

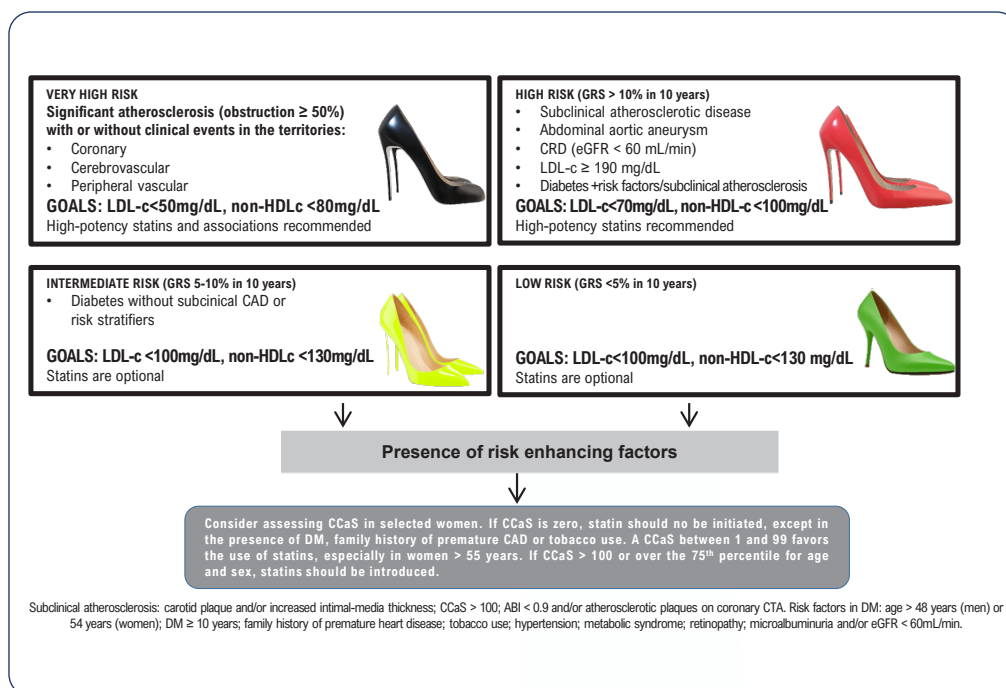


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Atrial Flutter in PRKAG2 Syndrome: Clinical and Electrophysiological Characteristics

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Abstract

Background: PRKAG2 syndrome is a rare autosomal dominant disease, a phenocopy of hypertrophic cardiomyopathy characterized by intracellular glycogen accumulation. Clinical manifestations include ventricular preexcitation, cardiac conduction disorder, ventricular hypertrophy, and atrial arrhythmias.

Objective: To compare the clinical and electrophysiological characteristics observed in patients with atrial flutter, with and without PRKAG2 syndrome.

Methods: An observational study comparing patients with atrial flutter: group A consisted of five patients with PRKAG2 syndrome from a family, and group B consisted of 25 patients without phenotype of PRKAG2 syndrome. The level of significance was 5%.

Results: All patients in group A had ventricular preexcitation and right branch block, and four had pacemakers (80%). Patients in group A were younger (39 ± 5.4 vs 58.6 ± 17.6 years, $p=0.021$), had greater interventricular septum (median=18 vs 10 mm; $p<0.001$) and posterior wall thickness (median=14 vs 10 mm; $p=0.001$). In group A, four patients were submitted to an electrophysiological study, showing a fasciculoventricular pathway, and atrial flutter ablation was performed in tree. All patients in group B were submitted to ablation of atrial flutter, with no evidence of accessory pathway. Group B had a higher prevalence of hypertension, diabetes mellitus, coronary artery disease and sleep apnea, with no statistically significant difference.

Conclusion: Patients with PRKAG2 syndrome presented atrial flutter at an earlier age and had fewer comorbidities when compared to patients with atrial flutter without mutation phenotype. The occurrence of atrial flutter in young individuals, especially in the presence of ventricular preexcitation and familial ventricular hypertrophy, should raise the suspicion of PRKAG2 syndrome.

Keywords: Cardiac Arrhythmias; Atrial Flutter; Hypertrophy, Left Ventricular; Cardiomyopathy, Hypertrophic; Atrioventricular Block; Glycogen Storage Disease.

