2017; 109(2 Supl 1):1-76.
53. Grundy SM, Stone NJ, Bailey AL et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. *Circulation.* 2019; 139(25):e1082-e1143.
54. Landmesser U, Chapman MJ, Stock JK et al. 2017 update of ESC/EAS task force on practical clinical guidance for proprotein convertase subtilisin/kexin type 9 inhibition in patients with atherosclerotic cardiovascular disease or in familial hypercholesterolemia. *Eur Heart J.* 2018; 39(14):1131-43.
55. Sociedade Brasileira de Cardiologia. Calculadora para diagnóstico de hipercolesterolemia familiar. Disponível em: <http://departamentos.cardiol.br/sbc-da/2015/CALCULADORAHF2017/etapa1.html> e <http://departamentos.cardiol.br/sbc-da/2015/CALCULADORAHF2017/etapa1.html>. Acesso em 9 jun 2019.

56. Santos RD, Gidding SS, Hegele RA et al. International Atherosclerosis Society Severe Familial Hypercholesterolemia Panel. Defining severe familial hypercholesterolemia and the implications for clinical management: a consensus statement from the International Atherosclerosis Society Severe Familial Hypercholesterolemia Panel. *Lancet Diabetes Endocrinol.* 2016; 4(10):850-61.
57. Humphries SE, Cooper JA, Capps N et al. Simon broome familial hyperlipidemia register Group. Coronary heart disease mortality in severe vs. non-severe familial hypercholesterolemia in the simon broome register. *Atherosclerosis.* 2019; 281:207-12.
58. Watts GF, Gidding S, Wierzbicki AS et al. Integrated guidance on the care of familial hypercholesterolemia from the International FH Foundation. *Int J Cardiol.* 2014; 171(3):309-25.
59. Wiegman A, Gidding SS, Watts GF et al. European Atherosclerosis Society Consensus Panel. Familial hypercholesterolemia in children and adolescents: gaining decades of life by optimizing detection and treatment. *Eur Heart J.* 2015; 36(36):2425-37.
60. World Health Organization (WHO). Human Genetics Programme (1999). Familial hypercholesterolemia (FH): report of a second WHO consultation. Geneva; 1999.
61. Williams RR, Hunt SC, Schumacher MC et al. Diagnosing heterozygous familial hypercholesterolemia using new practical criteria validated by molecular genetics. *Am J Cardiol.* 1993; 72(2):171-6.
62. National Collaborating Centre for Primary Care (UK). Identification and management of familial hypercholesterolemia (FH). London: Royal College of General Practitioners (UK); 2008. Disponível em: <http://www.nice.org.uk/CG71>. 29 abr 2018.
63. Hopkins PN, Toth PP, Ballantyne CM et al. National Lipid Association Expert Panel on Familial Hypercholesterolemia. Familial hypercholesterolemias: prevalence, genetics, diagnosis and screening recommendations from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. *J Clin Lipidol.* 2011; 5(3 Suppl):S9-S17.
64. Scartezini M, Ferreira CEDS, Izar MCO et al. Posicionamento sobre a flexibilização do jejum para o perfil lipídico. *Arq Bras Cardiol.* 2017; 108(3):195-7.
65. Seidah NG, Awan Z, Chrétien M et al. PCSK9: a key modulator of cardiovascular health. *Circ Res.* 2014; 114(6):1022-36.
66. Usifo E, Leigh SE, Whittall RA et al. Low-density lipoprotein receptor gene familial hypercholesterolemia variant database: update and pathological assessment. *Ann Hum Genet.* 2012; 76(5):387-401.
67. Humphries SE, Whittall RA, Hubbart CS et al. Genetic causes of familial hypercholesterolemia in patients in the UK: relation to plasma lipid levels and coronary heart disease risk. *J Med Genet.* 2006; 43(12):943-9.
68. Heath KE, Gudnason V, Humphries SE et al. The type of mutation in the low-density lipoprotein receptor gene influences the cholesterol-lowering response of the HMG-CoA reductase inhibitor simvastatin in patients with heterozygous familial hypercholesterolemia. *Atherosclerosis.* 1999; 143(1):41-54.
69. Gudnason V, Day IN, Humphries SE. Effect on plasma lipid levels of different classes of mutations in the low-density lipoprotein receptor gene in patients with familial hypercholesterolemia. *Arterioscler Thromb.* 1994; 14(11):1717-22.
70. Hobbs HH, Brown MS, Goldstein JL. Molecular genetics of the LDL receptor gene in familial hypercholesterolemia. *Hum Mutat.* 1992; 1(6):445-66.
71. Pisciotta L, Cantafora A, De Stefano F et al. A “de novo” mutation of the LDL-receptor gene as the cause of familial hypercholesterolemia. *Biochim Biophys Acta* 2002; 1587(1):7-11.
72. Goldstein JL, Brown MS. Familial hypercholesterolemia. In: Scriver CR, Beaudet AL, Sly WS, Valle D (eds.). *The metabolic basis of inherited disease.* New York (NY): McGraw-Hill; 1989. p. 1195-250.
73. Iacocca MA, Chora JR, Carrié A et al. ClinVar database of global familial hypercholesterolemia-associated DNA variants. *Hum Mutat.* 2018; 39(11):1631-40.
74. Horsthemke B, Dunning A, Humphries S. Identification of deletions in the human low-density lipoprotein receptor gene. *J Med Genet.* 1987; 24(3):144-7.
75. Hobbs HH, Leidersdorf E, Goldstein JL et al. Multiple crm-mutations in familial hypercholesterolemia. Evidence for 13 alleles, including four deletions. *J Clin Invest.* 1988; 81(3):909-17.
76. Hobbs HH, Russell DW, Brown MS et al. The LDL receptor locus in familial hypercholesterolemia: mutational analysis of a membrane protein. *Annu Rev Genet.* 1990; 24:133-70.
77. Langlois S, Kastelein JJ, Hayden MR. Characterization of six partial deletions in the low-density-lipoprotein (LDL) receptor gene causing familial hypercholesterolemia (FH). *Am J Hum Genet.* 1988; 43(1):60-8.
78. Iacocca MA, Chora JR, Carrié A et al. ClinGen FH Variant Curation Expert Panel. ClinVar database of global familial hypercholesterolemia-associated DNA variants. *Hum Mutat.* 2018; 39(11):1631-40.
79. Villéger L, Abifadel M, Allard D et al. The UMD-LDLR database: additions to the software and 490 new entries to the database. *Hum Mutat.* 2002; 20(2):81-7.
80. Varret M, Abifadel M, Rabès JP et al. Genetic heterogeneity of autosomal dominant hypercholesterolemia. *Clin Genet.* 2008; 73(1):1-13.
81. Horton JD, Cohen JC, Hobbs HH. Molecular biology of PCSK9: its role in LDL metabolism. *Trends Biochem Sci.* 2007; 32(2):71-7.
82. Garcia CK, Wilund K, Arca M et al. Autosomal recessive hypercholesterolemia caused by mutations in a putative LDL receptor adaptor protein. *Science.* 2001; 292(5520):1394-8.
83. He G, Gupta S, Yi M et al. ARH is a modular adaptor protein that interacts with the LDL receptor, clathrin, and AP-2. *J Biol Chem.* 2002; 277(46):44044-9.
84. Pisciotta L, Priore Oliva C, Pes GM et al. Autosomal recessive hypercholesterolemia (ARH) and homozygous familial hypercholesterolemia (FH): a phenotypic comparison. *Atherosclerosis.* 2006; 188(2):398-405.
85. Brautbar A, Leary E, Rasmussen K et al. Genetics of familial hypercholesterolemia. *Curr Atheroscler Rep.* 2015; 17(4):491.
86. Wang J, Joy T, Mymin D et al. Phenotypic heterogeneity of sitosterolemia. *J Lipid Res.* 2004; 45(12):2361-7.
87. Soutar AK, Naoumova RP. Mechanisms of disease: genetic causes of familial hypercholesterolemia. *Nat Clin Pract Cardiovasc Med.* 2007; 4(4):214-25.
88. Foody JM, Vishwanath R. Familial hypercholesterolemia/autosomal dominant hypercholesterolemia: molecular defects, the LDL-C continuum, and gradients of phenotypic severity. *J Clin Lipidol.* 2016; 10(4):970-86.
89. Talmud PJ, Shah S, Whittall R et al. Use of low-density lipoprotein cholesterol gene score to distinguish patients with polygenic and monogenic familial hypercholesterolaemia: a case-control study. *Lancet.* 2013; 381(9874):1293-301.
90. Futema M, Shah S, Cooper JA et al. Refinement of variant selection for the LDL cholesterol genetic risk score in the diagnosis of the polygenic form of clinical familial hypercholesterolemia and replication in samples from 6 countries. *Clin Chem.* 2015; 61(1):231-8.
91. Leren TP. Cascade genetic screening for familial hypercholesterolemia. *Clin Genet.* 2004; 66(6):483-7.
92. Fouchier SW, Defesche JC, Umans-Eckenhausen MW et al. The molecular basis of familial hypercholesterolemia in The Netherlands. *Hum Genet.* 2001; 109(6):602-15.

93. Marks D, Wonderling D, Thorogood M et al. Screening for hypercholesterolemia versus case finding for familial hypercholesterolemia: a systematic review and cost-effectiveness analysis. *Health Technol Assess.* 2000; 4(29):1-123.
94. Watts GF, Sullivan DR, Poplawski N et al. Familial hypercholesterolemia: a model of care for Australasia. *Atheroscler Suppl.* 2011; 12(2):221-63.
95. Watts GF, van Bockxmeer FM, Bates T et al. A new model of care for familial hypercholesterolemia from Western Australia: closing a major gap in preventive cardiology. *Heart Lung Circ.* 2010; 19(7):419-22.
96. Pocovi M, Civeira F, Alonso R et al. Familial hypercholesterolemia in Spain: case-finding program, clinical and genetic aspects. *Semin Vasc Med.* 2004; 4(1):67-74.
97. Kusters DM, Huijgen R, Defesche JC et al. Founder mutations in the Netherlands: geographical distribution of the most prevalent mutations in the low-density lipoprotein receptor and apolipoprotein B genes. *Neth Heart J.* 2011; 19(4):175-82.
98. Bourbon M, Alves AC, Medeiros AM et al. Investigators of Portuguese FH Study. Familial hypercholesterolemia in Portugal. *Atherosclerosis.* 2008; 196(2):633-42.
99. Jannes CE, Santos RD, de Souza Silva PR et al. Familial hypercholesterolemia in Brazil: cascade screening program, clinical and genetic aspects. *Atherosclerosis.* 2015; 238(1):101-7.
100. Pollex RL, Hegele RA. Genomic copy number variation and its potential role in lipoprotein and metabolic phenotypes. *Curr Opin Lipidol.* 2007; 18(2):174-80.
101. Leren TP, Manshaus T, Skovholt U et al. Application of molecular genetics for diagnosing familial hypercholesterolemia in Norway: results from a family-based screening program. *Semin Vasc Med.* 2004; 4(1):75-85.
102. MRC-Holland. MLPA (multiplex ligation-dependent probe amplification).® DNA general protocol instructions. General protocol for the detection and quantification DNA sequences. Disponível em: mrcolland.com/products/4838/MLPA%20PROTOCOL%20MDP-v007.pdf.
103. Wonderling D, Umans-Eckenhuisen MA, Marks D et al. Cost-effectiveness analysis of the genetic screening program for familial hypercholesterolemia in The Netherlands. *Semin Vasc Med.* 2004; 4(1):97-104.
104. Johannesson M, Jönsson B, Kjekshus J et al. Cost effectiveness of simvastatin treatment to lower cholesterol levels in patients with coronary heart disease. Scandinavian Simvastatin Survival Study Group. *N Engl J Med.* 1997; 336(5):332-6.
105. Slack J. Risks of ischaemic heart-disease in familial hyperlipoproteinemic states. *Lancet.* 1969; 2(7635):1380-2.
106. Trinder M, Li X, DeCastro ML et al. Risk of premature atherosclerotic disease in patients with monogenic versus polygenic familial hypercholesterolemia. *J Am Coll Cardiol.* 2019; 74(4):512-22.
107. Galema-Boers AM, Lenzen MJ, Engelkes SR et al. Cardiovascular risk in patients with familial hypercholesterolemia using optimal lipid-lowering therapy. *J Clin Lipidol.* 2018; 12(2):409-16.
108. Ray KK, Watts GF. FH Hypercholesterolemia Studies Collaboration. Improving the global care of familial hypercholesterolemia: starting the ball rolling. *Atherosclerosis.* 2018; 277:230-3.
109. Jansen AC, van Aalst-Cohen ES, Tanck MW et al. The contribution of classical risk factors to cardiovascular disease in familial hypercholesterolemia: data in 2400 patients. *J Intern Med.* 2004; 256(6):482-90.
110. Akioyamen LE, Genest J, Chu A et al. Risk factors for cardiovascular disease in heterozygous familial hypercholesterolemia: a systematic review and meta-analysis. *J Clin Lipidol.* 2019; 13(1):15-30.
111. Alonso R, Mata N, Castillo S et al. Cardiovascular disease in familial hypercholesterolemia: influence of low-density lipoprotein receptor mutation type and classic risk factors. *Atherosclerosis.* 2008; 200(2):315-21.
112. Di Angelantonio E, Gao P, Pennells L et al. Emerging Risk Factors C. Lipid-related markers and cardiovascular disease prediction. *JAMA.* 2012; 307(23):2499-506.
113. Clarke R, Peden JF, Hopewell JC et al. Genetic variants associated with Lp(a) lipoprotein level and coronary disease. *N Engl J Med.* 2009; 361(26):2518-28.
114. Langedest A, Kamstrup PR, Tybjaerg-Hansen A et al. High lipoprotein(a) as a possible cause of clinical familial hypercholesterolemia: a prospective cohort study. *Lancet Diabetes Endocrinol.* 2016; 4(7):577-87.
115. Civeira F, Castillo S, Alonso R et al. Tendon xanthomas in familial hypercholesterolemia are associated with cardiovascular risk independently of the low-density lipoprotein receptor gene mutation. *Arterioscler Thromb Vasc Biol.* 2005; 25(9):1960-5.
116. Oosterveer DM, Versmissen J, Yazdanpanah M et al. Differences in characteristics and risk of cardiovascular disease in familial hypercholesterolemia patients with and without tendon xanthomas: a systematic review and meta-analysis. *Atherosclerosis.* 2009; 207(2):311-7.
117. Mangili LC, Miname MH, Silva PRS et al. Achilles tendon xanthomas are associated with the presence and burden of subclinical coronary atherosclerosis in heterozygous familial hypercholesterolemia: A pilot study. *Atherosclerosis.* 2017; 263:393-7.
118. Martinez LR, Miname MH, Bortolotto LA et al. No correlation and low agreement of imaging and inflammatory atherosclerosis' markers in familial hypercholesterolemia. *Atherosclerosis.* 2008; 200(1):83-8.
119. Ye ZX, Cheng HM, Chiou KR et al. Relation of coronary artery calcium to flow-mediated dilation and C-reactive protein levels in asymptomatic patients with heterozygous familial hypercholesterolemia. *Am J Cardiol.* 2007; 100(7):1119-23.
120. Paquette M, Dufour R, Baass A. The Montreal-FH-score: a new score to predict cardiovascular events in familial hypercholesterolemia. *J Clin Lipidol.* 2017; 11(1):80-6.
121. Paquette M, Brisson D, Dufour R et al. Cardiovascular disease in familial hypercholesterolemia: validation and refinement of the Montreal-FH-SCORE. *J Clin Lipidol.* 2017; 11(5):1161-7e3.
122. Perez de Isla L, Alonso R, Mata N et al. Predicting cardiovascular events in familial hypercholesterolemia: the Safeheart Registry (Spanish Familial Hypercholesterolemia Cohort Study). *Circulation.* 2017; 135(22):2133-44.
123. Miname MH, Bittencourt MS, Nasir K et al. Subclinical coronary atherosclerosis and cardiovascular risk stratification in heterozygous familial hypercholesterolemia patients undergoing statin treatment. *Curr Opin Lipidol.* 2019; 30(2):82-7.
124. Neves PO, Andrade J, Moncao H. Coronary artery calcium score: current status. *Radiol Bras.* 2017; 50(3):182-9.
125. Detrano R, Guerci AD, Carr JJ et al. Coronary calcium as a predictor of coronary events in four racial or ethnic groups. *N Engl J Med.* 2008; 358(13):1336-45.
126. Erbel R, Mohlenkamp S, Moebus S et al. Coronary risk stratification, discrimination, and reclassification improvement based on quantification of subclinical coronary atherosclerosis: the Heinz Nixdorf Recall Study. *J Am Coll Cardiol.* 2010; 56(17):1397-406.
127. Pletcher MJ, Tice JA, Pignone M et al. Using the coronary artery calcium score to predict coronary heart disease events: a systematic review and meta-analysis. *Arch Int Med.* 2004; 164(12):1285-92.
128. Malik S, Zhao Y, Budoff M et al. Coronary artery calcium score for long-term risk classification in individuals with type 2 diabetes and metabolic syndrome from the Multi-Ethnic Study of Atherosclerosis. *JAMA cardiology.* 2017; 2(12):1332-40.
129. Mitchell JD, Fergstrom N, Gage BF et al. Impact of statins on cardiovascular outcomes following coronary artery calcium scoring. *J Am Coll Cardiol.* 2018; 72(25):3233-42.

Update

130. Arad Y, Spadaro LA, Roth M et al. Treatment of asymptomatic adults with elevated coronary calcium scores with atorvastatin, vitamin C, and vitamin E: the St. Francis Heart Study Randomized Clinical Trial. *J Am Coll Cardiol*. 2005; 46(1):166-72.
131. Gallo A, Giral P, Carrie A et al. Early coronary calcifications are related to cholesterol burden in heterozygous familial hypercholesterolemia. *J Clin Lipidol*. 2017; 11(3):704-11e2.
132. Mach F, Baigent C, Catapano AL et al. ESC Scientific Document Group. 2019 ESC/EAS Guidelines for the management of dyslipidemias: lipid modification to reduce cardiovascular risk. *Eur Heart J*. 2020; 41(1):111-86.
133. Miname MH, Bittencourt MS, Moraes SR et al. Coronary artery calcium and cardiovascular events in patients with familial hypercholesterolemia receiving standard lipid-lowering therapy. *JACC Cardiovascular imaging*. 2019; 12(9):1797-804.
134. Hsiao EM, Rybicki FJ, Steigner M. CT coronary angiography: 256-slice and 320-detector row scanners. *Curr Cardiol Rep*. 2010; 12(1):68-75.
135. Investigators S-H. CT coronary angiography in patients with suspected angina due to coronary heart disease (SCOT-HEART): an open-label, parallel-group, multicentre trial. *Lancet*. 2015; 385(9985):2383-91.
136. Cho I, Chang HJ, Sung JM et al. Coronary computed tomographic angiography and risk of all-cause mortality and nonfatal myocardial infarction in subjects without chest pain syndrome from the Confirm Registry (coronary CT angiography evaluation for clinical outcomes: an international multicenter registry). *Circulation*. 2012; 126(3):304-13.
137. Han D, Hartaigh BO, Gransar H et al. Incremental prognostic value of coronary computed tomography angiography over coronary calcium scoring for major adverse cardiac events in elderly asymptomatic individuals. *Eur Heart J Cardiovasc Imaging*. 2018; 19(6):675-83.
138. Cho I, Chang HJ, Hartaigh BO et al. Incremental prognostic utility of coronary CT angiography for asymptomatic patients based upon extent and severity of coronary artery calcium: results from the Coronary CT Angiography Evaluation for Clinical Outcomes International Multicenter (CONFIRM) Study. *Eur Heart J*. 2015; 36(8):501-8.
139. Miname MH, Ribeiro MS, Parga Filho J et al. Evaluation of subclinical atherosclerosis by computed tomography coronary angiography and its association with risk factors in familial hypercholesterolemia. *Atherosclerosis*. 2010; 213(2):486-91.
140. Neefjes LA, Ten Kate GJ, Rossi A et al. CT coronary plaque burden in asymptomatic patients with familial hypercholesterolemia. *Heart*. 2011; 97(14):1151-7.
141. Chow BJ, Small G, Yam Y et al. Incremental prognostic value of cardiac computed tomography in coronary artery disease using CONFIRM: coronary computed tomography angiography evaluation for clinical outcomes: an International Multicenter Registry. *Circulation Cardiovasc Imaging*. 2011; 4(5):463-72.
142. Tada H, Kawashiri MA, Okada H et al. Assessment of coronary atherosclerosis in patients with familial hypercholesterolemia by coronary computed tomography angiography. *Am J Cardiol*. 2015; 115(6):724-9.
143. Muhlestein JB, Lappe DL, Lima JA et al. Effect of screening for coronary artery disease using CT angiography on mortality and cardiac events in high-risk patients with diabetes: the FACTOR-64 randomized clinical trial. *JAMA*. 2014; 312(21):2234-43.
144. Luijckx IK, Kuipers IM, Hutten BA et al. Coronary computed tomography angiography and echocardiography in children with homozygous familial hypercholesterolemia. *Atherosclerosis*. 2019; 285:87-92.
145. Santos RD, Miname MH, Martinez LR et al. Non-invasive detection of aortic and coronary atherosclerosis in homozygous familial hypercholesterolemia by 64 slice multi-detector row computed tomography angiography. *Atherosclerosis*. 2008; 197(2):910-5.
146. de Groot E, Hovingh GK, Wiegman A et al. Measurement of arterial wall thickness as a surrogate marker for atherosclerosis. *Circulation*. 2004; 109(23 Suppl 1):III33-8.
147. Kastelein JJ, Akdim F, Stroes ES et al. Simvastatin with or without ezetimibe in familial hypercholesterolemia. *N Engl J Med*. 2008; 358(14):1431-43.
148. Smilde TJ, van Wissen S, Wollersheim H et al. Effect of aggressive versus conventional lipid lowering on atherosclerosis progression in familial hypercholesterolemia (ASAP): a prospective, randomized, double-blind trial. *Lancet*. 2001; 357(9256):577-81.
149. Wiegman A, Hutten BA, de Groot E et al. Efficacy and safety of statin therapy in children with familial hypercholesterolemia: a randomized controlled trial. *JAMA*. 2004; 292(3):331-7.
150. Braamskamp M, Langslet G, McCrindle BW et al. Effect of rosuvastatin on carotid intima-media thickness in children with heterozygous familial hypercholesterolemia: the Charon Study (hypercholesterolemia in children and adolescents taking rosuvastatin open label). *Circulation*. 2017; 136(4):359-66.
151. Polak JF, Post WS, Carr JJ et al. Associations of common carotid intima-media thickness with coronary heart disease risk factors and events vary with distance from the carotid bulb. *J Am Soc Echocardiography*. 2014; 27(9):991-7.
152. Yeboah J, McClelland RL, Polonsky TS et al. Comparison of novel risk markers for improvement in cardiovascular risk assessment in intermediate-risk individuals. *JAMA*. 2012; 308(8):788-95.
153. Naqvi TZ, Lee MS. Carotid intima-media thickness and plaque in cardiovascular risk assessment. *JACC Cardiovasc Imaging*. 2014; 7(10):1025-38.
154. Pitsavos CH, Chrysoschoou C, Panagiotakos DB et al. Exercise capacity and heart rate recovery as predictors of coronary heart disease events, in patients with heterozygous familial hypercholesterolemia. *Atherosclerosis*. 2004; 173(2):347-52.
155. Michaelides AP, Fourlas CA, Pitsavos C et al. Exercise testing in asymptomatic patients with heterozygous familial hypercholesterolemia. *Coron Artery Dis*. 2004; 15(8):461-5.
156. Nanchen D, Gencer B, Muller O et al. Prognosis of patients with familial hypercholesterolemia after acute coronary syndromes. *Circulation*. 2016; 134(10):698-709.
157. Anderson TJ, Grégoire J, Pearson GJ et al. 2016 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in the Adult. *Can J Cardiol*. 2016; 32(11):1263-82.
158. Eckel RH, Jakicic JM, Ard JD et al. American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 AHA/ACC guideline on lifestyle management to reduce cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014; 129(25 Suppl 2):S76-99.
159. Mensink RP. Effects of saturated fatty acids on serum lipids and lipoproteins: a systematic review and regression analysis. Geneva: World Health Organization (WHO); 2016.
160. World Health Organization (WHO). Draft guidelines on dietary saturated and trans fatty acids: time for a new approach? *BMJ*. 2019; 366:l5683.
161. Estruch R, Ros E, Salas-Salvado J et al. Retraction and republication: primary prevention of cardiovascular disease with a Mediterranean diet. *N Engl J Med*. 2018; 378(25):2441-2.
162. Echouffo-Tcheugui JB, Ahima RS. Does diet quality or nutrient quantity contribute more to health? *J Clin Invest*. 2019; 129(10):3969-70.
163. Moore TJ, Vollmer WM, Appel LJ et al. Effect of dietary patterns on ambulatory blood pressure: results from the dietary approaches to stop hypertension (DASH) trial. DASH Collaborative Research Group. *Hypertension*. 1999; 34:472-7.
164. Marklund M, Wu JHY, Imamura F et al. Cohorts for heart and aging research in genomic epidemiology (CHARGE) fatty acids and outcomes research consortium (FORCE). Biomarkers of dietary omega-6 fatty acids and incident cardiovascular disease and mortality. *Circulation*. 2019; 139(21):2422-36.

165. Wu JH, Lemaitre RN, King IB et al. Circulating omega-6 polyunsaturated fatty acids and total and cause-specific mortality: the Cardiovascular Health Study. *Circulation*. 2014; 130(15):1245-53.
166. U. S. Department of Agriculture and U. S. Department of Health and Human Services Dietary Guidelines for Americans. 8. ed. Washington, DC: U. S. Government Printing Office; 2015.
167. Rhee EJ, Ryu S, Lee JY et al. The association between dietary cholesterol intake and subclinical atherosclerosis in Korean adults: the Kangbuk Samsung Health Study. *J Clin Lipidol*. 2017; 11:432-41.
168. Virtanen JK, Mursu J, Tuomainen TP et al. Egg consumption and risk of incident type 2 diabetes in men: the Kuopio Ischaemic Heart Disease Risk Factor Study. *Am J Clin Nutr*. 2015; 101(5):1088-96.
169. Institute of Medicine. Dietary reference intakes for energy, carbohydrate, fiber, fat, fatty acids, cholesterol, protein, and amino acids. Washington, DC: The National Academies Press; 2002.
170. McNamara DJ, Kolb R, Parker TS et al. Heterogeneity of cholesterol homeostasis in man. Response to changes in dietary fat quality and cholesterol quantity. *J Clin Invest*. 1987; 79(6):1729-39.
171. Berger S, Raman G, Vishwanathan R et al. Dietary cholesterol and cardiovascular disease: a systematic review and meta-analysis. *Am J Clin Nutr*. 2015; 102(2):276-94.
172. Freeman AM, Morris PB, Barnard N et al. Trending cardiovascular nutrition controversies. *J Am Coll Cardiol*. 2017; 69(9):1172-87.
173. Blesso CN, Fernandez ML. Dietary cholesterol, serum lipids, and heart disease: Are eggs working for or against you? *Nutrients*. 2018; 10(4):426.
174. Radzeviciene L, Ostrauskas R. Egg consumption and the risk of type 2 diabetes mellitus: a case-control study. *Pub Health Nutr*. 2012; 15(8):1437-41.
175. Djoussé L, Gaziano JM, Buring JE et al. Egg consumption and risk of type 2 diabetes in men and women. *Diabetes Care*. 2009; 32(2):295-300.
176. Cheng P, Pan J, Xia J et al. Dietary cholesterol intake and stroke risk: a meta-analysis. *Oncotarget*. 2018; 9(39):25698-707.
177. Larsson SC, Åkesson A, Wolk A. Egg consumption and risk of heart failure, myocardial infarction, and stroke: results from 2 prospective cohorts. *Am J Clin Nutr*. 2015; 102(5):1007-13.
178. Xu L, Lam TH, Qiang C et al. Egg consumption and the risk of cardiovascular disease and all-cause mortality: Guangzhou Biobank Cohort Study and meta-analyses. *Eur J Nutr*. 2018; 58(2):785-96.
179. Zhong VW, Van Horn L, Cornelis MC et al. Associations of dietary cholesterol or egg consumption with incident cardiovascular disease and mortality. *JAMA*. 2019; 321(11):1081-95.
180. Eckel RH. Reconsidering the Importance of the Association of Egg Consumption and Dietary Cholesterol with Cardiovascular Disease Risk. *JAMA*. 2019; 321(11):1055-6.
181. Orsavova J, Misurcova L, Ambrozova JV et al. Fatty acids composition of vegetable oils and its contribution to dietary energy intake and dependence of cardiovascular mortality on dietary intake of fatty acids. *Int J Mol Sci*. 2015; 16(6):12871-90.
182. Tvřizcka E, Kremmyda LS, Stankova B et al. Fatty acids as biocompounds: their role in human metabolism, health and disease □ a review. Part 1: classification, dietary sources and biological functions. *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub*. 2011; 155(2):117-30.
183. de Oliveira Otto MC, Mozaffarian D, Kromhout D et al. Dietary intake of saturated fat by food source and incident cardiovascular disease: the Multi-Ethnic Study of Atherosclerosis. *Am J Clin Nutr*. 2012; 96(2):397-404.
184. Forouhi NG, Koulman A, Sharp SJ et al. Differences in the prospective association between individual plasma phospholipid saturated fatty acids and incident type 2 diabetes: the EPIC-InterAct case-cohort study. *Lancet Diabetes Endocrinol*. 2014; 2(10):810-8.
185. Lemaitre RN, McKnight B, Sotoodehnia N et al. Circulating verylong-chain saturated fatty acids and heart failure: the cardiovascular health study. *J Am Heart Assoc*. 2018; 7(21):e010019.
186. Mozaffarian D, Micha R, Wallace S. Effects on coronary heart disease of increasing polyunsaturated fat in place of saturated fat: a systematic review and meta-analysis of randomized controlled trials. *PLoS Med*. 2010; 7:e1000252.
187. Astrup A, Dyerberg J, Elwood P et al. The role of reducing intakes of saturated fat in the prevention of cardiovascular disease: where does the evidence stand in 2010? *Am J Clin Nutr*. 2011; 93(4):684-8.
188. Sacks FM, Lichtenstein AH, Wu JHY et al. American Heart Association. Dietary fats and cardiovascular disease: a presidential advisory from the American Heart Association. *Circulation*. 2017; 136(3):e1-e23.
189. Spritz N, Mishkel MA. Effects of dietary fats on plasma lipids and lipoproteins: an hypothesis for the lipid-lowering effect of unsaturated fatty acids. *J Clin Invest*. 1969; 48(1):78-86.
190. Horton JD, Cuthbert JA, Spady DK. Dietary fatty acids regulate hepatic low-density lipoprotein (LDL) transport by altering LDL receptor protein and mRNA levels. *J Clin Invest*. 1993; 92(2):743-9.
191. Srivastava RA, Ito H, Hess M et al. Regulation of low-density lipoprotein receptor gene expression in HepG2 and Caco2 cells by palmitate, oleate, and 25-hydroxycholesterol. *J Lipid Res*. 1995; 36(7):1434-46.
192. Mustad VA, Etherton TD, Cooper AD et al. Reducing saturated fat intake is associated with increased levels of LDL receptors on mononuclear cells in healthy men and women. *J Lipid Res*. 1997; 38(3):459-68.
193. Nicolosi RJ, Stucchi AF, Kowala MC et al. Effect of dietary fat saturation and cholesterol on LDL composition and metabolism. In vivo studies of receptor and nonreceptor-mediated catabolism of LDL in cebus monkeys. *Arteriosclerosis*. 1990; 10(1):119-28.
194. Bennett AJ, Billett MA, Salter AM et al. Modulation of hepatic apolipoprotein B, 3-hydroxy-3-methylglutaryl-CoA reductase and low-density lipoprotein receptor mRNA and plasma lipoprotein concentrations by defined dietary fats. Comparison of trimyristin, tripalmitin, tristearin and triolein. *Biochem J*. 1995; 311(Pt 1):167-73.
195. Piccinin E, Cariello M, De Santis S et al. Role of oleic acid in the gut-liver axis: from diet to the regulation of its synthesis via stearyl-CoA desaturase 1 (SCD1). *Nutrients*. 2019; 11(10):2283.
196. Mente A, Dehghan M, Rangarajan S et al. Prospective Urban Rural Epidemiology (PURE) Study investigators. Association of dietary nutrients with blood lipids and blood pressure in 18 countries: a cross-sectional analysis from the PURE study. *Lancet Diabetes Endocrinol*. 2017; 5(10):774-87.
197. Hooper L, Martin N, Abdelhamid A et al. Reduction in saturated fat intake for cardiovascular disease. *Cochrane Database Syst Rev*. 2015; 6:CD011737.
198. Forsyth S, Gautier S, Salem N Jr. Dietary intakes of arachidonic acid and docosahexaenoic acid in early life - with a special focus on complementary feeding in developing countries. *Ann Nutr Metab*. 2017; 70(3):217-27.
199. Balk EM, Lichtenstein AH, Chung M et al. Effects of omega-3 fatty acids on serum markers of cardiovascular disease risk: a systematic review. *Atherosclerosis*. 2006; 189(1):19-30.
200. Harris WS. n-3 fatty acids and serum lipoproteins: human studies. *Am J Clin Nutr*. 1997; 65(5 Suppl):1645S-1654S.
201. Hartweg J, Perera R, Montori V et al. Omega-3 polyunsaturated fatty acids (PUFA) for type 2 diabetes mellitus. *Cochrane Database Syst Rev*. 2008; (1):CD003205.
202. Abdelhamid AS, Brown TJ, Brainard JS et al. Omega-3 fatty acids for the primary and secondary prevention of cardiovascular disease. *Cochrane Database Syst Rev*. 2018; 11:CD003177.
203. Brinton EA, Mason RP. Prescription omega-3 fatty acid products containing highly purified eicosapentaenoic acid (EPA). *Lipids Health Dis*. 2017; 16(1):23.

204. Yokoyama M, Origasa H, Matsuzaki M et al. Effects of eicosapentaenoic acid on major coronary events in hypercholesterolemic patients (JELIS): a randomized open-label, blinded endpoint analysis. *Lancet*. 2007; 369(9567):1090-8.
205. Engler MM, Engler MG, Malloy M et al. Docosahexaenoic acid restores endothelial function in children with hyperlipidemia: results from the EARLY Study. *Int J Clin Pharmacol Ther*. 2004; 42(12):672-9.
206. Balestrieri GP, Maffi V, Sleiman I et al. Fish oil supplementation in patients with heterozygous familial hypercholesterolemia. *Recent Prog Med*. 1996; 87(3):102-5.
207. Malhotra A, Shafiq N, Arora A et al. Dietary interventions (plant sterols, stanols, omega-3 fatty acids, soy protein and dietary fibers) for familial hypercholesterolemia. *Cochrane Database Syst Rev*. 2014; (6):CD001918.
208. Matthan NR, Welty FK, Barrett PH et al. Dietary hydrogenated fat increases high-density lipoprotein Apo A-I catabolism and decreases low-density lipoprotein Apo B-100 catabolism in hypercholesterolemic women. *Arterioscler Thromb Vasc Biol*. 2004; 24(6):1092-7.
209. Ahmed S, Kharroubi W, Kaoubaa N et al. Correlation of trans fatty acids with the severity of coronary artery disease lesions. *Lipids Health Dis*. 2018; 17(1):52.
210. Zapolska-Downar D, Kosmider A, Naruszewicz M. Trans fatty acids induce apoptosis in human endothelial cells. *J Physiol Pharmacol*. 2005; 56(4):611-25.
211. Mozaffarian D, Clarke R. Quantitative effects on cardiovascular risk factors and coronary heart disease risk of replacing partially hydrogenated vegetable oils with other fats and oils. *Eur J Clin Nutr*. 2009; 63(Suppl 2):S22-33.
212. Wang Q, Afshin A, Yakoob MY et al. Global Burden of Diseases Nutrition and Chronic Diseases Expert Group (NutriCoDE). Impact of nonoptimal intakes of saturated, polyunsaturated, and trans fat on global burdens of coronary heart disease. *J Am Heart Assoc*. 2016; 5(1):pii:e002891.
213. GBD 2017 diet collaborators. Health effects of dietary risks in 195 countries, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet*. 2019; 393(10184):1958-72.
214. Han SN, Leka LS, Lichtenstein AH et al. Effect of hydrogenated and saturated, relative to polyunsaturated, fat on immune and inflammatory responses of adults with moderate hypercholesterolemia. *J Lipid Res*. 2002; 43(3):445-52.
215. Mensink RP, Zock PL, Kester AD et al. Effects of dietary fatty acids and carbohydrates on the ratio of serum total to HDL cholesterol and on serum lipids and apolipoproteins: a meta-analysis of 60 controlled trials. *Am J Clin Nutr*. 2003; 77(5):1146-55.
216. Largada MJ, García-Illatas G, Farré R. Analysis of phytosterols in foods. *J Pharm Biomed Anal*. 2006; 41(1):1486-96.
217. Gylling H, Plat J, Turley S et al. Plant sterols and plant stanols in the management of dyslipidemia and prevention of cardiovascular disease. *Atherosclerosis* 2014; 232(2):346-60.
218. Martins CM, Fonseca FA, Ballus CA et al. Common sources and composition of phytosterols and their estimated intake by the population in the city of Sao Paulo, Brazil. *Nutrition*. 2013; 29(6):865-71.
219. Lottenberg AM, Nunes VS, Nakandakare ER et al. The human cholesterol ester transfer protein I405V polymorphism is associated with plasma cholesterol concentration and its reduction by dietary phytosterol esters. *J Nutr*. 2003; 133(6):1800-5.
220. Lottenberg AM, Nunes VS, Nakandakare ER et al. Food phytosterol ester efficiency on the plasma lipid reduction in moderate hypercholesterolemic subjects. *Arq Bras Cardiol*. 2002; 79(2):139-42.
221. Noakes M, Clifton P, Ntanos F et al. An increase in dietary carotenoids when consuming plant sterols or stanols is effective in maintaining plasma carotenoid concentrations. *Am J Clin Nutr*. 2002; 75(1):79-86.
222. Machado VA, Fonseca FA, Fonseca HA et al. Plant sterol supplementation on top of lipid-lowering therapies in familial hypercholesterolemia. *Int J Cardiol*. 2015; 184:570-2.
223. Moruisi KG, Oosthuizen W, Opperman AM. Phytosterols/stanols lower cholesterol concentrations in familial hypercholesterolemic subjects: a systematic review with meta-analysis. *J Am Coll Nutr*. 2006; 25(1):41-8.
224. Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents; National Heart, Lung, and Blood Institute. Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents: summary report. *Pediatrics*. 2011; 128(Suppl 5):S213-56.
225. Laitinen K, Isolauri E, Kaipainen L et al. Plant stanol ester spreads as components of a balanced diet for pregnant and breast-feeding women: evaluation of clinical safety. *Br J Nutr*. 2009; 101(12):1797-804.
226. Vuksan V, Jenkins AL, Rogovik AL et al. Viscosity rather than quantity of dietary fibre predicts cholesterol-lowering effect in healthy individuals. *Br J Nutr*. 2011; 106(9):1349-52.
227. Gunness P, Michiels J, Vanhaecke L et al. Reduction in circulating bile acid and restricted diffusion across the intestinal epithelium are associated with a decrease in blood cholesterol in the presence of oat β -glucan. *Food Funct*. 2016; 30(12):4227-38.
228. Garcia-Diez F, Garcia-Mediavilla V, Bayon JE et al. Pectin feeding influences fecal bile acid excretion, hepatic bile acid and cholesterol synthesis and serum cholesterol in rats. *J Nutr*. 1996; 126(7):1766-71.
229. Wang Y, Harding SV, Thandapilly SJ et al. Barley β -glucan reduces blood cholesterol levels via interrupting bile acid metabolism. *Br J Nutr*. 2017; 118(10):822-9.
230. Tong LT, Zhong K, Liu L et al. Effects of dietary hull-less barley β -glucan on the cholesterol metabolism of hypercholesterolemic hamsters. *Food Chem*. 2015; 169:344-9.
231. Hsieh YL, Yao HT, Cheng RS et al. Chitosan reduces plasma adipocytokines and lipid accumulation in liver and adipose tissues and ameliorates insulin resistance in diabetic rats. *J Med Food*. 2012; 15(5):453-60.
232. Thandapilly SJ, Ndou SP, Wang Y et al. Barley β -glucan increases fecal bile acid excretion and short chain fatty acid levels in mildly hypercholesterolemic individuals. *Food Funct*. 2018; 9(6):3092-6.
233. Whitehead A, Beck EJ, Tosh S et al. Cholesterol-lowering effects of oat β -glucan: a meta-analysis of randomized controlled trials. *Am J Clin Nutr*. 2014; 100(6):1413-21.
234. Hartley L, May MD, Loveman E et al. Dietary fibre for the primary prevention of cardiovascular disease. *Cochrane Database Syst Rev*. 2016; (1):CD011472.
235. McVeigh BL, Dillingham BL, Lampe JW et al. Effect of soy protein varying in isoflavone content on serum lipids in healthy young men. *Am J Clin Nutr*. 2006; 83(2):244-51.
236. Høie LH, Morgenstern EC, Gruenewald J et al. A double-blind placebo-controlled clinical trial compares the cholesterol-lowering effects of two different soy protein preparations in hypercholesterolemic subjects. *Eur J Nutr*. 2005; 44(2):65-71.
237. Sacks FM, Lichtenstein A, Van Horn L, Harris W, Kris-Etherton P, Winston M, American Heart Association Nutrition Committee. Soy protein, isoflavones, and cardiovascular health: an American Heart Association Science Advisory for professionals from the Nutrition Committee. *Circulation*. 2006; 113(7):1034-44.
238. Torres-Moreno M, Torrecasana E, Salas-Salvadó J et al. Nutritional composition and fatty acids profile in cocoa beans and chocolates with different geographical origin and processing conditions. *Food Chem*. 2015; 166:125-32.
239. Jia L, Liu X, Bai YY et al. Short-term effect of cocoa product consumption on lipid profile: a meta-analysis of randomized controlled trials. *Am J Clin Nutr*. 2010; 92(1):218-25.

240. Tokede OA, Gaziano JM, Djoussé L. Effects of cocoa products/dark chocolate on serum lipids: a meta-analysis. *Eur J Clin Nutr.* 2011; 65(8):879-86.
241. Grundy SM. Influence of stearic acid on cholesterol metabolism relative to other long-chain fatty acids. *Am J Clin Nutr.* 1994; 60(6 Suppl):986S-990S.
242. U.S. Department of Agriculture. Agricultural Research Service. SR legacy, fats and oils - FDC ID:171142 NDB number: 4047. Disponível em: <https://fdc.nal.usda.gov/fdc-app.html#/food-details/171412/nutrients>. Acesso em: 12 fev 2020.
243. Eyres L, Eyres MF, Chisholm A et al. Coconut oil consumption and cardiovascular risk factors in humans. *Nutr Rev.* 2016; 74(4):267-80.
244. Voon PT, Ng TK, Lee VK et al. Diets high in palmitic acid (16:0), lauric and myristic acids (12:0 + 14:0), or oleic acid (18:1) do not alter postprandial or fasting plasma homocysteine and inflammatory markers in healthy Malaysian adults. *Am J Clin Nutr.* 2011; 94(6):1451-7.
245. Cox C, Sutherland W, Mann J et al. Effects of dietary coconut oil, butter and safflower oil on plasma lipids, lipoproteins and lathosterol levels. *Eur J Clin Nutr.* 1998; 52(9):650-4.
246. Mendis S, Kumarasundaram R. The effect of daily consumption of coconut fat and soya-bean fat on plasma lipids and lipoproteins of young normolipidaemic men. *Br J Clin Nutr.* 1990; 63(3):547-52.
247. Maki KC, Hasse W, Dicklin MR et al. Corn oil lowers plasma cholesterol compared with coconut oil in adults with above-desirable levels of cholesterol in a randomized crossover trial. *J Nutr.* 2018; 148(10):1556-63.
248. Feranil AB, Duazo PL, Kuzawa CW et al. Coconut oil is associated with a beneficial lipid profile in pre-menopausal women in the Philippines. *Asia Pac J Clin Nutr.* 2011; 20(2):190-5.
249. Lee JY, Sohn KH, Rhee SH et al. Saturated fatty acids, but not unsaturated fatty acids, induce the expression of cyclooxygenase-2 mediated through Toll-like receptor 4. *J Biol Chem.* 2001; 276(20):16683-9.
250. Velloso LA, Folli F, Saad MJ. TLR4 at the crossroads of nutrients, gut microbiota, and metabolic inflammation. *Endocr Rev.* 2015; 36(3):245-71.
251. Weatherill AR, Lee JY, Zhao L et al. Saturated and polyunsaturated fatty acids reciprocally modulate dendritic cell functions mediated through TLR4. *J Immunol.* 2005; 174(9):5390-7.
252. Lee JY, Ye J, Gao Z et al. Reciprocal modulation of toll-like receptor-4 signaling pathways involving MyD88 and phosphatidylinositol 3-kinase/AKT by saturated and polyunsaturated fatty acids. *J Biol Chem.* 2003; 278(39):37041-51.
253. Valente FX, Cândido FG, Lopes LL et al. Effects of coconut oil consumption on energy metabolism, cardiometabolic risk markers, and appetite responses in women with excess body fat. *Eur J Nutr.* 2017; 57(4):1627-37.
254. Karupaiah T, Chuah KA, Chinna K et al. Comparing effects of soybean oil- and palm olein-based mayonnaise consumption on the plasma lipid and lipoprotein profiles in human subjects: a double-blind randomized controlled trial with cross-over design. *Lipids Health Dis.* 2016; 15:131.
255. Sun Y, Neelakantan N, Wu Y et al. Palm oil consumption increases LDL-C cholesterol compared with vegetable oils low in saturated fat in a meta-analysis of clinical trials. *J Nutr.* 2015; 145(7):1549-58.
256. Tholstrup T, Hjerpested J, Raff M. Palm olein increases plasma cholesterol moderately compared with olive oil in healthy individuals. *Am J Clin Nutr.* 2011; 94(6):1426-32.
257. Yakoob MY, Shi P, Hu FB et al. Circulating biomarkers of dairy fat and risk of incident stroke in U. S. men and women in 2 large prospective cohorts. *Am J Clin Nutr.* 2014; 100(6):1437-47.
258. Pala V, Sieri S, Chiodini P et al. Associations of dairy product consumption with mortality in the European Prospective Investigation into Cancer and Nutrition (EPIC)-Italy cohort. *Am J Clin Nutr.* 2019; 110(5):1220-30.
259. Universidade Estadual de Campinas (Unicamp). Tabela brasileira de composição de alimentos - TACO. 4. ed. Campinas: Unicamp/NEPA; 2011. 161 p. Disponível em: <http://www.unicamp.br/nepa/taco/tabela>. Acesso em: 12 fev 2019.
260. Brassard D, Tessier-Grenier M, Allaire J et al. Comparison of the impact of SFAs from cheese and butter on cardiometabolic risk factors: a randomized controlled trial. *Am J Clin Nutr.* 2017; 105(4):800-9.
261. Avalos EE, Barrett-Connor E, Kritiz-Silverstein D et al. Is dairy product consumption associated with the incidence of CHD? *Public Health Nutr.* 2013; 16(11):2055-63.
262. Ericson U, Hellstrand S, Brunkwall L et al. Food sources of fat may clarify the inconsistent role of dietary fat intake for incidence of type 2 diabetes. *Am J Clin Nutr.* 2015; 101(5):1065-80.
263. Pimpin L, Wu JHY, Haskelberg H et al. Is butter back? A systematic review and meta-analysis of butter consumption and risk of cardiovascular disease, diabetes, and total mortality. *Plos One.* 2016; 11:e0158118.
264. Gidding SS, Champagne MA, de Ferranti SD et al. The agenda for familial hypercholesterolemia: a scientific statement from the American Heart Association. *Circulation.* 2015; 132(22):2167-92.
265. Sposito AC, Faria Neto JR, Carvalho LSF et al. On behalf of the Luso-Latin American Consortium on statin-associated muscle symptoms. Statin-associated muscle symptoms: position paper from the Luso-Latin American Consortium. *Curr Med Res Opin.* 2017; 33(2):239-51.
266. Cholesterol treatment trialists (CTT) collaboration, Baigent C, Blackwell L et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomized trials. *Lancet.* 2010; 376(9753):1670-81.
267. O'Regan C, Wu P, Arora P et al. Statin therapy in stroke prevention: a meta-analysis involving 121,000 patients. *Am J Med.* 2008; 121(1):24-33.
268. Cholesterol treatment trialists (CTT). The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomized trials. *Lancet.* 2012; 380(9841):P581-590.
269. Kearney PM, Blackwell L, Collins R et al. Efficacy of cholesterol-lowering therapy in 18,686 people with diabetes in 14 randomized trials of statins: a meta-analysis. *Lancet.* 2008; 371(9607):117-25.
270. Pijlman AH, Huijgen R, Verhagen SN et al. Evaluation of cholesterol lowering treatment of patients with familial hypercholesterolemia: a large cross-sectional study in The Netherlands. *Atherosclerosis.* 2010; 209(1):189-94.
271. Ito MK, McGowan MP, Moriarty PM. Management of familial hypercholesterolemia in adult patients: recommendations from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. *J Clin Lipidol.* 2011; 5(3 Suppl):S38-45.
272. Turley SD. Cholesterol metabolism and therapeutic targets: rationale for targeting multiple metabolic pathways. *Clin Cardiol.* 2004; 27(6 Suppl 3):III16-21.
273. Mikhailidis DP, Sibbring GC, Ballantyne CM et al. Meta-analysis of the cholesterol-lowering effect of ezetimibe added to ongoing statin therapy. *Curr Med Res Opin.* 2007; 23(8):2009-26.
274. Kastelein JJP, Akdim F, Stroes ESG et al. Simvastatin with or without ezetimibe in familial hypercholesterolemia. *N Engl J Med.* 2008; 358(14):1431-43.
275. Stein E, Stender S, Mata P et al. Achieving lipoprotein goals in patients at high risk with severe hypercholesterolemia: efficacy and safety of ezetimibe co-administered with atorvastatin. *Am Heart J.* 2004; 148(3):447-55.
276. Gagné C, Gaudet D, Bruckert E. Efficacy and safety of ezetimibe coadministered with atorvastatin or simvastatin in patients with homozygous familial hypercholesterolemia. *Circulation.* 2002; 105(21):2469-75.
277. Fleg JL, Mete M, Howard BV et al. Effect of statins alone versus statins plus ezetimibe on carotid atherosclerosis in type 2 diabetes: the SANDS (Stop Atherosclerosis in Native Diabetics Study) trial. *J Am Coll Cardiol.* 2008; 52(25):2198-205.