Introduction

PRKAG2 syndrome is a rare genetic disease of autosomal dominant inheritance caused by mutations in the gene encoding the γ_2 subunit of AMP-activated protein kinase (AMPK).^{1,2} The main histopathological finding in affected patients' hearts is intracellular myocardial glycogen deposition, which may trigger electrophysiological and structural cardiac changes that mimic Wolff-Parkinson-White syndrome (WPW) and hypertrophic cardiomyopathy.³ Studies indicate that the prevalence of

PRKAG2 syndrome is 0.23 to 1% of patients with suspected hypertrophic cardiomyopathy.^{3,4} The incidence of PRKAG2 syndrome may be underestimated in clinical practice, as many cases are mistakenly diagnosed as sarcomeric hypertrophic cardiomyopathy.

The phenotypic manifestation of PRKAG2 syndrome has great variability, consisting of ventricular preexcitation, left ventricular hypertrophy, conduction system disorders, and atrial tachyarrhythmias.⁵ The early identification of PRKAG2 syndrome is of particular interest, as it is related to a high risk of progression to complete atrioventricular block requiring pacemaker implantation and sudden death.⁶

Concerning atrial tachyarrhythmias, previous studies have shown that atrial flutter is less common than atrial fibrillation in the general population, affecting more men.⁷ From the electrocardiographic point of view, it is typically characterized by the presence of F waves in the lower leads and an approximate atrial frequency of 300 bpm.⁸ The electrophysiological mechanism of atrial flutter

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involves macroreentry in atria, using slow, anatomical or functional conduction areas. The incidence increases with age, being less than 5 cases per 100,000 inhabitants among people under 50 but reaching almost 600 cases per 100,000 inhabitants among those over 80.⁹ Although WPW syndrome and hypertrophic cardiomyopathy are related to increased prevalence of atrial fibrillation, the association of atrial flutter and ventricular pre-excitation is a rare phenomenon.^{10,11} In PRKAG2 syndrome, there are reports in the literature of the appearance of atrial flutter in patients with ventricular pre-excitation,¹² but there are few data on clinical and electrophysiological behavior of atrial flutter in the disease. Although atrial flutter may be the first manifestation of PRKAG2 syndrome, a delayed diagnosis of the syndrome can occur, especially when there is no evident ventricular hypertrophy.¹³

This study aimed to compare the clinical, electrocardiographic and electrophysiological characteristics observed in patients with atrial flutter, with and without PRKAG2 syndrome. Members of a family with atrial flutter and previously genotyped with the Arg302Gln mutation of the *PRKAG2* gene were analyzed and compared with a control group of patients with atrial flutter without the phenotype of PRKAG2 syndrome.

Methods

Study participants

This is an observational, retrospective, comparative study involving patients with atrial flutter, selected by convenience sampling. For this, the following criteria were selected: (1) patients with Arg302Gln mutation of the *PRKAG2* gene who developed atrial flutter; (2) patients with records of typical atrial flutter from our arrhythmia service in the last 5 years. Patients were divided into two groups. Group A was composed of five patients from the same family accompanied in our service, composed of 16 members with PRKAG2 syndrome, previously genotyped,¹⁴ who developed atrial flutter, with a mean follow-up time of 15.1 ± 2.9 years. Group B included 25 patients with typical atrial flutter, without the phenotype of PRKAG2 syndrome, consecutively submitted to catheter ablation from 2015 to 2020.

Data were obtained from physical examination, laboratory tests, electrocardiogram, echocardiogram, and electrophysiological study. Short PR interval on electrocardiogram was determined when less than 120 ms. The ventricular pre-excitation pattern was defined by the association of short PR interval with increased QRS duration (> 110 ms) or delta wave. The diagnostic criterion of atrial flutter was previously established. Typical atrial flutter on ECG was defined by the presence of negative F waves in IDI, DIII and aVF and positive in V1. The ECG was performed in 12 leads at a speed of 25mm/s, gain of 10mm:1mV and filter from 0.05Hz to 15Hz.⁸

The echocardiogram diagnosis of left ventricular hypertrophy was established against the thickness of the interventricular septum or posterior wall of the left

ventricle ≥ 13 mm, with no other apparent cause.¹⁵ The electrophysiological study and catheter ablation were performed according to previously described techniques, with atrial and ventricular stimulation, using multipolar diagnostic catheters and an 8 mm irrigated or tip ablation catheter. The cavotricuspid isthmus ablation was performed with bidirectional block and demonstration of atrial double potential (> 100 ms).¹⁶

Statistical analysis

After collecting the information, the data were stored in an Excel spreadsheet and submitted to statistical analysis, performed with R core Team software (Vienna, Austria) for Windows, free of charge. The descriptive statistical analysis expressed categorical variables in absolute frequency and percentage (%). Continuous variables were expressed by mean $\pm$ standard deviation or median (interquartile interval) in cases of non-normal distribution. Data normality was evaluated using the Shapiro-Wilk test. Fisher's exact test was used to compare categorical variables. As appropriate, continuous variables were compared by student's t-test for independent samples or Mann-Whitney U test. A value of $p < 0.05$ was considered significant.

Ethical issues

The Research Ethics Committee approved the study under number 3.044.277, and a free and informed consent form was obtained from the participants.

Results

Clinical characteristics

The clinical, electrocardiographic and echocardiographic characteristics of patients in group A with PRKAG2 syndrome are in Table 1. The analysis of the family heredogram (Figure 1) shows the pattern of autosomal dominant inheritance of the disease, with a report of three sudden unexplained deaths in the family, in individuals with a median age of 38 years. In all five patients included in this study, atrial flutter was identified as the first clinical manifestation of the disease, with a mean age at diagnosis of 39 ± 5.4 years. On the electrocardiogram, all patients in group A presented an electrocardiographic pattern compatible with ventricular preexcitation, associated with right branch block (BRD) in four (80%). Figure 2A shows a typical electrocardiogram of a patient with *PRKAG2* mutation in sinus rhythm, and Figure 2B demonstrates atrial flutter rhythm tracing. Progression to sinus node dysfunction or atrioventricular block led to pacemaker implantation in 4 (80%), with a mean age at implantation of 44 ± 6 years.

Group B consisted of 25 patients with typical atrial flutter, 19 (76%) men, six (24%) with a mean age at diagnosis of 58.6 ± 17.6 years, and one (4%) pacemaker-carrying by sinus node dysfunction. Atrial septal defect was documented in three (12%), and atrial flutter-induced

Table 1 – Clinical characteristics of group A

Patient	Sex	Age	Age at diagnosis	Symptoms	Atrial arrhythmia	PM	LVH
II:5	M	56	30	Palpitation	AFL, AF	+	+
II:6	M	60	42	Syncope, palpitation	AFL, AF	+	+
II:7	F	58	40	Syncope	AFL	+	+
II:10	M	53	44	Presyncope, palpitation	AFL	+	+
III:18	M	43	39	Palpitation	AFL	-	-

M: male; F: female; PM: pacemaker; AFL: atrial flutter; AF: atrial fibrillation; LVH: left ventricular hypertrophy.