278. Rossebo AB, Pedersen TR, Boman K et al. Intensive lipid lowering with simvastatin and ezetimibe in aortic stenosis. *N Engl J Med*. 2008; 359(13):1343-56.
279. Cannon CP, Blazing MA, Giugliano RP et al. Ezetimibe added to statin therapy after acute coronary syndromes. *N Engl J Med*. 2015; 372(25):2387-97.
280. Baigent C, Landray MJ, Reith C et al. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomized placebo-controlled trial. *Lancet*. 2011; 377(9784):2181-92.
281. Lambert G, Sjouke B, Choque B et al. The PCSK9 decade. *J Lip Res*. 2012; 53(12):2515-24.
282. Navarese EP, Kolodziejczak M, Schulze V et al. Effects of proprotein convertase subtilisin/kexin type 9 antibodies in adults with hypercholesterolemia: a systematic review and meta-analysis. *Ann Intern Med*. 2015; 163(1):40-51.
283. Raal FJ, Stein EA, Dufour R et al. PCSK9 inhibition with evolocumab (AMG 145) in heterozygous familial hypercholesterolemia (RUTHERFORD-2): a randomized, double-blind, placebo-controlled trial. *Lancet*. 2015; 385(9965):331-40.
284. Kastelein JJ, Ginsberg HN, Langslet G et al. ODYSSEY FH I and FH II: 78 week results with alirocumab treatment in 735 patients with heterozygous familial hypercholesterolemia. *Eur Heart J*. 2015; 36(43):2996-3003.
285. Santos RD, Stein EA, Hovingh GK et al. Long-term evolocumab in patients with familial hypercholesterolemia. *J Am Coll Cardiol*. 2020;75(6):565-574.
286. Raal FJ, Hovingh GK, Blom D et al. Long-term treatment with evolocumab added to conventional drug therapy, with or without apheresis, in patients with homozygous familial hypercholesterolemia: an interim subset analysis of the open-label TAUSIG study. *Lancet Diabetes Endocrinol*. 2017; 5(4):280-90.
287. Sabatine MS, Giugliano RP, Keech AC et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. *N Engl J Med*. 2017; 376(18):1713-22.
288. Schwartz GG, Steg PG, Szarek M et al. Alirocumab and cardiovascular outcomes after acute coronary syndrome. *N Engl J Med*. 2018; 379(22):2097-107.
289. Einarsson K, Ericsson S, Ewerth S et al. Bile acid sequestrants: mechanisms of action on bile acid and cholesterol metabolism. *Eur J Clin Pharmacol*. 1991; 40(Suppl 1):S53-8.
290. Feingold KR, Anawalt B, Boyce A et al. In: Cholesterol lowering drugs. Endotext. South Dartmouth (MA): MDText.Com, Inc.; 2000-2020.
291. The lipid research clinics coronary primary prevention trial results. II. The relationship of reduction in incidence of coronary heart disease to cholesterol lowering. *JAMA*. 1984; 251(3):365-74.
292. Buchwald H, Fitch LL, Campos CT. Partial ileal bypass in the treatment of hypercholesterolemia. *J Fam Pract*. 1992; 35(1):69-76.
293. Buchwald H, Varco RL, Matts JP et al. Effect of partial ileal bypass surgery on mortality and morbidity from coronary heart disease in patients with hypercholesterolemia. Report of the Program on the Surgical Control of the Hyperlipidemias (POSCH). *N Engl J Med*. 1990; 323(14):946-55.
294. Ohri SK, Keane PF, Swift I et al. Reappraisal of partial ileal bypass for the treatment of familial hypercholesterolemia. *Am J Gastroenterol*. 1989; 84(7):740-3.
295. Heffron SP, Parikh A, Volodarskiy A et al. Changes in lipid profile of obese patients following contemporary bariatric surgery: a meta-analysis. *Am J Med*. 2016; 129(9):952-9.
296. Health Quality Ontario. Low-density lipoprotein apheresis: an evidence-based analysis. *Ont Health Technol Assess Ser*. 2007; 7(5):1-101.
297. Winters JL. Lipid apheresis, indications, and principles. *J Clin Apheresis*. 2011; 26(5):269-75.
298. Wang A, Richhariya A, Gandra SR et al. Systematic review of low-density lipoprotein cholesterol apheresis for the treatment of familial hypercholesterolemia. *J Am Heart Assoc*. 2016; 5(7):e003294.
299. Thompson GR, Catapano A, Saheb S et al. Severe hypercholesterolemia: therapeutic goals and eligibility criteria for LDL apheresis in Europe. *Curr Opin Lipidol*. 2010; 21(6):492-6.
300. Julius U, Fischer S, Schatz U et al. Why an apheresis center should offer more than one lipoprotein apheresis method. *Ther. Apher. Dial*. 2013; 17(2):179-84.
301. Thompson GR, Barbir M, Davies D et al. Recommendations for the use of LDL apheresis. *Atherosclerosis*. 2008; 98(2):247-55.
302. Harada-Shiba M, Arai H, Oikawa S et al. Guidelines for the management of familial hypercholesterolemia. *J Atheroscler Thromb*. 2012; 19(12):1043-60.
303. Goldberg AC, Hopkins PN, Toth PP et al. National Lipid Association Expert Panel on Familial Hypercholesterolemia. Familial hypercholesterolemia: screening, diagnosis and management of pediatric and adult patients – clinical guidance from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. *J Clin Lipidol*. 2011; 5(3 Suppl):S1-S8.
304. Stefanutti C, Julius U. Lipoprotein apheresis: state of the art and novelties. *Atherosclerosis Suppl*. 2013; 14(1):19-27.
305. Schuff-Werner P, Fenger S, Kohlschein P. Role of lipid apheresis in changing times. *Clin Res Cardiol Suppl*. 2012; 7(Suppl 1):7-14.
306. Keller C, Grutzmacher P, Bahr F et al. LDL-apheresis with dextran sulphate and anaphylactoid reactions to ACE inhibitors. *Lancet*. 1993; 341(8836):60-1.
307. Stefanutti C, Morozzi C, Petta A. Lipid and low-density-lipoprotein apheresis. Effects on plasma inflammatory profile and on cytokine pattern in patients with severe dyslipidemia. *Cytokine*. 2011; 56(3):842-9.
308. Coker M, Ucar SK, Simsek DG et al. Low density lipoprotein apheresis in pediatric patients with homozygous familial hypercholesterolemia. *Ther Apher Dial*. 2009; 13(2):121-8.
309. Goldberg AC, Hopkins PN, Toth PP et al. Familial hypercholesterolemia: screening, diagnosis and management of pediatric and adult patients clinical guidance from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. *J Clin Lipidol*. 2011; 5(3 Suppl): S1-S8.
310. Thompson GR. LDL apheresis. *Atherosclerosis*. 2003; 167(1):1-13.
311. Tatami R, Inoue N, Itoh H et al. Regression of coronary atherosclerosis by combined LDL-apheresis and lipid-lowering drug therapy in patients with familial hypercholesterolemia: a multicenter study. The LARS Investigators. *Atherosclerosis*. 1992; 95(1):1-13.
312. Waidner T, Franzen D, Voelker W et al. The effect of LDL apheresis on progression of coronary artery disease in patients with familial hypercholesterolemia. Results of a multicenter LDL apheresis study. *Clin Invest*. 1994; 72(11):858-63.
313. Schuff-Werner P, Gohike H, Bartmann U et al. The HELP-LDL-apheresis multicentre study, an angiographically assessed trial on the role of LDL-apheresis in the secondary prevention of coronary heart disease. II. Final evaluation of the effect of regular treatment on LDL-cholesterol plasma concentrations and the course of coronary heart disease. The HELP-Study Group. Heparin induced extra-corporeal LDL-precipitation. *Eur J Clin Invest*. 1994; 24(11):724-32.
314. Thompson GR, Maher VM, Matthews S et al. Familial Hypercholesterolemia Regression Study: a randomized trial of low-density-lipoprotein apheresis. *Lancet*. 1995; 345(8953):811-6.
315. Kroon AA, Aengevaeren WR, van den Werf T et al. LDL-Apheresis Atherosclerosis Regression Study (LAARS). Effect of aggressive versus conventional lipid lowering treatment of coronary atherosclerosis. *Circulation*. 1996; 93(10):1826-35.

316. Mabuchi H, Koizumi J, Shimizu M et al. Long-term efficacy of low-density lipoprotein apheresis on coronary heart disease in familial hypercholesterolemia. Hokuriku-FH-LDL-Apheresis Study Group. *Am J Cardiol.* 1998; 82(12):1489-95.
317. Ritcher WO, Donner MG, Hofling B et al. Long-term effect of low-density lipoprotein apheresis on plasma lipoproteins and coronary heart disease in native vessels and coronary bypass in severe heterozygous familial hypercholesterolemia. *Metabolism.* 1998; 47(7):863-8.
318. Tamai O, Matsuoka H, Itabe H et al. Single LDL apheresis improves endothelium-dependent vasodilation in hypercholesterolemic humans. *Circulation.* 1997; 95(1):76-82.
319. Igarashi K, Tsuji M, Nishimura M et al. Improvement of endothelium-dependent coronary vasodilation after a single LDL apheresis in patients with hypercholesterolemia. *J Clin Apher.* 2004; 19(1):11-6.
320. Sato M, Amano I. Changes in oxidative stress and microcirculation by low-density lipoprotein apheresis. *Ther Apher Dial.* 2003; 7(4):419-24.
321. Kobayashi K, Yamashita K, Tasaki H et al. Evaluation of improved coronary flow velocity reserve using transthoracic doppler echocardiography after single LDL apheresis. *Ther Apher Dial.* 2004; 8(5):383-9.
322. Keller C. Apheresis in coronary heart disease with elevated Lp(a): a review of Lp(a) as a risk factor and its management. *Ther Apher Dial.* 2007; 11(1):2-8.
323. Bambauer R. Is lipoprotein(a)-apheresis useful? *Ther Apher Dial.* 2005; 9(2):142-7.
324. Thompson GR, Blom DJ, Marais AD et al. Survival in homozygous familial hypercholesterolemia is determined by the on-treatment level of serum cholesterol. *Eur Heart J.* 2018; 39(14):1162-8.
325. Barbir M, Khaghani A, Kehely A et al. Normal levels of lipoproteins including lipoprotein(a) after liver-heart transplantation in a patient with homozygous familial hypercholesterolemia. *Q J Med.* 1992; 85(307-308):807-12.
326. Gidding SS, Daniels SR, Kavey RE. Expert Panel on Cardiovascular Health and Risk Reduction in Youth. Developing the 2011 integrated pediatric guidelines for cardiovascular risk reduction. *Pediatrics.* 2012; 129(5):e1311-9.
327. Wiegman A, Gidding SS, Watts GF, Chapman MJ, Ginsberg HN, Cuchel M, et al. Familial hypercholesterolaemia in children and adolescents: gaining decades of life by optimizing detection and treatment. *Eur Heart J.* 2015; 36(36):2425-37.
328. Mata P, Alonso R, Ruiz A et al. Diagnosis and treatment of familial hypercholesterolemia in Spain: consensus document. *Aten Primaria.* 2015; 47(1):56-65.
329. Caballero P, Alonso R, Rosado P et al. Detection of subclinical atherosclerosis in familial hypercholesterolemia using non-invasive imaging modalities. *Atherosclerosis.* 2012; 222(2):468-72.
330. Dalla Pozza R, Ehringer-Schetitska D, Fritsch P et al. Association for European Paediatric Cardiology Working Group Cardiovascular Prevention. Intima media thickness measurement in children: a statement from the Association for European Paediatric Cardiology (AEPC) Working Group on Cardiovascular Prevention endorsed by the Association for European Paediatric Cardiology. *Atherosclerosis.* 2015; 238(2):380-7.
331. Narverud I, Retterstøl K, Iversen PO et al. Markers of atherosclerotic development in children with familial hypercholesterolemia: a literature review. *Atherosclerosis.* 2014; 235(2):299-309.
332. Riggio S, Mandraffino G, Sardo MA et al. Pulse wave velocity and augmentation index, but not intima-media thickness, are early indicators of vascular damage in hypercholesterolemic children. *Eur J Clin Invest.* 2010; 40(3):250-7.
333. Vitarelli A, Martino F, Capotosto L et al. Early myocardial deformation changes in hypercholesterolemic and obese children and adolescents: a 2D and 3D speckle tracking echocardiography study. *Medicine (Baltimore).* 2014; 93(12):e71.
334. Lebars MA, Rieu D, Girardet JP. Dietary recommendations for children with hypercholesterolemia. *Arch Pediatr.* 2010; 17(7):1126-32.
335. Shafiq N, Singh M, Kaur S et al. Dietary treatment for familial hypercholesterolemia. *Cochrane Database Syst Rev.* 2010; (1):CD001918.
336. Sánchez-Bayle M, Soriano-Guillén L. Influence of dietary intervention on growth in children with hypercholesterolemia. *Acta Paediatr.* 2003; 92(9):1043-6.
337. Piercy KL, Troiano RP, Ballard RM et al. The Physical Activity Guidelines for Americans. *JAMA.* 2018; 320(19):2020-8.
338. Dias KA, Green DJ, Ingul CB et al. Exercise and vascular function in child obesity: a meta-analysis. *Pediatrics.* 2015; 136(3):e648-59.
339. Vázquez MA, Vázquez BY, Intaglietta M et al. Nonobese, exercising children diagnosed with dyslipidemia have normal C-reactive protein. *Vasc Health Risk Manag.* 2009; 5(1):65-9; quiz 70-2.
340. Ambrosetti M, Malfatto G, Cremona MA et al. Familial hypercholesterolemia in cardiac rehabilitation: a new field of interest. *Monaldi Arch Chest Dis.* 2014; 82(2):87-92.
341. Avis HJ, Vissers MN, Stein EA et al. A systematic review and meta-analysis of statin therapy in children with familial hypercholesterolemia. *Arterioscler Thromb Vasc Biol.* 2007; 27(8):1803-10.
342. Martin AC, Gidding SS, Wiegman A et al. Knowns and unknowns in the care of pediatric familial hypercholesterolemia. *J Lipid Res.* 2017; 58(9):1765-76.
343. Arambepola C, Farmer AJ, Perera R et al. Statin treatment for children and adolescents with heterozygous familial hypercholesterolemia: a systematic review and meta-analysis. *Atherosclerosis.* 2007; 195(2):339-47.
344. Avis HJ, Hargreaves IP, Ruiters JP et al. Rosuvastatin lowers coenzyme Q10 levels, but not mitochondrial adenosine triphosphate synthesis, in children with familial hypercholesterolemia. *J Pediatr.* 2011; 158(3):458-62.
345. Avis HJ, Hutten BA, Gagné C et al. Efficacy and safety of rosuvastatin therapy for children with familial hypercholesterolemia. *J Am Coll Cardiol.* 2010; 55(11):1121-6.
346. Clauss SB, Holmes KW, Hopkins P et al. Efficacy and safety of lovastatin therapy in adolescent girls with heterozygous familial hypercholesterolemia. *Pediatrics.* 2005; 116(3):682-8.
347. Ferreira WP, Bertolami MC, Santos SN et al. One-month therapy with simvastatin restores endothelial function in hypercholesterolemic children and adolescents. *Pediatr Cardiol.* 2007; 28(1):8-13.
348. Gandelman K, Glue P, Laskey R et al. An eight-week trial investigating the efficacy and tolerability of atorvastatin for children and adolescents with heterozygous familial hypercholesterolemia. *Pediatr Cardiol.* 2011; 32(4):433-41.
349. Xavier HT, Izar MC, Faria Neto JR et al. V Brazilian Guidelines on Dyslipidemias and Prevention of Atherosclerosis. *Arq. Bras. Cardiol.* 2013; 101(4 Suppl 1):1-20.
350. Clauss S, Wai KM, Kavey RE et al. Ezetimibe treatment of pediatric patients with hypercholesterolemia. *J Pediatr.* 2009; 154(6):869-72.
351. Davidson MH. A systematic review of bile acid sequestrant therapy in children with familial hypercholesterolemia. *J Clin Lipidol.* 2011; 5(2):76-81.
352. Amundsen AL, Ose L, Nenseter MS et al. Plant sterol ester-enriched spread lowers plasma total and LDL cholesterol in children with familial hypercholesterolemia. *Am J Clin Nutr.* 2002; 76(2):338-44.
353. Santos RD, Ruzza A, Hovingh GK et al; HAUSER-RCT Investigators. Evolocumab in pediatric heterozygous familial hypercholesterolemia. *N Engl J Med.* 2020; 383(14):1317-1327.
354. Daniels S, Caprio S, Chaudhari U et al. PCSK9 inhibition with alirocumab in pediatric patients with heterozygous familial hypercholesterolemia: The ODYSSEY KIDS study. *J Clin Lipidol.* 2020; 14(3):322-330.e5.

355. Sabatine MS, Giugliano RP, Wiviott SD et al. Open-Label Study of Long-Term Evaluation against LDL Cholesterol (OSLER) Investigators. Efficacy and safety of evolocumab in reducing lipids and cardiovascular events. *N Engl J Med* 2015; 372(16):1500-9.
356. Robinson JG, Farnier M, Krempf M et al. Odyssey long term investigators. Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. *N Engl J Med*. 2015; 372(16):1489-99.
357. Vuorio A, Watts GF, Petri T. Initiation of PCSK9 inhibition in patients with heterozygous familial hypercholesterolemia entering adulthood: a new design for living with a high-risk condition? *Eur Heart J*. 2016; 37(17):1353-6.
358. France M, Rees A, Datta D et al. Heart UK Medical Scientific and Research Committee. HEART UK statement on the management of homozygous familial hypercholesterolaemia in the United Kingdom. *Atherosclerosis*. 2016; 255:128-39.
359. Nemati MH, Astaneh B, Joubah A. Triple coronary artery bypass graft in a 10-year-old child with familial hypercholesterolemia. *Gen Thorac Cardiovasc Surg*. 2009; 57(2):94-7.
360. Winkler B, Kuhn S, Kunzmann S et al. Severe hypertriglyceridemia in a 6-year-old boy with ALL relapse: successfully treated with plasmapheresis. *Klin Padiatr*. 2013; 225(6):364-5.
361. Bilal MS, Aydemir NA, Turan T. Rosskono procedure and postal pasty in a child with homozygous hypercholesterolemia: case report. *J Heart Valve Dis*. 2005; 14(6):855-8.
362. Radaelli G, Sausen G, Cesa CC et al. Statin treatments and dosages in children with familial hypercholesterolemia: meta-analysis. *Arq Bras Cardiol*. 2018; 111(6):810-21.
363. de Jongh S, Kerckhoffs MC, Grootenhuis MA et al. Quality of life, anxiety and concerns among statin-treated children with familial hypercholesterolemia and their parents. *Acta Paediatr*. 2003; 92(9):1096-101.
364. Toleikyte I, Retterstøl K, Leren TP et al. Pregnancy outcomes in familial hypercholesterolemia: a registry-based study. *Circulation*. 2011; 124(15):1606-14.
365. Ito MK, McGowan MP, Moriarty PM; National Lipid Association Expert Panel on Familial Hypercholesterolemia. Management of familial hypercholesterolemia in adult patients: recommendations form the National Lipid Association Expert Panel on Familial Hypercholesterolemia. *J Clin Lipidol*. 2011; 5(3Suppl):S38-45.
366. Klingel R, Göhlen B, Schwarting A et al. Differential indication of lipoprotein apheresis during pregnancy. *Ther Apher Dial*. 2003; 7(3):359-64.
367. Thorogood M, Seed M, De Mott K; Guideline Development Group. Management of fertility in women with familial hypercholesterolemia: summary of NICE guidance. *BJOG*. 2009; 116(4):478-9.
368. Simonson SG, Martin PD, Warwick MJ et al. The effect of rosuvastatin on oestrogen & progestin pharmacokinetics in healthy women taking an oral contraceptive. *Br J Clin Pharmacol*. 2004; 57(3):279-86.
369. Kusters DM, Homsma SJ, Hutten BA et al. Dilemmas in treatment of women with familial hypercholesterolemia during pregnancy. *Neth J Med*. 2010; 68(1):299-303.
370. Catov JM, Bodnar LM, Kip KE et al. Early pregnancy lipid concentrations and spontaneous preterm birth. *Am J Obstet Gynecol*. 2007; 197(6):610.e1-7.
371. Amundsen AL, Khoury J, Iversen PO et al. Marked changes in plasma lipids and lipoproteins during pregnancy in women with familial hypercholesterolemia. *Atherosclerosis*. 2006; 189(2):451-7.
372. Hameed AB, Tummala PP, Goodwin TM et al. Unstable angina during pregnancy in two patients with premature coronary atherosclerosis and aortic stenosis in association with familial hypercholesterolemia. *Am J Obstet Gynecol*. 2000; 182(5):1152-5.
373. Khoury J, Amundsen AL, Tonstad S et al. Evidence for impaired physiological decrease in the uteroplacental vascular resistance in pregnant women with familial hypercholesterolemia. *Acta Obstet Gynecol Scand*. 2009; 88(2):222-6.
374. Liguori A, D'Armiento FP, Palagiano A et al. Effect of gestational hypercholesterolemia on omental vasoreactivity, placental enzyme activity and transplacental passage of normal and oxidised fatty acids. *BJOG*. 2007; 114(12):1547-56.
375. Varret M, Rabes JP, Saint-Jore B et al. A third major locus for autosomal dominant hypercholesterolemia maps to 1p34.1-p32. *Am J Hum Genet*. 1999; 64(5):1378-87.
376. Horton JD, Cohen JC, Hobbs HH. PCSK9: a convertase that coordinates LDL catabolism. *J Lipid Res*. 2009; 50 (Suppl):S172-7.
377. Maxwell KN, Fisher EA, Breslow JL. Overexpression of PCSK9 accelerates the degradation of the LDLR in a post-endoplasmic reticulum compartment. *Proc Natl Acad Sci USA*. 2005; 102(6):2069-74.
378. Cohen JC, Boerwinkle E, Mosley TH Jr. et al. Sequence variations in PCSK9, low LDL, and protection against coronary heart disease. *N Engl J Med*. 2006; 354(12):1264-72.
379. Robinson JG, Nedergaard BS, Rogers WJ et al. Effect of evolocumab or ezetimibe added to moderate or high-intensity statin therapy on LDL-C lowering in patients with hypercholesterolemia: the LAPLACE-2 randomized clinical trial. *JAMA*. 2014; 311(18):1870-82.
380. Raal FJ, Honarpour N, Blom DJ et al. Inhibition of PCSK9 with evolocumab in homozygous familial hypercholesterolemia (TESLA Part B): a randomized, double-blind, placebo-controlled trial. *Lancet*. 2015; 385(9965):341-50.
381. Roth EM, Taskinen MR, Ginsberg HN et al. Monotherapy with the PCSK9 inhibitor alirocumab versus ezetimibe in patients with hypercholesterolemia: results of a 24 week, double-blind, randomized Phase 3 trial. *Int J Cardiol*. 2014; 176(1):55-61.
382. Cannon CP, Cariou B, Blom D et al. Efficacy and safety of alirocumab in high cardiovascular risk patients with inadequately controlled hypercholesterolemia on maximally tolerated doses of statins: the ODYSSEY COMBO II randomized controlled trial. *Eur Heart J*. 2015; 36(19):1186-94.
383. Roth EM, Moriarty PM, Bergeron J et al. A phase III randomized trial evaluating alirocumab 300 mg every 4 weeks as monotherapy or add-on to statin: ODYSSEY CHOICE I. *Atherosclerosis*. 2016; 254:254-62.
384. Ginsberg HN, Rader DJ, Raal FJ et al. Efficacy and safety of alirocumab in patients with heterozygous familial hypercholesterolemia and LDL-C of 160 mg/dl or higher. *Cardiovasc Drugs Ther*. 2016; 30(5):473-83.
385. Hartgers ML, Defesche JC, Langslet G et al. Alirocumab efficacy in patients with double heterozygous, compound heterozygous, or homozygous familial hypercholesterolemia. *J Clin Lipidol*. 2018; 12(2):390-6e8.
386. Sabatine MS, Giugliano RP, Keech A et al. Rationale and design of the further cardiovascular outcomes research with PCSK9 inhibition in subjects with elevated risk trial. *Am Heart J*. 2016; 173:94-101.
387. Giugliano RP, Mach F, Zavitz K et al; EBBINGHAUS Investigators. Cognitive function in a randomized trial of evolocumab. *N Engl J Med*. 2017; 377(7):633-43.
388. Ridker PM, Revkin J, Amarenco P et al. Cardiovascular efficacy and safety of bococizumab in high-risk patients. *N Engl J Med*. 2017; 376(16):1527-39.
389. Ridker PM, Tardif JC, Amarenco P et al. Lipid-reduction variability and antidrug-antibody formation with bococizumab. *N Engl J Med*. 2017; 376(16):1517-26.
390. Ridker PM, Rose LM, Kastelein JJP et al. Cardiovascular event reduction with PCSK9 inhibition among 1578 patients with familial hypercholesterolemia: results from the SPIRE randomized trials of bococizumab. *J Clin Lipidol*. 2018; 12(4):958-65.

391. Schwartz GG, Bessac L, Berdan LG et al. Effect of alirocumab, a monoclonal antibody to PCSK9, on long-term cardiovascular outcomes following acute coronary syndromes: rationale and design of the ODYSSEY outcomes trial. *Am Heart J*. 2014; 168(5):682-9.
392. Neef D, Berthold HK, Gouni-Berthold I. Lomitapide for use in patients with homozygous familial hypercholesterolemia: a narrative review. *Expert Rev*. 2016; 9(5):655-63.
393. Hussain MM, Rava P, Walsh M et al. Multiple functions of microsomal triglyceride transfer protein. *Nutr Metab (Lond)*. 2012; 9(14):1-16.
394. Chacra APM, Ferrari MC, Rocha VZ et al. Case report: the efficiency and safety of lomitapide in a homozygous familial hypercholesterolemic child. *J Clin Lipidol*. 2019; 13(3):397-401.
395. Cuchel M, Meagher EA, du Toit Theron H et al; Phase 3 HoFH Lomitapide Study investigators. Efficacy and safety of a microsomal triglyceride transfer protein inhibitor in patients with homozygous familial hypercholesterolemia: a single-arm, open-label, phase 3 study. *Lancet*. 2013; 381(9860):40-6.
396. Chandler CE, Wilder DE, Pettini JL et al. CP346086: an MTP inhibitor that lowers plasma cholesterol and triglycerides in experimental animals and in humans. *J Lipid Res*. 2003; 44(10):1887-901.
397. Blom DJ, Cuchel M, Ager M, Phillips H. Target achievement and cardiovascular event rates with lomitapide in homozygous familial hypercholesterolaemia. *Orphanet J Rare Dis*. 2018; 13(1):96.
398. Blom DJ, Aversa MR, Meagher EA et al. Long-term efficacy and safety of the microsomal triglyceride transfer protein inhibitor lomitapide in patients with homozygous familial hypercholesterolemia. *Circulation*. 2017; 136(3):332-5.
399. D'Erasmo L, Cefalu AB, Noto D et al. Efficacy of lomitapide in the treatment of familial homozygous hypercholesterolemia: results of a real-world clinical experience in Italy. *Adv Ther*. 2017; 34(5):1200-1210.
400. Underberg JA, Cannon CP, Larrey D et al. Long-term safety and efficacy of lomitapide in patients with homozygous familial hypercholesterolemia: Five-year data from the Lomitapide Observational Worldwide Evaluation Registry (LOWER). *J Clin Lipidol*. 2020; 14(6):807-817.
401. Santos RD, Valenti L, Romeo S. Does nonalcoholic fatty liver disease cause cardiovascular disease? Current knowledge and gaps. *Atherosclerosis*. 2019; 282:110-20.
402. Roeters van Lennep J, Aversa M, Alonso R. Treating homozygous familial hypercholesterolemia in a real-world setting: experiences with lomitapide. *J Clin Lipidol*. 2015; 9(4):607-17.
403. Tuteja S, Duffy D, Dunbar RL et al. Pharmacokinetic interactions of the microsomal triglyceride transfer protein inhibitor, lomitapide, with drugs commonly used in the management of hypercholesterolemia. *Pharmacotherapy*. 2014; 34(3):227-39.
404. Rader DJ, Kastelein JJ. Lomitapide and mipomersen: two first-in-class drugs for reducing low-density lipoprotein cholesterol in patients with homozygous familial hypercholesterolemia. *Circulation*. 2014; 129(9):1022-32.
405. Goldberg AC. Novel therapies and new targets of treatment for familial hypercholesterolemia. *J Clin Lipidol*. 2010; 4(5):350-6.
406. Raal FJ, Santos RD, Blom DJ et al. Mipomersen, an apolipoprotein B synthesis inhibitor, for lowering of LDL cholesterol concentrations in patients with homozygous familial hypercholesterolemia: a randomized, double-blind, placebo-controlled trial. *Lancet*. 2010; 375(9719):998-1006.
407. Santos RD, Raal FJ, Catapano AL et al. Mipomersen, an antisense oligonucleotide to apolipoprotein B-100, reduces lipoprotein(a) in various populations with hypercholesterolemia: results of 4 phase III trials. *Arterioscler Thromb Vasc Biol*. 2015; 35(3):689-99.
408. Miller M, Wright CC, Browne B. Lipid-lowering medications for children and adolescents. *J Clin Lipidol*. 2015; 9(Suppl 5):S67-S76.
409. Brandts J, Ray KK. Clinical implications and outcomes of the ORION Phase III trials. *Future Cardiol*. 2020. doi: 10.2217/fca-2020-0150. Online ahead of print.
410. Ray KK, Landmesser U, Leiter LA et al. Inclisiran in Patients at High Cardiovascular Risk with Elevated LDL Cholesterol. *N Engl J Med*. 2017; 376(15):1430-40.
411. Raal FJ, Kallend D, Ray KK et al. Inclisiran for the treatment of heterozygous familial hypercholesterolemia. *N Engl J Med* 2020; 382(16):1520-1530.
412. Raal FJ, Rosenson RS, Reeskamp LF et al. Evinacumab for homozygous familial hypercholesterolemia. *N Engl J Med* 2020; 383(8):711-720.
413. Rosenson RS, Burgess LJ, Ebenbichler CF et al. Evinacumab in patients with refractory hypercholesterolemia. *N Engl J Med* 2020; 383(24):2307-2319.
414. Pinkosky SL, Newton RS, Day EA, Ford RJ, Lhotak S, Austin RC, et al. Liver-specific ATP-citrate lyase inhibition by bempedoic acid decreases LDL-C and attenuates atherosclerosis. *Nat Commun* 2016; 7(1):13457.
415. Goldberg AC, Leiter LA, Stroes ESG et al. Effect of bempedoic acid vs placebo added to maximally tolerated statins on low-density lipoprotein cholesterol in patients at high risk for cardiovascular disease: The CLEAR Wisdom randomized clinical trial. *JAMA*. 2019; 322(18):1780-1788.
416. Ballantyne CM, Laufs U, Ray KK et al. Bempedoic acid plus ezetimibe fixed-dose combination in patients with hypercholesterolemia and high CVD risk treated with maximally tolerated statin therapy. *Eur J Prev Cardiol*. 2020; 27(6):593-603.
417. Detsky AS, Naglie G. A clinician's guide to cost-effectiveness analysis. *Ann Intern Med*. 1990; 113:147-54.
418. World Health Organization (WHO). Macroeconomics and health: investing in health for economic development. Report of the Commission on Macroeconomics and Health. Geneva; 2001.
419. Siqueira ASE, Siqueira-Filho AC, Land MGP. Analysis of the economic impact of cardiovascular diseases in the last five years in Brazil. *Arq Bras Cardiol*. 2017; 109(1):39-46.
420. Bahia LR, Rosa RS, Santos RD et al. Estimated costs of hospitalization due to coronary artery disease attributable to familial hypercholesterolemia in the Brazilian public health system. *Arch Endocrinol Metab*. 2018; 62(3):303-8.
421. Neil HA, Hammond T, Huxley R et al. Extent of underdiagnosis of familial hypercholesterolemia in routine practice: prospective registry study. *BMJ*. 2000; 321(7254):148.
422. Rosso A, Pitini E, D'Andrea E et al. The cost-effectiveness of genetic screening for familial hypercholesterolemia: a systematic review. *Ann Ig*. 2017; 29(5):464-80.
423. Chen CH, Hay JW. Cost-effectiveness analysis of alternative screening and treatment for heterozygous familial hypercholesterolemia in the United States. *Int J Cardiol*. 2015; 181:417-24.
424. Nherera L, Calvert NW, Demott K et al. Cost-effectiveness analysis of the use of a high-intensity statin compared to a low-intensity statin in the management of patients with familial hypercholesterolemia. *Curr Med Res Opin*. 2010; 26(3):529-36.
425. Odden MC, Pletcher MJ, Coxson PG et al. Cost-effectiveness and population impact of statins for primary prevention in adults aged 75 years or older in the United States. *Ann Intern Med*. 2015; 162(8):533-41.
426. Ward S, Lloyd Jones M, Pandor A et al. A systematic review and economic evaluation of statins for the prevention of coronary events. *Health Technol Ass*. 2007; 11(14):1-160.

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427. Ribeiro R, Duncan BB, Ziegelman PK et al. Cost-effectiveness of high, moderate and low-dose statins in the prevention of vascular events in the Brazilian Public Health System. *Arq Bras Cardiol.* 2015; 104(1):32-44.
428. Fonarow GC, Keech AC, Pedersen TR et al. Cost-effectiveness of evolocumab therapy for reducing cardiovascular events in patients with atherosclerotic cardiovascular disease. *JAMA Cardiol.* 2017; 2(10):1069-78.
429. Kazi DS, Moran AE, Coxson PG. Cost-effectiveness of PCSK9 inhibitor therapy in patients with heterozygous familial hypercholesterolemia or atherosclerotic cardiovascular disease. *JAMA.* 2016; 316(7):743-53.
430. Arrieta H, Page TF, Veledar E et al. Economic evaluation of PCSK9 inhibitors in reducing cardiovascular risk from health system and private payer perspectives. *PLoS One.* 2017; 12(1):e0169761.

Update



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Brazilian Position Statement on the Use Of Multimodality Imaging in Cardio-Oncology – 2021

Development: Cardiovascular Imaging Department (Departamento de Imagem Cardiovascular – DIC) of the Brazilian Society of Cardiology (Sociedade Brasileira de Cardiologia – SBC) endorsed by the Sociedad Interamericana de Imágenes Cardiovasculares (SiSIAC) of the Sociedad Interamericana de Cardiología (SIAC)

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Note: These statements are for information purposes and should not replace the clinical judgment of a physician, who must ultimately determine the appropriate treatment for each patient.

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If, within the last 3 years, the author/collaborator of the statement:

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List of Abbreviations

¹⁸ F-FDG	¹⁸ F-fluorodeoxyglucose	LVCR	Left ventricular contractile reserve
AMI	Acute myocardial infarction	LVEF	Left ventricular ejection fraction
BMT	Bone marrow transplantation	AL amyloidosis	Light-chain amyloidosis
CHD	Carcinoid heart disease	MRI	Magnetic resonance imaging
CTX	Cardiotoxicity	SUV _{max}	Maximum standardized uptake value
CVD	Cardiovascular disease	NM	Nuclear medicine
CRT	Catheter-related thrombosis	PCT	Primary cardiac tumor
CT	Computed tomography	RICAD	Radiation-induced coronary artery disease
CAD	Coronary artery disease	RIHD	Radiation-induced heart disease
DVT	Deep venous thrombosis	RIVD	Radiation-induced valve disease
DM	Diabetes mellitus	RA	Right atrium/atrial
ECV	Extracellular volume	RV	Right ventricle/ventricular
GLS	Global longitudinal strain	TTS	Takotsubo syndrome
GvHD	Graft-versus-host disease	^{99m} Tc	Technetium-99m
HF	Heart failure	TEE	Transesophageal echocardiography
IE	Infective endocarditis	TTE	Transthoracic echocardiography
IMT	Intima-media thickness	ATTR amyloidosis	Transthyretin amyloidosis
LA	Left atrium/atrial	Top2	Topoisomerase 2
LV	Left ventricle/ventricular	VTE	Venous thromboembolism

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1. General Aspects

1.1. Current Situation of Cardio-Oncology in Brazil and Worldwide

The estimated incidence of cancer in Brazil was 600 thousand cases per year in 2018 and 2019.¹ Only as of 2005, the survival rate surpassed that of overall cancer mortality, leading to an increased number of survivors exposed to the risk of cardiotoxicity (CTX), which is currently the second leading cause of morbidity and mortality in this population.²

Cardiovascular complications resulting from cancer treatment, which are the focus of this consensus statement, may result in premature deaths, costly hospitalizations, and absence from work, leading to the need for early diagnosis and interventions.³

Age (children and older adults), previous myocardial or coronary heart disease, hypertension, diabetes mellitus (DM), smoking, alcohol consumption, and sedentary lifestyle are factors associated with increased risk of CTX.⁴

Recent studies suggest that genotypic variants may modify the susceptibility to CTX, turning genetic mapping into a promising field for identification of risk subgroups.⁵

It is recommended that patients at high-risk for development of CTX be considered those whose treatment includes:⁶

- High-dose anthracycline (doxorubicin > 250 mg/m² or epirubicin > 600 mg/m²);
- Radiotherapy at a dose ≥ 30 Gy (involving the heart) or > 2 Gy/session;
- Lower doses of combined anthracycline and radiotherapy;
 - Lower doses of anthracyclines or trastuzumab alone, but associated with:
 - More than two cardiovascular risk factors (smoking, hypertension, DM, dyslipidemia, obesity – during or after therapy);

- Age ≥ 60 years;
- Structural heart disease before or during treatment (ejection fraction: 50% to 55%, acute myocardial infarction [AMI], moderate/important valve disease);
- Combination of low doses of anthracycline and trastuzumab.

1.2. Definition of Cardiotoxicity

The definition of CTX based on the degree of left ventricular ejection fraction (LVEF) reduction ignores the changes that precede the fall in LVEF and all other toxic effects that occur in addition to this parameter.⁶⁻⁸ Lack of a more comprehensive definition and, sometimes, clinical, laboratory, and imaging limitations to document some events in the initial stage make CTX an underdiagnosed clinical condition. The European Society of Cardiology revised in 2017 the definition of CTX to cover any structural or functional changes in the heart and circulation, both in the presence or in the immediate or late post-treatment of cancer, and considered chemotherapy, radiotherapy, or the disease itself as aggressive agents.⁴

1.3. Mechanisms of Cardiotoxicity

Although we are aware of some CTX-related mechanisms, identifying the predominant mechanism remains a great challenge, as the combination of different drugs and treatment protocols as well as constitutional factors inherent to each patient account for a complex interaction that results in damage to the cardiovascular system (Table 1). Depending on the chemotherapy agent class, cell damage may occur directly or indirectly and with or without potential for reversibility.⁹ Ewer et al.¹⁰ proposed in 2005 a classification of CTX in types 1 and 2; despite being the subject of much criticism, it has helped divide CTX into irreversible cell damage (type 1), attributed to anthracyclines, and reversible dysfunctions (type 2), attributed to trastuzumab. With the development of new anticancer therapies, including Bruton tyrosine kinase inhibitors, proteasome inhibitors, checkpoint inhibitors, among others known to be potentially cardiotoxic, it seems that this classification proposal deserves to be revised and expanded.

1.4. Clinical Manifestations of Cardiotoxicity

The cardiovascular clinical manifestations arising from cancer treatment are the tip of an iceberg whose base consists of structural and functional changes that precede signs and symptoms. For didactic purposes, we chose to divide CTX manifestations into three subgroups: clinical, laboratory, and imaging/tracing (Table 2). It should be noted that such proposal may be criticized at first, as routine genetic mapping is not yet feasible to determine more accurately the culpability of the phenotypic expression.

Anthracyclines and anti-HER2 monoclonal antibodies account for most documented cases of left ventricular (LV) dysfunction. Cardinale et al.¹¹ demonstrated that the incidence of CTX for anthracycline use in a population of 2,625 patients was 9%, with 98% of cases occurring in the first year of treatment.¹¹ Alkylating agents, proteasome inhibitors,

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Table 1 – Summary of the main suggested mechanisms of cardiotoxicity by group of drugs

Anthracyclines	DNA double-strand break (topoisomerase IIB)
	Oxidative stress (reactive oxygen species)
	Cell membrane hyperpermeability (lipid peroxidation)
	Ultrastructural changes
	Cytoplasmic vacuolization
	Apoptosis
Trastuzumab	Interruption of HER-2/ERBB2 receptor signaling – Neuregulin 1
	Inhibits cell repair
	Cell dysfunction
Cisplatin Cyclophosphamide	Direct endothelial injury
	Platelet activation and aggregation
	Coronary thrombosis
5-Fluorouracil	Acts on the molecular signaling pathway that regulates smooth muscle tone
	Vasospasm – vasoconstriction
Vascular endothelial growth factor (VEGF) inhibitors	Inhibit nitric oxide synthase activity
	Increase endothelin production
	Inhibit rho-kinase activation
	Vasospasm
Protease inhibitors	Interference with the degradation of dysfunctional proteins
	Functional changes in the myocyte
Immune checkpoint inhibitors	Increased T-cell activity
	Autoimmune activity in the heart muscle

Table – Cardiotoxicity phenotypes

Clinical status	• Hypertension
	• Pulmonary hypertension
	• Venous and arterial embolic events
	• Carotid artery disease
	• Heart failure/myocarditis
	• Pericardial effusion/pericarditis
	• Valve dysfunctions
	• Myocardial ischemia/infarction
	• Pericardial disease
Laboratory	• Elevated troponins (T or I) and/or CK-MB
	• Elevated natriuretic peptide (BNP/NT-proBNP)
Imaging/Tracing	• Heart rhythm disorders (extrasystoles, blocks, supraventricular and ventricular tachycardias, bradyarrhythmias, increased corrected QT interval on electrocardiogram)
	• Dilated cardiac chambers with preserved LVEF
	• LVEF reduction > 10% (baseline) or > 15% (global longitudinal strain)
	• Left ventricular diastolic dysfunction
	• Pericardial thickening and/or effusion
	• Valve dysfunctions (stenosis, failures)
	• Changes in imaging tests that indicate active inflammatory signs or necrosis (scintigraphy/cardiac MRI)
	• Changes in coronary CT angiography or calcium score that were initiated or aggravated during or after cancer treatment (chemotherapy and/or radiotherapy)

BNP: brain natriuretic peptide; CT: computed tomography; LVEF: left ventricular ejection fraction; MRI: magnetic resonance imaging.

and some tyrosine kinase inhibitors also cause dysfunction by means of several mechanisms.⁴ Severe inflammatory myocarditis may be associated with immune checkpoint inhibitors in 0.27% of patients in use of a combination of nivolumab and ipilimumab.¹²

Coronary artery disease (CAD), clinically manifested as stable or unstable angina or AML, may be secondary to direct endothelial injury, acute arterial thrombosis, or vasospasm, depending on the therapeutic class that was used. Obstructive atherosclerosis, plaque rupture and coronary thrombosis, annular/valvular degenerations, and pericarditis are related to mediastinal radiotherapy and are dependent on the radiation dose that was used. Hypertension is closely linked to the use of endothelial growth factor inhibitors. Deep venous thrombosis (DVT), peripheral artery disease, and pulmonary hypertension are also within the range of clinical manifestations of CTX.⁴

2. Myocardial Cardiotoxicity

2.1. Contribution from Echocardiography

2.1.1. Myocardial Structural and Functional Assessment of the Left Ventricle

2.1.1.1. Standard Doppler Echocardiography

When myocardial dysfunction was recognized as a potential adverse effect of cancer treatment, several strategies were then tested to monitor myocardial function. Initially considered to be the most accurate method, endomyocardial biopsy quickly fell into disuse because of its invasive nature, being then replaced by serial monitoring of LV systolic function by noninvasive cardiovascular imaging tests.

Echocardiography has become a consolidated method for monitoring CTX using LVEF, as it is widely available, cost-effective, and harmless, allowing for it to be repeated multiple times. Additionally, it provides several other anatomical and functional findings.

Administration of the Simpson method improves the estimation of ventricular volumes, overcoming the limitations of fractional shortening and the Teichholz formula, obtained from linear measurements of M-mode or two-dimensional (2D) echocardiography. However, sensitivity to detect small longitudinal variations in systolic function remains low, mainly because of frequent preload and afterload variations during chemotherapy and intra- and inter-observer variability (one of the most accepted parameters for diagnosis of CTX), which may reach up to 10%.¹³ It is important to remember that, because of those variations, tests with results outside the expected parameters should be repeated and confirmed 2 to 3 weeks after the initial finding.

The risk of CTX is considered to range from 3.6 to 11.8 times for use of cardiotoxic drugs (especially anthracyclines) if pre-treatment LVEF is between 50% and 55%. During monitoring and after cancer treatment, CTX identification should be based on a fall > 10% in LVEF (compared to pre-treatment values) to less than 50%.¹⁴ This situation is the subject of an important

debate in medical teams regarding cardiological risk and cancer benefit. The discussed approaches include replacing it with lower cardiotoxic risk treatments, using cardioprotective measures, and even discontinuing treatment (if LVEF < 45% for anthracyclines and < 40% for the other classes), a decision always made together with the oncologist.^{14,15}

The assessment of longitudinal systolic function, especially when advanced methods (three-dimensional [3D] echocardiography and myocardial deformation analysis) are unavailable, should be performed jointly. Although there are no reference ranges for diagnosis, a progressive decline in the measurement of mitral annular peak systolic velocity by tissue Doppler imaging (s' wave) and mitral annular plane systolic excursion (MAPSE) is significant.¹⁶

The number of times that echocardiographic imaging is required remains controversial in the literature, varying according to individual risk, therapeutic protocol (drugs used and total dosage), and identification of CTX signs and symptoms.

It is important to remember that CTX, in the form of quantitative changes in conventional parameters for assessing systolic function, may not be evident until there is a substantial reduction in myocardial reserve. Thus, cardiac damage may not become apparent for years or even decades after the end of cardiotoxic treatment, a fact that is particularly applicable to adult survivors of tumors during childhood.

2.1.1.2. Myocardial Strain

Strain, or deformation, is defined as the amount of deformation or the fractional change in the length of a myocardial segment from initial length. Such parameter is expressed as a percentage (%) and with the negative sign.¹⁷

Two-dimensional strain imaging, deriving from speckle tracking, is not dependent on the angle (a limiting factor when tissue Doppler imaging is used), which makes it more reproducible and more commonly used in general clinical practice to detect early changes in myocardial mechanics.¹⁷ Three-dimensional strain imaging represents an improvement of the technique. In this modality, an entire pyramidal volume is obtained from the apical view and then analyzed, being much faster than the other modalities but having lower spatial and temporal resolution.

The fall in LVEF is a late marker of myocardial damage and translates into a poor prognosis, with reduced chance of ventricular function recovery in 58% of patients, despite any intervention with cardioprotective drugs. Cardiac dysfunction only becomes evident when myocardial damage is significant; therefore, absence of LVEF reduction does not exclude CTX.^{18,19}

Thus, administration of speckle-tracking strain imaging to analyze ventricular mechanics is gradually extending to all heart diseases, especially those associated with the use of anticancer agents, such as anthracyclines and trastuzumab.²⁰ The possibility of detecting subclinical lesions has been one of the great advantages. Overall, although early change detection is conceptually important, the value of actual changes must be proven to correlate with the outcomes.

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A review of several studies demonstrated the ability of strain imaging to detect myocardial deformation changes earlier than the fall in LVEF, either immediately after therapy infusion or in later stages.²¹

Ganame et al.²² demonstrated the acute effects of anthracyclines, which are able to induce systolic dysfunction.²² The same group of investigators studied 56 patients without any risk factors for cardiovascular disease (CVD), diagnosed with lymphoma, leukemia, and other malignant tumors, treated only with anthracyclines (dose lower than 300 mg/m²), and compared them with a control group.²³ After a mean follow-up of 5.2 years, a significant reduction in global longitudinal strain (GLS) was demonstrated at a time point when LVEF was still normal, showing that new diagnostic tools are able to predict this decline early in time.

Sawaya et al.²⁴ used 2D speckle tracking to demonstrate that GLS and troponin were predictors of systolic dysfunction in patients with breast cancer treated with anthracyclines and trastuzumab.²⁴ Forty-three patients underwent echocardiography at baseline and at three and six months of treatment. LVEF using the Simpson biplane method, GLS, radial and circumferential strain, and biomarkers were assessed. In that study, GLS was able to predict CTX in seven out of nine patients, with a sensitivity of 78% and a specificity of 79%. The event occurred at three months of follow-up in one of the patients and at six months in the others.

Tan et al.²⁵ examined LVEF and GLS in 19 patients with breast cancer using trastuzumab and followed-up for 34 months (mean 24.7 months). They observed that changes in ventricular function persisted for a long period, with increased LV chamber dimensions and reduced GLS throughout the entire follow-up, questioning the reversibility of the damage caused by trastuzumab.²⁵

Almeida et al. evaluated 40 patients with breast cancer who had used doxorubicin two years prior to undergoing an echocardiogram and compared them with 41 healthy women. The authors demonstrated that GLS and S' wave of the mitral annulus were reduced in patients who underwent chemotherapy, but LVEF remained normal, suggesting the presence of subclinical ventricular dysfunction. The authors also showed that age and previous use of doxorubicin were independent markers of GLS reduction.²⁶

Recently, Piveta et al.²⁷ evaluated the role of 3D strain in patients with breast cancer treated with anthracyclines. After exposure to a low anthracycline dose (120 mg/m²), only 3D circumferential strain and 3D area strain showed changes, while 2D strain parameters remained unchanged.²⁷

A systematic review of 1,504 patients showed that a relative reduction of 10% to 15% in GLS from baseline was an important predictor for a decline in LVEF. Radial and circumferential strain measurements also show changes, but such variables are not yet routinely used. When pre-chemotherapy values are not available for comparison, GLS values greater than -19% are suggestive of CTX, and the association with biomarkers, especially ultrasensitive troponin, increases the sensitivity for diagnosis of CTX. It is worth noting that reference ranges may vary depending on the software used in the devices and age and sex of the patients, hence the recommendation to repeat

the tests using always the same device and, preferably, the same examiner.²¹

An expert consensus of the American and European Cardiovascular Imaging Societies suggests that changes in deformation precede ventricular dysfunction.²⁸ A reduction > 15% in GLS immediately after or during anthracycline therapy is the most useful parameter in predicting CTX, while a reduction > 8% will probably exclude the diagnosis of CTX (Figure 1).

Liu et al.²⁹ described in 2018 an algorithm to follow-up patients treated with anticancer agents that used LVEF and GLS as echocardiographic measures. In patients with LVEF > 60%, the recommendation was to optimize the control of existing cardiovascular risk factors. Those with LVEF between 50% and 59% and with GLS lower than -16% or at the lower limit of normal were classified as preserved myocardial function; those with GLS greater than -16% or a 15% reduction from baseline were considered to have subclinical dysfunction. Patients with LVEF between 40% and 49% were considered to have myocardial dysfunction; thus, this specific group was indicated for initiation of cardioprotective therapy and a joint evaluation with the oncologist on the risks and benefits of anticancer therapy, with an occasional dose reduction or medication change. In patients with LVEF < 40%, it is recommended that cardioprotective therapy is initiated and the use of a noncardiotoxic alternative therapy is discussed with the oncologist.

There is no consensus on systolic function indices to be monitored during treatment.^{14,15,29} However, recently, the SUCCOUR (Strain sUveillance of Chemotherapy for improving Cardiovascular Outcomes) study was published. It showed that treatment guided by a greater than 12% drop in the LV global longitudinal strain in patients treated with anthracyclines is able to prevent the drop in ejection fraction and cardiotoxicity in 1 year.³⁰ In addition to the diagnosis of CTX, the identification of GLS reduction has prognostic value, as it has been associated with higher late mortality in a retrospective study involving 120 patients followed-up for 21.6 ± 13.9 months.³¹

2.1.1.3. Left Ventricular Ejection Fraction by 3D Imaging

Three-dimensional echocardiographic imaging is the method of choice for calculating LVEF during cancer treatment (Figure 2).³² By providing greater resemblance to cardiac anatomy, it is much consistent with cardiac magnetic resonance imaging (MRI) in the calculation of volumes, mass, and LVEF.³³ The 3D analysis is not dependent on geometric assumptions, as is the case of 2D analysis, in addition to minimizing limitations related to that technique such as "apical shortening."

The predominant CTX change for a consequent decrease in LVEF is an increase in LV end-systolic volume.¹⁵ In the oncology population, studies suggest that 3D imaging is preferable to 2D imaging mainly because the former has demonstrated greater reproducibility and greater accuracy in the recognition of borderline or slightly reduced LVEF. In survivors of cancer treated with anthracyclines, Armstrong et al.³⁴ demonstrated that 3D imaging had greater ability to identify patients with

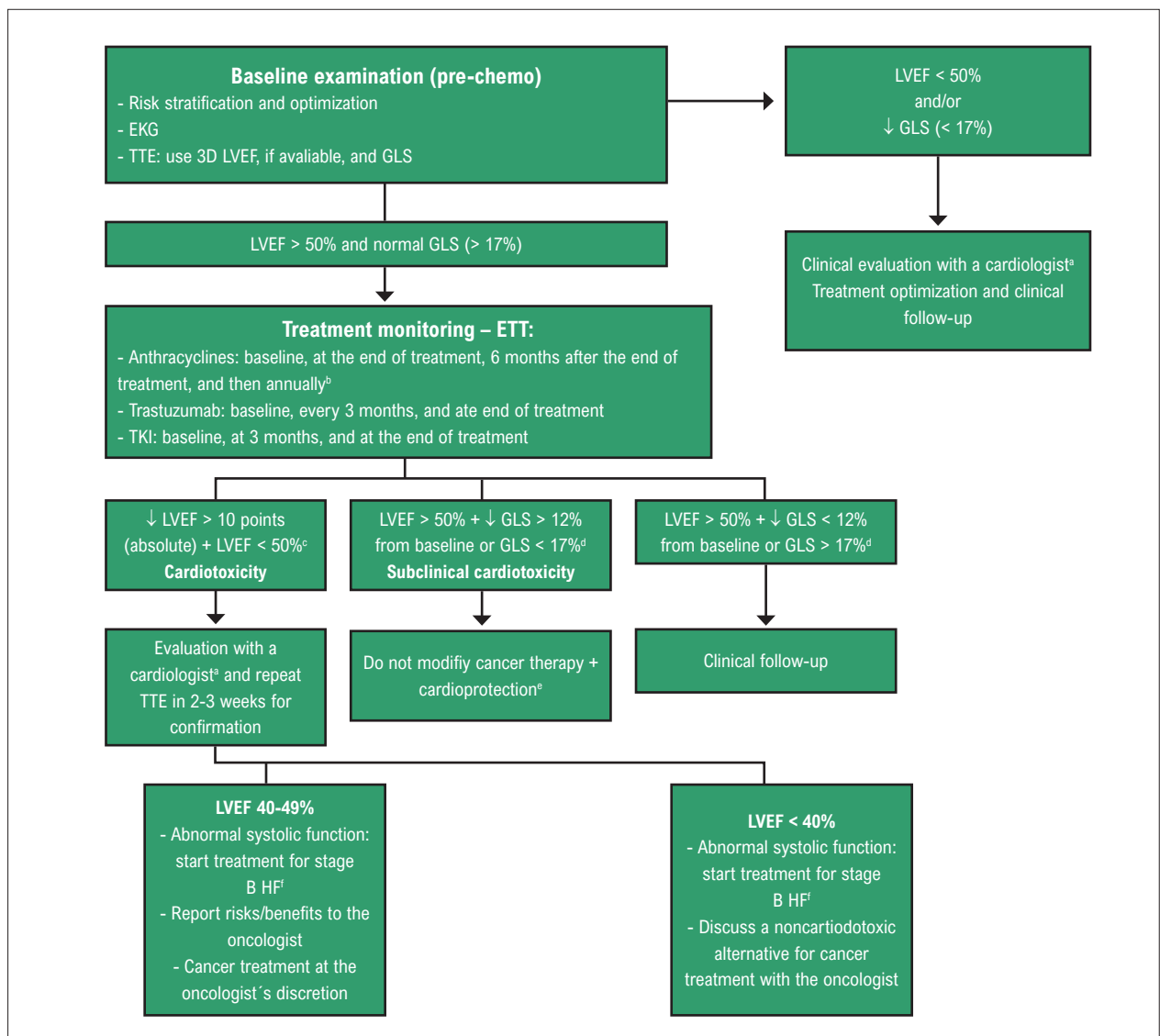


Figure 1 – Clinical monitoring and management during cardiotoxic therapy.

Adapted from: JACC Cardiovasc Imaging. 2018 Aug;11(8):1122-1131; Rev Esp Cardiol (Engl Ed) 2017; J Am Soc Echocardiogr. 2014 Sep;27(9):911-39; Arq Bras Cardiol 2020; [online]. DOI: <https://doi.org/10.36660/abc.20201006>; Journal of the American College of Cardiology (2020), DOI: <https://doi.org/10.1016/j.jacc.2020.11.020>

^a preferably a cardio-oncologist

^b if the cumulative dose is greater than 240 mg/m² (or equivalent), reevaluation of LVEF and SLG is recommended for each new chemotherapy cycle (50-60 mg/m²)

^c if using 3D echo, consider LVEF fall greater than 5% to less than 55% in symptomatic patients or greater than 10% in asymptomatic patients.

^d in the absence of baseline SLG (pre-chemotherapy) for comparison, use absolute value of SLG < 17% as representative of significant change.

^e it is suggested to start cardioprotective treatment with ACE inhibitors and/or beta-blockers.

^f follow the recommendations of 2013 ACC/AHA guideline on the management of the treatment of HF stage B.

EKG: electrocardiogram; 3D: three-dimensional echocardiogram; CVRF: cardiovascular risk factors; LVEF: left ventricular ejection fraction; GLS: global longitudinal strain; TTE: two-dimensional transthoracic echocardiogram; TKI: tyrosine kinase inhibitors; HF: heart failure; ACE: angiotensin-converting enzyme; ACC/AHA: American College of Cardiology and American Heart Association.

LVEF < 50% than 2D imaging, with an accuracy very similar to that of cardiac MRI, allowing for earlier identification of subclinical CTX.³⁴ The SUCCOUR study used two criteria of cardiotoxicity by preferentially 3D echocardiography: a fall of more than 5% in patients with symptoms of heart failure, or greater than 10% in asymptomatic patients, compared with the baseline test for values of ejection fraction lower than 55%.³⁰

In patients undergoing chemotherapy, Thavendiranathan et al.¹³ compared different echocardiographic techniques for

sequential assessment of LVEF over 1 year and demonstrated that 3D imaging had the lowest intra- and inter-observer temporal variability (5.6%).¹³ This finding suggests that, in addition to being reliable, 3D imaging is a consistent and reproducible method for evaluation of patients with cancer.³² Other papers also highlight the greater reproducibility of 3D imaging in the calculation of LVEF, mainly because, as a semiautomatic technique for endocardial tracing, it is less affected by variability in image acquisition.³⁵

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Figure 2 – Example of a three-dimensional echocardiogram with full volume analysis and estimated volumes and left ventricular ejection fraction.

2.1.1.4. Contrast Echocardiography

Inadequate visualization of LV endocardial borders often occurs in patients undergoing chemotherapy for breast cancer, particularly when following mastectomy and radiotherapy. Consequently, underestimated volumes and inaccurate LVEF determination may occur. According to international guidelines, an ultrasound contrast agent should be used to improve the definition of endocardial borders and the analysis of LV function when endocardial visualization is limited in two or more segments.³⁶ Conversely, contrast agents are not recommended when LVEF is estimated on 3D echocardiogram, as they lead to less reproducibility and greater temporal variability in LVEF compared to 3D imaging alone.¹³

2.1.1.5. Stress Echocardiography

Exercise or pharmacological stress echocardiography is an established method for detecting obstructive CAD and subclinical changes in myocardial function. Patients with cancer often have a decrease in global cardiovascular reserve, attributed to the direct effects of adjuvant cancer therapy and/or the indirect effects of lifestyle changes associated with treatment.³⁷ Thus, the potential uses for stress echocardiography in patients undergoing cancer therapy include the following: (a) initial investigation of presence of obstructive CAD in patients with intermediate-to-high pre-test probability, noninterpretable ECG (exercise) or unable to exercise (dobutamine), especially if receiving chemotherapy associated with ischemia or after long-term radiotherapy; (b) determination of left ventricular contractile reserve (LVCR) as a predictor of CTX in patients with normal rest LVEF and GLS; (c) determination of LVCR in established CTX, as transient recovery of LV function during stress could indicate a better prognosis.²⁸ Despite those potentialities, stress echocardiography has been scarcely used in the field of cardio-oncology.

Using exercise stress echocardiography in 57 asymptomatic women with normal LVEF treated for breast cancer with anthracyclines, Khouri et al.³⁸ found a 12% reduction in stroke volume and a 24% reduction in cardiac index from rest when compared to controls, suggesting impaired LVCR.³⁸

Civelli et al.³⁹ prospectively measured LVCR (defined as the difference between peak and rest LVEF) using low-dose dobutamine stress echocardiography during and after high-dose

chemotherapy in 49 women with advanced breast cancer. An asymptomatic decline $\geq 5\%$ in LVCR from baseline was able to predict a fall in LVEF to $< 50\%$.³⁹

The only published systematic review on the utility of cardiac stress methods for detecting CVD in survivors of breast cancer concluded that there seems to be evidence that stress echocardiography is beneficial to early prognostic evaluation and late follow-up after anthracycline therapy.⁴⁰

Before stress echocardiography can be routinely added to clinical practice in cardio-oncology, further studies are needed to determine the best stressor, which parameters should be measured during the test, the best time to perform the test according to the different types of treatment, cost-benefit and feasibility in the oncology population, and, finally, the presence of incremental prognostic value over traditional parameters measured at rest (LVEF and GLS).

2.1.1.6. Diastolic Function

Abnormal parameters related to diastolic function, such as E and A waves, E/A ratio, isovolumic relaxation time, and myocardial performance index, have been described early after chemotherapy.^{41,42} However, longitudinal studies have not been able to reproduce the prognostic value of those findings and there is insufficient evidence to recommend such assessment in the diagnosis of chemotherapy-induced CTX.⁴³

Studies have demonstrated the utility of tissue Doppler-derived measurements in the assessment of diastolic function in patients undergoing cancer treatment. Some papers have shown a reduction in tissue Doppler-derived early diastolic velocity (e' wave) of the mitral annulus in patients treated with anthracyclines, which remained reduced during treatment and years later, but no predictive value for CTX was demonstrated.¹⁶ Negishi et al.⁴⁴ revealed that a 10% reduction in e' wave velocity was observed in patients who developed CTX after treatment with higher cumulative doses of doxorubicin, but this parameter was not shown to have a predictive role for LVEF fall.⁴⁴

The use of diastolic dysfunction as a specific CTX marker has been questioned. Abnormalities may occur due to preload changes resulting from volume replacements associated with cancer treatment or volume depletion associated with side effects of chemotherapy, such as nausea, vomiting, and diarrhea. In such

cases, they may not represent an actual change in LV diastolic performance.

2.1.2. Myocardial Structural and Functional Assessment of the Right Ventricle

The prevalence and prognostic value of right ventricular (RV) involvement have not yet been properly studied. Data on the influence of chemotherapy on RV remodeling, function, and mechanics are scarce and, at times, conflicting.

The difficulty inherent to RV assessment and hemodynamic variations suggests that parameters such as tricuspid annular plane systolic excursion (TAPSE), tissue velocity of the basal segment of the RV free wall (S' wave), RV fractional area change (FAC), as well as myocardial strain are ideally measured by echocardiography, while the assessment of right ventricular ejection fraction (RVEF) is left to MRI or 3D echocardiography.

The drugs most frequently related to RV dysfunction and changes in pulmonary circulation are anthracyclines, trastuzumab, cyclophosphamide, and dasatinib.⁴⁵ Boczar et al. assessed RV longitudinal strain in patients with breast cancer treated with anthracycline. After 3 months, they observed that strain reduced from -16.2% to -13.81%.⁴⁶ The difference in RV longitudinal strain is more pronounced when the septum is excluded, suggesting a greater sensitivity of the RV myocardium.⁴⁷

2.1.3. Late Echocardiographic Follow-up

Recommendations regarding patient follow-up after completion of chemotherapy will vary according to the clinical characteristics of the study population, the protocol used in chemotherapy (with or without radiotherapy), and the cumulative dose of drugs (especially trastuzumab and anthracyclines). Because of the increased risk of developing CTX within 12 months of anthracycline use, the fall in LVEF during trastuzumab use, and the appearance of late complications following radiotherapy, we suggest performing late follow-up as shown in Figure 3.

2.2. Contribution from Nuclear Medicine

2.2.1. Radionuclide Ventriculography

Radionuclide ventriculography, often referred to as a multigated acquisition (MUGA) scan, is a scintigraphic test performed using a gamma chamber in the nuclear medicine (NM) department. This is a noninvasive method that produces low radiation exposure and does not cause severe side effects, with excellent reproducibility and low inter- and intra-observer variability in assessing ventricular function.⁴⁸

Together with echocardiography, radionuclide ventriculography is the most widely accepted method for assessing LVEF in patients

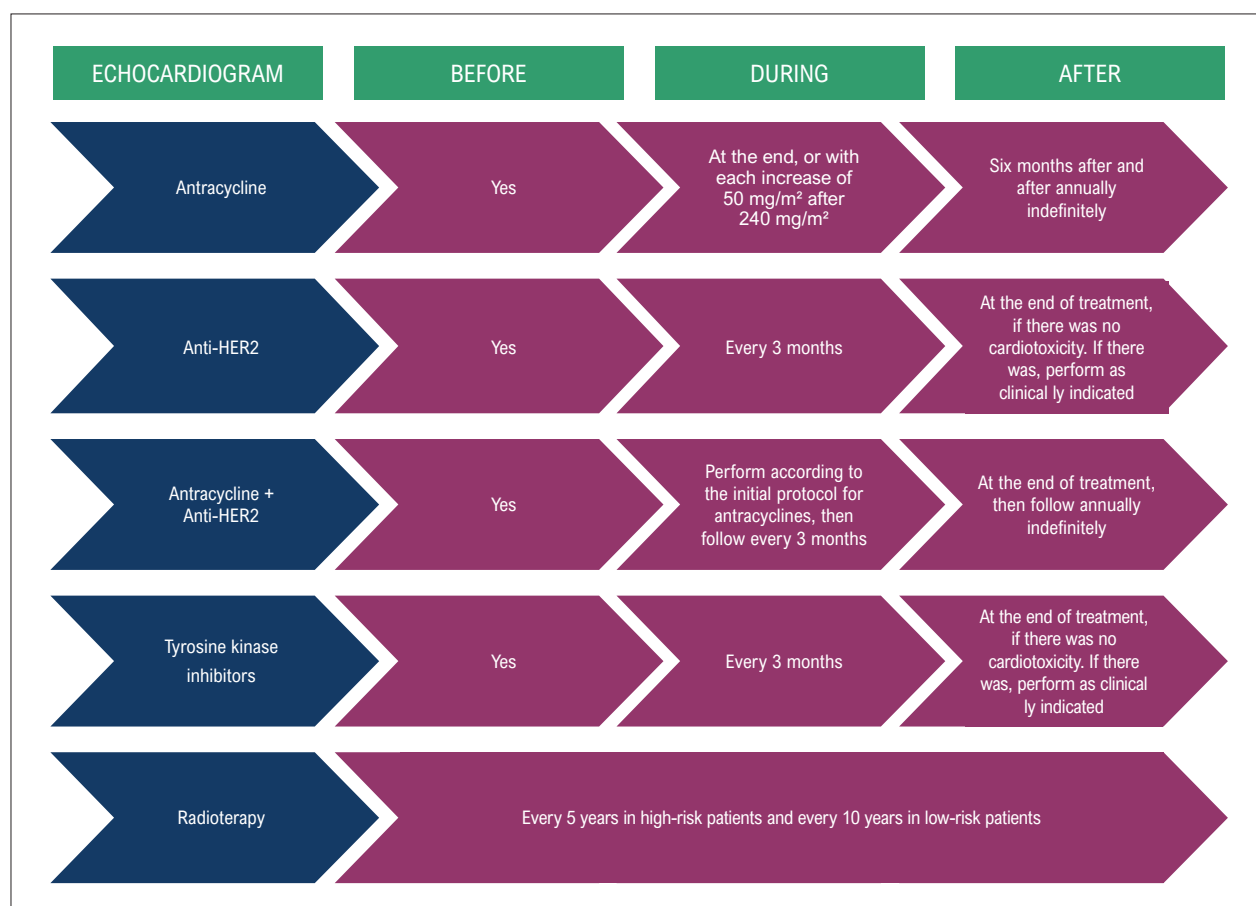


Figure 3 – Recommendations for late echocardiographic follow-up.

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before and during cancer treatment and identifying the risk for chronic HF (90% sensitivity and 72% specificity).⁴⁹

With a normal baseline LVEF, the next measurements should be made at cumulative doses of 250 to 300 and 400 to 450 mg/m². For patients with abnormal baseline LVEF (< 50%), serial studies are recommended before each subsequent dose of doxorubicin. Figure 4 shows examples of LVEF behavior assessed by radionuclide ventriculography in patients undergoing chemotherapy.

2.2.2. Assessment of Cardiac Sympathetic Activity with mIBG

Meta-iodobenzylguanidine (mIBG) is a molecule with a structure similar to that of norepinephrine and selectively acts on sympathetic nerves without, however, being metabolized by monoamine oxidase or catechol-O-methyltransferase, and

not having a stimulatory effect as norepinephrine does. Cardiac ¹²³I-mIBG scintigraphy directly assesses the global and regional sympathetic function of the heart, including uptake, reuptake, storage, and release processes of norepinephrine at presynaptic nerve terminals.⁵⁰

Guimarães et al.⁵¹ performed cardiac ¹²³I-mIBG scintigraphy in 20 women with breast cancer and normal LVEF who had been treated with anthracycline derivatives combined with trastuzumab or alone. The authors observed that the combined use of anthracycline and trastuzumab provided a higher frequency and intensity of cardiac adrenergic hyperactivity.⁵¹ Another study identified abnormal ¹²³I-mIBG uptake in patients who used anthracycline. Additionally, ¹²³I-mIBG uptake from heart-to-mediastinum ratio decreased as the cumulative dose of the drug increased.⁵² Those results support the hypothesis that early cardioprotection with beta-blockers may be beneficial for those patients.

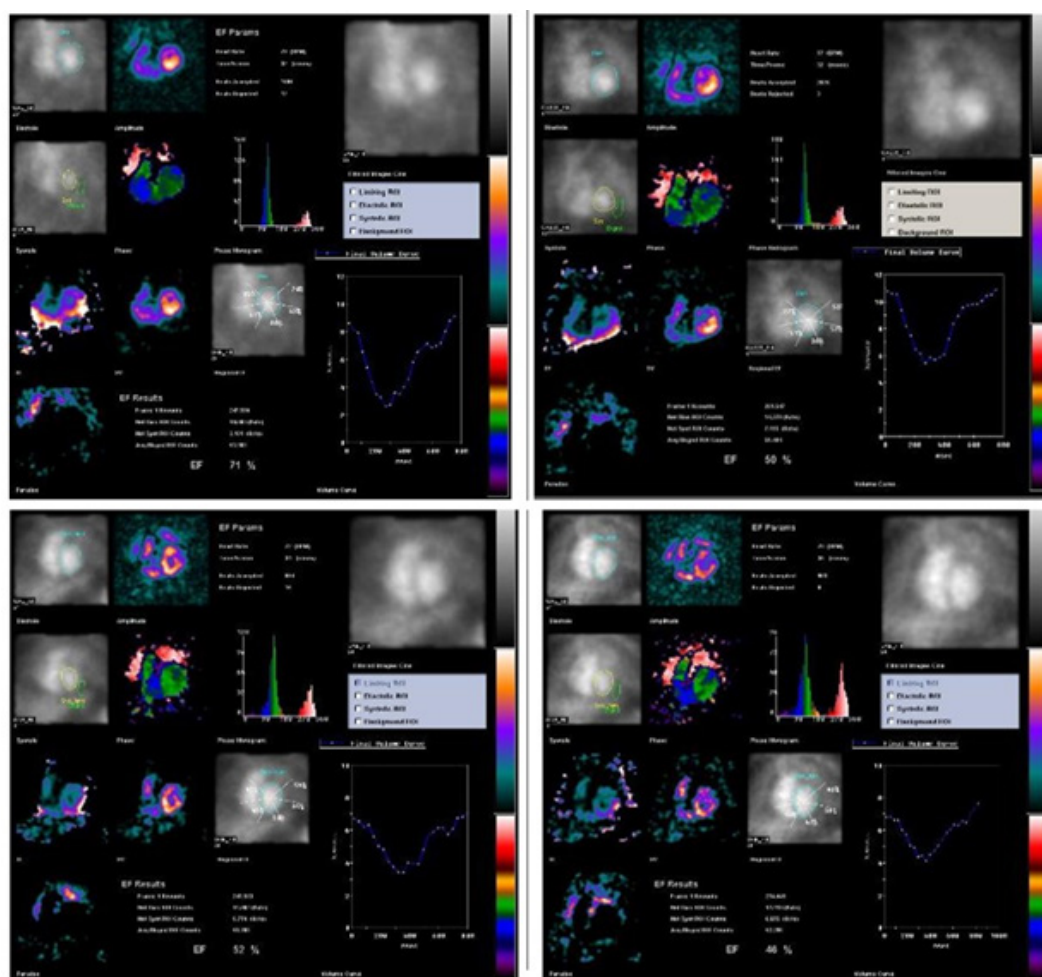


Figure 4 – Examples of two patients who underwent radionuclide ventriculography to measure left ventricular ejection fraction (LVEF) before and after anthracycline chemotherapy. The upper left image shows the baseline LVEF of the first patient, which was 71% (normal) and then decreased to 50% after the end of chemotherapy and start of trastuzumab therapy (upper right). The lower left image shows the baseline LVEF (52%) of a patient with breast cancer before the start of chemotherapy, which decreased to 46% during follow-up (lower right), leading to the use of cardioprotective medication. The images were kindly provided by Dr. Márcia Modesto (Nuclear Medicine Department of the Instituto Brasileiro de Controle do Câncer, São Paulo, Brazil).

2.2.3. Myocardial Metabolism – ^{18}F -FDG PET-CT

Recently, Borde et al.⁵³ retrospectively analyzed myocardial uptake of ^{18}F -fluorodeoxyglucose (FDG) in patients with lymphoma treated with adriamycin-based chemotherapy.⁵³ The authors demonstrated that increased myocardial metabolic activity may be a potential marker of cell alteration preceding the CTX cascade. In that study, the increase in glucose metabolism in the heart muscle was directly proportional to the cumulative dose of doxorubicin (in mg/m^2). Similar findings have also been suggested in patients with radiation-induced cardiac damage.⁵⁴ Toubert et al.⁵⁵ demonstrated a change in myocardial ^{18}F -FDG uptake in a patient treated with a combination of tyrosine kinase inhibitors (imatinib and sorafenib) who subsequently developed fatal HF (Table 3).⁵⁵

Positron emission tomography with computed tomography (PET-CT) scans using ^{18}F -FDG, as well as those obtained by MRI, may be useful in the diagnosis of CTX induced by immune checkpoint inhibitors, as they allow detecting, evaluating the extent, and even quantifying the inflammatory process of several CVDs, such as myocarditis, pericarditis, and vasculitis.⁵⁶⁻⁵⁸

2.3. Contribution from Cardiac Magnetic Resonance Imaging

2.3.1. Assessment of Cardiotoxicity during Antineoplastic Treatment

Cardiac MRI is considered the gold standard for measuring LVEF and ventricular mass and volume, making it a valuable tool to assess chemotherapy-induced CTX.^{34,59,60} LVEF may be reduced by changing one or both volumes. In general, reduced diastolic volume is related to preload status that undergoes dynamic, constant changes in a patient with cancer due to vomiting, bleeding, diarrhea, or dehydration. These are readily reversible with blood volume restoration. However, a progressive increase in stroke volume is considered a marker of chemotherapy-related myocardial injury. Another important parameter that should be monitored during chemotherapy is ventricular mass. CTX causes an initial increase in ventricular mass, probably due to induction of inflammatory response by chemotherapy, leading to an increased volume of the interstitium and cardiomyocytes. However, in later stages, usually after 6 months, there is a process of ventricular mass reduction (apoptosis, fibrosis, cardiomyocyte hypotrophy, etc.). Thus, when we are facing an increase in stroke volume

and a reduction in ventricular mass, this combination is very suggestive of CTX, even if ejection fraction is preserved.

More recently, myocardial strain analysis by cardiac MRI has been gaining prominence. In the population undergoing chemotherapy, the literature highlights the potential of the test to diagnose subclinical changes.⁶¹⁻⁶³ Jolly et al.⁶¹ studied 72 patients undergoing chemotherapy for breast cancer, sarcoma, or lymphoma with serial cardiac MRI.⁶¹ There was a significant impairment in global circumferential strain 3 months after treatment compared to baseline. Moreover, global circumferential strain strongly correlated with a subclinical fall in LVEF. In a different study of 41 patients with breast cancer treated with trastuzumab, both GLS and global circumferential strain decreased during treatment and correlated with a fall in LVEF.⁶² Cardiac MRI strain is not yet widely used in clinical practice, but studies have demonstrated that the method is potentially applicable to cardio-oncology patients.

2.3.2. Cardiac Magnetic Resonance Imaging in Late Follow-up

Late evaluation with cardiac MRI provides important diagnostic and prognostic findings when complemented with tissue analysis. It is important to understand that early changes during treatment are markers of some late changes, such as presence of delayed enhancement. Myocardial edema is suggestive of an inflammatory process in the myocardium, and the greater the water content, the greater the local signal intensity.⁶⁴ A useful sequence in this context is triple inversion recovery, which is obtained by adding a third saturation pulse, to eliminate any adipose tissue signal (fat saturation) from the image.^{64,65} Some studies have shown myocardial edema in cardiac MRI soon after anthracycline therapy using T2-weighted sequences.⁶⁶ Early increase in edema and subacute increase in fibrosis seen in mice that received anthracyclines were strongly related and are both indicators of late mortality.⁶⁷

Delayed enhancement imaging is a widely validated noninvasive technique to identify and quantify myocardial fibrosis using gadolinium, a paramagnetic contrast agent. Different delayed enhancement patterns are recognized in cardiac MRI, which allows for identification of different types of myocardial involvement, thus distinguishing between ischemic and nonischemic cardiomyopathies.⁶⁸ This is of particular importance when assessing chemotherapy-induced cardiomyopathy in individuals with preexisting cardiac conditions, such as CAD.

Table 3 – PET-CT studies that assessed the relationship of ^{18}F -FDG myocardial uptake in patients undergoing chemotherapy or radiotherapy⁵⁵

Myocardial ^{18}F -FDG PET-CT vs. drugs: what do the studies show?	
Borde et al. ⁵³	Adriamycin: increased ^{18}F -FDG uptake in the myocardium may precede a reduction in left ventricular function, and the degree of cardiotoxicity is proportional to the received dose.
Toubert et al. ⁵⁵	Tyrosine kinase inhibitors (imatinib and sorafenib): a case report showed a change in ^{18}F -FDG myocardial uptake prior to a fatal cardiac event.
Evans et al. ⁵⁸	Increased ^{18}F -FDG uptake in patients who received thoracic radiotherapy of > 20 Gy to > 5 cm^2 of the heart: indicator of myocardial injury.

^{18}F -FDG: ^{18}F -fluorodeoxyglucose; PET-CT: positron emission tomography–computed tomography.

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The prevalence of delayed enhancement in CTX is low.⁵⁹ Despite being the gold standard for identifying focal areas of myocardial fibrosis, delayed enhancement imaging is not suitable for assessing diffuse interstitial fibrosis, which is generally found in cardiomyopathy caused by CTX. There is no typical pattern of delayed enhancement for CTX related to anthracyclines and trastuzumab, and LVEF may fall even without delayed enhancement.^{60,69} If present, its characteristics resemble the known patterns of nonischemic cardiomyopathies (epicardial, mesocardial, focal, and/or junctional) (Figure 5).^{68,70}

Myocarditis is a severe, potentially fatal complication in patients undergoing immunotherapy, with a mortality rate of approximately 40%.⁷¹ It may have a higher incidence and even manifest as a fulminant condition in patients using immune checkpoint inhibitors, especially if they are in combination therapy and on average 34 days after therapy is initiated.⁷²

2.3.3. Tissue Characterization by Cardiac Magnetic Resonance Imaging

2.3.3.1. T2 Mapping

Cardiac MRI has the advantage of providing detailed information on cardiac remodeling, which is complementary to the traditional morphological and functional assessment of the myocardium. Consistent data suggest that edema, inflammation, expansion of connective tissue matrix, and change in regional myocardial deformation occur before myocardial dysfunction in patients undergoing cardiotoxic treatment, reinforcing the potential applicability of that imaging modality in individuals exposed to cardiotoxic therapies.

Clinical studies have recently shown that the use of cardiac MRI protocols that incorporate multiparametric T1 and T2 mapping sequences led to the detection of preclinical and early changes in CTX.^{73,74} The detection of myocardial edema, which is usually based on increased signal intensity on T2-weighted images in the myocardium normalized to skeletal muscle values, has been successfully used for ischemic and nonischemic heart muscle disease.⁷⁵⁻⁷⁷

Using sequences widely available and simpler than T2 mapping, Ferreira de Souza et al. documented a significant increase in T2 signal intensity in women treated with moderate doses of doxorubicin (240 mg/m²).⁷⁴ Several groups are currently investigating whether T2 mapping is applicable to the assessment of myocardial edema in survivors of cancer treated with antineoplastic therapies, but, to date, limited clinical data are available to warrant their use in everyday practice.

2.3.3.2. T1 Mapping

Although delayed enhancement imaging accurately demonstrates the presence of scarring and replacement fibrosis, this technique is not able to provide complete and definitive data on the total amount of fibrosis in the myocardium, especially on interstitial fibrosis.⁷⁸ Because delayed enhancement imaging is based on relative differences in T1 signal intensity after administration of gadolinium-based contrast agents, visualization of diffuse interstitial fibrosis may be incomplete or limited by this technique.

In both retrospective and prospective studies, delayed enhancement has not been uniformly detected in patients treated with anthracycline-based chemotherapy.^{79,80} In fact, a cardiac MRI scan with negative delayed enhancement or without areas of fibrosis does not necessarily exclude the presence of myocardial fibrosis, thus reinforcing the limitation of this method in this context. Although Fallah-Rad et al. have demonstrated the presence of subepicardial delayed enhancement in all patients who had LV dysfunction induced by trastuzumab,⁷⁹ other studies have found conflicting results. Lawley et al.⁸¹ showed that < 10% of women treated with trastuzumab had positive delayed enhancement.⁸¹

New techniques based on sequential T1 measurements performed before and after the administration of gadolinium-based contrast agents provide a more accurate assessment of myocardial extracellular volume (ECV), a marker of connective tissue matrix in the myocardium and interstitial fibrosis. Even before the introduction of T1 mapping, authors had already shown that T1 measurements were able to detect increased distribution of gadolinium in the myocardium in survivors of cancer treated with chemotherapy.⁷⁹ These findings suggest

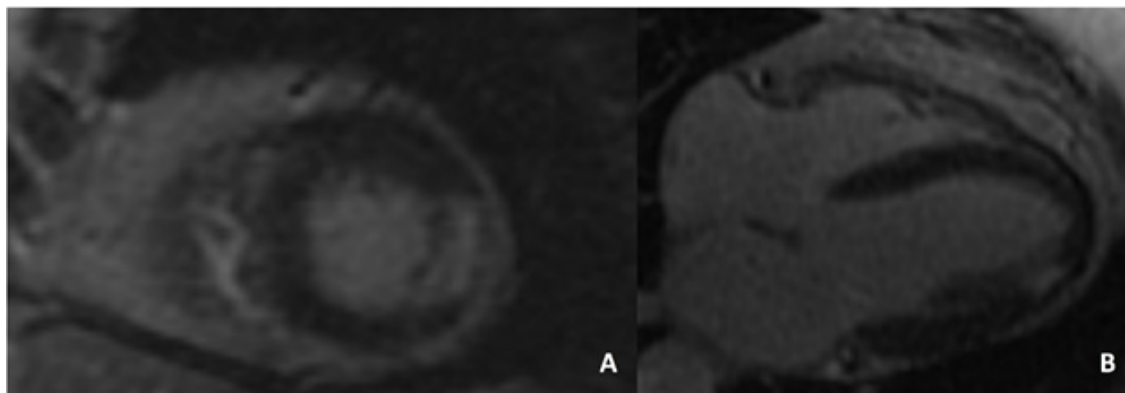


Figure 5 – Focal delayed enhancement in the left ventricular inferolateral wall of a patient with breast cancer treated with anthracycline and trastuzumab.

that the expansion of connective tissue matrix assessed by T1 mapping emerges as an early marker of CTX and is able to predict impaired functional status.

Patients previously exposed to anthracyclines have significantly higher ECV values when compared to healthy controls matched for age and sex. Jordan et al. investigated patients with and without cancer, including some treated and not treated with anthracycline as well as some treated with other chemotherapy agents.⁸² Native T1 values (prior to contrast administration) were consistently higher before and after treatment in those with cancer compared to those without cancer. The study also demonstrated that ECV increased significantly after anthracycline therapy ($30.4 \pm 0.7\%$ vs. $27.8 \pm 0.7\%$; $P < 0.01$). Moreover, in multivariate statistical models, both native T1 and ECV values remained consistently higher in patients with cancer regardless of adjusting for other variables.

As recently demonstrated, quantifying intracellular water lifetime (T1) in the myocardium emerges as an innovative approach to detect myocardial remodeling following cancer treatment, providing additional information to the assessment of ECV alone.¹⁵ A recent study evaluated 27 women with breast cancer before and after a cumulative doxorubicin dose of 240 mg/m^2 , including the measurement of biomarkers. From 1 to 2 years following doxorubicin use, there was a decrease in LVEF and indexed LV mass. Conversely, there was an increase in ECV and a reduction in intracellular water lifetime.⁷⁴

3. Vascular Toxicity

3.1. Contribution from Vascular Ultrasonography

3.1.1. Venous Thromboembolism and Cancer

3.1.1.1. Introduction

The association between cancer and superficial venous thrombosis or DVT was first reported by Armand Trousseau in 1865.⁸³ The relative risk of venous thromboembolism (VTE) is approximately seven times higher in patients with active cancer, and VTE may be the first manifestation of occult cancer (7% to 12% of cases), consisting of a “paraneoplastic phenomenon.”^{84,85}

Occurrence of thrombosis complicates the management of patients with cancer because of the need for anticoagulant therapy and the potential risk of bleeding. Patients with cancer and acute VTE are at a higher risk of recurrent thrombosis than those without cancer. Finally, an episode of VTE increases the mortality of patients with cancer and this may be the result of massive pulmonary embolism or tumor progression.⁸⁶

3.1.1.2. Epidemiology

There are several associated factors that may increase the risk of thrombosis in patients with cancer, such as treatment (radiotherapy and/or chemotherapy), postoperative period, and intravascular devices.⁸⁷ The incidence of DVT in patients with cancer is 4.7-fold higher than in those without cancer

after adjusting for comorbidities, as demonstrated in a general population in Denmark.⁸⁸ Two-year incidence rate ranges from 0.8% to 8.0% and is associated with high rates of recurrence and mortality. A higher incidence of VTE within 1 year of diagnosis occurs in those with advanced neoplastic disease of the brain, lung, uterus, bladder, pancreas, stomach, and kidney (4- to 13-fold higher in metastatic disease than in localized disease). Chemotherapy increases the risk of VTE by 7 times in patients with cancer.

3.1.1.3. Diagnosis of Deep Venous Thrombosis

Venous ultrasonography is the standard imaging test for patients with suspected (deep and/or superficial) venous thrombosis in central vessels, abdominal vessels, or extremities (cervical spine, upper and lower limbs). In addition to confirming or discarding the presence of thrombi, it allows for a differential diagnosis against other diseases.

In clinical practice, the definition of the body segment to be examined depends on the signs and symptoms presented by the patient. In cases of suspected pulmonary embolism and no evidence of the location of the thrombi, venous ultrasound screening should prioritize the vessels in the lower limbs (site of 85% of DVT cases). If the result is negative for that site, the investigation will then include the iliac veins and the inferior vena cava, and, finally, cervical and upper limb vessels.

3.1.1.4. Venous Ultrasound Protocols

It is recommended that patients with a Wells score ≥ 2 undergo venous ultrasonography (involving the compression of the entire lower limb every 2 cm from the inguinal ligament to the ankle, including the posterior tibial and peroneal veins as well as the gastrocnemius and soleus muscle veins in the calf; and color images with a spectral analysis of at least the common femoral and popliteal veins) because if only the femoropopliteal segment is examined and doubt remains, a complete examination should be repeated within 5 to 7 days to discard DVT (delaying diagnosis and increasing risks and costs). If there are symptomatic areas not included in the protocol, these must be assessed (e.g., anterior tibial veins, plantar veins, etc.).⁸⁹

If a complete examination cannot be promptly conducted, a two-point compression ultrasound should be initially performed until a new test with complete protocol can be carried out. It is known that the availability of this diagnostic modality is limited in smaller medical centers and outpatient clinics as well as in the evenings and weekends.

Specific examinations of the iliac veins and the inferior vena cava should be reserved for doubtful cases; rhizomelic thrombosis initiating in the upper thigh (Figure 6 A-B); or when spectral flow curves (pulsed-wave Doppler) in the common femoral vein have a continuous pattern (loss of phasicity), suggesting proximal involvement.

3.1.1.5. Differential Diagnosis of Deep Venous Thrombosis

Patients with cancer (occult or active, bedridden or not, undergoing chemotherapy or radiotherapy, using

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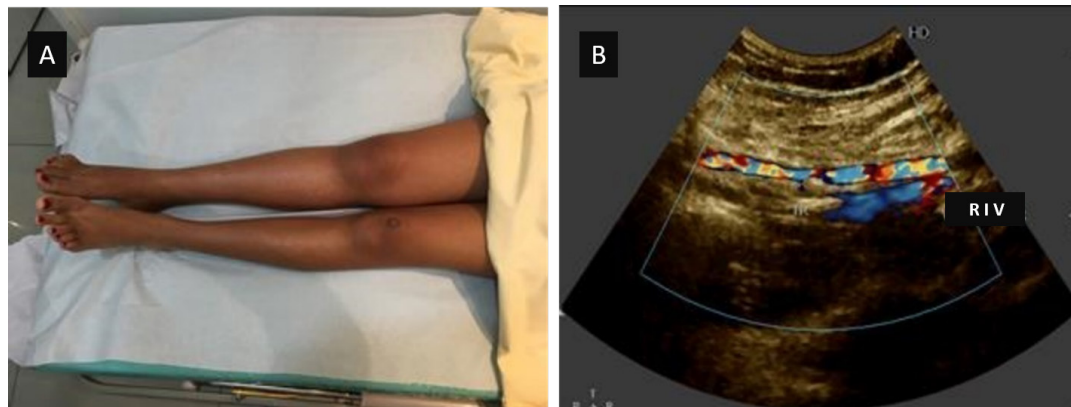


Figure 6 A and B – Rhizomelic edema in an adolescent with cancer and thrombotic occlusion of the right iliac vein (RIV).

anticoagulants, with a venous catheter for drug infusion) and other comorbidities may have complications that require a differential diagnosis against venous thrombosis. The most frequent complications are unilateral or bilateral edema at any site and calf pain.