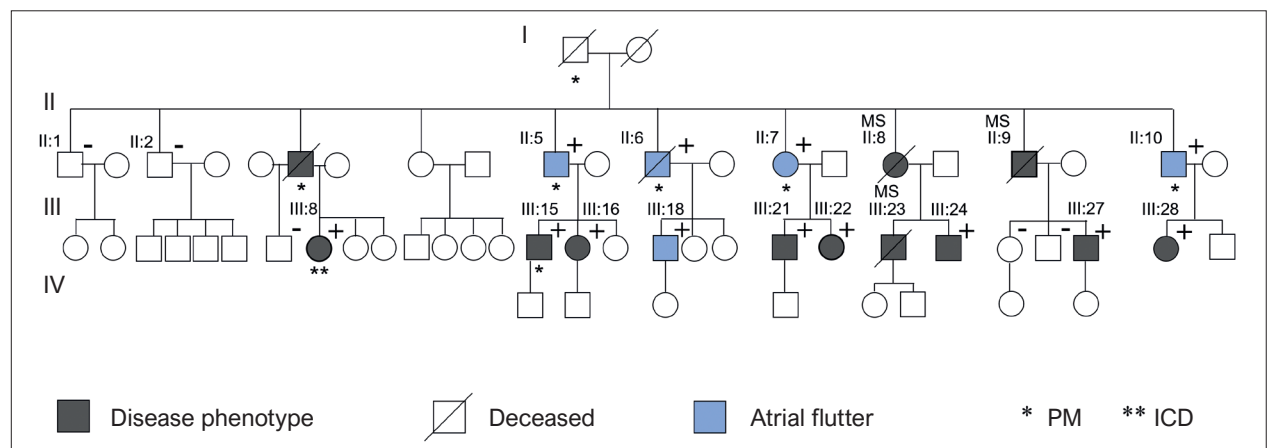


Figure 1 – Heredogram of the family with PRKAG2 syndrome, with identification of the five patients with atrial flutter. PM: pacemaker; ICD: cardioverter implantable defibrillator. Individuals tested for a PRKAG2 mutation are identified as carriers (+) or non-carriers (-). A patient underwent ICD implantation due to a misdiagnosis of hypertrophic cardiomyopathy.

tachycardiomyopathy in three (12%). Only two (8%) group B patients had right branch block, and none had ventricular pre-excitation.

Electrophysiological aspects

Four patients from group A underwent electrophysiological study, three of them male. Short AH and HV intervals were recorded, with fixed HV (median=30 ms), during basic rhythm and rapid atrial stimulation (Figure 3). The Wenckebach point was obtained in four patients, with a mean of 302.5 ± 31 ms. The test with adenosine was performed, with a record of anterograde and retrograde AV block. Decremental ventricle-atrial retrograde conduction was observed during ventricular stimulation in all. The findings were compatible with the presence of fasciculoventricular accessory pathway. Three patients underwent atrial flutter ablation during the procedure, and an arrhythmogenic circuit dependent on the cavotricuspid isthmus was demonstrated. Success was achieved in 100%, without recurrence after 18 months. All patients in Group B were submitted to ablation with a catheter of the typical atrial flutter (cavotricuspid isthmus). The presence of an accessory pathway was not evidenced.

Comparative aspects of groups A and B

The clinical, electrocardiographic, and echocardiographic characteristics of groups A and B (Table 2) were compared. The mean age at the diagnosis of atrial flutter in group A was significantly lower than in group B (39 ± 5.4 vs. 58.6 ± 17.6 years; $p = 0.021$). Among the symptoms, a higher prevalence of syncope/presyncope was observed in group A ($p = 0.004$). Risk factors established for the development of atrial flutter, such as arterial hypertension, diabetes mellitus, sleep apnea, obesity and coronary artery disease, were more prevalent in group B but without statistical significance. There was no statistically significant difference between the groups concerning renal function.

On baseline electrocardiogram in sinus rhythm, it was observed that group A had lower heart rate, shorter PR interval and higher prevalence of BRD. Regarding echocardiographic characteristics, left ventricular hypertrophy was observed in 80% of patients in group A and only 6% of group B ($p=0.001$). There was no statistically significant difference in relation to the ejection fraction and left atrium size.

In addition, total atrioventricular block was observed only in patients in group A (80% vs 0%, $p < 0.001$), as well as more often required PM implantation in relation to group B (80% vs 8%, $p = 0.002$).