Ultrasonography, in addition to discarding the presence of thrombi in the lumen of vessels in edematous segments, allows for diagnosis of tumor masses compressing the iliac veins and causing unilateral or bilateral edema; May-Thurner syndrome and left lower limb edema; extensive cellulite; and mediastinal masses compressing the superior vena cava and causing upper limb and neck edema. As bilateral edema is rarely caused by thrombosis, systemic conditions (heart failure [HF], liver failure, kidney failure, hypothyroidism) or medication use should be discarded.

Another advantage of ultrasonography in cases of significant increase in limb volume due to tumor mass compression, extensive DVT, or large hematomas is the rapid assessment of possible impairment associated with regional arterial flow (i.e., compartment syndrome), which may lead to severe ischemia.

3.1.2. Catheter-Related Thrombosis in Patients with Cancer

3.1.2.1. Introduction

Long-term catheter use is frequent in patients with cancer because of the need for infusion of chemotherapy agents and intravenous administration of supportive therapies. Catheter-related thrombosis (CRT) is defined as a mural thrombus that extends from the catheter to the lumen of the vessel, leading to partial obstruction or occlusion of the catheter, with or without clinical symptoms.⁹⁰

Most cases of CRT occur within 100 days of catheter insertion. CRT rate is between 14% and 18% when venography or vascular ultrasound screening is performed. Of those, less than 5% of patients are symptomatic.⁹¹

CRT may cause pulmonary embolism and loss of vascular access in 15% and 10% of patients, respectively, which

significantly increases the costs related to treatment and management.⁹²

3.1.2.2. Risk Factors

A meta-analysis that included five randomized studies of individuals with and without cancer prospectively evaluated CRT-related variables and found that the following were significant:⁹³

- Subclavian vein × upper limb insertion (odds ratio [OR] 2.16; 95% confidence interval [CI] 1.07-4.34);
- Previous history of DVT (OR 2.03; 95% CI 1.05-3.92);
- Improper catheter tip position (OR 1.92; 95% CI 1.22-3.02).

In multivariate analysis, implanted ports showed a 57% reduction in the risk of CRT when compared to peripherally implanted central venous catheters.⁹³

3.1.2.3. Diagnosis and Complications

In thrombosis involving veins of the arm, axillary vein, distal subclavian vein, or jugular vein, sensitivity and specificity are very high (> 95%) (Figure 7). These values, however, fall to about 55% in thrombosis involving the proximal subclavian vein, the brachiocephalic veins, and the superior vena cava. This is due to a naturally difficult approach imposed by the anatomical barrier of bone and lung in this region. An alternative approach is the use of probes with a smaller contact surface area such as pediatric and/or adult sector probes and microconvex probes. The most frequent complications of thrombi are secondary infection (bacterial colonization), pulmonary embolism, and postthrombotic syndrome.^{94,95}

3.1.3. Pulmonary Hypertension in Patients with Cancer

Pulmonary hypertension is defined as an increase in mean arterial pressure greater than 20 mm Hg detected through an invasive procedure of right heart catheterization. The most common form is due to LV involvement (World Health Organization group II).

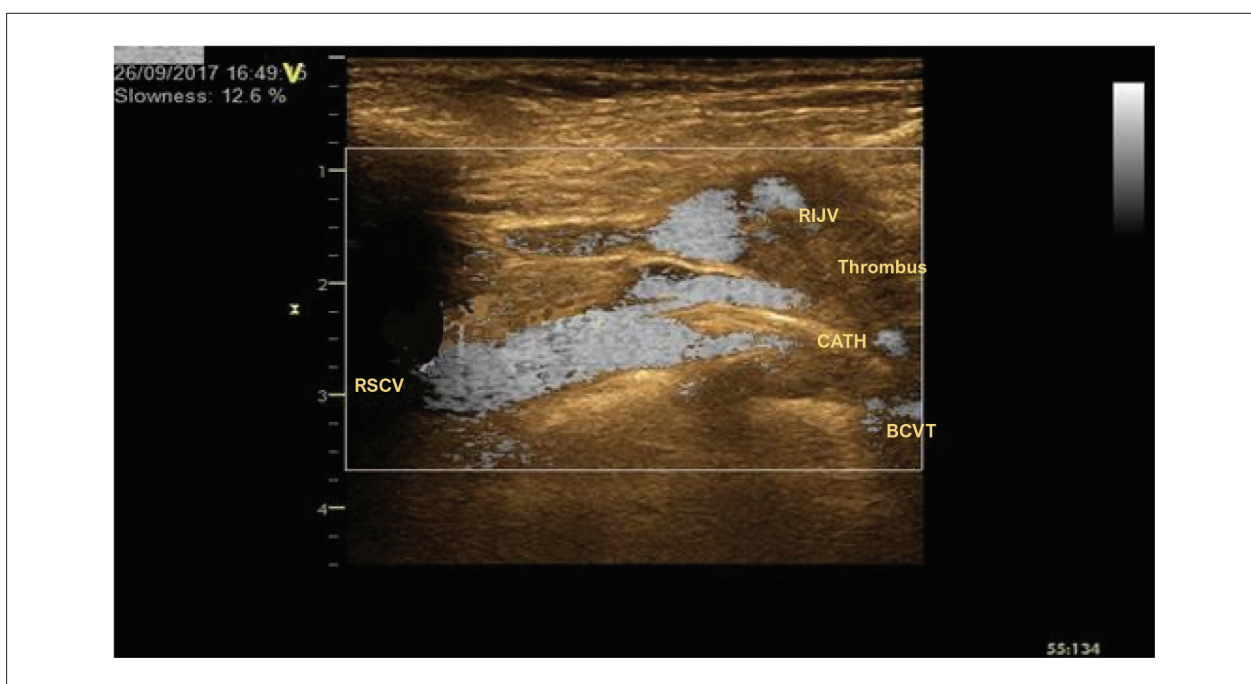


Figure 7 – Vascular ultrasound of the proximal supraclavicular region showing thrombus in the proximal right internal jugular vein (RIJV), brachiocephalic venous trunk (BCVT), and proximal right subclavian vein (RSCV). A central venous catheter (CATH) is observed in the RSCV directed towards the BCVT.

Echocardiogram remains the first-line test in the diagnostic investigation of pulmonary hypertension; however, it is important to reinforce that etiological diagnosis of pulmonary hypertension in patients with cancer is clinically complex, as we may find:

- Masses or tumors in the left atrium (LA) causing obstruction and thereby leading to increased capillary pressure;
- Extrinsic tumor compression, as seen in cases of large thymomas, lymphomas, or fibrosing mediastinitis;
- Pulmonary thromboembolism secondary to the use of tyrosine kinase inhibitors such as dasatinib or to LV involvement (CTX, preexisting heart disease, valve diseases, etc.).⁹⁶

In patients with pulmonary hypertension, computed tomography (CT) has a special value for assessing pulmonary vascularization and pulmonary parenchyma, providing information on possible mechanisms and consequences of pulmonary hypertension. Pulmonary parenchymal findings on CT scans of patients with pulmonary hypertension may vary and depend on the etiology.⁹⁷

Noncontrast CT allows for detection of abnormalities related to pulmonary hypertension, such as enlarged pulmonary artery and dilated right chambers, and identifies conditions secondary to pulmonary disease, thus being sufficient for assessing most lung diseases. The test is indicated for assessing pulmonary parenchyma in diffuse lung diseases, such as interstitial lung diseases and chronic obstructive pulmonary disease, for detecting arteriovenous malformations, and for diagnosing veno-occlusive disease or pulmonary capillary hemangiomatosis.

Contrast CT can define the pulmonary vascular anatomy and structure, obtaining accurate angiographic images from the pulmonary artery down to the subsegmental vessels. The technique is widely available, easy to perform, and more sensitive than invasive angiography in the detection of pulmonary emboli and thus has become the standard modality for noninvasive diagnosis of acute pulmonary embolism.

In pulmonary hypertension, the RV will reflect pressure overload with hypertrophy and dilation, and may show ventricular dysfunction. Significant distortion of ventricular geometry may be present, with the RV taking on a globose shape, leading to LV compression in more advanced stages. Patients with pulmonary hypertension with RV dilation and reduced RV ejection fraction have a poorer prognosis.⁹⁸

Cine imaging provides an accurate assessment of ventricular morphology and function with images acquired in short-axis orientation, obtaining complete volumetric coverage of the RV, although images acquired in transaxial orientation may also be used. Several data are obtained, such as end-systolic and end-diastolic volumes, ejection fraction, cardiac output, and myocardial mass.⁹⁹ RV mass is measured by tracing the epicardial and endocardial borders, and ventricular mass index is usually calculated as the ratio between RV mass and LV mass.

Interventricular septal geometry is also assessed by MRI, and projection to the left during systole indicates increased pressure in the right chambers. As the pressure in the lungs increases, systolic pressure of the RV may exceed that of the LV and lead to impaired LV stroke volume. In cases of more severe pulmonary hypertension, progressive RV failure affects

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LV diastolic function because the interventricular septum projects also during diastole, thus compromising LV diastolic filling and further reducing cardiac output. Interventricular septal curvature is an effective measure of geometric deformation involving the ventricles, with a strong correlation between paradoxical interventricular septal curvature and severity of pulmonary hypertension.¹⁰⁰

New techniques are being implemented, such as myocardial strain analysis, phase-contrast imaging, and delayed enhancement imaging, with potential application in cases of patients with pulmonary hypertension, allowing for analysis of regional myocardial function, hemodynamic repercussions, and extent of RV impairment.¹⁰¹

4. Radiotherapy-Induced Cardiotoxicity

4.1. Role of Echocardiography

4.1.1. Epidemiology

Radiotherapy holds an important place in cancer treatment. In the United States (US), over 3 million survivors of cancer underwent radiotherapy in 2016, accounting for 29% of all survivors 5 years after the initial diagnosis. The proportion of patients with cancer undergoing thoracic radiotherapy reaches 45.6% if those with breast cancer and lymphoma are included. Several studies have demonstrated an increased incidence of CAD, AMI, and sudden cardiac death in patients undergoing radiotherapy, especially those with Hodgkin lymphoma or breast cancer, reinforcing the potential side effects of the treatment.^{102,103}

Radiation-induced heart disease (RIHD) is known as the multiple deleterious effects generated by the total cumulative dose of radiotherapy and enhanced by adjuvant chemotherapy on the cardiovascular system. The spectrum is highly variable and includes the involvement of any cardiovascular system structure, and late manifestation is much more frequent. Acute complications, usually more subtle and clinically less important, consist of myopericarditis

and pericarditis. Late findings, which appear years or decades after exposure, tend to be clinically relevant and include cases of chronic pericarditis, valve diseases, medium- and large-vessel diseases (porcelain aorta and carotid stenosis), cardiomyopathies (dilated and restrictive types), conduction disorders, and CAD.¹⁰⁴ There is abundant literature demonstrating that exposure to radiation, especially of the left chest, is associated with increased cardiovascular mortality, attributed mainly to CAD and a higher risk of developing HF.^{105,106} The most relevant risk factors for developing RIHD are shown in Table 4.

4.1.2. Pathophysiology

Cardiomyocytes are relatively resistant to radiation damage because of their postmitotic state. However, endothelial cells remain sensitive to radiation, and the pathophysiology of most forms of RIHD seems to be related to these cells. Other mechanisms that perpetuate cellular injury also seem to be implicated, such as ischemia and tissue hypoxia, in addition to the direct injury manifested by accelerated atherosclerosis, thrombosis, oxidative stress induction, myocytolysis, and activation of neurohumoral mechanisms leading to atherosclerosis and, finally, fibrosis.¹⁰⁷

4.1.3. Initial Evaluation and Follow-Up

In patients with cancer, complementary cardiovascular evaluation is classically dictated by symptom status or by suggestive findings on physical examination. Echocardiography plays a key role in the assessment of heart morphology and function and is considered the first imaging modality in most cases.

Regarding post-radiotherapy follow-up, annual clinical evaluations are recommended, including targeted history taking, clinical examination, and resting electrocardiogram. In the presence of symptoms and/or new suggestive findings on physical examination, a new transthoracic echocardiogram (TTE) is suggested. In asymptomatic patients classified as low risk for developing RIHD, TTE surveillance is recommended after 10 years of exposure with subsequent reassessments

Table 4 – Risk factors for radiation-induced heart disease (RIHD)

RISK FACTORS FOR RIHD
< 50 years of age
Cumulative radiation dose > 30 Gy
High fractional doses of radiation > 2 Gy/day
Presence and extent of a tumor close to the heart
Concomitant use of chemotherapy agents (mainly anthracyclines)
Risk factors for cardiovascular disease (hypertension, DM, dyslipidemia, smoking)
Preexisting cardiovascular disease
Inadequate cardiac protection
Irradiation in the anterior region or left hemithorax
Definition of high risk: exposure to thoracic radiotherapy in the anterior or left chest region in addition to at least one of the listed factors

DM: diabetes mellitus.

every 5 years. In asymptomatic individuals classified as high risk, however, evaluation should be anticipated, including the investigation of myocardial ischemia using a noninvasive functional test, as shown in Figure 8.^{104,108,109}

4.1.4. Radiation-Induced Heart Disease and Role of Echocardiogram

4.1.4.1. Radiation-Induced Pericardial and Myocardial Disease

Pericardial disease is described as the most common side effect of thoracic radiotherapy, usually appearing a few weeks after treatment. New protocols including lower doses and implementation of cardioprotective techniques decreased the incidence from 20% to 2.5%, with a correlation proportional to the dose and volume exposed during treatment.^{103,104} Pericarditis is typically self-limiting. However, 10% to 20% of patients develop chronic or constrictive pericarditis 5 to 10 years after treatment, which is indicative of a more reserved prognosis.¹⁰⁹ TTE provides diagnosis, allows for quantification of pericardial effusions, and serves as a guide to pericardiocentesis. A great advantage of the method is allowing for analysis of constrictive physiology, characterized

by echocardiographic findings such as pericardial thickening, septal bounce, restrictive diastolic filling pattern, significant inspiratory variation in mitral inflow (> 25%), inferior vena cava plethora, reduced circumferential strain, and hepatic vein diastolic expiratory flow reversal. The impact on survival has been attributed to the concomitant finding of other radiation-associated cardiac injuries, being commonly accompanied by myocardial fibrosis, premature coronary artery stenosis, and important valve injuries.

4.1.4.2. Radiation-Induced Coronary Artery Disease

Treatment of Hodgkin lymphoma and breast cancer typically includes thoracic radiotherapy, resulting in cardiac tissue exposure to radiation. The cumulative incidence of radiation-induced coronary artery disease (RICAD) is estimated to reach almost 60% in survivors of Hodgkin lymphoma, with a relative risk 3.2 times greater than that of the general population.¹⁰⁹ Regarding breast cancer, which is the most frequent cancer among women, meta-analyses showed that the relative risk of developing RICAD is higher in patients undergoing left thoracic radiotherapy.¹¹⁰

Therefore, patients with thoracic neoplasms are at a considerably higher risk of developing RICAD compared

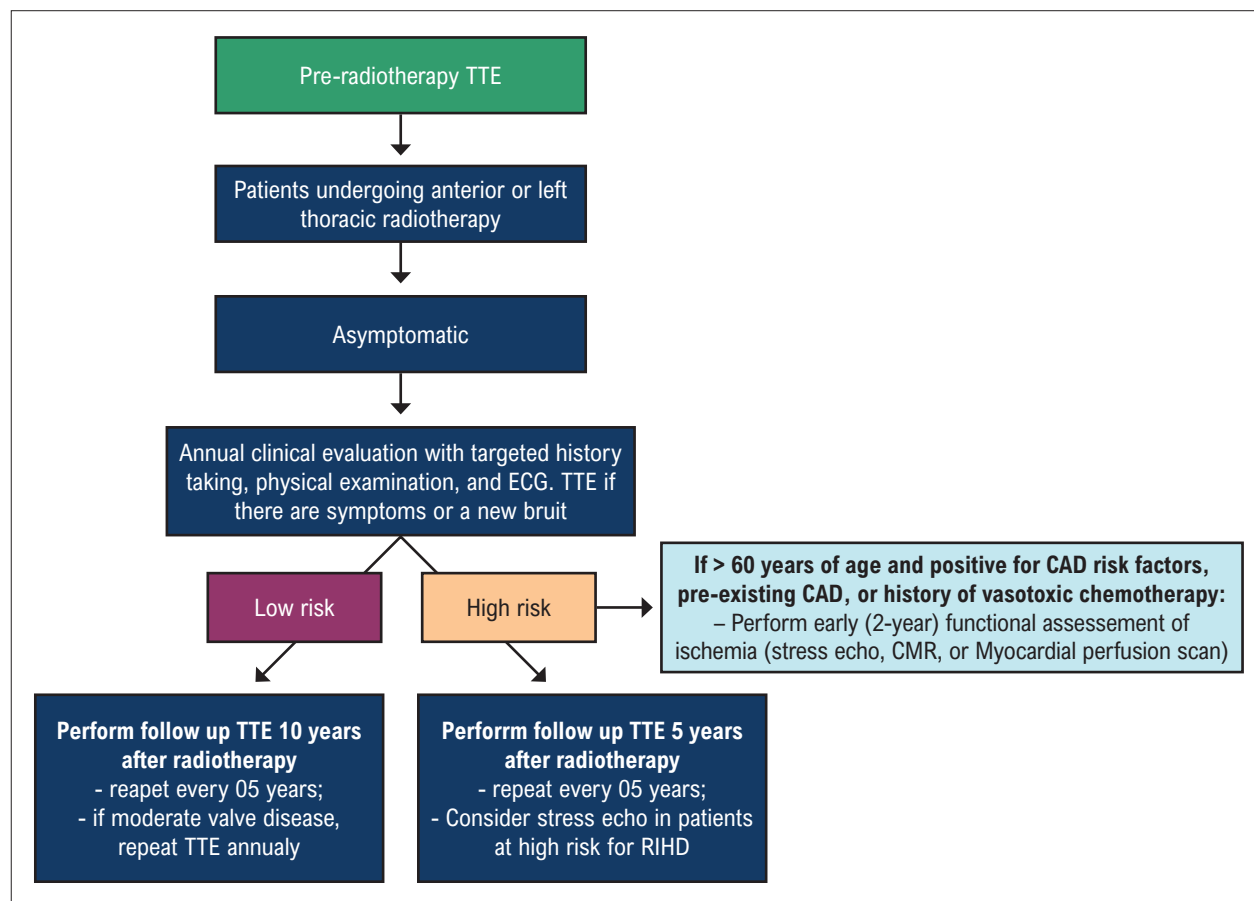


Figure 8 – Algorithm for echocardiographic monitoring following thoracic radiotherapy.^{104,108,109} CAD: coronary artery disease; ECG: electrocardiogram; echo: echocardiogram; RF: risk factor; RIHD: radiation-induced heart disease; TTE: transthoracic echocardiogram.

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to the general population, especially in the presence of risk factors such as the cumulative dose used (in general > 30 Gy), early age at exposure, affected tissue volume, lack of cardiac protection, and presence of preexisting traditional cardiovascular risk factors.^{104,105,109}

Although RIHD manifests late, CAD, in particular, may appear earlier, as of the fifth year after exposure.¹⁰⁵ RICAD is known to mostly exhibit ostial and proximal involvement, typically affecting the left main coronary artery, the left anterior descending artery, or the right coronary artery.^{107,111} Radiotherapy predisposes to or accelerates atherosclerosis, even in those without classic cardiovascular risk factors, and may have sudden death as the first clinical presentation. Because of high morbidity and mortality rates and heterogeneous and sometimes atypical clinical presentation, we thus recommend performing stress TTE screening using exercise or pharmacological (dobutamine) stress whenever relevant. This noninvasive functional method offers advantages such as satisfactory accuracy, no radiation, relatively low cost, and high availability.

4.1.4.3. Radiation-Induced Valve Disease

A higher prevalence of radiation-induced valve disease (RIVD) is reported in the subgroups of patients with Hodgkin lymphoma (17%) and breast cancer (4.2%). Similar to RICAD, the risk is related to total radiation dose and radiation field.

Valve involvement with hemodynamic repercussions usually occurs after 10 years of radiotherapy and most commonly affects left heart valves. The aortic valve is more frequently affected than the mitral valve. Valve regurgitation manifests earlier than stenosis, which usually appears about 20 years after radiotherapy. Echocardiographic findings are variable and may range from minimal changes without any associated valve dysfunction to diffuse fibrosis, thickening, and calcification. The involvement of any component of the valve apparatus is typical, but the commissures are spared, thus allowing for differentiation from a rheumatic etiology. Aortomitral curtain impairment (i.e., thickening and calcification) is a typical post-radiotherapy finding associated with poor long-term survival.^{103,108}

With the progression of symptoms and severity of the lesions, surgical intervention or percutaneous management may be required. Specific echocardiographic techniques such as 3D echocardiography and transesophageal echocardiography (TEE) contribute to improved anatomical and functional assessment, especially in valve lesions with greater hemodynamic and structural repercussions. However, caution is recommended when performing TEE in patients undergoing thoracic radiotherapy, given the possibility of associated esophageal impairment.

4.2. Radiation-Induced Arteritis – Actinic Arteritis

Radiation-induced arteritis, also known as actinic arteritis, is the result of changes in the arterial wall leading to stenosis or occlusion. These phenomena may lead to an accelerated atherosclerotic process of inflammatory etiology, secondary to endothelial cell injury, which can

occur in medium- or large-sized arteries. In cases of radiotherapy for head and neck tumors, the affected arteries may be both intracranial and extracranial.

Radiation-induced carotid artery stenosis had its course investigated by Cheng et al.¹¹² The authors demonstrated that there was an annual progression of the degree of stenosis from less than 50% to more than 50% in 15.4% of irradiated patients versus 4.8% of nonirradiated patients. There was no difference in symptom onset or mortality between the study groups. However, such changes may lead to the onset of cerebrovascular symptoms, and symptomatic patients with carotid artery lesions following radiotherapy have been shown to exhibit reduced cerebral flow.¹¹³

Peripheral artery disease, although rare, has also been reported following radiotherapy for the treatment of cervical cancer, with involvement of the iliac and femoral arteries. Symptoms may be those of chronic ischemia, although cases of acute arterial occlusion have been observed.¹¹⁴

Peripheral artery disease, although comparatively rare, has also been reported following radiotherapy, e.g., for the treatment of cervical cancer, with involvement of the iliac and femoral arteries. Symptoms may be those of chronic ischemia, although cases of acute arterial occlusion have been observed.¹¹⁴

4.2.1. Diagnosis

The diagnosis of carotid artery stenosis may be clinically inferred by neck auscultation for a bruit in the irradiated region. Imaging modalities such as vascular ultrasonography, CT angiography, MRI, or conventional contrast angiography are able to detect and quantify a stenotic lesion.¹¹⁵

Vascular ultrasonography has the advantages of being noninvasive and low-cost, using no nephrotoxic contrast, and thus being safe for medium- and long-term follow-up.

4.2.2. Ultrasonographic Features

Arterial injuries induced by ionizing radiation may occur in the various arteries of the body, and have been described especially in the supraaortic vessels (i.e., the carotid and subclavian arteries). In the first year after treatment of localized head and neck cancers with radiotherapy, a process of accelerated and progressive intima-media thickening occurs in both carotid arteries, which may lead to significant luminal narrowing.¹¹⁶ Wilbers et al. found similar results 7 years after radiotherapy was used in this region.¹¹⁷ A 20-year follow-up study of young adults who underwent radiotherapy showed the following findings: a higher prevalence of atherosclerotic plaques in the irradiated vessels than the nonirradiated vessels (18% vs. 2%), greater intima-media thickness (IMT) in treated patients than controls, and a linear increase in IMT over time after radiotherapy¹¹⁸ (Figures 9 and 10).

This accelerated atherosclerotic process often affects the common carotid artery, although the internal carotid artery may also be involved. Differential diagnosis using ultrasound imaging alone is not always possible, and a history of radiotherapy in the affected region is crucial for

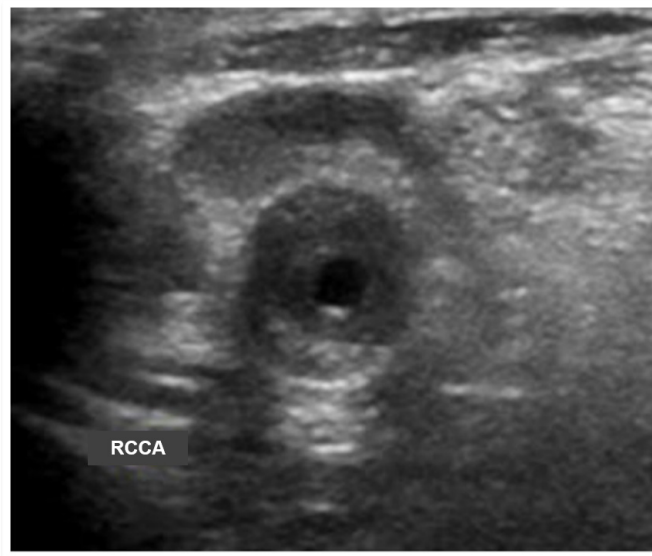


Figure 9 – Transverse plane of the right common carotid artery showing significant intima-media thickening with consequent luminal narrowing.

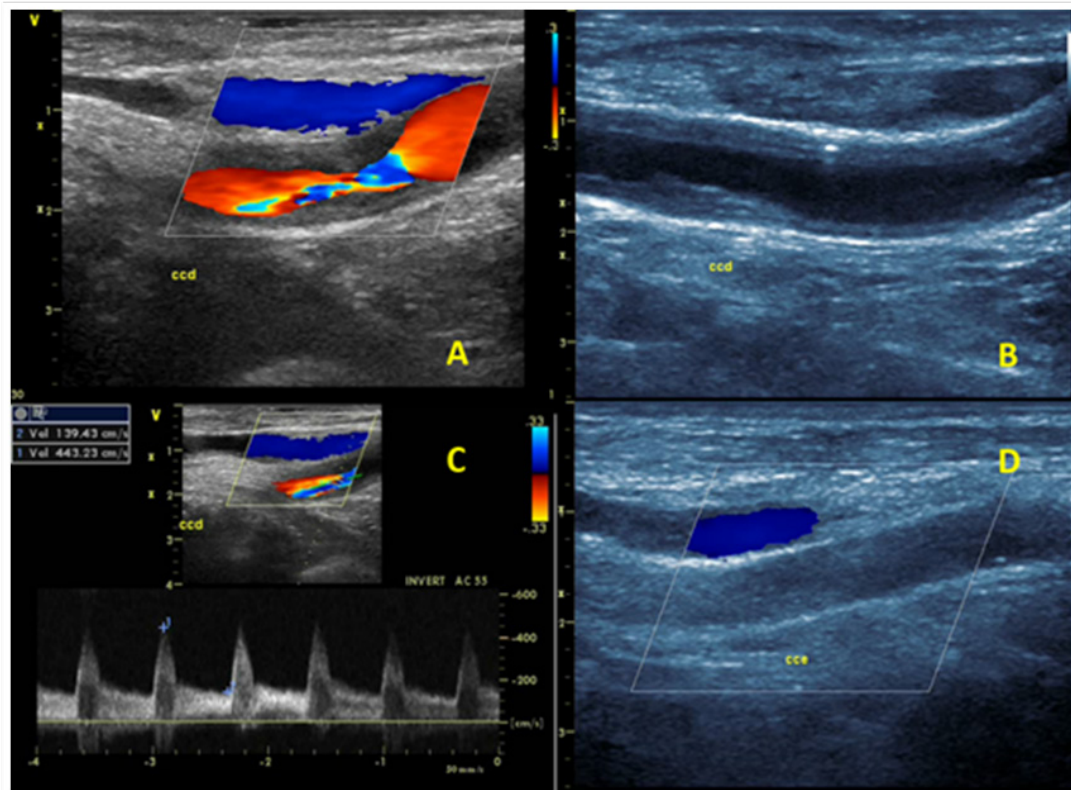


Figure 10 – Patient with actinic arteritis 6 years after radiotherapy. A. Stenosis > 70% of the right common carotid artery on color Doppler image – significant luminal narrowing and turbulent flow are observed. B. Large increase in intima-media thickness of the right common carotid artery on B-mode image causing luminal narrowing. C. Pulsed-wave Doppler image showing increased flow velocity. D. Occluded left common carotid artery.

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the diagnosis to be established. Chronic atherosclerotic disease and Takayasu arteritis are the main differential diagnoses. In chronic atherosclerotic disease, involvement is more common in the carotid bifurcation and the internal carotid artery. The common carotid artery may also be affected (Figure 11). In actinic arteritis, involvement of the common carotid artery is more evident, with more diffuse, pronounced, and progressive atherosclerosis^{112,115}.

In Takayasu arteritis, there is a homogeneous and concentric thickening that may lead to significant stenosis and occlusion of the vessel, and there may also be dilations (aneurysms). It typically affects the common carotid artery

up to the bifurcation, but spares the internal carotid¹¹⁹ (Figure 12 A-B).

4.2.3. Arterial Stenosis Follow-Up

Because of the progressive nature of radiation-induced arterial stenoses, a more rigorous follow-up using imaging methods is suggested to detect significant but still treatable stenoses. Initially, vascular ultrasonography may be performed annually and then individualized, with shorter intervals in case of rapid disease progression as well as after treatment.¹²⁰

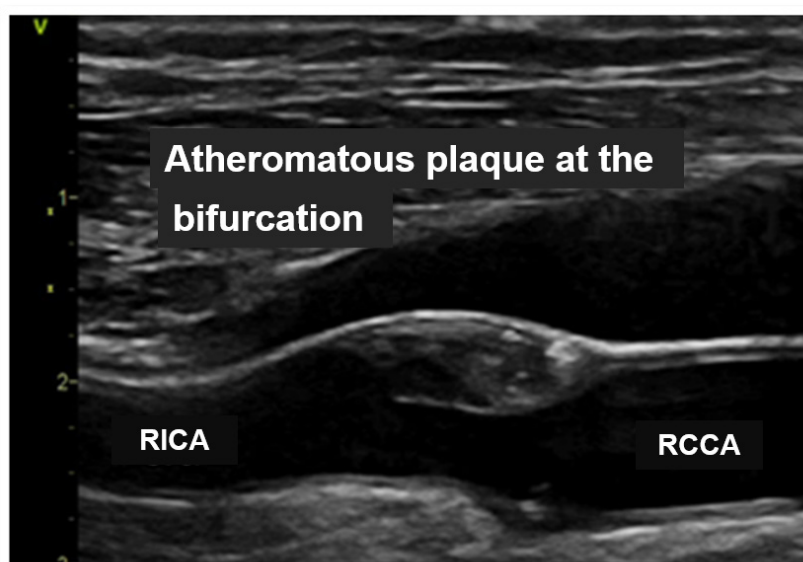


Figure 11 – Atherosclerotic plaque in the carotid bifurcation.

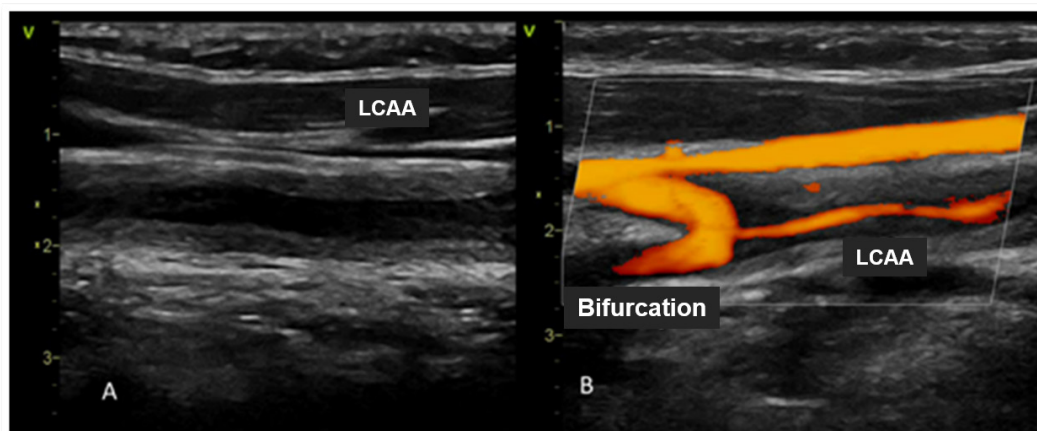


Figure 12 – Takayasu arteritis in a 17-year-old female patient. A. Longitudinal plane of the left common carotid artery (LCCA) showing a significant concentric wall thickening.¹¹⁹ B. Power Doppler image showing great luminal narrowing of the common carotid artery with preserved lumen from the carotid bifurcation.

Carotid endarterectomy (ECA) and endovascular approaches (carotid angioplasty and stenting) have proven effective in the treatment of radiotherapy-induced stenosis.¹²¹ The extent of the disease and a large arterial area affected may facilitate the development of embolic phenomena during stenting, with consequent cerebrovascular events. Moreover, stenting may favor intimal hyperplasia with restenosis (Figure 13). The mechanism that leads to the emergence of intrastent intimal hyperplasia in those patients seems to be related to the proliferation of smooth muscle cells.¹²² Restenosis has been shown to be a problem following endovascular treatment, appearing to be greater in previously irradiated patients compared to controls. The rate of restenosis >50% is higher in patients treated with stenting compared to those treated with carotid endarterectomy.¹²³

The treatment of involved arteries other than cervical arteries should be individualized. There are case reports of patients treated with surgery and endovascularly, with angioplasty and stenting.^{114,124}

4.3. Cardiovascular Evaluation after Radiotherapy and Role of Nuclear Medicine

4.3.1. Coronary Artery Disease Evaluation and Follow-Up after Radiotherapy

Lind et al.¹²⁵ evaluated 69 women undergoing thoracic radiotherapy at doses of 46 to 50 Gy, with fractions of up to 2 Gy per session, using proper cardiac shielding. They underwent rest myocardial perfusion imaging with technetium-99m (^{99m}Tc) sestamibi or ^{99m}Tc tetrofosmin before and at 6, 12, and 18 months following radiotherapy. Myocardial perfusion changes were observed at 6 months, especially in the left anterior descending artery.¹²⁵ This finding

is consistent with that of Hardenbergh et al.,¹²⁶ who showed myocardial perfusion changes in about 60% of patients 6 months after thoracic radiotherapy.¹²⁶ Ventricular function analysis on echocardiography showed that only one of the patients had a reduction of over 10% in LVEF. Although an association with microcirculation damage was found, the authors highlighted the importance of those changes, which may subsequently lead to diastolic and systolic dysfunction.

Both microvascular and macrovascular changes in the coronary arteries are recognized late sequelae of thoracic radiotherapy. The importance of regular coronary artery screening for effects of radiotherapy is known. However, specific screening regimens for this population are still lacking, despite a large arsenal of noninvasive methods available.^{127,128}

4.4. Coronary Artery Disease Evaluation after Radiotherapy – Role of Computed Tomography

Radiotherapy-induced cardiotoxicity involves several pathophysiological mechanisms that trigger various forms of harm to the cardiovascular system. In the coronary arteries, there may be a direct vasospastic effect, endothelial damage or changes in lipid metabolism and consequent premature atherosclerosis. The risk of subsequent coronary events is proportional to the radiation dose.

The high accuracy of coronary CT angiography for detection of CAD gives this method the potential to provide accurate information on suspected CAD in cancer patients, especially in those presenting with chest pain and symptoms of heart failure of potentially ischemic etiology.

Several studies have reported an increased incidence of CAD, acute myocardial infarction, and sudden cardiac death in patients undergoing radiotherapy, especially in patients with Hodgkin lymphoma or breast cancer, which highlights the

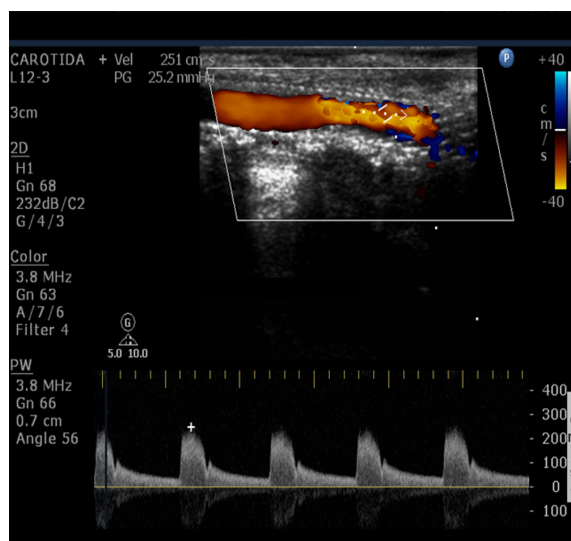


Figure 13 – Patient after 10 years of radiotherapy with a stent in the left common carotid artery; longitudinal color Doppler image showing intimal hyperplasia and intrastent flow; pulsed-wave Doppler image showing increased local velocity.

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potential of this treatment modality to cause harm. Current guidelines suggest screening for CAD within 5 to 10 years after irradiation of the chest to screen for late cardiotoxicity.¹²⁹ Multiple studies, including CT studies, have confirmed these clinical and epidemiological findings in patients with Hodgkin lymphoma. Mulrooney et al.¹³⁰ identified plaque on CT angiography in 39% of survivors. In a prospective study of 179 patients with a mean follow-up of 9.5 years, Girinsky et al.¹³¹ found plaque in 26% of those who had undergone radiotherapy. On multivariate analysis, the radiation dose applied to the origin of the coronary arteries was associated with subsequent detection of plaque. Van Rosendael et al.¹³² compared 71 patients undergoing radiotherapy versus 237 nonirradiated controls, matched for multiple CAD risk factors, and found a higher prevalence of plaques, more proximal disease, greater degree of stenosis, and a greater number of vessels with significant lesions in the group undergoing radiotherapy.

4.5. Coronary Artery Disease Evaluation after Radiotherapy – Role of Magnetic Resonance Imaging

CMR has excellent accuracy for the diagnosis of myocardial ischemia when combined with pharmacological stress testing, and is considered the gold standard for assessment of infarction areas, myocardial viability, and ventricular function, with prognostic value in predicting cardiovascular events.

The CE-MARC study compared investigation of ischemia by stress myocardial perfusion CMR versus scintigraphy in 628 patients undergoing cine coronary angiography as the gold-standard reference, in a population with a 39% baseline prevalence of obstructive CAD.¹³³ Both methods had similar specificities (CMR, 83.4%; SPECT, 82.6%, $p = 0.916$), but CMR was significantly more sensitive for the diagnosis of myocardial ischemia (86.5%) than SPECT (66.5%) ($p < 0.0001$).

The late gadolinium enhancement (LGE) technique, in which images are acquired after infusion of gadolinium contrast without the need for stressors, is considered the leading noninvasive method for detection of myocardial fibrosis. Analysis of the extent of myocardial infarction predicts myocardial viability in the segment under investigation. Assessment of the presence and extent of infarction by CMR has established prognostic value; detection of previously unknown infarcts in patients undergoing CMR is associated with worse cardiovascular prognosis and mortality.¹³⁴

5. Cardiac Tumors and Masses

5.1. Contribution from Echocardiography

Cardiac masses are often challenging to echocardiographic diagnosis. Thrombi, vegetations, and pseudotumors account for 75% of cases. Primary cardiac tumors (PCTs), in turn, are extremely rare with an estimated frequency of 0.02%. They may be benign or malignant in terms of histology. Cardiac metastases are up to 100 times more frequent. The World Health Organization recently updated the classification of cardiac and pericardial tumors.¹³⁵

Transthoracic echocardiography (TTE) assesses location, morphology, dimensions, echogenicity, mobility, extent, calcifications, type of insertion, and presence or absence of pericardial effusion.¹³⁶ Different Doppler imaging modalities allow for assessment of blood flow and consequent hemodynamic repercussions, such as flow obstruction or valve dysfunction. Color flow mapping reveals the presence of vascularization in some types of tumors, and the use of contrast perfusion allows for identification and differentiation of thrombi from tumors. In general, thrombi do not enhance and are well delineated in the contrasted chamber. Contrast agents also assist in the differentiation of benign from malignant tumors.¹³⁷ Malignant tumors tend to be completely enhanced, while benign tumors are only partially enhanced. Perfusion imaging analysis of post-impulse contrast replenishment may be qualitative using visual inspection or quantitative using time-signal intensity curves and parametric maps (color-coded signal intensity). The difference in post-impulse (A) maximal steady-state pixel intensity between the mass and the adjacent myocardium ($\Delta A_{\text{mass-myocardium}}$) is calculated. Reported sensitivity and specificity of $\Delta A_{\text{mass-myocardium}}$ in differentiating thrombi from benign and malignant tumors were 93% and 100%, respectively, with a cutoff value of 23.2 dB, and were 100% and 97%, with a cutoff value of 0.45 dB.¹³⁸ Estimated volume, velocity, and microvascular blood flow of the masses may also be obtained. Strain imaging can differentiate the nature and contractile pattern of some types of tumors, such as fibroma and rhabdomyoma. In rhabdomyomas, deformation is opposite to that of the myocardium, while fibromas have no deformation.¹³⁹ TEE has greater sensitivity (> 95%) and acoustic resolution than TTE, providing a better characterization of tumors and masses in terms of location, insertion, and relationship with the vena cava, especially in atrial and valvular lesions. TEE plays an important role in cases of systemic embolization, in intraoperative assessment of tumor resection, as well as in ventricular lesions in patients with limited thoracic acoustic window. Real-time 3D echocardiogram is the latest technique for assessing cardiac masses, providing more accurate data on volume, morphology, and relationship with adjacent structures, as well as aspects such as location and type of insertion, homogeneity, vascularization, calcification, and areas of necrosis.¹⁴⁰

Any cardiac mass detected on echocardiography must be analyzed within the respective clinical and epidemiological context. Age, sex, symptoms, and concomitant oncology disease are important inputs for diagnosis. Artifacts should be excluded by analyzing multiple cut planes and adjusting the imaging parameters. Eustachian valve and prominent crista terminalis, Chiari network, and coumadin ridge are anatomic variants that may be misinterpreted as masses. Lambl excrescences are filiform structures ranging from 3 to 5 mm found at sites of valve closure, downstream of valve. They do not cause valve dysfunction but may embolize. Lipomatous hypertrophy of the interatrial septum is characterized by infiltration of mature fat, which spares the fossa ovalis resulting in a typical dumbbell shape. Calcified amorphous tumors are heterogeneous,

hyperechoic, nonneoplastic masses with hypoechoic or isoechoic areas, of variable mobility, often associated with mitral annular calcification and considered to be potential sources of embolism.¹⁴¹ Pericardial cysts are hypoechoic, usually loculated masses with varying dimensions that are adjacent to the cardiac border. Thrombi may be found in any chamber and vary in size, morphology, and mobility but do not usually occur outside predisposing conditions. When inside the LA, they are present mainly in patients who have spontaneous echo contrast, atrial fibrillation, stenosis, or mitral prosthesis. In the right atrium (RA), they are relatively common in oncology patients with a long-term catheter and a hypercoagulable state. Migrating thrombi are seen on the right side of the heart in patients with DVT and pulmonary embolism. LV thrombus is associated with changes in segmental contractility and dilated cardiomyopathy. Vegetations mainly affect the left heart valves, have great mobility, and move independently. They are found on the atrial surface of the atrioventricular valves and on the ventricular surface of the semilunar valves, often causing valve dysfunction in endocarditis.

5.1.1. Benign Primary Cardiac Tumors

From 85% to 90% of all PCTs are benign. Of these, nearly 50% are myxomas.¹³⁶ Rhabdomyoma is the most common type in children, accounting for approximately 50% of cases, followed by fibroma and myxoma.¹⁴²

5.1.1.1. Cardiac Myxomas

These are more frequent in patients aged from 30 to 60 years, presenting with constitutional, obstructive, or embolic symptoms. They are in the LA in 75% of cases, in the RA in 20%, and in the ventricles in 5%. Typically, they are described as oscillating polypoid masses attached to the interatrial septum through a narrow pedicle. They are heterogeneous tumors with echogenic nuclei, cystic areas, and smooth surfaces. Depending on their size, they may obstruct the flow of the atrioventricular valve. Papillary myxomas are smaller and have a stretched appearance, irregular surface, greater mobility, and greater risk of embolization. Both 2D and 3D TEE and the use of contrast perfusion assist in the characterization of those tumors. Cardiac myxomas may be recurrent when associated with Carney complex. In such cases, TTE is the optimal imaging technique for follow-up.¹⁴³

5.1.1.2. Papillary Fibroelastomas

These are small (usually < 10mm) sessile or pedunculated, rounded, gelatinous, avascular tumors with multiple narrow, elongated, branched papillary projections. They resemble sea anemones when placed under water. These characteristics provide them with friability and predispose them to adherent thrombi.¹⁴⁴ Embolization is more common in tumors larger than 10 mm and may be due to adherent thrombi or fragmented papillae. They are usually single, mobile, and attached to any endocardial surface by a short pedicle. They affect the endocardial surface of valve

in 77% of cases and occur mainly in older adults. They are commonly seen in the middle section of the left heart valve leaflets. They usually project into the arterial lumen in the aortic valve and into the atrial surface in the mitral valve.^{144,145} On echocardiogram, they exhibit independent mobility, stippled and sparkling edges, and a narrow central pedicle. They usually cause no valve dysfunction. TEE plays an important role in the assessment of those tumors.

5.1.1.3. Rhabdomyomas

These are usually diagnosed in the first year of life or during fetal life. They are associated with tuberous sclerosis, are usually multiple, and tend to regress spontaneously.¹⁴⁶ They mainly affect the interventricular septum, ventricular walls, and atrioventricular valves. They appear as multiple nodular or pedunculated, lobulated, well-defined, homogeneous masses that are hyperechogenic to the surrounding myocardium. They show deformation opposite to that of the myocardium on strain imaging.¹³⁹

5.1.1.4. Cardiac Fibromas

These rarely occur in adults. Approximately 3% to 5% of cases are associated with Gorlin syndrome (also called nevoid basal cell carcinoma syndrome).¹⁴⁷ They are characterized as a single intramural, hyperechogenic, well-defined, noncontractile solid mass with calcifications that extend into the LV chamber. They may cause arrhythmia, ventricular dysfunction, and flow obstruction. They show no deformation on strain imaging.¹³⁹

5.1.1.5. Cardiac Lipomas

These are masses of encapsulated adipose tissue that are found mainly in the LV subendocardium but also occur in other chambers, the pericardium, and cardiac valves, reaching several centimeters in size. They are broad-based, homogeneous, immobile tumors without calcification. They are hyperechoic in the chamber and hypoechoic in the pericardium.¹⁴⁸

5.1.1.6. Teratomas

These are germ cell tumors found in infants, children, and fetuses.¹⁴⁷ They may be mature or immature and rarely occur in adults. They are preferably located in the pericardial space and may cause cardiac tamponade or compression of adjacent structures.¹⁴⁹ They are characterized as heterogeneous masses containing solid, cystic areas and calcifications, often accompanied by pericardial effusion.

5.1.1.7. Cardiac Hemangiomas

These vascular tumors are rarely found and may occur at any age, including fetal life. They are located mainly in the LV and RA, measuring between 2 and 10 cm in most cases. They are pedunculated and mobile in half of the cases. They appear as well circumscribed masses that may be cystic or solid, unilobulated or multilobulated, depending on their type, i.e., cavernous, capillary, or arteriovenous.¹⁵⁰

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5.1.1.8. Cardiac Paragangliomas

These are very rare neuroendocrine tumors. They are associated with several syndromes, such as Von Hippel-Lindau disease, neurofibromatosis type I, and Carney complex. They may be benign or malignant and hormonally active or inactive. They are extremely vascularized and nonencapsulated. They occur most often between the 4th and 5th decades of life and are located mainly in the pericardial space, next to the atrioventricular groove, at the root of the great vessels, and in the LA. They are characterized as broad-based, usually ovoid, well-demarcated echogenic masses with an average size of 5cm, surrounding the coronary artery and possibly compressing adjacent structures.¹⁵¹

5.1.1.9. Cardiac Schwannomas

These are extremely rare slow-growing tumors with only 25 cases reported in the English literature (18 intracardiac and 7 intrapericardial tumors). They arise from the cardiac plexus or branches of the vagus nerve and involve the right side of the heart more often. They are benign but may exhibit malignant behavior. They are echogenic, hypodense, nonpedunculated, demarcated masses that may reach several centimeters in size and cause signs and symptoms related to the compression of adjacent structures.¹⁵²

5.1.2. Malignant Primary Cardiac Tumors

These are extremely rare tumors whose frequency is 0.008%. From 10% to 15% of all PCTs are malignant. They are represented by different types of sarcomas, lymphomas, and mesotheliomas. They mainly affect adults in the fifth decade of life. Sarcomas account for 65% to 95% of cases in adults and 70% in children and adolescents (< 18 years).^{143,154} Angiosarcoma is the most common type. Usually it produces symptoms such as dyspnea and pleuritic chest pain.¹⁵⁵

5.1.2.1. Angiosarcomas

These exhibit an aggressive behavior and may metastasize. They are preferably located in the RA. They present as voluminous, homogeneous, immobile, nonpedunculated, stalkless, lobulated, echogenic masses with a broad base of endocardial insertion and smooth intracardiac borders. Because they are located next to the atrioventricular groove, angiosarcomas usually cause obstructions in the tricuspid valve and, in most cases, affect the pericardium causing hemorrhagic effusions. Partly because of their slender vascular channels, they do not significantly enhance with the use of contrast perfusion. The sensitivity of TTE for identification is 75%.¹⁵⁵

5.1.2.1.1. Undifferentiated Sarcomas

These are typically located in the LA and may mimic myxomas. They tend to involve the mitral valve causing flow obstruction. They have a broad base, some mobility, and a smooth and homogeneous appearance.¹⁵⁶

5.1.2.1.2. Rhabdomyosarcomas

These are the most common type in children. They usually arise from the ventricular walls and often interfere with valve function because of intracavitary growth.¹⁴⁸ They tend to occur in more than one location causing obstruction at multiple levels. They grow rapidly and usually invade the pericardium.¹³⁶

5.1.2.1.3. Leiomyosarcomas

These arise most commonly from vessels such as the inferior vena cava and pulmonary artery but may also occur in the LA.

5.1.2.2. Primary Cardiac Lymphomas

These account for approximately 27% of malignant PCTs, and diffuse large B-cell lymphoma is the most common type.¹⁵³ They predominate in the 6th decade of life but also occur between the 1st and 9th decades, and are frequently seen in immunocompromised patients. They are located mainly on the right side of the heart and in the pericardium. They involve the superior vena cava and the interatrial septum in 25% and 48% of cases, respectively. They appear as infiltrating or nodular masses. Infiltrating forms are homogeneous and lead to wall thickening and restrictive hemodynamics. Nodular forms intrude into the chambers and may compromise the atrioventricular node, right coronary artery, and pericardium.¹³⁶ More than one chamber is involved in 75% of cases. Depending on the location and dimensions, they may cause inflow obstruction, superior vena cava syndrome, arrhythmias, atrioventricular block, restrictive or constrictive syndromes, pericardial effusion, and embolic phenomena. Both 2D and 3D TEE and the use of contrast perfusion are useful for the characterization of those tumors.¹⁵⁷

5.1.2.3. Primary Malignant Pericardial Mesotheliomas

These account for 8% of malignant PCTs and approximately 50% of primary pericardial tumors.^{153,158} They are more frequent between the 5th and 7th decades of life and show low survival. In many cases, they are associated with exposure to asbestos and radiation.¹⁵⁹ Symptoms are vague and include constrictive pericarditis and pericardial effusion with cardiac tamponade. Myocardial infiltration may occur and lead to conduction abnormalities. TTE has low sensitivity for detection.¹⁵⁸

5.1.3. Metastatic Cardiac Tumors

These are by definition malignant, and their incidence has increased in recent decades, reaching 18.35% in patients with advanced cancer.^{159,160} They predominate between the 6th and 7th decade of life. Cardiac metastases may occur by direct extension of the tumor, hematogenous spread, lymphatic spread, or intracavitary extension from the inferior vena cava or pulmonary veins. With the exception of central nervous system tumors, any malignant tumor may spread to the heart, but carcinomas of the

lung, breast, and esophagus, melanoma, and hematologic neoplasms (leukemia and lymphoma) are responsible for most cases.^{159,161} Malignant melanomas are the most likely tumors to affect the heart. Pericardium, epicardium, myocardium, and endocardium are, in descending order of frequency, the most affected sites. If intracavitary, they are preferably located in the right chambers. Pericardial effusions are frequent and may be asymptomatic. Cardiac involvement should be suspected in all patients with cancer who develop new cardiovascular symptoms.¹⁶² TTE is the initial assessment method for detecting tumor thrombi in the inferior vena cava and cardiac chambers as well as pericardial effusion. Other imaging modalities are required to better characterize the lesions, including their extent and relationship with adjacent structures, as well as to reveal the primary tumor site.¹⁶¹

5.2. Contribution from Cardiac Magnetic Resonance Imaging

Cardiac MRI, mainly because of the property of tissue characterization, has been established as a robust method in the assessment of cardiac masses, especially in differentiating benign from malignant tumors. In addition to tissue characterization, cardiac MRI will provide important information regarding location, dimensions, extent, and signs of compression or obstruction of cardiac structures.¹⁶³

Steady-state free precession MRI sequences are used to assess the morphology and mobility of the mass and its relationship with the myocardium, as well as whether the mass is causing hemodynamic obstruction to the valve structures. Pre-contrast T1- and T2-weighted black-blood sequences assist in defining the relationship with the adjacent anatomy, size, extent, and characterization of the mass. Signal intensity of the mass on MRI depends on T1 and T2 relaxation time. The signal intensity should be evaluated in relation to that of the myocardium, i.e., whether the mass signal is isointense, hypointense, or hyperintense to the myocardial signal.¹⁶⁴

Fat saturation allows for identification of a fat signal in the composition of the mass, as this is hyperintense on T1- and T2-weighted sequences; saturation of the signal suggests a fatty component in the mass. This technique can detect benign structures such as lipomatous infiltration of the interatrial septum, benign tumors such as lipoma, and the presence of fat as a component of a liposarcoma.

Vascularization of the tumor may be assessed using first-pass perfusion imaging for presence or absence of perfusion and whether this is isoperfused, hypoperfused, or hyperperfused in relation to the LV myocardium, while delayed enhancement detects the presence of fibrosis in the mass composition.¹⁶⁵

The cardiac MRI protocol for assessing a cardiac or pericardial mass should be initiated with high-resolution axial slices, followed by cine sequences for location and analysis of cardiac function and hemodynamic repercussions. Then, according to the diagnostic suspicion, slices are made over the mass for proper tissue characterization. T1- and T2-

weighted sequences may be used, as well as fat suppression sequences to assess the lipid component of the suspected mass, first-pass perfusion with gadolinium to assess vascularization, and delayed enhancement sequences to assess fibrosis.

If a thrombus is suspected, delayed enhancement sequences with a long inversion time may also be used to confirm the diagnosis. Cardiac MRI allows for differentiation of thrombus from tumor, as there is no perfusion in the thrombus by the paramagnetic contrast agent. The thrombus appears very dark on delayed enhancement sequences, even with a prolonged inversion time of up to 600 ms, and an adjacent hyperintense area may be observed by the surrounding blood. A slight delayed enhancement may be present in very organized, old thrombi.

5.2.1. Benign Primary Tumors

5.2.1.1. Myxomas

Pre-contrast findings may be explained by their histology: high signal intensity on T2-weighted sequences is related to the myxoid matrix with a high content of water and polysaccharides, while low signal intensity is related to areas of hemorrhage, hemosiderin (degradation of hemoglobin), calcifications, and surface thrombi. Myxomas are isointense on T1-weighted images and hyperintense on T2-weighted images (Figure 14). A slight enhancement on first-pass perfusion imaging was observed in 16% to 66% of cases. Delayed enhancement has a variable and heterogeneous pattern, with a more diffuse distribution (> 50% of the tumor – more frequent) and a less intense pattern (< 50% of the tumor).¹⁶⁶ From 10% to 20% of myxomas have calcifications and some may have thrombi on their surface.

5.2.1.2. Lipomas

These arise from the subendocardial layer in 50% of cases and from the mesocardial or epicardial layers in the other 50%. They may determine hemodynamic changes, depending on their size. They show a homogeneous signal similar to that of fatty tissue: hyperintense on T1-weighted images and with signal dropout on fat saturation sequences and isointense or hyperintense on T2-weighted images.¹⁶⁷ There is no first-pass perfusion or delayed enhancement on contrasted sequences¹⁶⁸ (Figure 15).

5.2.1.3. Papillary Fibroelastomas

On cine imaging, they present as a hypointense and extremely mobile mass, without necessarily causing a functional impact on the valve. Assessing tissue characteristics of those tumors is difficult because of their small size and great mobility, but intermediate signal intensity on T1- and high signal intensity on T2-weighted images can be observed, with no first-pass perfusion or high signal intensity on delayed enhancement images¹⁶⁷ (Figure 16).

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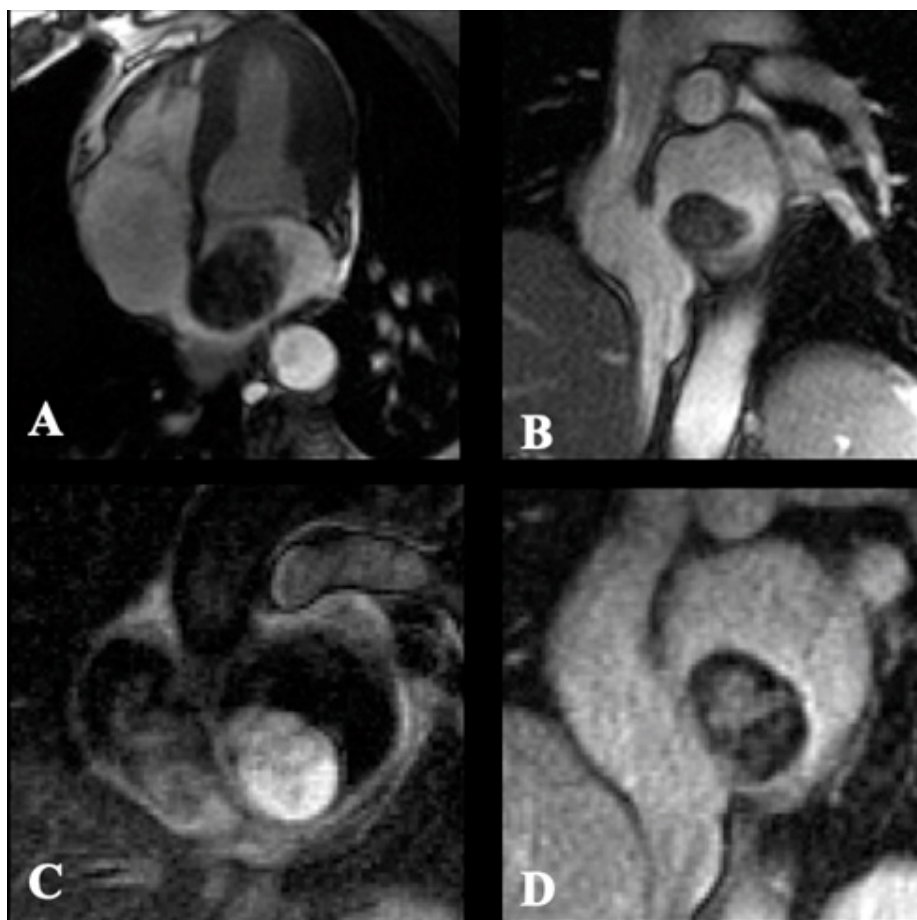


Figure 14 – Myxoma in the left atrium.



Figure 15 – Lipoma in the right atrium. A. Four-chamber cine image of a large lipoma in the right atrium. B. T1-weighted image showing that the lipoma is hyperintense. C. No local delayed enhancement.

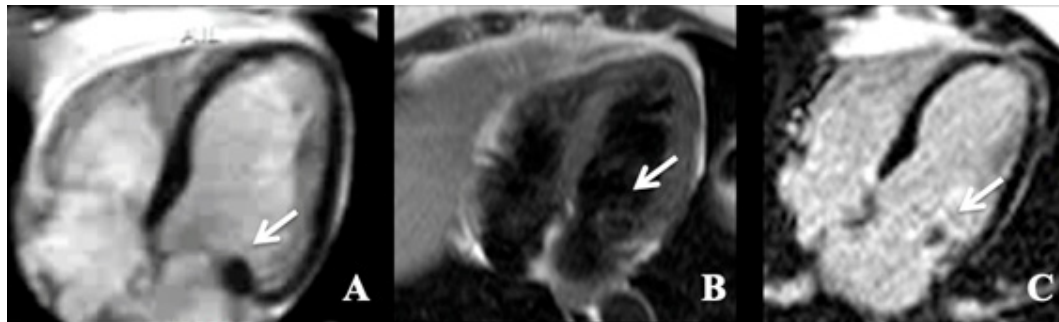


Figure 16 – Papillary fibroelastoma in the mitral valve. A. Four-chamber cine image of a hypointense mass. B. T1-weighted image showing intermediate signal intensity. C. Early late gadolinium enhancement sequence showing a slight local enhancement.

5.2.1.4. Rhabdomyomas

These are slightly hyperintense on T1-weighted images and hyperintense on T2-weighted images. They show minimal or even no enhancement with gadolinium (Figure 17).

5.2.1.5. Fibromas

These are usually isointense or hypointense on T1-weighted images and homogeneously hypointense on T2-weighted images. In general, they do not appear on first-pass perfusion imaging because of their low vascularity. On delayed enhancement imaging, fibromas are intensely and homogeneously enhanced, although sometimes the lesions may have a central component of low signal intensity that may be associated with local calcification¹⁶⁹ (Figure 18).

5.2.1.6. Hemangiomas

These are heterogeneously isointense or hyperintense on T1-weighted images and usually hyperintense on T2-weighted images, and heterogeneous areas of low signal intensity may also occur. The delayed enhancement pattern is typically heterogeneous and hyperintense with a marked first-pass perfusion.^{168,169}

5.2.2. Malignant Tumors

Malignant tumors tend to be larger, are more frequently perfused with gadolinium, and have a higher prevalence of delayed enhancement.¹⁷⁰

5.2.2.1. Sarcomas

Most sarcomas have characteristics suggestive of malignancy, such as a heterogeneous signal due to necrosis and internal hemorrhage, nodular or irregular shape, ill-defined borders, infiltration of the myocardium and adjacent structures, extension to the pericardium, and associated pericardial effusion. Angiosarcoma accounts for 40% of cardiac sarcomas and is mostly located in the RA with infiltration of the atrial wall and the pericardium associated with pericardial

effusion (Figure 19). On cardiac MRI, it is shown as a large heterogeneous lobular mass that is isointense or hyperintense on T1-weighted images, hyperintense on T2-weighted images, perfused with gadolinium on first-pass images, and heterogeneously hyperintense on delayed enhancement images (Figure 20).^{147,169}

5.2.2.2. Lymphomas

These are isointense or hypointense on T1-weighted images, isointense or hyperintense on T2-weighted images, and heterogeneously enhanced on delayed enhancement images.

5.3. Contribution from Nuclear Medicine

5.3.1. ¹⁸F-FDG PET-CT

Scanning with ¹⁸F-FDG PET-CT remains seldom used in cardiac tumors, especially malignant PCTs. In secondary malignant cardiac tumors (metastases), which are most frequent, ¹⁸F-FDG PET-CT is an established technique.¹⁷¹

A case series conducted by Rahbar et al.¹⁷² evaluated 24 consecutive patients with cardiac tumors using ¹⁸F-FDG PET-CT scanning before treatment.¹⁷² The patients were divided according to histological subtype of the tumors, obtained by surgical resection or biopsy, into: benign (n = 7), primary malignant (n = 8), or secondary malignant (n = 9). Tumor ¹⁸F-FDG uptake was observed between groups. Then, to assess sensitivity and specificity of the method in differentiating benign from malignant tumors, they were divided into malignant (n = 17) or benign (n = 7) only. ¹⁸F-FDG uptake was quantified according to the maximum standardized uptake value (SUV_{max}) of 3D volumes covering the tumor mass. In case of low tumor ¹⁸F-FDG uptake, CT images were used to identify and obtain tumor volumes. Additionally, because of physiological myocardial ¹⁸F-FDG uptake, uptake in the normal myocardium and blood pool were measured and compared with SUV_{max} of the tumors. They found that ¹⁸F-FDG uptake was low in the blood pool and normal myocardium, and significantly high in the primary malignant tumors compared to the

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Figure 17 – Rhabdomyoma in the left ventricle: A. Short-axis cine image of an intramural mass in the interventricular septum. B. T2-weighted image showing high signal intensity. C. Delayed enhancement sequence showing a slight local enhancement.

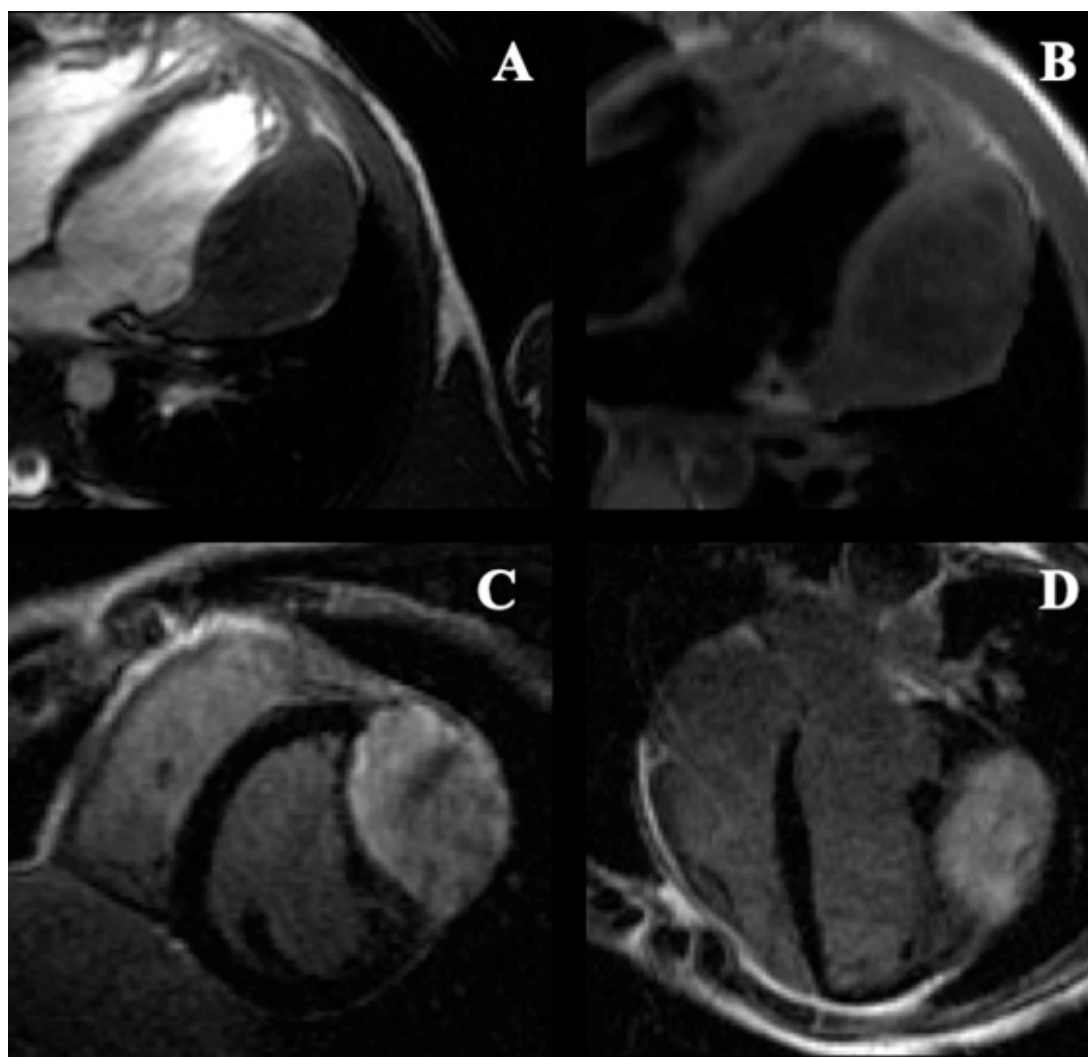


Figure 18 – Intramural fibroma. A. Four-chamber cine image of an intramural tumor on the lateral wall. B. T2-weighted image of a hypointense mass in relation to the myocardium. C and D. Short- and long-axis delayed enhancement image showing homogeneously high signal intensity of the tumor compatible with fibrous tissue.

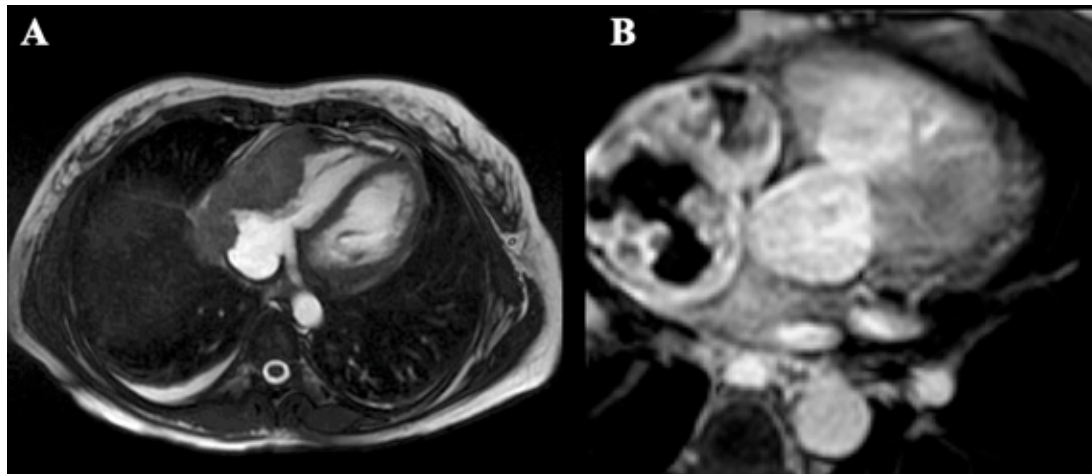


Figure 19 – Angiosarcoma in the right atrium. A. Four-chamber cine image of a sarcoma arising from the posterior wall of the right atrium and invading the walls, the basal portion of the right ventricle, and the pericardium. B. Delayed enhancement image of a heterogeneously hyperintense mass on upper axial plane.

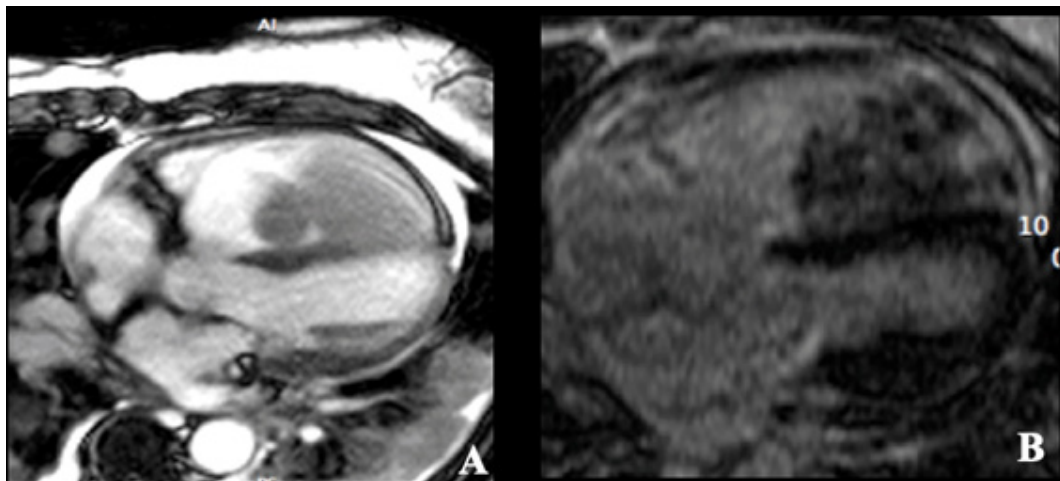


Figure 20 – Rhabdomyosarcoma in the right ventricle. A. Four-chamber cine image of a large multilobulated intracavitary mass in the right ventricle. B. Delayed enhancement image showing a heterogeneously hyperintense mass.

benign ones. Secondary malignant tumors showed an uptake comparable to that of primary malignant tumors but with a considerably higher SUV_{max} variation. The mean SUV_{max} was 2.8 ± 0.6 in the benign cardiac tumor group. Such tumors usually show no positive contrast to the normal myocardium and are only seen on morphologic CT images. In contrast, SUV_{max} of primary malignant tumors is 2.5 times greater than that of benign tumors. Among metastatic cardiac tumors, SUV_{max} was 10.8 ± 4.9 with a significant variation in ^{18}F -FDG uptake from 3.4 to 16.7. In primary malignant tumors, ^{18}F -FDG uptake was greater than that of benign tumors and similar to that of secondary malignant tumors.¹⁷²

5.3.1.1. Cutoff SUV_{max} value for ^{18}F -FDG to better differentiate benign from malignant cardiac tumors

Different cutoff SUV_{max} values have been suggested for determination of malignancy using ^{18}F -FDG PET-CT scanning. Rahbar et al.¹⁷² demonstrated that a value of 3.5 reached a sensitivity of 100%, a specificity of 86%, a positive predictive value of 94%, and a negative predictive value of 100%.¹⁷² When they increased this value to 4.6, they found a specificity of 100%, a sensitivity of 94%, and a positive predictive value of 100% for malignancy. The main limitations of that study were the retrospective nature, the lack of a diagnostic pattern for cardiac tumors, and the heterogeneity of the results. Also, several myxomas were

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not included in the analysis because they were diagnosed on echocardiogram and cardiac MRI.

6. Special Situations

6.1. Carcinoid Heart Disease

Neuroendocrine tumors are rare neoplasms (2.5 to 5 cases per 100,000 population) that may occur anywhere but often involve the gastrointestinal tract (carcinoid tumors).¹⁷³ In about 30% to 40% of cases, mostly in the small intestine and proximal colon, patients experience vasomotor changes (hypotension, hypertension, flushing), diarrhea, and bronchospasm. This is called carcinoid syndrome, and it is usually associated with hepatic metastasis.¹⁷⁴ The presence of biomarkers such as N-terminal pro-B-type natriuretic peptide (NT-proBNP), chromogranin A (CgA), and 5-hydroxyindoleacetic acid (5-HIAA) is useful both in diagnosis and prognosis of carcinoid disease.¹⁷⁵

Carcinoid heart disease (CHD), manifested by plaque formation, thickening, and endocardial fibrosis, is probably related to chronic exposure to 5-HIAA and preferably affects the right chambers and the tricuspid and pulmonary valves. Impairment of left chambers (15% of cases) and mitral and aortic valves is seen in the presence of a right-to-left shunt

(e.g., patent foramen ovale) or a bronchial carcinoid tumor.¹⁷⁶ Early diagnosis and monitoring of disease progression have a dramatic impact on prognosis and long-term survival (mean survival of 1.6 years vs. 4.6 years in patients without CHD), as early surgical intervention is essential for a successful management.

Echocardiography is considered the gold standard for the diagnosis and monitoring of CHD.¹⁷³ The assessment of right heart chambers (atrium and ventricle), RV function, thickening, leaflet mobility, and presence of valve regurgitation or stenosis (individually analyzed) should be performed on initial clinical suspicion, in case of a new bruit, new symptoms, or every 3 to 6 months according to CHD severity (Figure 21).

Tricuspid valve involvement leading to regurgitation is the most frequent alteration, followed by pulmonary regurgitation, tricuspid stenosis and, finally, pulmonary stenosis. In the tricuspid valve, there is main involvement of the anterior and septal leaflets, and the posterior leaflet is relatively preserved. RV dilation and dysfunction are consequences of the severity of the valve lesions. Cardiac metastases (4% of cases) may be identified on echocardiography but are more visible on MRI.^{173,176}

Several echocardiographic scores have been proposed for CHD assessment. Among the simplest ones, Westberg et al.¹⁷⁷ (Table 5) evaluates only tricuspid valve regurgitation

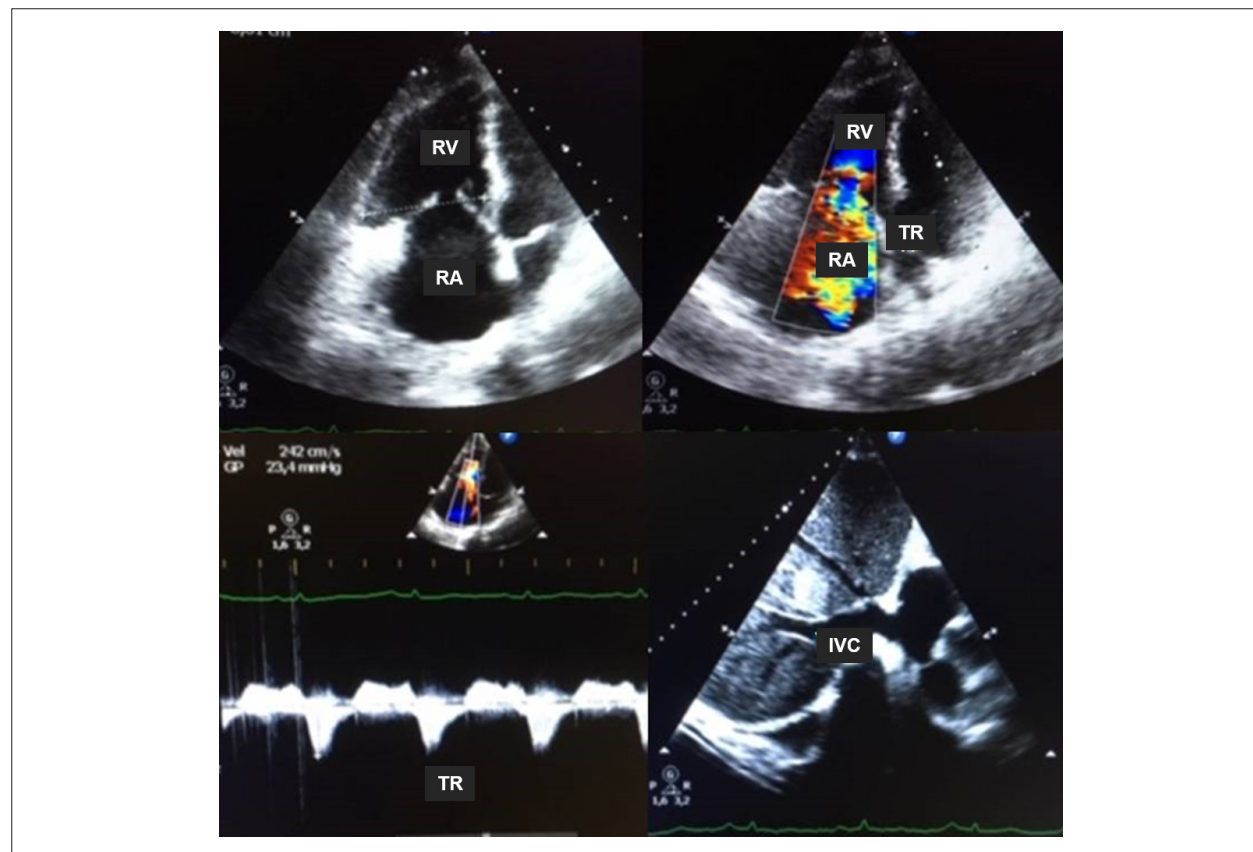


Figure 21 – Patient with a carcinoid tumor, liver metastasis, and clinical status of right heart failure. RV: right ventricle, RA: right atrium, TR: tricuspid regurgitation, IVC: inferior vena cava.

Table 5 – Westberg score¹⁷¹

Characteristics	Severity and scoring				
	Normal	Mild	Moderate	Severe	Severe with valve retraction
Valve thickening	0	1	2	3	4
Regurgitation	Normal 0	Mild 1	Moderate 2	Significant 3	Extreme 4

and anatomy. A score > 1 is considered pathological (87% accuracy). A score > 4 has a 3-year survival rate < 45% vs. 75% for a score of 0.¹⁷⁷

More complex scores provide a greater amount of information and are useful for surgical monitoring and planning. In Bhattacharyya et al.¹⁷³ (Table 6), a score > 8 has a diagnostic accuracy of 96% for CHD, and a 5-point increase in the score is an independent predictor of CHD progression (RR 2.95) and mortality (RR 2.66), according to Dobson et al.^{176,178}

Surgical cardiac intervention is indicated in case of RV dilation and dysfunction and signs of HF refractory to drug treatment. Closure of the patent foramen ovale, aiming to reduce right-to-left shunt, and removal of metastases are recommended during the approach.¹⁷⁵

6.2. Cardiac Amyloidosis

6.2.1. Introduction

Amyloidosis is a multisystemic disease arising from the deposition of compound proteinaceous material in the extracellular space that is difficult to diagnose and, once cardiac involvement is proven, has a poor prognosis. According to the type of precursor protein, it can be classified as light-chain (AL) amyloidosis (when the deposits originate from light-chain proteins) and transthyretin (ATTR) amyloidosis (when the protein carries thyroxine and retinol).¹⁷⁹

6.2.2. Clinical Types and Cardiac Involvement

Besides the heart, AL amyloidosis may affect several organs such as the kidneys, the gastrointestinal tract, and the autonomic nervous system. It is caused by the deposition of proteins deriving from immunoglobulin light chains produced by plasma cells in cases of plasma dyscrasia, such as in multiple myeloma. Approximately 10% of patients with multiple myeloma may develop AL amyloidosis, and more than half of them may have cardiac amyloidosis. Cardiac involvement is second to kidney involvement in AL amyloidosis.^{180,181}

The pathological mechanism of ATTR amyloidosis is the deposition of transthyretin derivatives produced by the liver. It is further divided into two subtypes: a) wild-type ATTR (ATTRwt), with predominant involvement of the heart and often causing carpal tunnel syndrome, biceps tendon rupture, and spinal stenosis; and b) mutant ATTR (ATTRm), associated with specific substitutions of transthyretin-coding genes that may affect, besides the heart, the autonomic and peripheral nervous systems.¹⁸²

6.2.3. Contribution from Echocardiography

TTE is the most widely used diagnostic option when cardiac amyloidosis is suspected, being also used to screen for cases in family members. It is highly available in medical services of variable complexity, has a relatively low cost, and allows for serial repetition with good reproducibility and consistent findings. Cardiac involvement has the poorest prognosis in this group of patients.

6.2.3.1. Increased Myocardial Thickness

The myocardium has a bright or speckled granular appearance, which is more visible on conventional imaging without harmonics. The increase in myocardial thickness is often concentric and symmetrical, unlike that of hypertrophic cardiomyopathy, which tends to show greater asymmetry in distribution (Figure 22). The presence of increased myocardial thickness and low-voltage waves on electrocardiogram is a finding that leads to suspected cardiac amyloidosis.¹⁸³ The term "increased myocardial thickness" must be distinguished from secondary myocardial hypertrophy: there is myocellular hypertrophy in the latter, while in the former it is the extracellular space that is increased by the deposition of amyloid protein material.¹⁸⁴ The increase in myocardial thickness is diffuse and may include all LV walls, RV free wall, interatrial septum, and valves with or without associated regurgitation. Myocardial thickness ≥ 12 mm may be used as a cutoff value for suspected cardiac amyloidosis.¹⁸⁵ The clinical value and prognosis of increased myocardial thickness are already known: the more exuberant, the greater the occurrence of congestive HF and the poorer the survival.

6.2.3.2. Left Atrium

There may also be changes in the LA, and the increase in LA volume may be due not only to high degrees of diastolic dysfunction but also to the deposition of amyloid fibrils.

Changes in atrial myocardial deformation (strain and strain rate) and in atrial systolic function parameters are frequently observed in patients with few echocardiographic characteristics related to cardiac amyloidosis and in those with congestive HF symptoms, which are associated with a poor prognosis.¹⁸⁶

6.2.3.3. Diastolic Function

In more advanced stages, the assessment of diastolic function usually reveals increased E/e' ratio compatible with increased LV filling pressures. However, diastolic function parameters are abnormal even in the early

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Table 6 – Bhattacharyya score¹⁶⁷

Characteristics	Severity and scoring			
	< 3 mm 0	≥ 3 and < 4 mm 1	≥ 4 and < 5 mm 2	≥ 5 mm 3
Valve thickening				
Valve mobility	Normal 0	Mild 1	Moderate 2	Severe/fixed 3
Valve morphology	Normal 0	Rectified 1	Slight retraction 2	Moderate/severe retraction 3
Valve stenosis	Normal 0	Mild 1	Moderate 2	Significant 3
Valve regurgitation	Normal 0	Mild 1	Moderate 2	Significant 3
Right ventricle diameter	Normal 0	Slight increase 1	Moderate increase 2	Significant increase 3
Right ventricle function	Normal 0	Slight reduction 1	Moderate reduction 2	Significant reduction 3

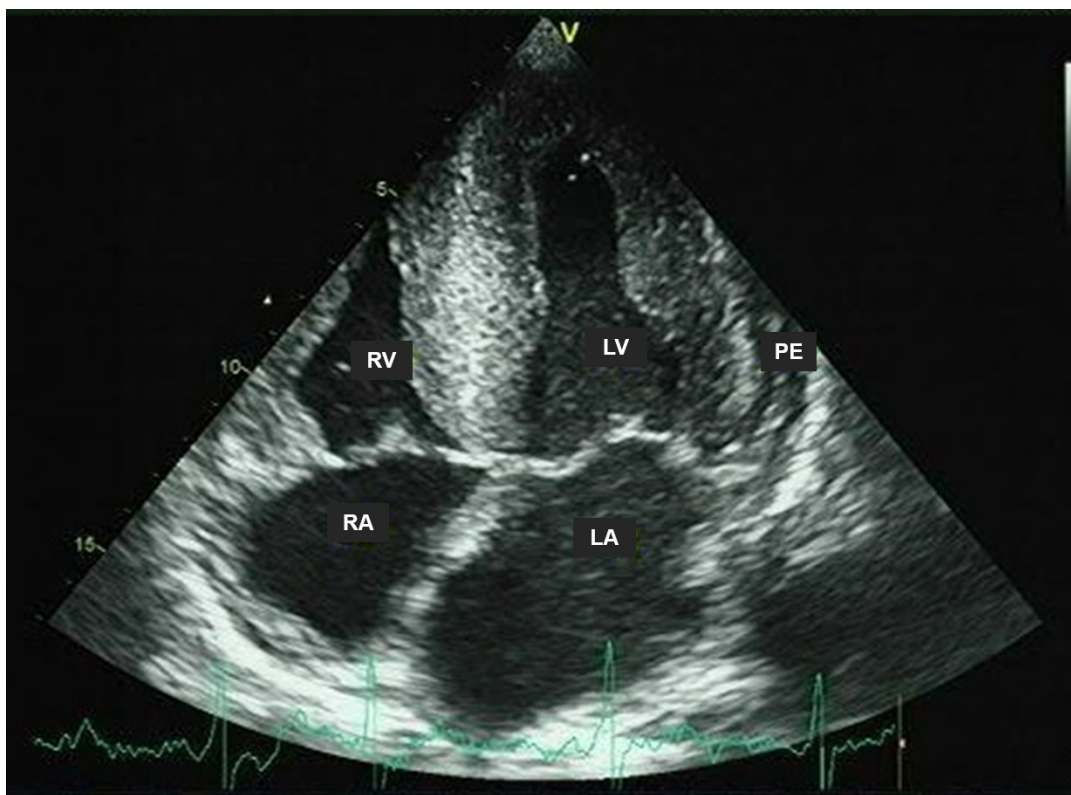


Figure 22 – Patient with left ventricular hypertrophy with no determined cause. Echocardiogram showing shiny or granular scintillating aspect of the myocardium suggestive of cardiac amyloidosis. PE: pericardial effusion; LA: left atrium; LV: left ventricle; RV: right ventricle; RA: right atrium.

stages of cardiac amyloidosis. The presence of diastolic dysfunction is associated with poor clinical outcomes, as already demonstrated, and suggests greater risk of thromboembolism.¹⁸⁷⁻¹⁸⁹

6.3.3.4. Left Ventricular Systolic Function

LVEF may still be within normal limits, and this feature allows for cardiac amyloidosis to be included as a cause of HF with preserved ejection fraction. Deteriorated systolic

function occurs in later stages and is associated with poor clinical outcomes and prognosis.^{187,189}

Regarding myocardial deformation measurements, cardiac amyloidosis exhibits a reduction in myocardial GLS mainly in the basal and middle segments of the LV with preserved values in the apical segment (i.e., apical sparing).^{188,190} It is useful to calculate the ratio of the mean apical GLS values by the sum of mean GLS values in the basal and middle LV segments. A ratio > 1 means a high specificity for diagnosis of cardiac amyloidosis.¹⁹⁰ When considering the relationship between LVEF measurements and myocardial strain values (referred to as ejection fraction-to-strain ratio [EFSR]), there is an inversion of the ratio with lower values of myocardial deformation and preserved LVEF, regardless of clear congestive HF symptoms. An EFSR ≥ 4 is useful in differentiating cardiac amyloidosis from hypertrophic cardiomyopathy, with 89.7% sensitivity and 91.7% specificity.^{187,188}

In cardiac amyloidosis, isolated myocardial GLS values $> -15\%$ have been associated with greater severity and increased mortality.¹⁹¹ In another study, a strain value $> -17\%$ managed to separate groups of patients with unfavorable clinical response after autologous bone marrow transplantation (BMT). An apical sparing index ≥ 1.19 was associated with higher mortality and need for heart transplantation at 5 years of follow-up. This index also showed a predictive value in the survival curves and the need for heart transplantation when associated with a lower LVEF value.¹⁹²

Liu et al.¹⁹³ analyzed the value of the diastolic wave peak of the strain rate curve alone (rapid diastolic filling phase) in 41 patients with cardiac amyloidosis, demonstrating that the global value of the diastolic strain rate (global $LSR_{dias} > -0.85 S^{-1}$) was predictive of a 4-fold increase in mortality in patients with cardiac amyloidosis with preserved LVEF (LVEF $> 50\%$).¹⁹³

Strain measurements are highly sensitive and exhibit good specificity in cases of cardiac amyloidosis; however, it should be noted that conventional echocardiographic measurements of systolic function are still important and demonstrate excellent prognostic correlation in such cases. Thus, stroke volume index (SVi) and the measure that associates stroke volume with total myocardial mass volume (referred to as myocardial contraction fraction [MCF]) showed a good prognostic value in patients with cardiac amyloidosis, regardless of type and comparable to that of strain measurements. Therefore, in this group of patients, SVi $< 33 mL/min$ and MCF $< 34\%$ with cardiac index $< 2.4 L/min/m^2$ were the best predictors of overall survival with an accuracy comparable to that of strain measurements¹⁹⁴ (Figure 23).

6.2.3.5. Other Findings

Despite not having a notable incidence in cases of cardiac amyloidosis, the presence of intracardiac thrombi has been reported and, of note, is not necessarily associated with the presence of atrial fibrillation.¹⁹⁵ Some authors have

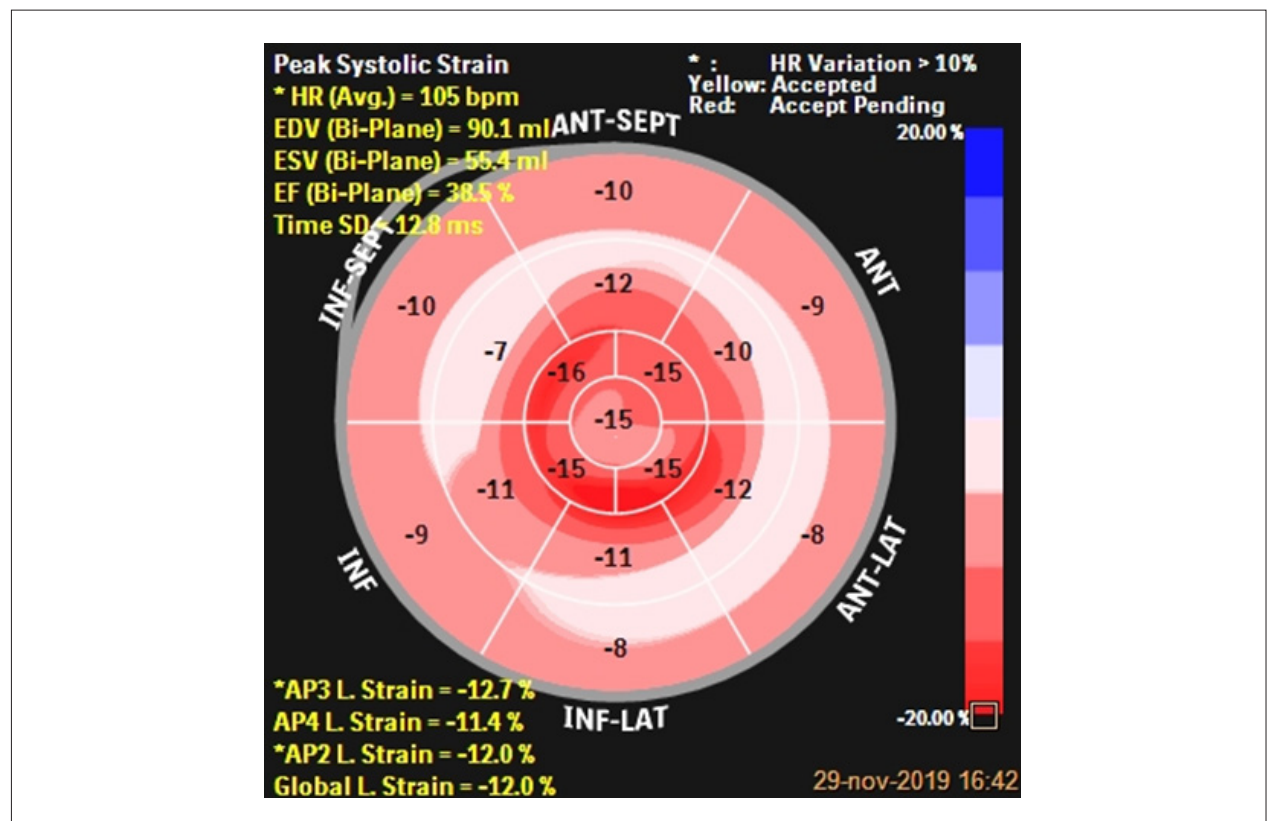


Figure 23 – Global longitudinal strain of the left ventricle in a patient with transthyretin amyloidosis, demonstrating a peculiar pattern that preserves the apex and majorly affects the middle and basal segments.

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demonstrated that AL amyloidosis and diastolic dysfunction are independent risk factors for intracardiac thrombi.¹⁹⁶ The search for thrombi should always be considered in patients who have criteria for severe cardiac amyloidosis (e.g., high degrees of increased myocardial thickness, decreased LVEF, and advanced stages of diastolic dysfunction). Several mechanisms have already been proposed to explain the occurrence of thrombi in addition to the presence of atrial fibrillation, such as: amyloid deposits in the subendocardial region that produce damage and greater parietal stiffness; hemodynamic stasis as a consequence of important diastolic dysfunction, usually of the restrictive type; and plasma hypercoagulability as a systemic mechanism resulting from various conditions.

Cardiac tamponade due to major pericardial effusion is rare, and diagnosis is predominantly clinical, as the high pressures in the right chambers decrease the chances of classic echocardiographic collapse. Less intense pericardial effusion is more common. Heart valves may also be infiltrated but rarely exhibit severe valve regurgitation.¹⁸⁷

6.2.3.6. Diagnostic Approach

In several clinical situations, the diagnosis of cardiac amyloidosis is initiated with an echocardiographic examination but very often occurs in one out of two contexts of cardiac evaluation.

The first situation concerns the need for cardiac evaluation in patients with multiple myeloma. In such cases, confirmation of cardiac involvement is imperative, as the survival rate in AL amyloidosis may be extremely unfavorable. Even if the classic echocardiographic findings are absent in the first examination, it is recommended that the examination is repeated in a follow-up visit.

In the second situation, patients undergo cardiac evaluation because they have either clinical manifestations of HF with preserved ejection fraction or “hypertrophy” on echocardiogram (often associated with low-voltage complexes on electrocardiogram).

In such cases, in addition to the echocardiographic findings described above, investigation should continue with other imaging tests (MRI and NM imaging) and laboratory tests such as protein electrophoresis and light-chain protein testing.

In centers where myocardial deformation analysis is available, the presence of apical sparing is typical but not exclusive. Other causes of LV hypertrophy may exhibit the same pattern, such as hypertrophy secondary to hypertension and aortic stenosis.

6.2.4. Contribution from Cardiac Magnetic Resonance Imaging

Cardiac MRI allows for diagnosis of cardiac amyloidosis by morphological and functional changes on cine sequences, as is the case with TTE, and more accurately through delayed enhancement and T1 map sequences.

A delayed enhancement sequence usually detects the deposition of amyloid protein in the myocardial interstitial space through the presence of hyperenhancement (white

color) against the usually black muscle on the images.¹⁹⁷ Syed et al.¹⁹⁸ analyzed cardiac MRIs of 120 patients with amyloidosis,¹⁹⁸ of which 35 had confirmed cardiac involvement by histology. The other 85 patients were divided into those with or without echocardiographic evidence of cardiac amyloidosis. In the 35 patients with histological diagnosis, 97% showed delayed enhancement and 91% had increased wall thickness on echocardiography. Transmural or subendocardial delayed enhancement was the most common pattern (83%), associated with greater interstitial amyloid deposition; focal delayed enhancement (6%) and difficulty in canceling the myocardial signal (8%) were other patterns associated with cardiac involvement. In the 85 patients without histological diagnosis, delayed enhancement was present in 86% of those with echocardiographic abnormalities and in 47% of those without evidence of cardiac amyloidosis on TTE. The presence and pattern of delayed enhancement were associated with the New York Heart Association (NYHA) functional class, low voltage on electrocardiogram, LV mass index, RV wall thickness, and serum troponin and type B natriuretic peptide (BNP) values.¹⁹⁸

Austin et al.¹⁹⁹ evaluated 47 patients with suspected cardiac amyloidosis who underwent cardiac MRI, electrocardiogram, TTE, and biopsy.¹⁹⁹ Compared to biopsy, delayed enhancement had a sensitivity of 88%, a specificity of 90%, a positive predictive value of 88%, and a negative predictive value of 90%, thus being the only parameter with significant diagnostic accuracy in multivariate analysis. One year after biopsy, 19% of patients died, and delayed enhancement was the only significant predictor of mortality in this period, showing the prognostic role of this parameter in amyloidosis.

Regarding the differentiation of types of cardiac amyloidosis, cardiac MRI is useful in predicting AL and ATTR amyloidosis. Dungu et al.²⁰⁰ showed a greater increase in myocardial thickness (228 g vs. 167 g) and a greater extent of delayed enhancement in patients with ATTR amyloidosis, although mortality in patients with AL amyloidosis was higher. In that study, 90% of patients with ATTR amyloidosis had some segment with transmural delayed enhancement compared to 37% of patients with AL amyloidosis. In addition, 100% of patients had delayed RV enhancement in ATTR amyloidosis compared to 72% in AL amyloidosis. The authors created a score called Query Amyloid Late Enhancement (QALE) with values ranging from 0 to 18. Values ≥ 13 can predict ATTR instead of AL amyloidosis, with a sensitivity of 82% and a specificity of 76%.

T1 mapping sequence, the most recent MRI technique, is useful in the diagnosis and prognosis of patients with cardiac amyloidosis. It may also be used to monitor the treatment of new therapeutic agents in this disease. Pre-contrast T1 values are increased in patients with cardiac amyloidosis; this is a diagnostic option for patients without delayed enhancement or those who do not undergo the delayed enhancement sequence because of contraindication to gadolinium injection. In addition, the gadolinium injection makes it possible to calculate myocardial ECV, which is expanded in cardiac amyloidosis by the deposition of amyloid fibrils in the interstitium, showing a good correlation with biopsy, with proven prognostic value.^{201,202}

6.2.5. Contribution from Nuclear Medicine

NM has gained new relevance in the diagnosis of cardiac amyloidosis, with studies showing that radiotracers with affinity for bone, such as 3,3-diphosphono-1,2-propanedicarboxylic acid (DPD) and pyrophosphate, both labeled with technetium-99m [^{99m}Tc], have very high sensitivity for the detection of ATTR. Scintigraphy with those tracers allows for noninvasive differentiation of amyloid protein subtypes based on the concentration levels of the tracer in the cardiac area. This differentiation has prognostic and therapeutic implications.²⁰³ Gilmore et al.²⁰⁴ have conducted the most important study on the subject to date. They evaluated the results of scintigraphy with bone-affine radiotracers in 1,217 patients with suspected cardiac amyloidosis referred for evaluation in specialty centers, and obtained sensitivity values of up to 99% when AL amyloidosis had already been ruled out by biochemical testing.²⁰⁴ The examination technique consists of injecting the tracer into a peripheral vein and then acquiring planar images of the chest

in the anterior projection 1 hour post radiopharmaceutical administration (Figure 24). This allows for a quantitative analysis to be performed in which two mirrored regions of interest (ROIs) are drawn, one over the cardiac area in the left hemithorax and another in the right hemithorax. A ratio between left and right hemithorax counts (representing the amount of tracer present in each area) > 1.5 has a high diagnostic sensitivity (95% sensitivity and 79% specificity),²⁰³ as well as prognostic value; ratios > 1.6 are associated with poor prognosis on 5-year follow-up. After 3 hours, whole-body images are acquired in the anterior, posterior, oblique, and left lateral projections. The level of concentration of the tracer in the cardiac area is compared to that of the ribcage and graded on a scale of 0 to 3, in which grade 0 denotes no cardiac concentration; grade 1, slight cardiac concentration, lower than that of the ribcage; grade 2, equal to that of the ribcage; and grade 3, greater than that of the ribcage. Grades 2 and 3 are strongly associated with ATTR amyloidosis ($> 99\%$ sensitivity and 86% specificity) (Figure 25) if AL disease

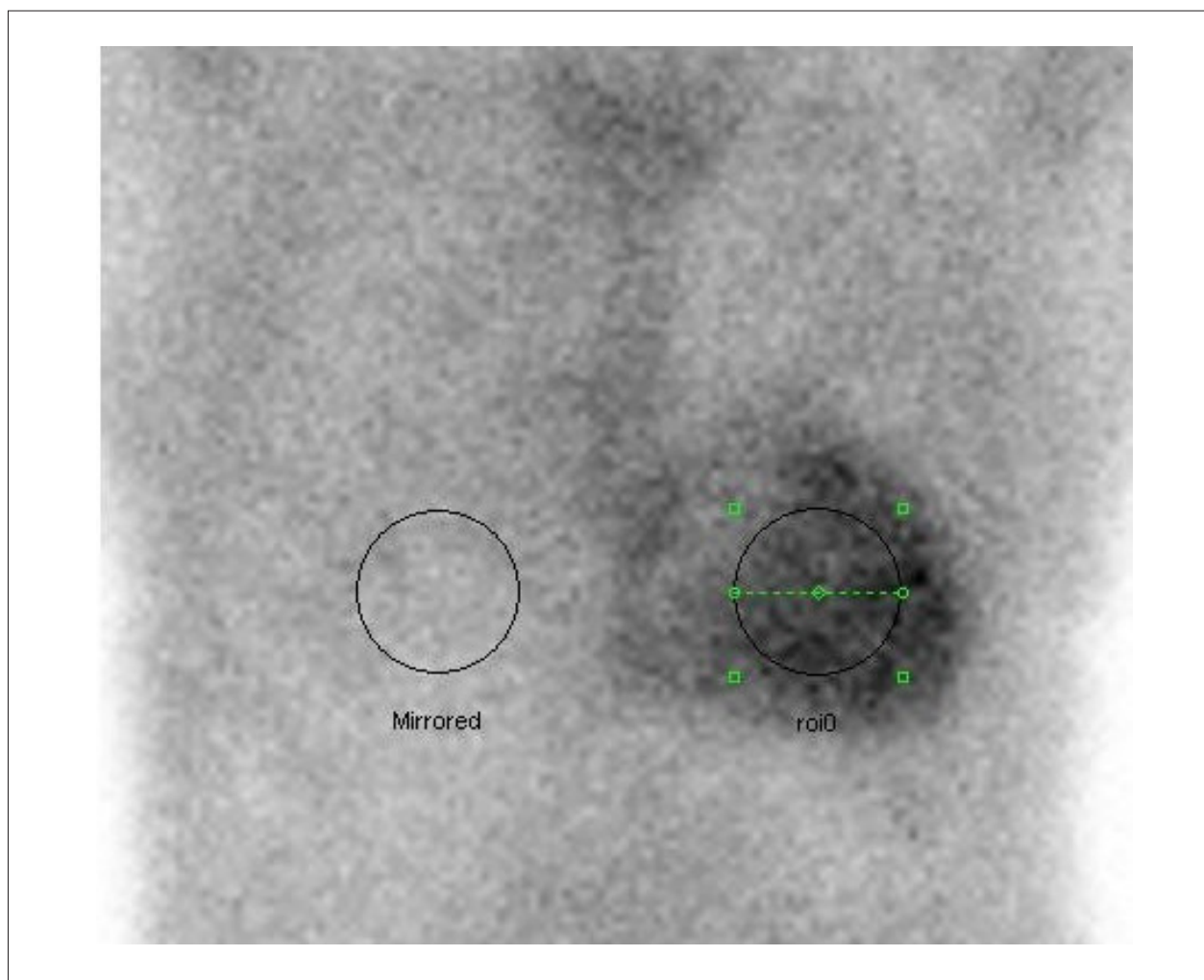


Figure 24 – Anterior image of the chest 1 hour after intravenous administration of technetium-99m-labeled pyrophosphate. Each of the circles represents a region of interest (ROI) and allows for quantification of tracer concentration. The ratio between left and right hemithorax counts, in this case, was 1.75, therefore positive for transthyretin amyloidosis.

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Figure 25 – Whole-body scintigraphy and planar chest images with technetium-99m-labeled pyrophosphate show abnormal radiopharmaceutical accumulation projecting from the heart (arrows) of a patient with advanced heart failure with preserved ejection fraction. Serum light-chain measurements were negative, and abdominal fat biopsy was positive for amyloidosis. The definitive diagnosis was transthyretin amyloidosis.

has already been ruled out. Grades 0 and 1 may be related to AL amyloidosis (Figure 26) or early-stage familial ATTR amyloidosis. Three-hour imaging has greater diagnostic specificity for ATTR amyloidosis (58% sensitivity and 100% specificity).^{205,206} Three-hour single-photon emission computed tomography (SPECT) of the chest has been frequently used because it improves the ability to distinguish the presence of activity in the LV (blood pool) and assess the interventricular septum, which is the usual site of myocardial biopsy if this procedure is necessary. This additional scan also allows for a more accurate quantitative comparison of the myocardial concentration of radiotracer to that of the ribcage. Figure 27 shows RV involvement by familial ATTR amyloidosis, best evaluated on SPECT images. Technetium-99m-labeled methylene diphosphonate (^{99m}Tc MDP) is the most widely available bone-affine radiotracer in Brazil, but its use for assessment of cardiac amyloidosis is discouraged. A study compared ^{99m}Tc MDP and DPD in a group of patients with familial amyloidosis and found that MDP performed suboptimally, with occasional false-negative findings.²⁰⁷

Figure 28 shows an algorithm for NM diagnosis of suspected cases of cardiac amyloidosis.

6.3. Takotsubo Syndrome

Takotsubo syndrome (TTS) is characterized by acute and reversible LV dysfunction with a behavior similar to that of acute coronary syndrome, usually with abrupt onset of precordial pain and dyspnea. It is a stress-induced cardiac syndrome without any evidence of obstructive CAD that usually resolves spontaneously within days or weeks.

In recent years, there has been a growing interest in studying the relationship between cancer and TTS. This happened especially after some published studies showed a strong association between the two conditions.²⁰⁸

The prevalence of neoplasms seems to be higher in patients with TTS when compared to individuals of the same age and sex, both at the time of diagnosis and at follow-up. While the diagnosis of TTS is around 1% to 2% in the general population, it reaches 10% in individuals with malignancies.²⁰⁹

In most cases, TTS involves apical and middle LV segments, which are akinetic or dyskinetic (apical ballooning pattern), as opposed to basal segments, which are generally hyperkinetic. Some forms with a variant pattern have been described such as the midventricular and inverted variants. The midventricular variant is characterized by akinesia of the midventricular

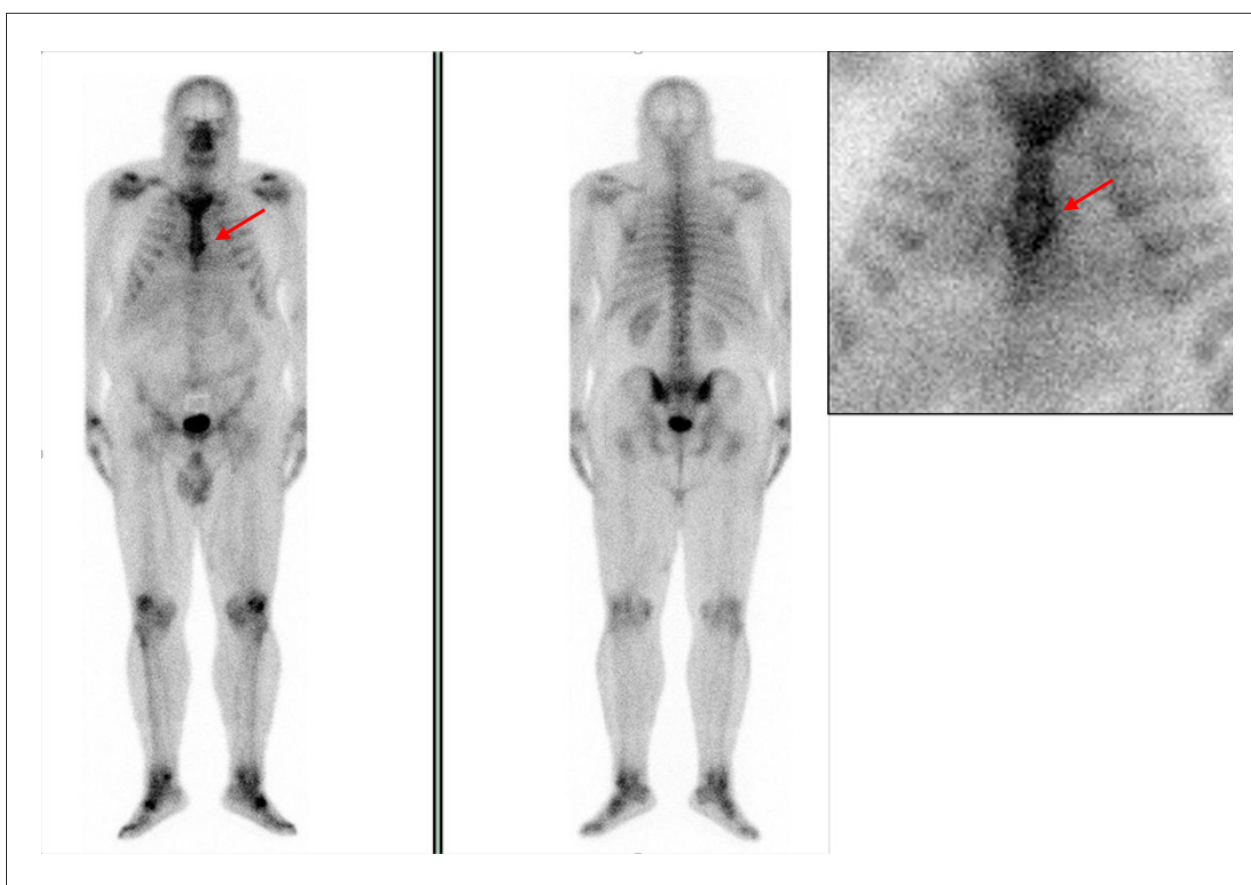


Figure 26 – Whole-body scintigraphy and planar chest images with technetium-99m-labeled pyrophosphate showing light-intensity accumulation (grade 1) projecting from the heart (arrow) of a patient with subsequent confirmation of light-chain amyloidosis due to a monoclonal spike in serum and urine electrophoresis, increased serum free light-chain antibodies, and bone marrow aspirate showing plasma cell infiltrate < 10%. Final confirmation was performed by abdominal fat biopsy, which was positive for amyloidosis.

segments, with hypokinesia or normal contraction of the apical segments and hypercontractility of the base. The inverted variant has two different forms: the first is characterized by apical sparing, presenting with hypokinesia of the remaining walls, and the second by hypokinesia limited to the basal segments.

Speckle tracking echocardiography allows for the assessment of multidirectional LV deformation. In typical cases (apical ballooning pattern), there is a compromise of apical and midventricular longitudinal deformation, with a base-to-apex strain gradient. In this phase, all components of the LV torsion mechanics involving the systolic and diastolic phases are compromised. Given its greater sensitivity in detecting subtle abnormalities compared to that of more traditional parameters, such as LVEF and wall motility index, speckle tracking echocardiography is useful in the diagnosis of TTS.²¹⁰

Three-dimensional echocardiography enabled a more accurate demonstration of LV volumes and LVEF compared to 2D echocardiography and angiography. However, further studies using this technology during the course of TTS are still required to establish its role in clinical practice.

The most prevalent tumors among patients with TTS are colorectal, breast, and bronchial malignancies and

melanoma.²⁰⁸ Hematologic neoplasms are less prevalent. Regarding potential triggering factors, a relationship with cancer treatment was identified in 57% of cases, including surgical stress (33%), chemotherapy (17%), and radiotherapy (7%); the others were emotional stress (30%) and the presence of another acute illness (13%).²⁰⁹

Patients with malignancies have a reduced tolerance threshold for stressors and an increased sensitivity of cardiac adrenergic receptors. In this context, the addition of physical (pain secondary to cancer, diagnostic procedures, cancer surgery) and emotional (fear of illness or death, changes in family dynamics) stressors, which are common to the disease, contributes to a greater predisposition to TTS. Some malignancies, such as pheochromocytoma and paraganglioma, cause hypercatecholaminemia and may be a trigger of TTS.²¹¹

6.4. Siderotic Cardiomyopathy (Iron Overload)

The prevalence of anemia in patients with cancer is high, and the condition is found in more than half of patients during the course of the disease, especially in those with hematologic neoplasms. Moderate-to-severe anemia occurs in approximately 40% of patients, and the cause is multifactorial; it may be secondary to treatment-related myelosuppression,

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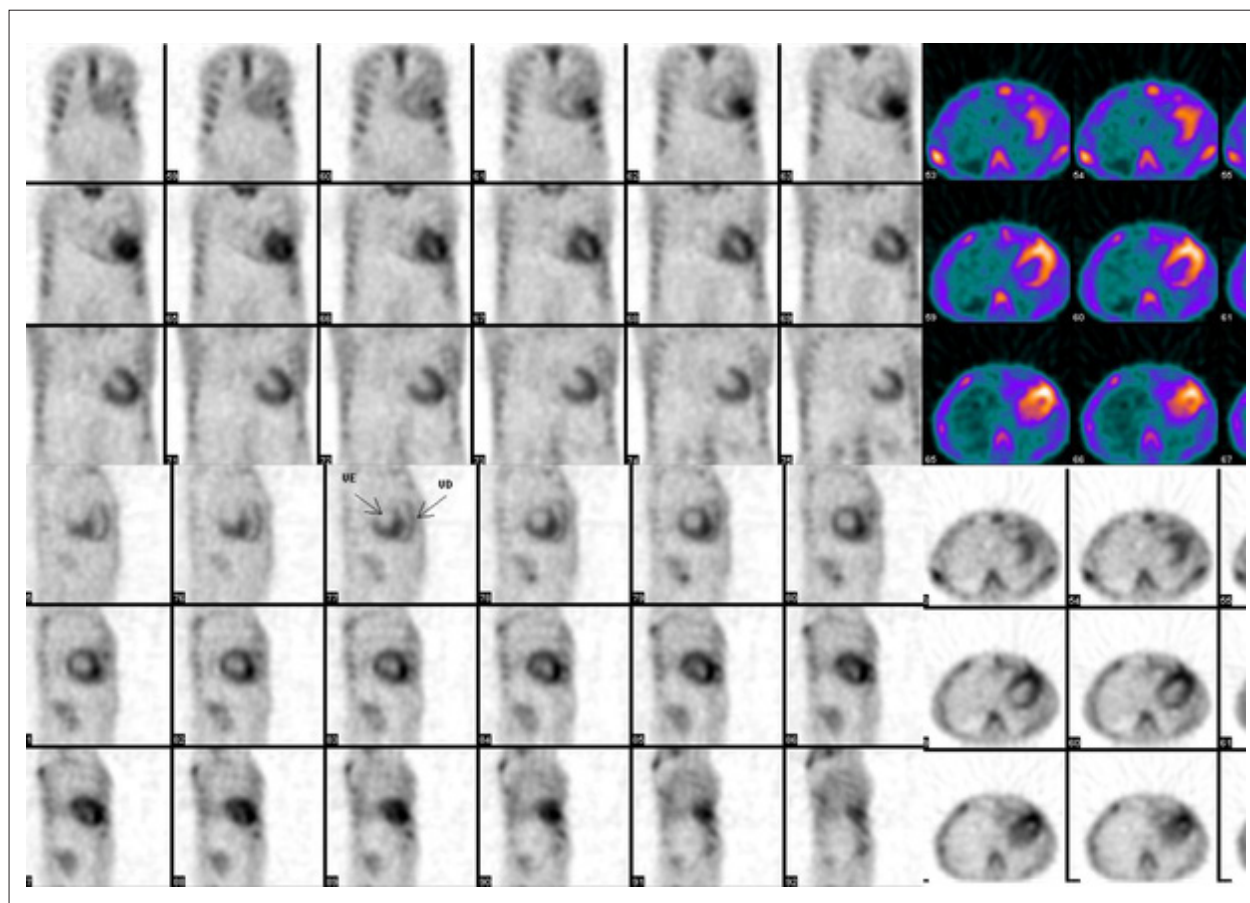


Figure 27 – Reconstructed single-photon emission computed tomography scans of the axial, coronal, and sagittal axes showing accumulation of technetium-99m-labeled pyrophosphate in the left ventricle and simultaneous involvement of the right ventricle (arrows) in a patient with suspected mutant transthyretin amyloidosis, confirmed by a genetic test.

occult bleeding, functional iron deficiency, erythropoietin deficiency due to kidney disease, and/or marrow involvement with tumor.²¹² The main oncologic disease leading to iron overload is myelodysplastic syndrome, due to both increased absorption and regular transfusions. Consequently, patients or survivors of cancer may experience iron overload in the liver, heart, and adrenal gland. Patients with cardiac iron overload usually have poorer cardiovascular prognosis compared to the general population, with outcomes present in 73.2% versus 54.5% over a 3-year period.²¹³

Iron overload cardiomyopathy in early stages commonly presents with normal ventricular function. Echocardiographic diagnosis is often challenging, but some findings may suggest a diagnosis compatible with clinical history. Ventricular diastolic dysfunction may progress to restrictive physiology, leading to dilated heart disease with reduced LVEF. It may manifest as pericardial constriction due to iron deposition in the pericardium. Speckle tracking still has a conflicting role in this context, but increased cardiac iron overload may be associated with a reduced absolute GLS value. There is no description in the literature of a strain pattern that is specific to myocardial iron overload. The results of studies that attempted to correlate circumferential and radial strain with

iron deposits were conflicting. Three-dimensional speckle tracking echocardiography also has no established role in these patients but has been showing favorable results for the detection of early subclinical dysfunction.²¹⁴⁻²¹⁶

Although echocardiography may be used to screen for iron overload, the method is not able to accurately predict myocardial iron content, unlike cardiac MRI (Table 7).

Because of this limitation, current guidelines of several international societies for different diseases recommend routine use of MRI to determine and monitor the level of iron overload in different organs. MRI is recommended for patients with cancer with detected serum ferritin levels > 1,000 ng/mL or for patients with a life expectancy > 12 months who received > 10 transfusion bags.^{217,218}

The MRI scan should evaluate both liver and heart, and be repeated annually or according to therapeutic changes in the iron chelator or transfusion load. The quantification is made by the indirect effect that the iron molecules exert on the local magnetic field in the tissue under analysis. Therefore, the higher the concentration of tissue iron, the lower the signal of the measured tissue (darker); thus, iron quantification in proportion to signal intensity is obtained from several images with consecutive modifications of echo time (Figure 29).

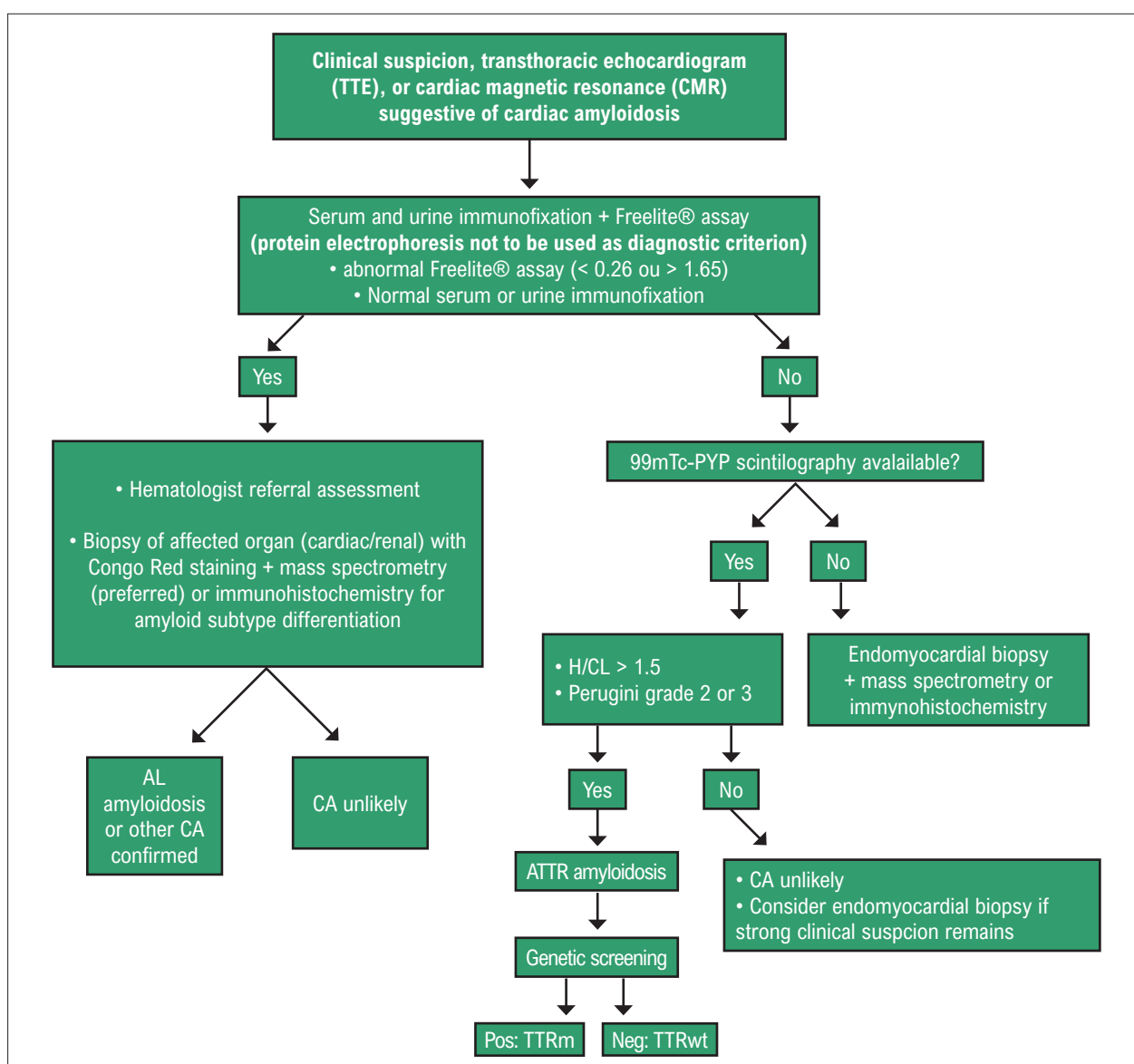


Figure 28 – Proposed nuclear medicine diagnostic sequence for suspected cases of cardiac amyloidosis (CA). TTE: transthoracic echocardiogram; MRI: magnetic resonance imaging; TTR: transthyretin amyloidosis (TTRm: mutant TTR; TTRwt: wild-type TTR); AL: light-chain amyloidosis; PYP: pyrophosphate; DPD: 3,3-diphosphono-1,2-propanodicarboxylic acid; ^{99m}Tc: technetium-99m.

Table 7 – Classification of myocardial and hepatic iron overload (MIO/HIO) by magnetic resonance imaging

T2* (ms) 1.5 T	R2* (Hz) 1.5 T	T2* (ms) 3.0 T	R2* (Hz) 3.0 T	MIO/HIO (mg/g DW)	Classification
Heart					
> 20	≤ 50	> 12.6	≤ 79	≤ 1.16	Normal
10 to 20	50 to 100	5.8 to 12.6	79 to 172	1.16 to 2.71	Slight/moderate overload
< 10	> 100	< 5.8	> 172	> 2.71	Severe overload
Liver					
> 15.4	≤ 65	> 8.4	≤ 119	≤ 2.0	Normal
4.5 to 15.4	66 to 224	2.3 to 8.4	120 to 435	2.0 to 7.0	Mild
2.1 to 4.5	225 to 475	1.05 to 2.3	436 to 952	7.0 to 15	Moderate
< 2.1	> 475	< 1.05	> 952	> 15	Severe

DW: dry weight.

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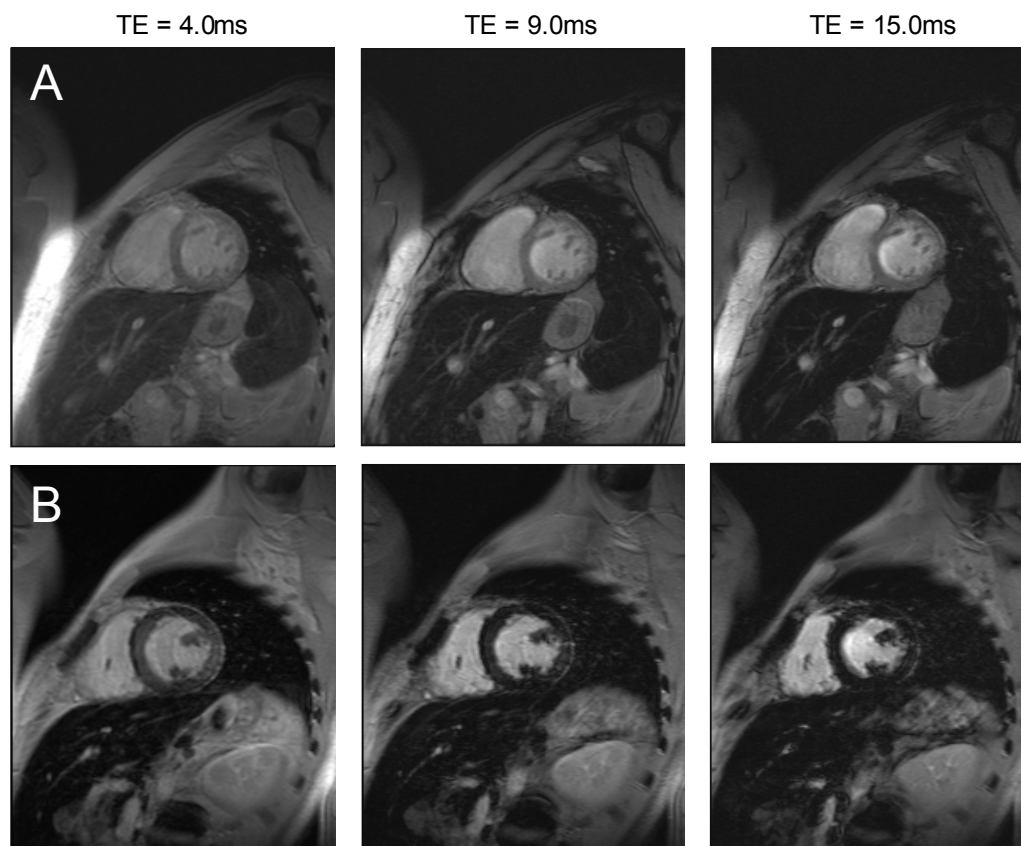


Figure 29 – Example of patients with cancer with normal myocardial iron levels (A) and significant iron overload (B). $T2^*$ in patient A was 22.8 ms with a myocardial iron concentration (MIC) of 0.98 mg/g; in patient B, $T2^*$ was 11.9 ms with an MIC of 2.2 mg/g. More myocardial darkening is observed in patient B with increased echo time values, visually determining the highest degree of myocardial overload. Patient B was initiated on oral iron chelation therapy after myocardial overload was determined by magnetic resonance imaging.

Currently, the MRI scan has no specific substitute, being the only test capable of quantitatively determining the levels of iron overload in different organs simultaneously, noninvasively, and without any contrast or ionizing radiation.

7. Pericardial Diseases

7.1. Pericardial Tumors

Although usually asymptomatic, pericardial malignancy may manifest as nonspecific symptoms such as dyspnea and tachycardia, which are often related to pericarditis, pericardial constriction, myocardial invasion, or, more commonly, pericardial effusion (with or without tamponade). Tamponade occurs in patients with major effusion and no previous symptoms in up to one third of cases.²¹⁹

In 20% to 50% of patients with cancer and pericardial effusion, the latter is caused by neoplastic involvement; in 30%, it may be due to lymphatic impairment secondary to radiotherapy or viral infection. In 10% to 25% of cases, pericardial effusion is the first sign of cancer.²²⁰

The tumors may be either primary pericardial neoplasms or metastases involving the pericardium (secondary pericardial neoplasm). The dissemination may occur through hematogenic spread, lymphatic spread, or direct invasion of the lung and mediastinum. The most common metastatic tumors involving the pericardium are lymphomas, melanomas, and lung, breast, and renal cell carcinomas; adenocarcinoma is the most common histological pattern.²²¹

A recent study showed that the presence of occult hematologic, colorectal, ovarian, kidney, pancreas, breast, and bladder neoplasms should be suspected in older adults, obese patients, and/or smokers who present with acute pericarditis and need for hospitalization. The cancer diagnosis was usually made 3 to 12 months following the episode of pericarditis.²²²

7.1.1. Echocardiogram in Patients with Pericardial Neoplasm

Pericardial effusion may be assessed semiquantitatively by TTE. Rapid volume increase and presence of spontaneous contrast on TTE, with or without identification of pericardial mass, are suggestive of pericardial neoplasm. It usually has a solid appearance, increased echogenicity, and may infiltrate

the myocardium.²²⁰ As a differential diagnosis, pericardial fat has low echogenicity and may be seen adjacent to the RV free wall and atrioventricular junction.

Among the primary tumors, mesothelioma, arising from the mesothelial cells of visceral or parietal pericardium, presents with pericardial effusion, tamponade, or constriction, and the nodules in the pericardium may invade the myocardium. A retrospective study of 64 patients with primary malignant pericardial mesothelioma showed that echocardiographic presentations were nonspecific, with pericardial effusion in 86% of cases (of which 67% were massive and 95% were bloody), pericardial masses in 36%, and thickening in 17%. Tamponade and constrictive pericarditis occurred in 37% and 27% of cases, respectively. Tamponade may be associated with the proliferation of diffuse mesothelial cells and myocardial infiltration, which may cause decreased relaxation and complacency. Reaccumulation of effusion following pericardiocentesis occurred in 73% of cases.²²³

The measurement of pericardial thickness is limited on echocardiography, except when the measures are greater than 5 mm. In general, the measurement of pericardial thickness is best performed by CT or cardiac MRI, which allow for a better evaluation of the implant and tumor extent. Thus, the use of multimodality imaging shows incremental value. Speckle tracking, in turn, can detect subclinical myocardial dysfunction because of early myocardial infiltration.

Usually, pericardial fluid should only be seen on systole, but accumulation makes it present during the entire cardiac cycle. Pericardial effusion is considered significant in the presence of at least 2cm of pericardial fluid around the heart. In cardiac tamponade, the heart is compressed by the accumulation of fluid in the pericardial space, which leads to increased intrapericardial pressure that exceeds the intracavitary pressure. Such accumulation may occur rapidly or gradually. The consequent collapse of the right heart chambers, secondary to increased intrapericardial pressure, is more prominent on expiration, when RA and RV filling is reduced.

However, in the presence of pulmonary hypertension, RA collapse is delayed, resisting until the intrapericardial pressure exceeds the high pressures in the right chambers. In cases of massive effusions, the heart tends to “swing” inside the pericardial fluid at each heartbeat and may have an electrical alternation on the electrocardiographic record. There are also respiratory changes in cardiac flows. The pressure increase inside the RV during inspiration leads to a deviation of the interventricular septum to the left and a consequent increase in the flow and volume of the right chambers, in addition to dilation of the inferior vena cava (Figure 30 A-B).

Subxiphoid incision is the gold standard for surgical approach in biopsy or pericardial drainage. However, pericardiocentesis is routinely guided by fluoroscopy or echocardiography, with a complication rate of 4% to 10%. During echocardiography-guided pericardiocentesis, agitated saline is useful to assess the position of the needle before inserting the catheter and then to assess the position of the catheter.²²⁴ Pericardial effusion is considered to be recurrent if reaccumulation of fluid occurs within 3 months of drainage.

8. Cardio-Oncology in Children and Adolescents

8.1. General Considerations

The number of new cases of childhood and adolescent cancer expected in Brazil, for each year of the 2020-2022 triennium, is of 4,310 new cases in males and 4,150 in females. These figures correspond to an estimated risk of 137 new cases per million in males and 139 per million in females. Childhood and adolescent cancer consists of a set of diseases with their own characteristics in relation to histopathology and clinical behavior. The predominant types of pediatric cancer (aged 0 to 19 years) are leukemia (28%), central nervous system neoplasms (26%), and lymphomas (8%), followed by tumors of the peripheral nervous system (neuroblastomas), Wilms’

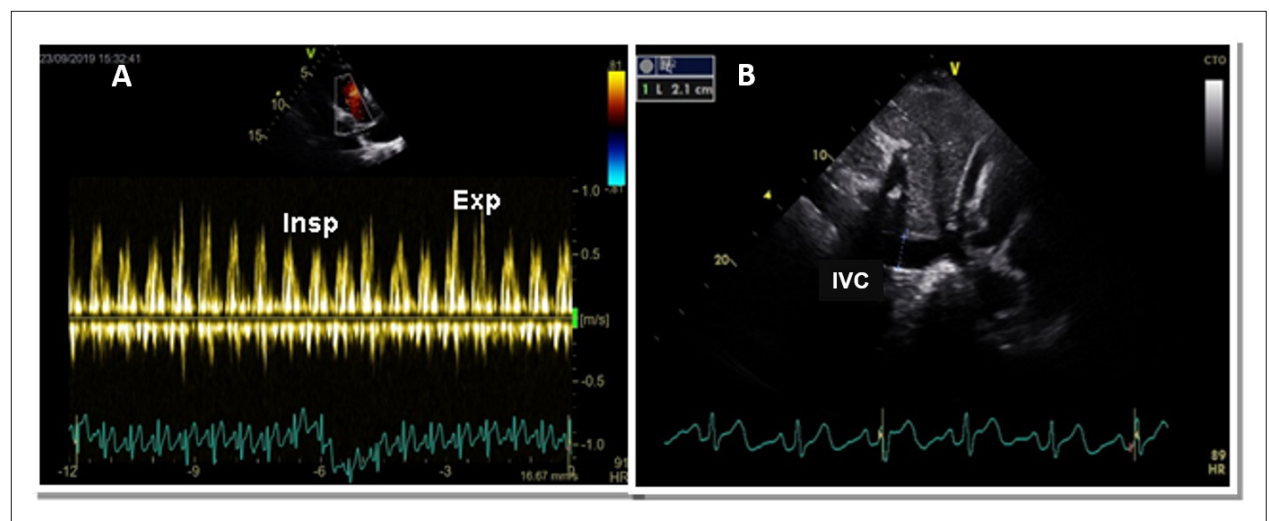


Figure 30 – A. Tricuspid valve flow variation > 40%. B. Dilated inferior vena cava (IVC) with no caliber variation with respiratory maneuvers (patient with breast cancer).

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tumor, retinoblastoma, germ cell tumors (ovaries and testes), soft tissue sarcomas, and osteosarcoma.²²⁵

The prospects for childhood and adolescent cancer cure are promising, with current survival rates approaching 80% in high-quality institutions if diagnosed early.²²⁶ Despite successful treatment, complications inherent to chemotherapy drugs and/or radiotherapy compromise several organ systems in the short, medium, or long term. There is clear evidence that survivors of cancer treated during childhood with anthracyclines and/or radiotherapy are significantly more likely to develop cardiovascular complications during their lifetime, estimated at 5% to 30%, especially considering the protocol used and certain risk factors. The cumulative incidence of severe chronic problems may reach 40% in the 30-year follow-up period for survivors.²²⁷

Cancer is the second most common cause of death among children aged 1 to 14 years in the US, second only to accidents and violent deaths. In Brazil, cancer accounted for 8% of the total deaths among children and adolescents aged 1 to 19 years and 12% of deaths in the age range of 1 to 14 years between 2009 and 2013. In 2014, 2,724 deaths from childhood and adolescent cancer occurred in Brazil.²²⁵ This reality demonstrates how important the interaction between hematologist-oncologists and cardiologists is for safety in the treatment of this type of cancer.

Cardiovascular complications are the main causes of morbidity and mortality in survivors of cancer treated during childhood, second only to disease recurrences and secondary neoplasms. The mechanisms of action of the various chemotherapy agents as well as the physical injuries caused by radiotherapy are comparable among adults, children, and adolescents. However, the younger age group is particularly more vulnerable in view of the ongoing process of growth and physical development. In addition, cardiomyocytes have a limited regeneration capacity, and the drug metabolism in this population behaves differently from that of adults.²²⁸ Therefore, injuries considered to be minor at the time of treatment may progressively compromise myocardial function over time, leading to decompensation in adulthood. Inadequate gain in LV mass, decreased contractile function, and possible development of progressive restrictive cardiomyopathy over the years lead to cardiovascular sequelae that are often irreversible in some of these patients.

In addition to ventricular myocardial dysfunction, other complications can result from the use of chemotherapy agents: arterial endothelial injuries (related to the effects of systemic and pulmonary hypertension), impaired coronary blood flow, venous endothelial injuries (related to thrombotic effects), valve dysfunction, arrhythmias, and pericardial diseases.²²⁹

Pericardial impairment may be directly related to the neoplasm, may result from the action of some chemotherapy agents, or may be secondary to cardiac metastasis. Pericarditis, with or without stroke, may or may not be associated with myocarditis. Constrictive pericarditis is more commonly associated with radiotherapy-induced CTX, and it is necessary to differentiate it from restrictive myocarditis. Cardiovascular imaging examinations are essential to elucidate these changes, especially in subclinical stages.

Anthracyclines (doxorubicin, daunorubicin, epirubicin, idarubicin, and mitoxantrone) are extremely potent chemotherapy agents widely used in most childhood cancer treatment protocols. There is a strong relationship between the cumulative dose of anthracyclines and the risk of HF, and in some cases there may be a long latency period between exposure to chemotherapy and the onset of cardiovascular symptoms.²²⁷ Myocardial injury is progressive and usually irreversible, culminating in severe cardiac dysfunction. There are several mechanisms by which the cardiotoxic action of anthracyclines may occur. The most common ones are the formation of cytoplasmic free radicals, resulting in oxidative stress in myocytes, and a direct action on the nucleus, in which anthracyclines act on topoisomerase 2 (Top2) by preventing the replication of DNA that induces cell death. Although the Top2 α fraction, which is the focus of anticancer treatment, is expressed in tumor cells, the Top2 β fraction is expressed in cardiomyocytes, thus allowing a similar toxic action.²³⁰ Current hematology-oncology treatment protocols follow a trend toward the use of lower doses of anthracyclines. However, even at doses that are considered low, some pediatric patients have cardiotoxic reactions during the course of treatment and/or late follow-up, so that some authors believe that there is no safe dose.²³¹ Individual susceptibility is not yet fully elucidated, but there are hypotheses that some genetic characteristics increase vulnerability and early occurrence of myocardial dysfunction. Some preventive actions are recommended, especially in patients stratified as being at high risk of developing cardiovascular complications. The primary strategy, specifically against the cardiotoxic effects of anthracyclines, is given by infusion of dexrazoxane or by using liposomal doxorubicin (not commonly used in young patients). The secondary strategy, represented by the administration of drugs with hemodynamic effects, such as beta-blockers (in particular carvedilol), angiotensin-converting enzyme inhibitors, and spironolactone, has been considered an adjuvant in the prevention or treatment of established lesions, whose prospective studies in children are still ongoing.²²⁸

Other potentially cardiotoxic substances are used to treat neoplasms in children and adolescents, often in combination with anthracyclines. CTX is not uncommon with the use of alkylating agents, such as cyclophosphamide, cisplatin, and ifosfamide, with the most frequent presentations being myocarditis, arrhythmias, and HF. The most common cardiovascular complication of antimetabolites, such as 5-fluorouracil, is myocardial ischemia, reported mainly in adults. Biological agents such as tyrosine kinase inhibitors can cause QT interval prolongation, HF, hypertension, and AMI. Etoposide is a synthetic podophyllotoxin approved for the treatment of some neoplasms such as Ewing's sarcoma and lymphomas. Cardiovascular complications are rare, but chest pain, angina, and AMI have been reported in adults receiving etoposide in combination with bleomycin, cisplatin, and ifosfamide. Biological agents such as interleukins and interferon may cause hypotension or arrhythmias. The main cardiovascular effect of vinca alkaloids, such as vincristine

and vinblastine, is myocardial ischemia due to coronary vasospasm. Immunotherapy has also been important in the treatment of childhood and adolescent cancer, with the potential to trigger myocarditis, although rare (< 1%), and pericarditis.^{232,233}

Radiotherapy is a therapeutic method often used in pediatric cancer treatment (about 40% of protocols). Cardiac complications resulting from radiotherapy are due to inflammation and fibrosis of cardiac structures, which may involve the pericardium, myocardium, heart valves, and coronary arteries. The pericardium is the most frequently affected structure. Although the lesions may remain asymptomatic for 5 to 15 years, they are usually progressive. Lesion severity is proportional to the dose, irradiated volume, and the combination with chemotherapy agents, which confers greater risk. Advances in radiotherapy techniques in the past two decades have allowed a reduction in the volume and doses of radiation in the cardiac area. With the emergence of 3D planning techniques, the demarcation of adjacent structures, dose adjustments, and field modifications have allowed a significant reduction in the doses applied to organs at risk, such as the heart.^{227,234}

8.2. Main Risk Factors for the Development of Cardiotoxicity in Children and Adolescents

Cumulative dose: even at relatively low doses, anthracyclines have been reported to trigger CTX. The concept of a safe anthracycline dose has been disregarded by some authors, as observed in a study that showed a 30% increase in subclinical echocardiographic abnormalities 13 years after leukemia treatment, even with cumulative doses of anthracyclines ranging from 180 to 240mg/m².^{234,235}

Combination of chemotherapy agents: concomitant administration of more than one chemotherapy agent known to be cardiotoxic not only facilitates but also potentiates adverse cardiovascular effects.

Age at treatment: children treated before 5 years of age are more likely to have cardiovascular complications in the short or long term, especially due to progressive myocardial functional limitation resulting from the demands of physical growth.

Sex: girls have a 2-fold higher incidence of CTX than boys, probably due to a higher percentage of body fat that allows longer exposure time and body concentration of anthracyclines.

Infusion rate: some studies in adults suggested a reduction in the prevalence of CTX by continuous infusion of anthracyclines, compared to bolus administration. This mode of infusion, however, was not cardioprotective in the long term in the pediatric population.²³¹

Mediastinal and neuroaxis radiotherapy: radiotherapy doses ≥ 30 Gy or the combination of anthracycline with radiotherapy, even at low doses, may also aggravate the risk of developing cardiovascular complications. Exposure to radiation at a young age is also an important factor. These patients may progress with valve complications, pericardial complications, restrictive cardiomyopathy,

CAD, and arrhythmias that can induce sudden cardiac death.^{227,234}

Radiotherapy of the central nervous system: in the long term, children who received cranial irradiation showed greater loss of ventricular mass, a fact attributed to the impairment of the pituitary gland with consequent secondary deficiency in the production of insulin-like growth factor 1, a precursor of growth hormone.²³⁶

Comorbidities: the presence of two or more comorbidities increases cardiovascular risk in adults surviving cancer treatment in the pediatric age. The development of hypertension, DM, dyslipidemia, and CAD, especially in association with obesity and smoking, increases the risk of early onset of complications when compared to their siblings. The presence of liver dysfunction, renal dysfunction, and electrolyte disturbances compromises drug clearance, slows down its elimination, and increases drug exposure time.

Genetic variants: individual predisposition to CTX has been reported in several studies. Some genetic variants, such as RARG and UGT1A6, increase Top2 or slow down drug metabolism. The incidence of myocardial dysfunction is increased 9-fold in patients with C282Y mutation for hereditary hemochromatosis. People with trisomy 21 are more likely to develop acute myeloid leukemia and more sensitive to the toxic effects of chemotherapy agents. Familial (hypertrophic, arrhythmogenic) cardiomyopathies and patients with congenital heart defects may have a more vulnerable myocardium.^{237,238}

8.3. Cardiac Monitoring during Treatment

The method of cardiovascular imaging tests, definitions, and parameters used in the evaluation of children and adolescents or survivors of cancer treatment at pediatric age is the same method that is used in the adult population.

Echocardiography is the main imaging test indicated for monitoring those patients, as it provides information on the main parameters of diastolic and systolic function of both ventricles, anatomical and functional status of the valve structures and the pericardium, in addition to investigating masses, thrombi, and vegetations. The ventricular myocardial function is quantified using several parameters and methods. The most recommended ones are LVEF using the Simpson biplane method and myocardial strain analysis using the speckle tracking technique. Myocardial deformation measurements are obtained using 2D and 3D echocardiography and then analyzed on longitudinal, radial, or circumferential modes, as they do not depend on the angle of ultrasound incidence. This method has been the subject of several studies that seek to detect early subclinical changes that may be predictors of CTX in children and adolescents.²³⁹ The longitudinal mode has been the one with best reproducibility used in the vast majority of studies. Despite its advantages (availability, accessibility, and low cost), echocardiography has some limitations, especially interobserver variability and compromised quality of the images obtained because of inadequate acoustic windows. Another limitation is related to ejection fraction, which has

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been proven to be of low sensitivity in the context of early detection of myocardial functional changes. In contrast, myocardial strain analysis using speckle tracking allows for the identification of subclinical lesions that precede the decrease in LVEF.^{239,240}

Cardiac MRI is another important diagnostic test in childhood and adolescent cardio-oncology. In addition to being the gold standard for LVEF quantification, it can detect early interstitial edema and myocardial fibrosis using contemporary methods associated with the use of gadolinium contrast by T1 mapping and delayed enhancement identification. Also, it plays an important role in the characterization of intracardiac and extracardiac masses. However, because of intrinsic characteristics, it has limitations for routine use.

The use of NM imaging in the pediatric area requires, in addition to technical knowledge, a joint assessment with the pediatric team on risk versus benefit of the exposure of children and adolescents to radiation doses (although low, based on radiation safety principles).²⁴¹ Radionuclide ventriculography, a noninvasive technique that uses ^{99m}Tc-labeled red blood cells as a radiopharmaceutical, allows for analysis of several ventricular function parameters (time activity curve, phase analysis, and amplitude), providing a refined assessment of the regions with better contractile performance (amplitude) and the time point when this contraction occurred (phase analysis), detecting the presence of interventricular and left intraventricular contractile dyssynchrony. However, information on diastolic function is limited. The timing for performing radionuclide ventriculography during cancer treatment to minimize the confounding variables is debatable. The suggestion is to perform it at least 3 weeks after anthracycline therapy, when patients have no fever and hemoglobin above 9 g/dL.²⁴² Regarding other NM imaging methods used to detect CTX such as myocardial uptake of ¹²³I-MIBG and PET-CT, there are still no robust data for indication in the pediatric population.

The diagnosis of CTX using cardiovascular imaging methods is based on the changes detected in the baseline examination. Thus, it is recommended that the functional assessment is conducted before the start of cancer treatment and then during the course of treatment for comparison purposes, making an effort to always use the same equipment, the same methods, and the same variables used in previous assessments.

Table 8 shows the international recommendations for echocardiographic monitoring of patients during and after treatment with anthracyclines (main representatives of CTX in children and adolescents).

Each patient's hemodynamic status must be considered at the time of assessment. Whenever possible, the status should be stable. The frailty of the pediatric patient in the face of certain situations, such as changes in blood volume (dehydration, hyperhydration), anemia, fever, hypothermia, shock, sepsis, abnormal heart rate, and changes in rhythm, may occasionally influence the interpretation of results. These conditions affect preload and afterload and can promote a variation of 5% to 10% in stroke volume per cardiac cycle, influencing the ejection fraction. Changes in global and segmental contractility during chemotherapy may be related to secondary cardiomyopathy induced by transient stress (idiopathic cause, sepsis, neurological injury, catecholamine release).²⁴³ Functional changes due to clinical complications may be transient or definitive. The recommendation is to reevaluate the patient soon after compensation.

The definition of subclinical CTX remains challenging for children and adolescents. Some studies have reported segmental changes even before the fall in GLS, which has suggested the greater accuracy of this method for early detection of myocardial dysfunction. Current international recommendations consider a 15% fall in GLS from baseline as indicative of subclinical dysfunction, provided that hemodynamic conditions are comparatively similar.²³⁹

Table 8 – Echocardiographic monitoring of patients treated with anthracyclines in childhood

CD (kg/m ²)	During treatment		After treatment	
	No PRF	At least 1 PRF	No PRF	At least 1 PRF
Baseline	Yes	Yes	N/A	N/A
< 200	- Clinical criterion	- Every 2/3 cycles	- 1 month after treatment - Evaluate in 1, 2, and 5 years - Individualize if required	- 1 month after treatment - Evaluate in 1, 2, and 5 years
200 to 300	- Clinical criterion	- Every 2/3 cycles	- 1, 6, and 12 months after treatment - Then every 2 years (asymptomatic)	- 1, 6, and 12 months after treatment - Then annually - Individualize
300 to 450	- Clinical criterion - Individualize if required	- Every 2 cycles	- 1, 6, and 12 months after treatment - Then annually - Individualize	- 1 month after treatment - Then every 6 months - Individualize if required
> 450	- Halfway through treatment - Individualize if required	- Every 2 cycles - Individualize if required	- 1 month after treatment - Then every 6 months - Individualize if required	

CD: cumulative dose; PRF: preexisting risk factor; N/A: not applicable.

8.4. Long Term Follow-up of Survivors

The risk of developing cardiovascular complications and the severity of lesions increase over time. Studies have shown that, among survivors of cancer treated during childhood and followed-up for 30 years, 8% had HF. The early detection of CTX induced by antineoplastic therapy seems to have a significant effect on the control of outcomes and on the hemodynamic effects resulting from myocardial injury. The identification of the best method for early detection of CTX in those patients is extremely important. Echocardiography and cardiac MRI are the most recommended tests by the main international guidelines and studies.^{28,227,239}

Despite the lack of randomized controlled studies in children and adolescents, early detection of subclinical lesions is of fundamental importance to stop their progression, which will then allow for prevention or reversal of LV pathological remodeling.²²⁸

The American Society of Clinical Oncology (ASCO) proposes five clinical questions that will guide management planning and cardiovascular monitoring of survivors:⁶

1. Which patients are at increased risk for developing cardiac dysfunction?
2. Which preventative strategies will minimize risk BEFORE initiation of therapy?
3. Which preventive strategies will minimize risk DURING potentially cardiotoxic therapy?
4. What are the preferred surveillance and monitoring approaches DURING treatment?
5. What are the preferred surveillance and monitoring approaches AFTER treatment?

Late follow-up planning based on risk stratification contributes to the choice of the best method for monitoring myocardial function (biomarkers and imaging tests). The aim is to detect subclinical dysfunction early, with consequent use of drugs that can prevent or reverse cardiac remodeling.

With regard to late follow-up after radiotherapy—which is one of the pillars of pediatric cancer treatment and about 40% of children, adolescents, and young adults undergo at some stage of the treatment—incidence and severity are directly proportional to the dose and irradiated volume and inversely proportional to age. Occurrence also increases with elapsed radiotherapy time and associated use of cardiotoxic agents, in particular anthracyclines, in addition to possible previous heart disease.^{34,234} Radiation leads to diffuse interstitial myocardial fibrosis related to the irradiated area, especially of the LV anterior wall, and clinical manifestation will consist of restrictive cardiomyopathy. In view of the difficulty in assessing diastolic function in children, each patient's follow-up values must be compared to baseline values. Endothelial damage favors early development of atherosclerotic plaques complicated by hemorrhage and inflammation with risk of rupture and thrombosis. The pericardium is the main target of injury usually initiated by fibrinous pericarditis and pericardial effusion, followed by fibrous thickening, preferably in the parietal pericardium and RV, and may extend to the mediastinum. Valve involvement is less frequent and, unlike pericardial involvement,

affects the left side of the heart more often. The cusps become thickened and may calcify and lead to insufficiency and stenosis, especially of the mitral and aortic valves, sparing the tips of the cusps and the valve commissures.²⁴⁴

Survivors of cancer treatment in childhood and adolescence are more vulnerable to the development of premature CAD, including in subclinical stages, with a risk of myocardial infarction 2 to 8 times greater than that of the general population. As coronary events are rare in younger patients, even in those at increased risk, pharmacological stress echocardiography and NM imaging tests to assess myocardial perfusion and viability are recommended.²⁴⁵

Late follow-up of individuals without ventricular dysfunction should be performed routinely after 6 months to 1 year and then periodically, given that the incidence of HF related to the use of anthracycline and radiotherapy increases with late monitoring; the condition may appear after 15 years or more. Although the ideal frequency for assessing LV structure and function in survivors exposed to cardiac radiation is not yet well established in consensus statements, the greater the number of risk factors, the greater the frequency that assessments should be conducted.²⁴⁶

8.5. Pregnancy in Survivors of Childhood and Adolescent Cancer

With advances in cancer treatment and the remarkable number of survivors of childhood and adolescent cancer, more women reach the childbearing age, and many will choose to become pregnant. Some have undiagnosed subclinical lesions and others are undergoing treatment for HF or other late complications of antineoplastic treatment. Pregnancy is associated with substantial changes in the cardiovascular system, as there is an increased metabolic demand in the pregnant woman's heart. Marked increases in circulating blood volume contribute to an additional 30% to 40% in cardiac output in a relatively early period of pregnancy (20 to 24 weeks), and these changes will influence the interpretation of cardiovascular status. The consequences are tachycardia, relative anemia, and hypercoagulability phenomena. The risk of developing cardiac events during pregnancy in women previously exposed to anthracyclines and/or thoracic radiotherapy in childhood is not clearly known, with limited data available in the literature.^{247,248}

Physiological multivalve regurgitations, especially in the right heart chambers, due to chamber enlargement, annular dilation, as well as mild pericardial effusion, are frequent in late pregnancy and postpartum, and seem to be caused by hypervolemia resulting from this period.

Table 9 lists maternal physiological cardiovascular changes according to each trimester of pregnancy.

8.5.1. Cardiac Outcomes in Pregnant Survivors of Childhood and Adolescent Cancer

Some clinical studies have evaluated cardiac outcomes in pregnant women previously exposed to cardiotoxic cancer therapy.

Van Dalen et al.²⁴⁷ retrospectively evaluated 53 female survivors of childhood and adolescent cancer who had one

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or more children. Data on LV systolic function and other echocardiographic parameters were not available for analysis. HF diagnosis was defined based on signs and symptoms. No patient developed HF during pregnancy or within 5 months of delivery.²⁴⁷

Hines et al.²⁴⁸ administered a questionnaire to 847 female survivors of childhood and adolescent cancer who had at least one complete pregnancy. The authors found that most female survivors of childhood and adolescent cancer did not experience cardiac complications during or after delivery; however, pregnant women with a history of cardiotoxic therapy should be followed-up carefully during pregnancy, especially those with a history of anthracycline exposure and who have been diagnosed with previous or current subclinical or symptomatic cardiomyopathy.²⁴⁸

In another study, 37 women who received doxorubicin as part of a chemotherapy protocol for a childhood neoplastic disorder were followed-up at the same center during pregnancy (72 gestations) and after delivery. The authors concluded that the pregnancy outcome in women who received doxorubicin for childhood malignancy is generally favorable. However, those with LV dysfunction before pregnancy should be considered at increased risk of a poor pregnancy outcome and further deterioration of myocardial function.²⁴⁹

Thompson et al.²⁵⁰ evaluated a cohort of 58 women who were treated with anthracyclines and/or thoracic radiotherapy before the age of 20 at the MD Anderson Cancer Center. The incidence of adverse cardiac events (defined as LVEF < 50% on at least two echocardiograms or CAD) was significantly higher in women who had at least one pregnancy (29%) compared to nulliparous controls matched for anthracycline dose and follow-up period (15%), with $p < 0.05$. Among the 58 pregnant women, nine were diagnosed with CVD during pregnancy and five were diagnosed after pregnancy. In this small cohort, the time from exposure to anthracyclines to the first pregnancy and the total anthracycline dose were associated with an increased risk of adverse cardiac events. In addition, pregnancy was associated with a 2.4-fold increase in the risk of developing adverse cardiac events (95% CI: 1.02-5.41, $p = 0.045$).²⁵⁰

8.5.2. Cardiovascular Monitoring Recommendation in Survivors of Childhood and Adolescent Cancer Wanting to Become Pregnant

Studies of non-cancer populations with preexisting cardiomyopathies have reported a high risk of cardiac

decompensation due to changes in cardiac physiology during pregnancy. Pregnancy is not recommended in patients with cardiomyopathies with LVEF < 40%.²⁵¹

In survivors of childhood and adolescent cancer, there is limited evidence on cardiac monitoring during pregnancy. International guidelines recommend a cardiovascular evaluation before pregnancy and in the first trimester for all women who were treated during childhood with anthracyclines and/or thoracic radiotherapy. The Children's Oncology Group recommends performing an echocardiogram before and then periodically during pregnancy (especially during the third trimester), in addition to cardiac monitoring during labor and delivery in patients receiving anthracycline doses > 300 mg/m², thoracic radiation doses > 30 Gy, and those who received both cancer treatments, i.e., anthracyclines and thoracic radiotherapy.^{246,251}

Recommendations are as follows:

- Echocardiographic assessment of cardiac function before pregnancy and then periodically, every trimester, in women who were treated with anthracyclines (especially at doses > 300 mg/m²) and/or thoracic radiotherapy (especially at doses > 30 Gy) with previous LVEF ≥ 50%.
- Echocardiographic assessment of cardiac function before pregnancy and in the last trimester of pregnancy, or when clinically indicated, in women who were treated with anthracyclines (doses < 300 mg/m²) and/or thoracic radiotherapy (doses < 30 Gy) with previous LVEF ≥ 50%.
- Echocardiographic assessment of cardiac function before pregnancy and then periodically, every trimester, or when clinically indicated, in addition to cardiac monitoring during labor and delivery in women with LVEF between 40% and 50%. Consider repeating the echocardiogram 1 month after delivery.
- Pregnancy is not recommended for patients with LVEF < 40%.

8.6. Predisposing Situations to Thrombotic Events Related to Childhood and Adolescent Cancer Treatment

8.6.1. Intracardiac thrombus

Much of the chemotherapy treatment of patients with childhood and adolescent cancer is performed

Table 9 – Physiological echocardiographic changes during pregnancy

1 st trimester	2 nd trimester	2 nd trimester	Postpartum
↓ SVR	↓ SVR	↓ SVR GLS	↓ HR LV end-diastolic diameter LV mass CO
↑ HR LV end-diastolic diameter LV mass CO	↑ HR LV end-diastolic diameter LV mass CO	↑ HR LV end-diastolic diameter LV mass CO	↑ SVR GLS

SVR: systemic vascular resistance; HR: heart rate; LV: left ventricle; GLS: global longitudinal strain; CO: cardiac output; ↑ = increases; ↓ = decreases.

intravenously using long-term catheters, which increase the risk of thrombus or vegetation formation. In Also, the procoagulant properties of tumor cells favor tumor invasion and metastasis.²⁵²

In the pediatric population, the mean incidence of cancer-associated thrombotic events is 8%, most frequently in acute leukemias, followed by sarcomas, lymphomas, acute myeloid leukemia, Wilms' tumor, neuroblastomas, and central nervous system tumors. Occurrence may reach 36.7% among leukemias and 16% among lymphomas (due to extrinsic mass compression in the mediastinum), solid tumors and central nervous system tumors. Among sarcomas, Ewing's is the one at most risk for thrombotic events, followed by rhabdomyosarcoma and osteosarcoma.²⁵³

Several clinical conditions are related to the etiology of thrombotic events in children and adolescents, such as recent surgery, congenital heart disease, immobilization, trauma, nephrotic syndrome, use of oral contraceptives, congenital thrombophilia, and presence of a central venous catheter, which is the most important predisposing factor alone.²⁵² L-asparaginase, used in acute lymphoblastic leukemia protocols, may suppress natural anticoagulants, particularly antithrombin and plasminogen. Corticosteroid use may lead to activation of both factor VIII-von Willebrand factor complex and plasminogen activator inhibitor-1. The combination of L-asparaginase and corticosteroids is a high-risk factor for the development of thrombotic events, especially in the induction phase, when there is reduced ability to inhibit thrombin.²⁵³

Pulmonary thromboembolism is much less reported among children and adolescents compared to adults. In a Canadian study, an incidence of 0.86 per 10,000 hospital admissions was demonstrated; however, there are limited data on long-term follow-up.²⁵⁴

The genetic characteristics of the host also contribute to a greater vulnerability to thrombotic events. A deficiency in natural anticoagulants such as antithrombin, protein C, and protein S is the genetic factor most often related to thrombotic events in the pediatric population.²⁵²

TTE is an important tool for the investigation of intracardiac thrombi and vegetations, being complemented by TEE, which is more sensitive. The use of microbubble contrast agents helps detect thrombi and differentiate avascular thrombus from vascularized tumors. Intracardiac thrombi are characterized by their hyperechogenic appearance and generally regular borders. MRI and CT angiography may be adjuvant for diagnostic clarification; however, it may remain difficult to differentiate thrombi from other cardiac tumors. A diagnosis of intracardiac thrombus results from a combination of image presentation, location, and clinical status. In uncertain cases, diagnosis is often made after a anticoagulation cycle and imaging reassessment.²⁵⁵

8.6.2. Central Venous Catheter

According to estimates, more than 5 million central venous catheters are implanted annually in the US. Children with cancer require intravenous administration of chemotherapy for a considerable amount of time. The use of central venous

catheters after the 1980s improved the quality of life of these patients, but use is associated with mechanical, infectious, and thrombotic complications. The incidence of CRT in pediatric patients with cancer reported in recent years has ranged from 4.6% to 7%.^{252,256}

Echocardiogram has a key role in the evaluation of this device. The tip of the catheter should ideally be in the superior vena cava close to the junction with the RA to prevent arrhythmias and thrombus formation. The entire visible venous path should be evaluated, as well as the flow behavior close to the device, in the cardiac chambers, and in the valves.²⁵⁶

8.6.3. Differential Diagnosis of Intracardiac Mass

8.6.3.1. Prominent Crista Terminalis

The crista terminalis is a fibromuscular tissue that demarcates the limits of the embryological venous sinus and the RA muscular wall. When prominent, it can be mistakenly diagnosed as an intracardiac mass. On echocardiography, it appears as a hyperechogenic image in the posterolateral portion of the RA. Identification avoids incorrect diagnosis of intracardiac thrombus.

8.6.3.2. Mitral Annular Calcification

Mitral annular calcification is the deposition of calcium and fat throughout the fibrous annulus, most commonly in the posterior portion of the mitral annulus, with a hyperechogenic appearance. It may be the basis for the formation of thrombi or vegetations and exhibits mobile calcified components with potential for embolization.

8.6.3.3. Infective Endocarditis

In patients undergoing cancer treatment with positive blood culture, infective endocarditis (IE) should be suspected, as these individuals are at high risk for hospital infections because of the number of hospitalizations and immunosuppression. TTE is mandatory in such cases. The investigation includes cardiac valves in search of signs of vegetation, abscess, or cardiac fistula, presence of new valve regurgitation, as well as the appearance of long-term intravenous devices. The specificity for diagnosis of endocardial vegetation using TTE is greater than 90%, but the sensitivity ranges from 62 to 79%, as images smaller than 2 to 3 mm may not be visible. TEE also has a specificity greater than 90%; however, it has a higher sensitivity for diagnosis of IE (> 80% to 90%).

Endocardial vegetations are characterized by very irregular shapes and chaotic movement that is independent from valve movement. They are usually located on the atrial side of atrioventricular valves and on the ventricular side of semilunar valves and are associated with the destruction of the valve apparatus, leading to valve regurgitation or abscess. Valve abscesses most commonly affect the aortic valve and may fistulate to the LV or the atrium. There is an increased risk for stroke and AMI in patients diagnosed with

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IE. The main agents responsible for stroke are endocardial vegetations with dimensions greater than 10 to 15 mm that affect more than one valve, have excessive mobility, and show positive blood culture for fungus, *Staphylococcus aureus*, and *Streptococcus bovis*.

8.6.3.4. Nonbacterial Thrombotic Endocarditis

Libman-Sacks endocarditis: this consists of granular material with immune complexes and platelets, without bacteria; it usually has small dimensions (1 to 4 mm), is found at the same sites as endocarditis, but is usually less irregular and better defined and is not associated with valve destruction. These lesions are usually asymptomatic and are more common in patients diagnosed with lupus.

Marantic endocarditis: this is a type of noninfectious endocarditis associated with malignancy, especially solid metastatic carcinomas and adenocarcinomas of the lung, pancreas, stomach, and other adenocarcinomas. There are descriptions of association with myelodysplastic syndromes. Marantic vegetations are composed of fibrin and platelets and rarely lead to valve dysfunction; classically, they affect the atrial face of the mitral valve and the ventricular face of the aortic valve. They may embolize in more than 50% of cases. Echotexture, dimensions, and location are no different from those of IE. However, significant diffuse valve thickening is frequently observed, which may help in the diagnosis.

8.6.3.5. Lambl Excrecences

Lambl excrecences are defined as filiform structures, less than 2 mm wide and 3 to 10 mm long, with undulating motion, located on the atrial face of the mitral valve and on the ventricular face of the aortic valve. They are not associated with thromboembolic events.

8.6. Cardiovascular Evaluation in Case of Bone Marrow Transplantation in Children and Adolescents

BMT, or hematopoietic stem cell transplantation, either autologous or allogeneic, plays an important role in the treatment of various neoplasms during childhood and adolescence. The most frequent ones are leukemias, some solid tumors, bone marrow aplasia, immunodeficiencies, and some inherited diseases that affect the hematopoietic system.

Autologous transplants are, in general, less susceptible to cardiovascular complications compared to allogeneic

transplants. The incidence of cardiovascular complications increases according to the time of cure of these patients, reaching up to 17% after 15 years of treatment. BMT survivors are at a 13-fold higher risk for cardiovascular complications compared to their siblings.²⁵⁷ The following factors favor CTX after BMT:

- Age at BMT;
- Anterior cardiotoxic chemotherapy (e.g., anthracyclines);
- Myeloablative conditioning regimen (e.g., cyclophosphamide);
- Prior chest irradiation;
- Total body irradiation;
- Type of transplant;
- Presence of graft-versus-host disease (GvHD);
- Comorbidities (e.g., hypertension, DM, dyslipidemia, smoking, obesity).

GvHD is the most common complication in allogeneic BMT and requires regular assessments using cardiovascular imaging methods. It triggers immune responses that lead to endothelial damage and chronic inflammatory processes, affects several organs, including the lungs, and may simulate pulmonary arterial hypertension. It favors the development of vasculitis, early atherosclerosis, hypertension, cerebrovascular diseases, angina, and AML.²⁵⁸ Prolonged use of corticosteroids and other immunosuppressants in GvHD treatment accelerates those events, and presence of conventional cardiovascular risk factors contributes to the appearance of these complications. Cardiac involvement alone in GvHD is rare and may manifest as pericarditis, arrhythmias, and CAD.²⁵⁷

Another factor to be considered is the deposition of iron in the myocardium resulting from multiple blood transfusions, which may persist for years after BMT and is usually assessed by means of cardiac and liver MRI.²⁵⁹

Survivors of BMT treated with anthracyclines and/or chest irradiation should be examined annually for signs of cardiovascular complications. Both systolic and diastolic cardiac function should be assessed using echocardiography, either annually or every 5 years, depending on dosage and age of exposure. They must be preventively advised regarding modifiable cardiovascular risk factors (hypertension, DM, dyslipidemia, smoking).

APPENDIX 1

SUGGESTED ECHOCARDIOGRAM REPORT FOR CARDIO-ONCOLOGY

I – Patient identification:

- Name:
- Hospital registration/personal ID:
- Sex:
- Date of birth: // (... years old)

II – Cancer diagnosis:

III – Comorbidities:

IV – Treatment:

Date of start of treatment: / /
 Date of end of treatment: / /
 Treatment protocol (drugs used):
 Cumulative anthracycline dose: mg/m²
 Thoracic radiotherapy: Gy
 Other medications being used:

V – Timing of examination:

- ☐ Baseline examination
- ☐ Intermediate examination (routine). Delta chemo: days
- ☐ Examination due to complications. Describe:
- ☐ Examination at the end of treatment.
- ☐ Examination after treatment: months / ... years
- ☐ Date of last examination: / /

VI – Anthropometric data:

Weight: kg Height: m BSA: m² BMI:

VII – Vital signs:

HR: bpm BP: X mm Hg RR: bpm Temp.: °

VIII – Blood volume status:

- ☐ Hypervolemia
- ☐ Dehydration

IX – Conventional two-dimensional echocardiographic measurements: (...)

X – LVd volume: mL LVs volume: mL

XI – LV mass: g LV mass index: g/m²

XII – Cardiac anatomy: (sequential description)

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XIII – Valve devices: (structural description, mobility, Doppler)

XIV – Estimated pulmonary artery systolic pressure: (mm Hg)

XV – Parameters for diastolic function assessment:

- E/A:
- Septal E/e': cm/s
- Lateral E/e': cm/s
- S: cm/s
- LAVI: mL/m²
- LA GLS: %
- Others?

XVI – Parameters for systolic function assessment:

- LVEF (Simpson biplane method): %
- Ejection fraction by 3D imaging: %
- LV global longitudinal strain (GLS): %
- Changes in segmental contractility:
- RV global contractility (qualitative analysis):
- RVEF (Simpson): %
- RV global longitudinal strain (GLS) %
- Other?

XVII – Pericardium:

XVIII – Conclusions:

XIX – Functional comparative analysis:

- Decrease in LVEF from baseline: %
- Decrease in GLS from baseline: %

XX – Observations:

APPENDIX 2

IMPORTANT CONSIDERATIONS IN THE EVALUATION OF ECHOCARDIOGRAM REPORT IN CARDIO-ONCOLOGY

1) Echocardiography should always be performed before any hematology-oncology treatment to record the patient's initial functional status and identify preexisting heart disease. These data will serve as a comparative basis for subsequent examinations.

2) Before the next cycle of chemotherapy, echocardiographic tests should ideally be performed 3 weeks after the last infusion or as close as possible to the next.

3) Intermediate examinations are recommended according to the treatment protocol (cardiotoxic potential of the chemotherapeutic drugs used) or stratification of individual cardiovascular risk.

4) Consider the patient's blood volume status (preload and afterload) as it may influence the actual strain values.

- 5) Evaluations in case of complications that compromise the patient's hemodynamic status will serve as isolated information. The examination must be repeated after improvement of the patient's clinical symptoms.
- 6) In case of detected dysfunctions (decreased LVEF and/or GLS or changes in diastolic function), the examination must be repeated after 3 weeks for confirmation of suspected condition or interpretation as a transient condition that will require future consideration.
- 7) In case of decreased LVEF and/or GLS when using known noncardiotoxic drugs, other causes for myocardial dysfunction must be considered (e.g., infection, CAD).
- 8) A good ECG tracing must be obtained for adequate strain quantification.
- 9) Use adequate echocardiographic windows whenever possible, avoiding image shortening as it leads to overvalued myocardial deformation indices.
- 10) Ideally, the same examiner should assess the patient during the entire follow-up.
- 11) When assessing a patient, consider using equipment of the same manufacturer during the entire follow-up.
- 12) GLS should not be performed in patients with cardiac arrhythmia (atrial fibrillation, severe tachycardia, and atrioventricular block).

APPENDIX 3

WARNING SIGNS DURING ECHOCARDIOGRAM EVALUATION IN CARDIO-ONCOLOGY

● Favorable	● Attention	● Caution	● Unfavorable
● Normal LVEF + normal GLS + Troponin (-) ● Normal LVEF + normal GLS + type I diastolic dysfunction = transient change? Reassess situation during the next elective examination. - Changes in segmental contractility + normal LVEF + normal GLS = Subclinical dysfunction? Transient change? = Reassess situation during the next elective examination.	● LVEF in the lower limit of normal in tachycardic patient. ● Normal LVEF + GLS < 16% or > 15% decrease from baseline GLS = Subclinical dysfunction? Consider cardioprotective measures.	● Abnormal LVEF + GLS < 16% or > 15% decrease from baseline GLS + troponin (+) = Discuss risks/benefits of chemotherapy regimen + cardiovascular treatment. = Repeat echocardiogram soon.	● Abnormal LVEF (< 40%) = Discuss temporary cessation of chemotherapy regimen + cardiovascular treatment. = Repeat echocardiogram soon. ● Pulmonary hypertension with right ventricle involvement. ● Cardiac tamponade.

Statement

References

- Santos MO. Estimate 2018: Cancer Incidence in Brazil. *Revista Brasileira de Cancerologia*. 2018;64(1):119-20.
- DeVita VT, Jr., Rosenberg SA. Two hundred years of cancer research. *N Engl J Med*. 2012;366(23):2207-14.
- Siqueira ASE, Siqueira-Filho AG, Land MGP. Analysis of the Economic Impact of Cardiovascular Diseases in the Last Five Years in Brazil. *Arq Bras Cardiol*. 2017;109(1):39-46.
- Zamorano JL, Lancellotti P, Rodriguez Munoz D, 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 Heart J*. 2016;37(36):2768-801.
- Armenian S, Bhatia S. Predicting and Preventing Anthracycline-Related Cardiotoxicity. *Am Soc Clin Oncol Educ Book*. 2018;38:3-12.
- 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*. 2017;35(8):893-911.
- Grupo de Estudos em Insuficiência Cardíaca da Sociedade Brasileira de C, Sociedade Brasileira de Oncologia C, Instituto do Coracao - Faculdade de Medicina da Universidade de Sao P, Instituto do Cancer do Estado de Sao Paulo - Faculdade de Medicina da Universidade de Sao P, Kalil Filho R, Hajjar LA, et al. [Brazilian Guideline for Cardio-Oncology from Sociedade Brasileira de Cardiologia]. *Arq Bras Cardiol*. 2011;96(2 Suppl 1):1-52.
- Virani SA, Dent S, Brezden-Masley C, Clarke B, Davis MK, Jassal DS, et al. Canadian Cardiovascular Society Guidelines for Evaluation and Management of Cardiovascular Complications of Cancer Therapy. *Can J Cardiol*. 2016;32(7):831-41.
- Feldman AM, Lorell BH, Reis SE. Trastuzumab in the treatment of metastatic breast cancer : anticancer therapy versus cardiotoxicity. *Circulation*. 2000;102(3):272-4.
- Ewer MS, Lippman SM. Type II chemotherapy-related cardiac dysfunction: time to recognize a new entity. *J Clin Oncol*. 2005;23(13):2900-2.
- Cardinale D, Colombo A, Bacchiani G, Tedeschi I, Meroni CA, Veglia F, et al. Early detection of anthracycline cardiotoxicity and improvement with heart failure therapy. *Circulation*. 2015;131(22):1981-8.
- Johnson DB, Chandra S, Sosman JA. Immune Checkpoint Inhibitor Toxicity in 2018. *JAMA*. 2018;320(16):1702-3.
- 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(1):77-84.
- Hajjar LA, Costa IBSS, Lopes MACQ, Hoff PMG, Diz MDPE, Fonseca SMR, et al. Diretriz Brasileira de Cardio-oncologia – 2020. *Arq Bras Cardiol*. 2020; [online]. DOI: <https://doi.org/10.36660/abc.20201006>
- Plana JC, Thavendiranathan P, Bucciarelli-Ducci C, Lancellotti P. Multi-Modality Imaging in the Assessment of Cardiovascular Toxicity in the Cancer Patient. *JACC Cardiovasc Imaging*. 2018;11(8):1173-86.
- Tassan-Mangina S, Codorean D, Metivier M, Costa B, Himberlin C, Jouannaud C, et al. Tissue Doppler imaging and conventional echocardiography after anthracycline treatment in adults: early and late alterations of left ventricular function during a prospective study. *Eur J Echocardiogr*. 2006;7(2):141-6.
- Pavlopoulos H, Nihoyannopoulos P. Strain and strain rate deformation parameters: from tissue Doppler to 2D speckle tracking. *Int J Cardiovasc Imaging*. 2008;24(5):479-91.
- Eidem BW. Identification of anthracycline cardiotoxicity: left ventricular ejection fraction is not enough. *J Am Soc Echocardiogr*. 2008;21(12):1290-2.
- Force T. Introduction to cardiotoxicity review series. *Circ Res*. 2010;106(1):19-20.
- Mantovani G, Madeddu C, Cadeddu C, Dessi M, Piras A, Massa E, et al. Persistence, up to 18 months of follow-up, of epirubicin-induced myocardial dysfunction detected early by serial tissue Doppler echocardiography: correlation with inflammatory and oxidative stress markers. *Oncologist*. 2008;13(12):1296-305.
- Thavendiranathan P, Poulin F, Lim KD, Plana JC, Woo A, Marwick TH. Use of myocardial strain imaging by echocardiography for the early detection of cardiotoxicity in patients during and after cancer chemotherapy: a systematic review. *J Am Coll Cardiol*. 2014;63(25 Pt A):2751-68.
- Ganame J, Claus P, Eyskens B, Uyttebroeck A, Renard M, D'Hooge J, et al. Acute cardiac functional and morphological changes after Anthracycline infusions in children. *Am J Cardiol*. 2007;99(7):974-7.
- Ganame J, Claus P, Uyttebroeck A, Renard M, D'Hooge J, Bijnsens B, et al. Myocardial dysfunction late after low-dose anthracycline treatment in asymptomatic pediatric patients. *J Am Soc Echocardiogr*. 2007;20(12):1351-8.
- Sawaya 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.
- Tan TC, Bouras S, Sawaya H, Sebag IA, Cohen V, Picard MH, et al. Time Trends of Left Ventricular Ejection Fraction and Myocardial Deformation Indices in a Cohort of Women with Breast Cancer Treated with Anthracyclines, Taxanes, and Trastuzumab. *J Am Soc Echocardiogr*. 2015;28(5):509-14.
- Almeida ALC, Silva VA, de Souza Filho AT, Rios VG, Lopes JR, de Afonseca SO, et al. Subclinical ventricular dysfunction detected by speckle tracking two years after use of anthracycline. *Arq Bras Cardiol*. 2015;104(4):274-83.
- Piveta RB, Rodrigues ACT, Vieira MLC, Fischer CH, Afonso TR, Daminello E, et al. Early Changes in Myocardial Mechanics Detected by 3-Dimensional Speckle Tracking Echocardiography in Patients Treated With Low Doses of Anthracyclines. *JACC Cardiovasc Imaging*. 2018;11(11):1729-31.
- 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. *Eur Heart J Cardiovasc Imaging*. 2014;15(10):1063-93.
- Liu J, Banchs J, Mousavi N, Plana JC, Scherrer-Crosbie M, Thavendiranathan P, et al. Contemporary Role of Echocardiography for Clinical Decision Making in Patients During and After Cancer Therapy. *JACC Cardiovasc Imaging*. 2018;11(8):1122-31.
- Thavendiranathan P, Negishi T, Somerset E, Negishi K, Penicka M, Lemieux J, Aakhus S, Miyazaki S, Shirazi M, Galderisi M, Marwick TH, on behalf of the SUCCOUR investigators, Strain-Guided Management of Potentially Cardiotoxic Cancer Therapy, *Journal of the American College of Cardiology* (2020), doi: <https://doi.org/10.1016/j.jacc.2020.11.020>.
- Negishi K, Negishi T, Haluska BA, Hare JL, Plana JC, Marwick TH. Use of speckle strain to assess left ventricular responses to cardiotoxic chemotherapy and cardioprotection. *Eur Heart J Cardiovasc Imaging*. 2014;15(3):324-31.
- Mor-Avi V, Lang RM. Is echocardiography reliable for monitoring the adverse cardiac effects of chemotherapy? *J Am Coll Cardiol*. 2013;61(1):85-7.
- Nesser HJ, Mor-Avi V, Gorissen W, Weinert L, Steringer-Mascherbauer R, Niel J, et al. Quantification of left ventricular volumes using three-dimensional echocardiographic speckle tracking: comparison with MRI. *Eur Heart J*. 2009;30(13):1565-73.
- 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 resonance imaging. *J Clin Oncol*. 2012;30(23):2876-84.

35. 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.
36. Porter TR, Abdelmoneim S, Belcik JT, McCulloch ML, Mulvagh SL, Olson JJ, et al. Guidelines for the cardiac sonographer in the performance of contrast echocardiography: a focused update from the American Society of Echocardiography. *J Am Soc Echocardiogr*. 2014;27(8):797-810.
37. Peel AB, Thomas SM, Dittus K, Jones LW, Lakoski SG. Cardiorespiratory fitness in breast cancer patients: a call for normative values. *J Am Heart Assoc*. 2014;3(1):e000432.
38. Khouri MG, Hornsby WE, Risum N, Velazquez EJ, Thomas S, Lane A, et al. Utility of 3-dimensional echocardiography, global longitudinal strain, and exercise stress echocardiography to detect cardiac dysfunction in breast cancer patients treated with doxorubicin-containing adjuvant therapy. *Breast Cancer Res Treat*. 2014;143(3):531-9.
39. Civelli M, Cardinale D, Martinoni A, Lamantia G, Colombo N, Colombo A, et al. Early reduction in left ventricular contractile reserve detected by dobutamine stress echo predicts high-dose chemotherapy-induced cardiac toxicity. *Int J Cardiol*. 2006;111(1):120-6.
40. Kirkham AA, Virani SA, Campbell KL. The utility of cardiac stress testing for detection of cardiovascular disease in breast cancer survivors: a systematic review. *Int J Womens Health*. 2015;7:127-40.
41. Eidem BW, Sapp BG, Suarez CR, Cetta F. Usefulness of the myocardial performance index for early detection of anthracycline-induced cardiotoxicity in children. *Am J Cardiol*. 2001;87(9):1120-2, A9.
42. Ishii M, Tsutsumi T, Himeno W, Eto G, Furi J, Hashino K, et al. Sequential evaluation of left ventricular myocardial performance in children after anthracycline therapy. *Am J Cardiol*. 2000;86(11):1279-81, A9.
43. Dorup I, Levitt G, Sullivan I, Sorensen K. Prospective longitudinal assessment of late anthracycline cardiotoxicity after childhood cancer: the role of diastolic function. *Heart*. 2004;90(10):1214-6.
44. 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(5):493-8.
45. Tadic M, Cuspidi C, Hering D, Venneri L, Danylenko O. The influence of chemotherapy on the right ventricle: did we forget something? *Clin Cardiol*. 2017;40(7):437-43.
46. Boczar KE, Aseyev O, Sulpher J, Johnson C, Burwash IG, Turek M, et al. Right heart function deteriorates in breast cancer patients undergoing anthracycline-based chemotherapy. *Echo Res Pract*. 2016;3(3):79-84.
47. Calleja A, Poulin F, Khorolsky C, Shariat M, Bedard PL, Amir E, et al. Right Ventricular Dysfunction in Patients Experiencing Cardiotoxicity during Breast Cancer Therapy. *J Oncol*. 2015;2015:609194.
48. van Royen N, Jaffe CC, Krumholz HM, Johnson KM, Lynch PJ, Natale D, et al. Comparison and reproducibility of visual echocardiographic and quantitative radionuclide left ventricular ejection fractions. *Am J Cardiol*. 1996;77(10):843-50.
49. Nousiainen T, Jantunen E, Vanninen E, Hartikainen J. Early decline in left ventricular ejection fraction predicts doxorubicin cardiotoxicity in lymphoma patients. *Br J Cancer*. 2002;86(11):1697-700.
50. Angelidis G, Giamouzis G, Karagiannis G, Butler J, Tsougos I, Valotassiou V, et al. SPECT and PET in ischemic heart failure. *Heart Fail Rev*. 2017;22(2):243-61.
51. Guimaraes SL, Brandao SC, Andrade LR, Maia RJ, Markman Filho B. Cardiac sympathetic hyperactivity after chemotherapy: early sign of cardiotoxicity? *Arq Bras Cardiol*. 2015;105(3):228-34.
52. Carrio I, Cowie MR, Yamazaki J, Udelson J, Camici PG. Cardiac sympathetic imaging with mIBG in heart failure. *JACC Cardiovasc Imaging*. 2010;3(1):92-100.
53. Borde C, Kand P, Basu S. Enhanced myocardial fluorodeoxyglucose uptake following Adriamycin-based therapy: Evidence of early chemotherapeutic cardiotoxicity? *World J Radiol*. 2012;4(5):220-3.
54. Jingu K, Kaneta T, Nemoto K, Ichinose A, Oikawa M, Takai Y, et al. The utility of 18F-fluorodeoxyglucose positron emission tomography for early diagnosis of radiation-induced myocardial damage. *Int J Radiat Oncol Biol Phys*. 2006;66(3):845-51.
55. Toubert ME, Vercellino L, Faugeron I, Lussato D, Hindie E, Bousquet G. Fatal heart failure after a 26-month combination of tyrosine kinase inhibitors in a papillary thyroid cancer. *Thyroid*. 2011;21(4):451-4.
56. Hu JR, Florido R, Lipson EJ, Naidoo J, Ardehali R, Tocchetti CG, et al. Cardiovascular toxicities associated with immune checkpoint inhibitors. *Cardiovasc Res*. 2019;115(5):854-68.
57. Locatelli L, Cadamuro M, Spirli C, Fiorotto R, Lecchi S, Morell CM, et al. Macrophage recruitment by fibrocystin-defective biliary epithelial cells promotes portal fibrosis in congenital hepatic fibrosis. *Hepatology*. 2016;63(3):965-82.
58. Evans JD, Gomez DR, Chang JY, Gladish GW, Erasmus JJ, Rebuena N, et al. Cardiac (1)(8)F-fluorodeoxyglucose uptake on positron emission tomography after thoracic stereotactic body radiation therapy. *Radiother Oncol*. 2013;109(1):82-8.
59. Thavendiranathan P, Wintersperger BJ, Flamm SD, Marwick TH. Cardiac MRI in the assessment of cardiac injury and toxicity from cancer chemotherapy: a systematic review. *Circ Cardiovasc Imaging*. 2013;6(6):1080-91.
60. Jordan JH, Todd RM, Vasu S, Hundley WG. Cardiovascular Magnetic Resonance in the Oncology Patient. *JACC Cardiovasc Imaging*. 2018;11(8):1150-72.
61. Jolly MP, Jordan JH, Melendez GC, McNeal GR, D'Agostino RB, Jr., Hundley WG. Automated assessments of circumferential strain from cine CMR correlate with LVEF declines in cancer patients early after receipt of cardiotoxic chemotherapy. *J Cardiovasc Magn Reson*. 2017;19(1):59.
62. Ong G, Brezden-Masley C, Dhir V, Deva DP, Chan KKW, Chow CM, et al. Myocardial strain imaging by cardiac magnetic resonance for detection of subclinical myocardial dysfunction in breast cancer patients receiving trastuzumab and chemotherapy. *Int J Cardiol*. 2018;261:228-33.
63. Drafts BC, Twomley KM, D'Agostino R, Jr., Lawrence J, Avis N, Ellis LR, et al. Low to moderate dose anthracycline-based chemotherapy is associated with early noninvasive imaging evidence of subclinical cardiovascular disease. *JACC Cardiovasc Imaging*. 2013;6(8):877-85.
64. Schulz-Menger J, Bluemke DA, Bremerich J, Flamm SD, Fogel MA, Friedrich MG, et al. Standardized image interpretation and post processing in cardiovascular magnetic resonance: Society for Cardiovascular Magnetic Resonance (SCMR) board of trustees task force on standardized post processing. *J Cardiovasc Magn Reson*. 2013;15(1):35.
65. Sara L, Szarf G, Tachibana A, Shiozaki AA, Villa AV, de Oliveira AC, et al. [II Guidelines on Cardiovascular Magnetic Resonance and Computed Tomography of the Brazilian Society of Cardiology and the Brazilian College of Radiology]. *Arq Bras Cardiol*. 2014;103(6 Suppl 3):1-86.
66. Oberholzer K, Kunz RP, Dittrich M, Thelen M. [Anthracycline-induced cardiotoxicity: cardiac MRI after treatment for childhood cancer]. *Rofo*. 2004;176(9):1245-50.
67. Farhad H, Staziaki PV, Addison D, Coelho-Filho OR, Shah RV, Mitchell RN, et al. Characterization of the Changes in Cardiac Structure and Function in Mice Treated With Anthracyclines Using Serial Cardiac Magnetic Resonance Imaging. *Circ Cardiovasc Imaging*. 2016;9(12):e003584.
68. Mahrholdt H, Wagner A, Judd RM, Sechtem U, Kim RJ. Delayed enhancement cardiovascular magnetic resonance assessment of non-ischaemic cardiomyopathies. *Eur Heart J*. 2005;26(15):1461-74.
69. de Ville de Goyet M, Brichard B, Robert A, Renard L, Veyckemans F, Vanhoutte L, et al. Prospective cardiac MRI for the analysis of biventricular function in children undergoing cancer treatments. *Pediatr Blood Cancer*. 2015;62(5):867-74.

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70. Fallah-Rad N, Lytwyn M, Fang T, Kirkpatrick I, Jassal DS. Delayed contrast enhancement cardiac magnetic resonance imaging in trastuzumab induced cardiomyopathy. *J Cardiovasc Magn Reson*. 2008;10(1):5.
71. Neilan TG, Rothenberg ML, Amiri-Kordestani L, Sullivan RJ, Steingart RM, Gregory W, et al. Myocarditis Associated with Immune Checkpoint Inhibitors: An Expert Consensus on Data Gaps and a Call to Action. *Oncologist*. 2018;23(8):874-8.
72. Mahmood SS, Fradley MG, Cohen JV, Nohria A, Reynolds KL, Heinzerling LM, et al. Myocarditis in Patients Treated With Immune Checkpoint Inhibitors. *J Am Coll Cardiol*. 2018;71(16):1755-64.
73. Melendez GC, Jordan JH, D'Agostino RB, Jr., Vasu S, Hamilton CA, Hundley WG. Progressive 3-Month Increase in LV Myocardial ECV After Anthracycline-Based Chemotherapy. *JACC Cardiovasc Imaging*. 2017;10(6):708-9.
74. Ferreira de Souza T, Quinaglia ACST, Osorio Costa F, Shah R, Neilan TG, Velloso L, et al. Anthracycline Therapy Is Associated With Cardiomyocyte Atrophy and Preclinical Manifestations of Heart Disease. *JACC Cardiovasc Imaging*. 2018;11(8):1045-55.
75. Zagrosek A, Abdel-Aty H, Boye P, Wassmuth R, Messroghli D, Utz W, et al. Cardiac magnetic resonance monitors reversible and irreversible myocardial injury in myocarditis. *JACC Cardiovasc Imaging*. 2009;2(2):131-8.
76. Kim RJ, Fieno DS, Parrish TB, Harris K, Chen EL, Simonetti O, et al. Relationship of MRI delayed contrast enhancement to irreversible injury, infarct age, and contractile function. *Circulation*. 1999;100(19):1992-2002.
77. Assomull RG, Prasad SK, Lyne J, Smith G, Burman ED, Khan M, et al. Cardiovascular magnetic resonance, fibrosis, and prognosis in dilated cardiomyopathy. *J Am Coll Cardiol*. 2006;48(10):1977-85.
78. Ylanen K, Poutanen T, Savikurki-Heikkilä P, Rinta-Kiikka I, Eerola A, Vetteranta K. Cardiac magnetic resonance imaging in the evaluation of the late effects of anthracyclines among long-term survivors of childhood cancer. *J Am Coll Cardiol*. 2013;61(14):1539-47.
79. 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(22):2263-70.
80. Wassmuth R, Schulz-Menger J. Late gadolinium enhancement in left ventricular dysfunction after trastuzumab. *J Am Coll Cardiol*. 2011;58(25):2697-8; author reply 9-700.
81. Lawley C, Wainwright C, Segelov E, Lynch J, Beith J, McCrohon J. Pilot study evaluating the role of cardiac magnetic resonance imaging in monitoring adjuvant trastuzumab therapy for breast cancer. *Asia Pac J Clin Oncol*. 2012;8(1):95-100.
82. Jordan JH, Vasu S, Morgan TM, D'Agostino RB, Jr., Melendez 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(8).
83. Varki A. Trousseau's syndrome: multiple definitions and multiple mechanisms. *Blood*. 2007;110(6):1723-9.
84. Khalil J, Bensaid B, Elkacemi H, Afif M, Bensaid Y, Kebdani T, et al. Venous thromboembolism in cancer patients: an underestimated major health problem. *World J Surg Oncol*. 2015;13:204.
85. Sallah S, Wan JY, Nguyen NP. Venous thrombosis in patients with solid tumors: determination of frequency and characteristics. *Thromb Haemost*. 2002;87(4):575-9.
86. Cohen AT, Katholing A, Rietbrock S, Bamber L, Martinez C. Epidemiology of first and recurrent venous thromboembolism in patients with active cancer. A population-based cohort study. *Thromb Haemost*. 2017;117(1):57-65.
87. Timp JF, Braekkan SK, Versteeg HH, Cannegieter SC. Epidemiology of cancer-associated venous thrombosis. *Blood*. 2013;122(10):1712-23.
88. Cronin-Fenton DP, Sondergaard F, Pedersen LA, Fryzek JP, Cetin K, Acquavella J, et al. Hospitalisation for venous thromboembolism in cancer patients and the general population: a population-based cohort study in Denmark, 1997-2006. *Br J Cancer*. 2010;103(7):947-53.
89. Needleman L, Cronan JJ, Lilly MP, Merli GJ, Adhikari S, Hertzberg BS, et al. Ultrasound for Lower Extremity Deep Venous Thrombosis: Multidisciplinary Recommendations From the Society of Radiologists in Ultrasound Consensus Conference. *Circulation*. 2018;137(14):1505-15.
90. McGee DC, Gould MK. Preventing complications of central venous catheterization. *N Engl J Med*. 2003;348(12):1123-33.
91. Verso M, Agnelli G. Venous thromboembolism associated with long-term use of central venous catheters in cancer patients. *J Clin Oncol*. 2003;21(19):3665-75.
92. Monreal M, Raventos A, Lerma R, Ruiz J, Lafoz E, Alastrue A, et al. Pulmonary embolism in patients with upper extremity DVT associated to venous central lines—a prospective study. *Thromb Haemost*. 1994;72(4):548-50.
93. Saber W, Moua T, Williams EC, Verso M, Agnelli G, Couban S, et al. Risk factors for catheter-related thrombosis (CRT) in cancer patients: a patient-level data (IPD) meta-analysis of clinical trials and prospective studies. *J Thromb Haemost*. 2011;9(2):312-9.
94. Eastman ME, Khorsand M, Maki DG, Williams EC, Kim K, Sondel PM, et al. Central venous device-related infection and thrombosis in patients treated with moderate dose continuous-infusion interleukin-2. *Cancer*. 2001;91(4):806-14.
95. Murray J, Precious E, Ali Khan R. Catheter-related thrombosis in cancer patients. *Br J Haematol*. 2013;162(6):748-57.
96. Schmaier AA, Ambesh P, Campia U. Venous Thromboembolism and Cancer. *Curr Cardiol Rep*. 2018;20(10):89.
97. DelleGrottaglie S, Ostenfeld E, Sanz J, Scatteia A, Perrone-Filardi P, Bossone E. Imaging the Right Heart-Pulmonary Circulation Unit: The Role of MRI and Computed Tomography. *Heart Fail Clin*. 2018;14(3):377-91.
98. Johns CS, Kiely DG, Rajaram S, Hill C, Thomas S, Karunasaagarar K, et al. Diagnosis of Pulmonary Hypertension with Cardiac MRI: Derivation and Validation of Regression Models. *Radiology*. 2019;290(1):61-8.
99. Bane O, Shah SJ, Cuttica MJ, Collins JD, Selvaraj S, Chatterjee NR, et al. A non-invasive assessment of cardiopulmonary hemodynamics with MRI in pulmonary hypertension. *Magn Reson Imaging*. 2015;33(10):1224-35.
100. Johns CS, Kiely DG, Swift AJ. Novel imaging techniques in pulmonary hypertension. *Curr Opin Cardiol*. 2018;33(6):587-93.
101. Rengier F, Melzig C, Derlin T, Marra AM, Vogel-Claussen J. Advanced imaging in pulmonary hypertension: emerging techniques and applications. *Int J Cardiovasc Imaging*. 2019;35(8):1407-20.
102. Cutter DJ, Darby SC, Yusuf SW. Risks of heart disease after radiotherapy. *Tex Heart Inst J*. 2011;38(3):257-8.
103. Groarke JD, Nguyen PL, Nohria A, Ferrari R, Cheng S, Moslehi J. Cardiovascular complications of radiation therapy for thoracic malignancies: the role for non-invasive imaging for detection of cardiovascular disease. *Eur Heart J*. 2014;35(10):612-23.
104. Lee MS, Finch W, Mahmud E. Cardiovascular complications of radiotherapy. *Am J Cardiol*. 2013;112(10):1688-96.
105. Darby SC, Ewertz M, McGale P, Bennet AM, Blom-Goldman U, Bronnum D, et al. Risk of ischemic heart disease in women after radiotherapy for breast cancer. *N Engl J Med*. 2013;368(11):987-98.
106. Nolan MT, Russell DJ, Negishi K, Marwick TH. Meta-Analysis of Association Between Mediastinal Radiotherapy and Long-Term Heart Failure. *Am J Cardiol*. 2016;118(11):1685-91.
107. Venkatesulu BP, Mahadevan LS, Aliru ML, Yang X, Bodd MH, Singh PK, et al. Radiation-Induced Endothelial Vascular Injury: A Review of Possible Mechanisms. *JACC Basic Transl Sci*. 2018;3(4):563-72.

108. Gujral DM, Lloyd G, Bhattacharyya S. Radiation-induced valvular heart disease. *Heart*. 2016;102(4):269-76.
109. Jaworski C, Mariani JA, Wheeler G, Kaye DM. Cardiac complications of thoracic irradiation. *J Am Coll Cardiol*. 2013;61(23):2319-28.
110. Cheng YJ, Nie XY, Ji CC, Lin XX, Liu LJ, Chen XM, et al. Long-Term Cardiovascular Risk After Radiotherapy in Women With Breast Cancer. *J Am Heart Assoc*. 2017;6(5).
111. Cuomo JR, Javaheri SP, Sharma GK, Kapoor D, Berman AE, Weintraub NL. How to prevent and manage radiation-induced coronary artery disease. *Heart*. 2018;104(20):1647-53.
112. Cheng SW, Ting AC, Ho P, Wu LL. Accelerated progression of carotid stenosis in patients with previous external neck irradiation. *J Vasc Surg*. 2004;39(2):409-15.
113. Lam WW, Ho SS, Leung SF, Wong KS, Metreweli C. Cerebral blood flow measurement by color velocity imaging in radiation-induced carotid stenosis. *J Ultrasound Med*. 2003;22(10):1055-60.
114. Moutardier V, Christophe M, Lelong B, Houvenaeghel G, Delperio JR. Iliac atherosclerotic occlusive disease complicating radiation therapy for cervix cancer: a case series. *Gynecol Oncol*. 2002;84(3):456-9.
115. Xu J, Cao Y. Radiation-induced carotid artery stenosis: a comprehensive review of the literature. *Interv Neurol*. 2014;2(4):183-92.
116. Muzaffar K, Collins SL, Labropoulos N, Baker WH. A prospective study of the effects of irradiation on the carotid artery. *Laryngoscope*. 2000;110(11):1811-4.
117. Wilbers J, Dorresteyn LD, Haast R, Hoebers FJ, Kaanders JH, Boogerd W, et al. Progression of carotid intima media thickness after radiotherapy: a long-term prospective cohort study. *Radiother Oncol*. 2014;113(3):359-63.
118. Meeske KA, Siegel SE, Gilsanz V, Bernstein L, Nelson MB, Spoto R, et al. Premature carotid artery disease in pediatric cancer survivors treated with neck irradiation. *Pediatr Blood Cancer*. 2009;53(4):615-21.
119. Mavrogeni S, Dimitroulas T, Chatziioannou SN, Kitas G. The role of multimodality imaging in the evaluation of Takayasu arteritis. *Semin Arthritis Rheum*. 2013;42(4):401-12.
120. Carmody BJ, Arora S, Avena R, Curry KM, Simpkins J, Cosby K, et al. Accelerated carotid artery disease after high-dose head and neck radiotherapy: is there a role for routine carotid duplex surveillance? *J Vasc Surg*. 1999;30(6):1045-51.
121. Tallarita T, Oderich GS, Lanzino G, Cloft H, Kallmes D, Bower TC, et al. Outcomes of carotid artery stenting versus historical surgical controls for radiation-induced carotid stenosis. *J Vasc Surg*. 2011;53(3):629-36 e1-5.
122. Protack CD, Bakken AM, Saad WE, Illig KA, Waldman DL, Davies MG. Radiation arteritis: a contraindication to carotid stenting? *J Vasc Surg*. 2007;45(1):110-7.
123. Fokkema M, den Hartog AG, Bots ML, van der Tweel I, Moll FL, de Borst GJ. Stenting versus surgery in patients with carotid stenosis after previous cervical radiation therapy: systematic review and meta-analysis. *Stroke*. 2012;43(3):793-801.
124. Pham HD, Prather MG, Rush DS. Percutaneous Treatment of Superficial Femoral Artery Stenosis Secondary to Radiation Arteritis. *Am Surg*. 2016;82(11):1098-100.
125. Lind PA, Pagnanelli R, Marks LB, Borges-Neto S, Hu C, Zhou SM, et al. Myocardial perfusion changes in patients irradiated for left-sided breast cancer and correlation with coronary artery distribution. *Int J Radiat Oncol Biol Phys*. 2003;55(4):914-20.
126. Hardenbergh PH, Munley MT, Bentel GC, Kedem R, Borges-Neto S, Hollis D, et al. Cardiac perfusion changes in patients treated for breast cancer with radiation therapy and doxorubicin: preliminary results. *Int J Radiat Oncol Biol Phys*. 2001;49(4):1023-8.
127. Donnellan E, Phelan D, McCarthy CP, Collier P, Desai M, Griffin B. Radiation-induced heart disease: A practical guide to diagnosis and management. *Cleve Clin J Med*. 2016;83(12):914-22.
128. Adams MJ, Lipshultz SE, Schwartz C, Fajardo LF, Coen V, Constine LS. Radiation-associated cardiovascular disease: manifestations and management. *Semin Radiat Oncol*. 2003;13(3):346-56.
129. Lancellotti P, Nkomo VT, Badano LP, Bergler-Klein J, Bogaert J, Davin L, et al. Expert consensus for multi-modality imaging evaluation of cardiovascular complications of radiotherapy in adults: a report from the European Association of Cardiovascular Imaging and the American Society of Echocardiography. *Eur Heart J Cardiovasc Imaging*. 2013; 14(8):721-40.
130. Mulrooney DA, Nunnery SE, Armstrong GT, Ness KK, Srivastava D, Donovan FD, et al. Coronary artery disease detected by coronary computed tomography angiography in adult survivors of childhood Hodgkin lymphoma. *Cancer*. 2014;120(22):3536-44.
131. Girinsky T, M'Kacher R, Lessard N, Koscielny S, Elfassy E, Raoux F, et al. Prospective coronary heart disease screening in asymptomatic Hodgkin lymphoma patients using coronary computed tomography angiography: results and risk factor analysis. *Int J Radiat Oncol Biol Phys*. 2014;89(1):59-66.
132. van Rosendaal AR, Daniels LA, Dimitriu-Leen AC, Smit JM, van Rosendaal PJ, Schali J, et al. Different manifestation of irradiation induced coronary artery disease detected with coronary computed tomography compared with matched non-irradiated controls. *Radiother Oncol*. 2017;125(1):55-61.
133. Greenwood JP, Maredia N, Younger JF, Brown JM, Nixon J, Colin C Everett CC, et al. Cardiovascular magnetic resonance and single-photon emission computed tomography for diagnosis of coronary heart disease (CE-MARC): a prospective trial. *Lancet*. 2012; 379(9814):453-60.
134. Schelbert EB, Cao JJ, Sigurdsson S, Aspelund T, Kellman P, Aletras AH, et al. Prevalence and prognosis of unrecognized myocardial infarction determined by cardiac magnetic resonance in older adults. *JAMA*. 2012; 308(9): 890-6.
135. Burke A, Tavora F. The 2015 WHO Classification of Tumors of the Heart and Pericardium. *J Thorac Oncol*. 2016;11(4):441-52.
136. Mankad R, Herrmann J. Cardiac tumors: echo assessment. *Echo Res Pract*. 2016;3(4):R65-R77.
137. Strachinaru M, Damry N, Duttmann R, Wauthy P, Catez E, Lutea M, et al. Ultrasound Contrast Quantification for the Diagnosis of Intracardiac Masses. *JACC Cardiovasc Imaging*. 2016;9(6):747-50.
138. Tang QY, Guo LD, Wang WX, Zhou W, Liu YN, Liu HY, et al. Usefulness of contrast perfusion echocardiography for differential diagnosis of cardiac masses. *Ultrasound Med Biol*. 2015;41(9):2382-90.
139. Ganame J, D'Hooge J, Mertens L. Different deformation patterns in intracardiac tumors. *Eur J Echocardiogr*. 2005;6(6):461-4.
140. Zaragoza-Macias E, Chen MA, Gill EA. Real time three-dimensional echocardiography evaluation of intracardiac masses. *Echocardiography*. 2012;29(2):207-19.
141. Singu T, Inatomi Y, Yonehara T, Ando Y. Calcified Amorphous Tumor Causing Shower Embolism to the Brain: A Case Report with Serial Echocardiographic and Neuroradiologic Images and a Review of the Literature. *J Stroke Cerebrovasc Dis*. 2017;26(5):e85-e9.
142. Tzani A, Doulamis IP, Mylonas KS, Avgerinos DV, Nasioudis D. Cardiac Tumors in Pediatric Patients: A Systematic Review. *World J Pediatr Congenit Heart Surg*. 2017;8(5):624-32.
143. Jain S, Maleszewski JJ, Stephenson CR, Klarich KW. Current diagnosis and management of cardiac myxomas. *Expert Rev Cardiovasc Ther*. 2015;13(4):369-75.
144. Gowda RM, Khan IA, Nair CK, Mehta NJ, Vasavada BC, Sacchi TJ. Cardiac papillary fibroelastoma: a comprehensive analysis of 725 cases. *Am Heart J*. 2003;146(3):404-10.
145. Tamin SS, Maleszewski JJ, Scott CG, Khan SK, Edwards WD, Bruce CJ, et al. Prognostic and Bioepidemiologic Implications of Papillary Fibroelastomas. *J Am Coll Cardiol*. 2015;65(22):2420-9.

Statement

146. Shen Q, Shen J, Qiao Z, Yao Q, Huang G, Hu X. Cardiac rhabdomyomas associated with tuberous sclerosis complex in children. From presentation to outcome. *Herz*. 2015;40(4):675-8.
147. Tao TY, Yahyavi-Firouz-Abadi N, Singh GK, Bhalla S. Pediatric cardiac tumors: clinical and imaging features. *Radiographics*. 2014;34(4):1031-46.
148. Capotosto L, Elena G, Massoni F, De Sio S, Carnevale A, Ricci S, et al. Cardiac Tumors: Echocardiographic Diagnosis and Forensic Correlations. *Am J Forensic Med Pathol*. 2016;37(4):306-16.
149. Cetrano E, Polito A, Carotti A. Primitive intrapericardial teratoma associated with yolk sac tumour. *Cardiol Young*. 2015;25(1):158-60.
150. Li W, Teng P, Xu H, Ma L, Ni Y. Cardiac Hemangioma: A Comprehensive Analysis of 200 Cases. *Ann Thorac Surg*. 2015;99(6):2246-52.
151. Semionov A, Sayegh K. Multimodality imaging of a cardiac paraganglioma. *Radiol Case Rep*. 2016;11(4):277-81.
152. Almobarak AA, AlShammari A, Alhomoudi RI, Eshaq AM, Algain SM, Jensen EC, et al. Benign Pericardial Schwannoma: Case Report and Summary of Previously Reported Cases. *Am J Case Rep*. 2018;19:90-4.
153. Oliveira GH, Al-Kindi SG, Hoimes C, Park SJ. Characteristics and Survival of Malignant Cardiac Tumors: A 40-Year Analysis of > 500 Patients. *Circulation*. 2015;132(25):2395-402.
154. Randhawa JS, Budd GT, Randhawa M, Ahluwalia M, Jia X, Daw H, et al. Primary Cardiac Sarcoma: 25-Year Cleveland Clinic Experience. *Am J Clin Oncol*. 2016;39(6):593-9.
155. Kupsky DF, Newman DB, Kumar G, Maleszewski JJ, Edwards WD, Klarich KW. Echocardiographic Features of Cardiac Angiosarcomas: The Mayo Clinic Experience (1976-2013). *Echocardiography*. 2016;33(2):186-92.
156. Valles-Torres J, Izquierdo-Villarroya MB, Vallejo-Gil JM, Casado-Dominguez JM, Roche Latasa AB, Auquilla-Clavijo P. Cardiac Undifferentiated Pleomorphic Sarcoma Mimicking Left Atrial Myxoma. *J Cardiothorac Vasc Anesth*. 2019;33(2):493-6.
157. Jang JJ, Danik S, Goldman M. Primary cardiac lymphoma: diagnosis and treatment guided by transesophageal echocardiogram perfusion imaging. *J Am Soc Echocardiogr*. 2006;19(8):1073 e7-9.
158. Restrepo CS, Vargas D, Ocazonez D, Martinez-Jimenez S, Betancourt Cuellar SL, Gutierrez FR. Primary pericardial tumors. *Radiographics*. 2013;33(6):1613-30.
159. Hudzik B, Misalski-Jamka K, Glowacki J, Lekston A, Gierlotka M, Zembala M, et al. Malignant tumors of the heart. *Cancer Epidemiol*. 2015;39(5):665-72.
160. Bussani R, De-Giorgio F, Abbate A, Silvestri F. Cardiac metastases. *J Clin Pathol*. 2007;60(1):27-34.
161. Burazor I, Aviel-Ronen S, Imazio M, Goitein O, Perelman M, Shelestovich N, et al. Metastatic cardiac tumors: from clinical presentation through diagnosis to treatment. *BMC Cancer*. 2018;18(1):202.
162. Lestuzzi C, De Paoli A, Baresic T, Miolo G, Buonadonna A. Malignant cardiac tumors: diagnosis and treatment. *Future Cardiol*. 2015;11(4):485-500.
163. Mousavi N, Cheezum MK, Aghayev A, Padera R, Vita T, Steigner M, et al. Assessment of Cardiac Masses by Cardiac Magnetic Resonance Imaging: Histological Correlation and Clinical Outcomes. *J Am Heart Assoc*. 2019;8(1):e007829.
164. Pazos-Lopez P, Pozo E, Siqueira ME, Garcia-Lunar I, Cham M, Jacobi A, et al. Value of CMR for the differential diagnosis of cardiac masses. *JACC Cardiovasc Imaging*. 2014;7(9):896-905.
165. Kassi M, Polsani V, Schutt RC, Wong S, Nabi F, Reardon MJ, et al. Differentiating benign from malignant cardiac tumors with cardiac magnetic resonance imaging. *J Thorac Cardiovasc Surg*. 2019;157(5):1912-22 e2.
166. Colin GC, Dymarkowski S, Gerber B, Michoux N, Bogaert J. Cardiac myxoma imaging features and tissue characteristics at cardiovascular magnetic resonance. *Int J Cardiol*. 2016;202:950-1.
167. O'Donnell DH, Abbata S, Chaithiraphan V, Yared K, Killeen RP, Cury RC, et al. Cardiac tumors: optimal cardiac MR sequences and spectrum of imaging appearances. *AJR Am J Roentgenol*. 2009;193(2):377-87.
168. Sparrow PJ, Kurian JB, Jones TR, Sivanathan MU. MR imaging of cardiac tumors. *Radiographics*. 2005;25(5):1255-76.
169. Braggion-Santos MF, Koenigk-Santos M, Teixeira SR, Volpe GJ, Trad HS, Schmidt A. Magnetic resonance imaging evaluation of cardiac masses. *Arq Bras Cardiol*. 2013;101(3):263-72.
170. Esposito A, De Cobelli F, Ironi G, Marra P, Canu T, Mellone R, et al. CMR in the assessment of cardiac masses: primary malignant tumors. *JACC Cardiovasc Imaging*. 2014;7(10):1057-61.
171. Bhattacharyya S, Khattar RS, Gujral DM, Senior R. Cardiac tumors: the role of cardiovascular imaging. *Expert Rev Cardiovasc Ther*. 2014;12(1):37-43.
172. Rahbar K, Seifarth H, Schafers M, Stegger L, Hoffmeier A, Spieker T, et al. Differentiation of malignant and benign cardiac tumors using 18F-FDG PET/CT. *J Nucl Med*. 2012;53(6):856-63.
173. Bhattacharyya S, Toumpanakis C, Burke M, Taylor AM, Caplin ME, Davar J. Features of carcinoid heart disease identified by 2- and 3-dimensional echocardiography and cardiac MRI. *Circ Cardiovasc Imaging*. 2010;3(1):103-11.
174. Patel C, Mathur M, Escarcega RO, Bove AA. Carcinoid heart disease: current understanding and future directions. *Am Heart J*. 2014;167(6):789-95.
175. Davar J, Connolly HM, Caplin ME, Pavel M, Zacks J, Bhattacharyya S, et al. Diagnosing and Managing Carcinoid Heart Disease in Patients With Neuroendocrine Tumors: An Expert Statement. *J Am Coll Cardiol*. 2017;69(10):1288-304.
176. Dobson R, Burgess MI, Valle JW, Pritchard DM, Vora J, Wong C, et al. Serial surveillance of carcinoid heart disease: factors associated with echocardiographic progression and mortality. *Br J Cancer*. 2014;111(9):1703-9.
177. Westberg C, Wangberg B, Ahlman H, Bergh CH, Beckman-Suurkula M, Caidahl K. Prediction of prognosis by echocardiography in patients with midgut carcinoid syndrome. *Br J Surg*. 2001;88(6):865-72.
178. Dobson R, Cuthbertson DJ, Jones J, Valle JW, Keevil B, Chadwick C, et al. Determination of the optimal echocardiographic scoring system to quantify carcinoid heart disease. *Neuroendocrinology*. 2014;99(2):85-93.
179. Mesquita ET, Jorge AJL, Souza CVJ, Andrade TR. Cardiac Amyloidosis and its New Clinical Phenotype: Heart Failure with Preserved Ejection Fraction. *Arq Bras Cardiol*. 2017;109(1):71-80.
180. Sperry BW, Reyes BA, Ikram A, Donnelly JP, Phelan D, Jaber WA, et al. Tenosynovial and Cardiac Amyloidosis in Patients Undergoing Carpal Tunnel Release. *J Am Coll Cardiol*. 2018;72(17):2040-50.
181. Hasserjian RP, Goodman HJ, Lachmann HJ, Muzikansky A, Hawkins PN. Bone marrow findings correlate with clinical outcome in systemic AL amyloidosis patients. *Histopathology*. 2007;50(5):567-73.
182. Merlini G, Bellotti V. Molecular mechanisms of amyloidosis. *N Engl J Med*. 2003;349(6):583-96.
183. Agha AM, Parwani P, Guha A, Durand JB, Iliescu CA, Hassan S, et al. Role of cardiovascular imaging for the diagnosis and prognosis of cardiac amyloidosis. *Open Heart*. 2018;5(2):e000881.
184. Aljaroudi WA, Desai MY, Tang WH, Phelan D, Cerqueira MD, Jaber WA. Role of imaging in the diagnosis and management of patients with cardiac amyloidosis: state of the art review and focus on emerging nuclear techniques. *J Nucl Cardiol*. 2014;21(2):271-83.
185. Falk RH, Alexander KM, Liao R, Dorbala S. AL (Light-Chain) Cardiac Amyloidosis: A Review of Diagnosis and Therapy. *J Am Coll Cardiol*. 2016;68(12):1323-41.
186. Mohty D, Damy T, Cosnay P, Echahidi N, Casset-Senon D, Viot P, et al. Cardiac amyloidosis: updates in diagnosis and management. *Arch Cardiovasc Dis*. 2013;106(10):528-40.

187. Cueto-Garcia L, Reeder GS, Kyle RA, Wood DL, Seward JB, Naessens J, et al. Echocardiographic findings in systemic amyloidosis: spectrum of cardiac involvement and relation to survival. *J Am Coll Cardiol*. 1985;6(4):737-43.
188. Pagourelis ED, Mirea O, Duchenne J, Van Cleemput J, Delforge M, Bogaert J, et al. Echo Parameters for Differential Diagnosis in Cardiac Amyloidosis: A Head-to-Head Comparison of Deformation and Nondeformation Parameters. *Circ Cardiovasc Imaging*. 2017;10(3):e005588.
189. Barros-Gomes S, Williams B, Nhola LF, Grogan M, Maalouf JF, Dispenzieri A, et al. Prognosis of Light Chain Amyloidosis With Preserved LVEF: Added Value of 2D Speckle-Tracking Echocardiography to the Current Prognostic Staging System. *JACC Cardiovasc Imaging*. 2017;10(4):398-407.
190. Phelan D, Collier P, Thavendiranathan P, Popovic ZB, Hanna M, Plana JC, et al. Relative apical sparing of longitudinal strain using two-dimensional speckle-tracking echocardiography is both sensitive and specific for the diagnosis of cardiac amyloidosis. *Heart*. 2012;98(19):1442-8.
191. Senapati A, Sperry BW, Grodin JL, Kusunose K, Thavendiranathan P, Jaber W, et al. Prognostic implication of relative regional strain ratio in cardiac amyloidosis. *Heart*. 2016;102(10):748-54.
192. Pun SC, Landau HJ, Riedel ER, Jordan J, Yu AF, Hassoun H, et al. Prognostic and Added Value of Two-Dimensional Global Longitudinal Strain for Prediction of Survival in Patients with Light Chain Amyloidosis Undergoing Autologous Hematopoietic Cell Transplantation. *J Am Soc Echocardiogr*. 2018;31(1):64-70.
193. Liu D, Hu K, Stork S, Herrmann S, Kramer B, Cikes M, et al. Predictive value of assessing diastolic strain rate on survival in cardiac amyloidosis patients with preserved ejection fraction. *PLoS One*. 2014;9(12):e115910.
194. Milani P, Dispenzieri A, Scott CG, Gertz MA, Perlini S, Mussinelli R, et al. Independent Prognostic Value of Stroke Volume Index in Patients With Immunoglobulin Light Chain Amyloidosis. *Circ Cardiovasc Imaging*. 2018;11(5):e006588.
195. Feng D, Syed IS, Martinez M, Oh JK, Jaffe AS, Grogan M, et al. Intracardiac thrombosis and anticoagulation therapy in cardiac amyloidosis. *Circulation*. 2009;119(18):2490-7.
196. Dubrey S, Pollak A, Skinner M, Falk RH. Atrial thrombi occurring during sinus rhythm in cardiac amyloidosis: evidence for atrial electromechanical dissociation. *Br Heart J*. 1995;74(5):541-4.
197. Tuzovic M, Yang EH, Baas AS, Depasquale EC, Deng MC, Cruz D, et al. Cardiac Amyloidosis: Diagnosis and Treatment Strategies. *Curr Oncol Rep*. 2017;19(7):46.
198. Syed IS, Glockner JF, Feng D, Araoz PA, Martinez MW, Edwards WD, et al. Role of cardiac magnetic resonance imaging in the detection of cardiac amyloidosis. *JACC Cardiovasc Imaging*. 2010;3(2):155-64.
199. Austin BA, Tang WH, Rodriguez ER, Tan C, Flamm SD, Taylor DO, et al. Delayed hyper-enhancement magnetic resonance imaging provides incremental diagnostic and prognostic utility in suspected cardiac amyloidosis. *JACC Cardiovasc Imaging*. 2009;2(12):1369-77.
200. Dzung JN, Valencia O, Pinney JH, Gibbs SD, Rowczenio D, Gilbertson JA, et al. CMR-based differentiation of AL and ATTR cardiac amyloidosis. *JACC Cardiovasc Imaging*. 2014;7(2):133-42.
201. Karamitsos TD, Piechnik SK, Baniyarsad SM, Fontana M, Ntusi NB, Ferreira VM, et al. Noncontrast T1 mapping for the diagnosis of cardiac amyloidosis. *JACC Cardiovasc Imaging*. 2013;6(4):488-97.
202. Baniyarsad SM, Fontana M, Maestrini V, Sado DM, Captur G, Petrie A, et al. T1 mapping and survival in systemic light-chain amyloidosis. *Eur Heart J*. 2015;36(4):244-51.
203. Amyloidosis Support Groups - HOW FAR ARE YOU FROM TREATMENT AND SUPPORT? [Acessado em 04/07/2020]. Disponível em: <https://www.amyloidosisupport.org/>. 2020.
204. Gillmore JD, Maurer MS, Falk RH, Merlini G, Damy T, Dispenzieri A, et al. Nonbiopsy Diagnosis of Cardiac Transthyretin Amyloidosis. *Circulation*. 2016;133(24):2404-12.
205. Merlini G, Dispenzieri A, Sanchirawala V, Schonland SO, Palladini G, Hawkins PN, et al. Systemic immunoglobulin light chain amyloidosis. *Nat Rev Dis Primers*. 2018;4(1):38.
206. Milani P, Merlini G, Palladini G. Light Chain Amyloidosis. *Mediterr J Hematol Infect Dis*. 2018;10(1):e2018022.
207. Ribeiro-Silva C, Gilberto S, Gomes RA, Mateus E, Monteiro E, Barroso E, et al. The relative amounts of plasma transthyretin forms in familial transthyretin amyloidosis: a quantitative analysis by Fourier transform ion-cyclotron resonance mass spectrometry. *Amyloid*. 2011;18(4):191-9.
208. Burgdorf C, Kurowski V, Bonnemeier H, Schunkert H, Radke PW. Long-term prognosis of the transient left ventricular dysfunction syndrome (Tako-Tsubo cardiomyopathy): focus on malignancies. *Eur J Heart Fail*. 2008;10(10):1015-9.
209. Giza DE, Lopez-Mattei J, Vejpongsa P, Munoz E, Iliescu G, Kitkungvan D, et al. Stress-Induced Cardiomyopathy in Cancer Patients. *Am J Cardiol*. 2017;120(12):2284-8.
210. Heggemann F, Hamm K, Kaelsch T, Sueselbeck T, Papavassiliu T, Borggrefe M, et al. Global and regional myocardial function quantification in Takotsubo cardiomyopathy in comparison to acute anterior myocardial infarction using two-dimensional (2D) strain echocardiography. *Echocardiography*. 2011;28(7):715-9.
211. Frustaci A, Loperfido F, Gentiloni N, Caldarulo M, Morgante E, Russo MA. Catecholamine-induced cardiomyopathy in multiple endocrine neoplasia. A histologic, ultrastructural, and biochemical study. *Chest*. 1991;99(2):382-5.
212. Gilreath JA, Stenehjem DD, Rodgers GM. Diagnosis and treatment of cancer-related anemia. *Am J Hematol*. 2014;89(2):203-12.
213. Lutz K, von Komorowski G, Durken M, Engelhardt R, Dinter DJ. Myocardial iron overload in transfusion-dependent pediatric patients with acute leukemia. *Pediatr Blood Cancer*. 2008;51(5):691-3.
214. Wasserman AJ, Richardson DW, Baird CL, Wyso EM. Cardiac hemochromatosis simulating constrictive pericarditis. *Am J Med*. 1962;32:316-23.
215. Di Odoardo LAF, Giuditta M, Cassinerio E, Roghi A, Pedrotti P, Vicenzi M, et al. Myocardial deformation in iron overload cardiomyopathy: speckle tracking imaging in a beta-thalassemia major population. *Intern Emerg Med*. 2017;12(6):799-809.
216. Li SJ, Hwang YY, Ha SY, Chan GC, Mok AS, Wong SJ, et al. Role of Three-Dimensional Speckle Tracking Echocardiography in the Quantification of Myocardial Iron Overload in Patients with Beta-Thalassemia Major. *Echocardiography*. 2016;33(9):1361-7.
217. Schempp A, Lee J, Kearney S, Mulrooney DA, Smith AR. Iron Overload in Survivors of Childhood Cancer. *J Pediatr Hematol Oncol*. 2016;38(1):27-31.
218. Roy NB, Myerson S, Schuh AH, Bignell P, Patel R, Wainscoat JS, et al. Cardiac iron overload in transfusion-dependent patients with myelodysplastic syndromes. *Br J Haematol*. 2011;154(4):521-4.
219. El Haddad D, Iliescu C, Yusuf SW, William WN, Jr., Khair TH, Song J, et al. Outcomes of Cancer Patients Undergoing Percutaneous Pericardiocentesis for Pericardial Effusion. *J Am Coll Cardiol*. 2015;66(10):1119-28.
220. Lestuzzi C, Berretta M, Tomkowski W. 2015 update on the diagnosis and management of neoplastic pericardial disease. *Expert Rev Cardiovasc Ther*. 2015;13(4):377-89.
221. Yared K, Baggish AL, Picard MH, Hoffmann U, Hung J. Multimodality imaging of pericardial diseases. *JACC Cardiovasc Imaging*. 2010;3(6):650-60.
222. Sogaard KK, Sorensen HT, Smeeth L, Bhaskaran K. Acute Pericarditis and Cancer Risk: A Matched Cohort Study Using Linked UK Primary and Secondary Care Data. *J Am Heart Assoc*. 2018;7(16):e009428.

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223. Kong L, Li Z, Wang J, Lv X. Echocardiographic characteristics of primary malignant pericardial mesothelioma and outcomes analysis: a retrospective study. *Cardiovasc Ultrasound*. 2018;16(1):7.
224. Virk SA, Chandrakumar D, Villanueva C, Wolfenden H, Liou K, Cao C. Systematic review of percutaneous interventions for malignant pericardial effusion. *Heart*. 2015;101(20):1619-26.
225. Brasil. Ministério da Saúde Instituto Nacional de Cancer. Estimativa 2020. [Acessado em 05/07/2020]. Disponível em: <https://www.inca.gov.br>. 2020.
226. Chow EJ, Leger KJ, Bhatt NS, Mulrooney DA, Ross CJ, Aggarwal S, et al. Paediatric cardio-oncology: epidemiology, screening, prevention, and treatment. *Cardiovasc Res*. 2019;115(5):922-34.
227. Armenian SH, Hudson MM, Mulder RL, Chen MH, Constine LS, Dwyer M, et al. Recommendations for cardiomyopathy surveillance for survivors of childhood cancer: a report from the International Late Effects of Childhood Cancer Guideline Harmonization Group. *Lancet Oncol*. 2015;16(3):e123-36.
228. Lipshultz SE, Diamond MB, Franco VI, Aggarwal S, Leger K, Santos MV, et al. Managing chemotherapy-related cardiotoxicity in survivors of childhood cancers. *Paediatr Drugs*. 2014;16(5):373-89.
229. Yeh ET, Bickford CL. Cardiovascular complications of cancer therapy: incidence, pathogenesis, diagnosis, and management. *J Am Coll Cardiol*. 2009;53(24):2231-47.
230. Vejpongs P, Yeh ET. Topoisomerase 2beta: a promising molecular target for primary prevention of anthracycline-induced cardiotoxicity. *Clin Pharmacol Ther*. 2014;95(1):45-52.
231. Levitt GA, Dorup I, Sorensen K, Sullivan I. Does anthracycline administration by infusion in children affect late cardiotoxicity? *Br J Haematol*. 2004;124(4):463-8.
232. Manolis AA, Manolis TA, Mikhailidis DP, Manolis AS. Cardiovascular safety of oncologic agents: A double-edged sword even in the era of targeted therapies - part 1. *Expert Opin Drug Saf*. 2018;17(9):875-92.
233. Chow EJ, Antal Z, Constine LS, Gardner R, Wallace WH, Weil BR, et al. New Agents, Emerging Late Effects, and the Development of Precision Survivorship. *J Clin Oncol*. 2018;36(21):2231-40.
234. Mulrooney DA, Yeazel MW, Kawashima T, Mertens AC, Mitby P, Stovall M, et al. Cardiac outcomes in a cohort of adult survivors of childhood and adolescent cancer: retrospective analysis of the Childhood Cancer Survivor Study cohort. *BMJ*. 2009;339:b4606.
235. Vandecruys E, Mondelaers V, De Wolf D, Benoit Y, Suys B. Late cardiotoxicity after low dose of anthracycline therapy for acute lymphoblastic leukemia in childhood. *J Cancer Surviv*. 2012;6(1):95-101.
236. Landy DC, Miller TL, Lipsitz SR, Lopez-Mitnik G, Hinkle AS, Constine LS, et al. Cranial irradiation as an additional risk factor for anthracycline cardiotoxicity in childhood cancer survivors: an analysis from the cardiac risk factors in childhood cancer survivors study. *Pediatr Cardiol*. 2013;34(4):826-34.
237. Aminkeng F, Bhavsar AP, Visscher H, Rassekh SR, Li Y, Lee JW, et al. A coding variant in RARG confers susceptibility to anthracycline-induced cardiotoxicity in childhood cancer. *Nat Genet*. 2015;47(9):1079-84.
238. Hefti E, Blanco JG. Anthracycline-Related Cardiotoxicity in Patients with Acute Myeloid Leukemia and Down Syndrome: A Literature Review. *Cardiovasc Toxicol*. 2016;16(1):5-13.
239. Pignatelli RH, Ghazi P, Reddy SC, Thompson P, Cui Q, Castro J, et al. Abnormal Myocardial Strain Indices in Children Receiving Anthracycline Chemotherapy. *Pediatr Cardiol*. 2015;36(8):1610-6.
240. Colan SD, Shirali G, Margossian R, Gallagher D, Altmann K, Canter C, et al. The ventricular volume variability study of the Pediatric Heart Network: study design and impact of beat averaging and variable type on the reproducibility of echocardiographic measurements in children with chronic dilated cardiomyopathy. *J Am Soc Echocardiogr*. 2012;25(8):842-54 e6.
241. Roca-Bielsa I, Vlakovic M. Pediatric nuclear medicine and pediatric radiology: modalities, image quality, dosimetry and correlative imaging: new strategies. *Pediatr Radiol*. 2013;43(4):391-2.
242. Corbett JR, Akinboboye OO, Bacharach SL, Borer JS, Botvinick EH, DePuey EG, et al. Equilibrium radionuclide angiocardiology. *J Nucl Cardiol*. 2006;13(6):e56-79.
243. Bybee KA, Prasad A. Stress-related cardiomyopathy syndromes. *Circulation*. 2008;118(4):397-409.
244. Yusuf SW, Sami S, Daher IN. Radiation-induced heart disease: a clinical update. *Cardiol Res Pract*. 2011;2011:317659.
245. Heidenreich PA, Schnittger I, Strauss HW, Vagelos RH, Lee BK, Mariscal CS, et al. Screening for coronary artery disease after mediastinal irradiation for Hodgkin's disease. *J Clin Oncol*. 2007;25(1):43-9.
246. Shankar SM, Marina N, Hudson MM, Hodgson DC, Adams MJ, Landier W, et al. Monitoring for cardiovascular disease in survivors of childhood cancer: report from the Cardiovascular Disease Task Force of the Children's Oncology Group. *Pediatrics*. 2008;121(2):e387-96.
247. van Dalen EC, van der Pal HJ, van den Bos C, Kok WE, Caron HN, Kremer LC. Clinical heart failure during pregnancy and delivery in a cohort of female childhood cancer survivors treated with anthracyclines. *Eur J Cancer*. 2006;42(15):2549-53.
248. Hines MR, Mulrooney DA, Hudson MM, Ness KK, Green DM, Howard SC, et al. Pregnancy-associated cardiomyopathy in survivors of childhood cancer. *J Cancer Surviv*. 2016;10(1):113-21.
249. Bar J, Davidi O, Goshen Y, Hod M, Yaniv I, Hirsch R. Pregnancy outcome in women treated with doxorubicin for childhood cancer. *Am J Obstet Gynecol*. 2003;189(3):853-7.
250. Thompson KA, Hildebrandt MA, Ater JL. Cardiac Outcomes With Pregnancy After Cardiotoxic Therapy for Childhood Cancer. *J Am Coll Cardiol*. 2017;69(5):594-5.
251. Stergiopoulos K, Shiang E, Bench T. Pregnancy in patients with pre-existing cardiomyopathies. *J Am Coll Cardiol*. 2011;58(4):337-50.
252. Athale U, Siciliano S, Thabane L, Pai N, Cox S, Lathia A, et al. Epidemiology and clinical risk factors predisposing to thromboembolism in children with cancer. *Pediatr Blood Cancer*. 2008;51(6):792-7.
253. Caruso V, Iacoviello L, Di Castelnuovo A, Storti S, Mariani G, de Gaetano G, et al. Thrombotic complications in childhood acute lymphoblastic leukemia: a meta-analysis of 17 prospective studies comprising 1752 pediatric patients. *Blood*. 2006;108(7):2216-22.
254. Biss TT, Brandao LR, Kahr WH, Chan AK, Williams S. Clinical features and outcome of pulmonary embolism in children. *Br J Haematol*. 2008;142(5):808-18.
255. Kuderer NM, Ortel TL, Francis CW. Impact of venous thromboembolism and anticoagulation on cancer and cancer survival. *J Clin Oncol*. 2009;27(29):4902-11.
256. Revel-Vilk S, Yacovovich J, Tamary H, Goldstein G, Nemet S, Weintraub M, et al. Risk factors for central venous catheter thrombotic complications in children and adolescents with cancer. *Cancer*. 2010;116(17):4197-205.
257. Chow EJ, Anderson L, Baker KS, Bhatia S, Guilcher GM, Huang JT, et al. Late Effects Surveillance Recommendations among Survivors of Childhood Hematopoietic Cell Transplantation: A Children's Oncology Group Report. *Biol Blood Marrow Transplant*. 2016;22(5):782-95.
258. Armenian SH, Sun CL, Kawashima T, Arora M, Leisenring W, Sklar CA, et al. Long-term health-related outcomes in survivors of childhood cancer treated with HSCT versus conventional therapy: a report from the Bone Marrow Transplant Survivor Study (BMTSS) and Childhood Cancer Survivor Study (CCSS). *Blood*. 2011;118(5):1413-20.
259. Armand P, Kim HT, Cutler CS, Ho VT, Koreth J, Alyea EP, et al. Prognostic impact of elevated pretransplantation serum ferritin in patients undergoing myeloablative stem cell transplantation. *Blood*. 2007;109(10):4586-8.



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In Original Article “Lower Prevalence and Severity of Coronary Atherosclerosis in Chronic Chagas’ Disease by Coronary Computed Tomography Angiography” with DOI number: <https://doi.org/10.36660/abc.20200342>, published in the Journal Arquivos Brasileiros de Cardiologia, 115(6):1051-1060, on page 1059, change the information that there was no external funding to: This study was funded by Capes. Change information that is not associated to: This article is part of the thesis of doctoral submitted by Savio Cardoso from Universidade de São Paulo.

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In Original Article “Treated Hypertensive Patients Assessed by Home Blood Pressure Telemonitoring. TeleMRPA Study”, with DOI number: <https://doi.org/10.36660/abc.20200073>, published in the Journal Arquivos Brasileiros de Cardiologia, 117(3):520-527, on page 520, change the institution of Dr. Roberto Dischinger Miranda from: Universidade Federal de São Paulo Escola Paulista de Medicina, São Paulo, SP - Brasil to: Seção Cardiovascular, Disciplina de Geriatria e Gerontologia, Escola Paulista de Medicina, Universidade Federal de São Paulo, São Paulo, SP - Brasil and add for Dr. Roberto Dischinger Miranda the institution Hospital Israelita Albert Einstein, São Paulo, SP - Brasil. Thus, institution 7 became: Escola de Ciências Sociais e da Saúde - Pontifícia Universidade Católica de Goiás, Goiânia, GO – Brazil; institution 8 became: Estratégia de Saúde da Família - Secretaria Municipal de Saúde Campos do Jordão, Campos do Jordão, SP – Brazil; institution 9 became: Procape / MCor, Recife, PE – Brazil and institution 10 became: Centro Universitário CESMAC - Hospital do Coração, Maceió, AL – Brazil.

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