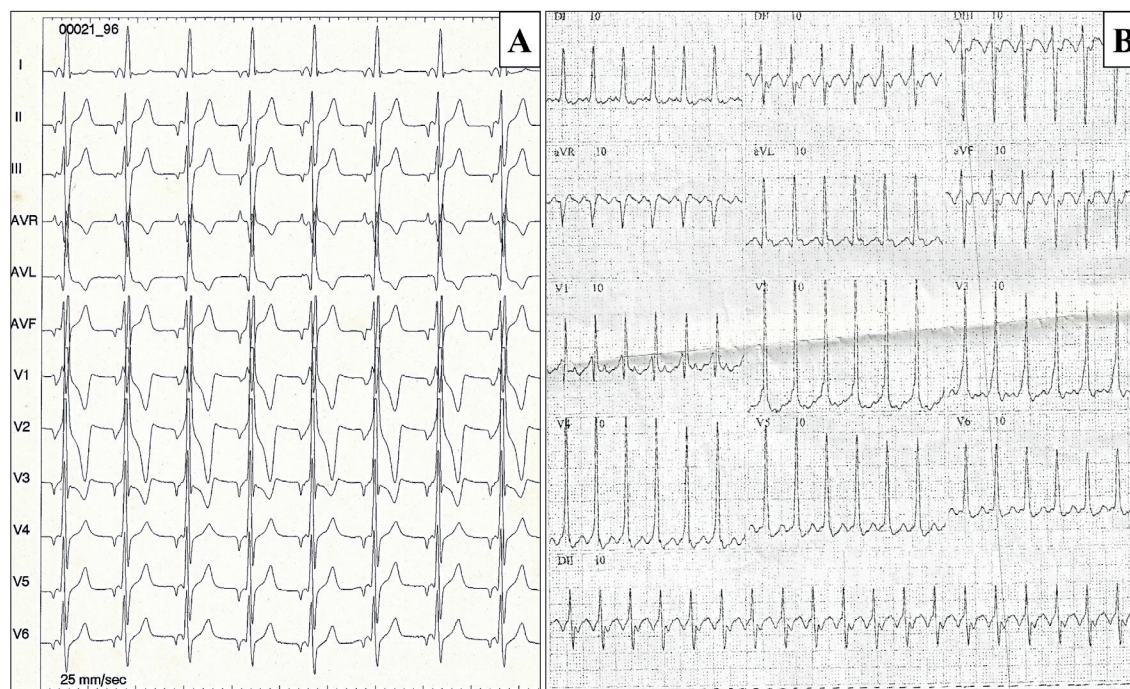


Figure 2 – A) Initial electrocardiogram of patient III:15, evidencing ectopic atrial rhythm and the aspect of ventricular preexcitation, with short PR interval followed by pseudo-delta wave, and QRS complex with right bundle block morphology. B) Electrocardiogram of patient II:10 with the typical pattern of PRKAG2 syndrome, showing atrial flutter with 2:1 conduction.

Discussion

PRKAG2 syndrome is a rare phenocopy of hypertrophic cardiomyopathy, mimicking WPW syndrome.¹⁷ However, the diagnostic distinction is crucial since the natural history, prognosis and treatment strategies are markedly different.¹⁸ Clinical manifestations of PRKAG2 syndrome include atrial tachyarrhythmias such as atrial flutter, conduction system disorders, and sudden death.^{2,3} This study compared the clinical and electrophysiological characteristics of patients with atrial flutter with PRKAG2 syndrome due to the Arg302Gln mutation and patients with atrial flutter without the syndrome phenotype.

One of the most striking characteristics of the electrocardiogram of patients with the PRKAG2 gene mutation is the presence of ventricular pre-excitation, mimicking WPW syndrome.¹ It is described that the incidence of atrial fibrillation in WPW syndrome is higher than in the general population, estimated between 10 and 23%, in the absence of structural heart disease.¹⁹ After catheter ablation of the accessory pathway, the risk of atrial arrhythmia is significantly reduced.²⁰ However, descriptions of atrial flutter in patients with WPW syndrome are rare in the literature.¹⁰ On the other hand, patients with hypertrophic cardiomyopathy have a high incidence of atrial fibrillation.¹⁵ PRKAG2 syndrome presents phenotypic aspects common to these two diseases, but the clinical characteristics and prognosis are peculiar.¹⁸ Regarding atrial tachyarrhythmias, it is estimated that 33% of PRKAG2

mutation carriers are affected by atrial fibrillation or atrial flutter.³ In our series, the prevalence of atrial flutter in patients with PRKAG2 syndrome was 100% from 50 years of age. Therefore, patients presented atrial flutter at an earlier age, with a much higher prevalence than in the general population.²¹

As for comorbidities and extracardiac manifestations that contribute to the increased prevalence of atrial arrhythmias, no statistically significant difference was observed in relation to the presence of hypertension and renal dysfunction between the two groups. However, it is important to note that patients with PRKAG2 syndrome may be susceptible to metabolic changes in the long term.²² There are descriptions in the literature of hypertension in young patients with PRKAG2 Syndrome,³ and renal involvement secondary to immunomediated nephropathy,²³ suggesting that systemic impairment is far more important than previously described.

The Arg302Gln mutation of the PRKAG2 gene found in the patients of this study is one of the most commonly reported in the literature.² However, the correlation between genotype and phenotype remains uncertain. Patients with Arg302Gln mutation presented a higher prevalence of ventricular preexcitation, syncope and pacemaker implantation compared to patients with Asn488Ile mutation, but with a lower prevalence of left ventricular hypertrophy.² As characteristically described in PRKAG2 syndrome, we observed that most patients in group A presented right branch

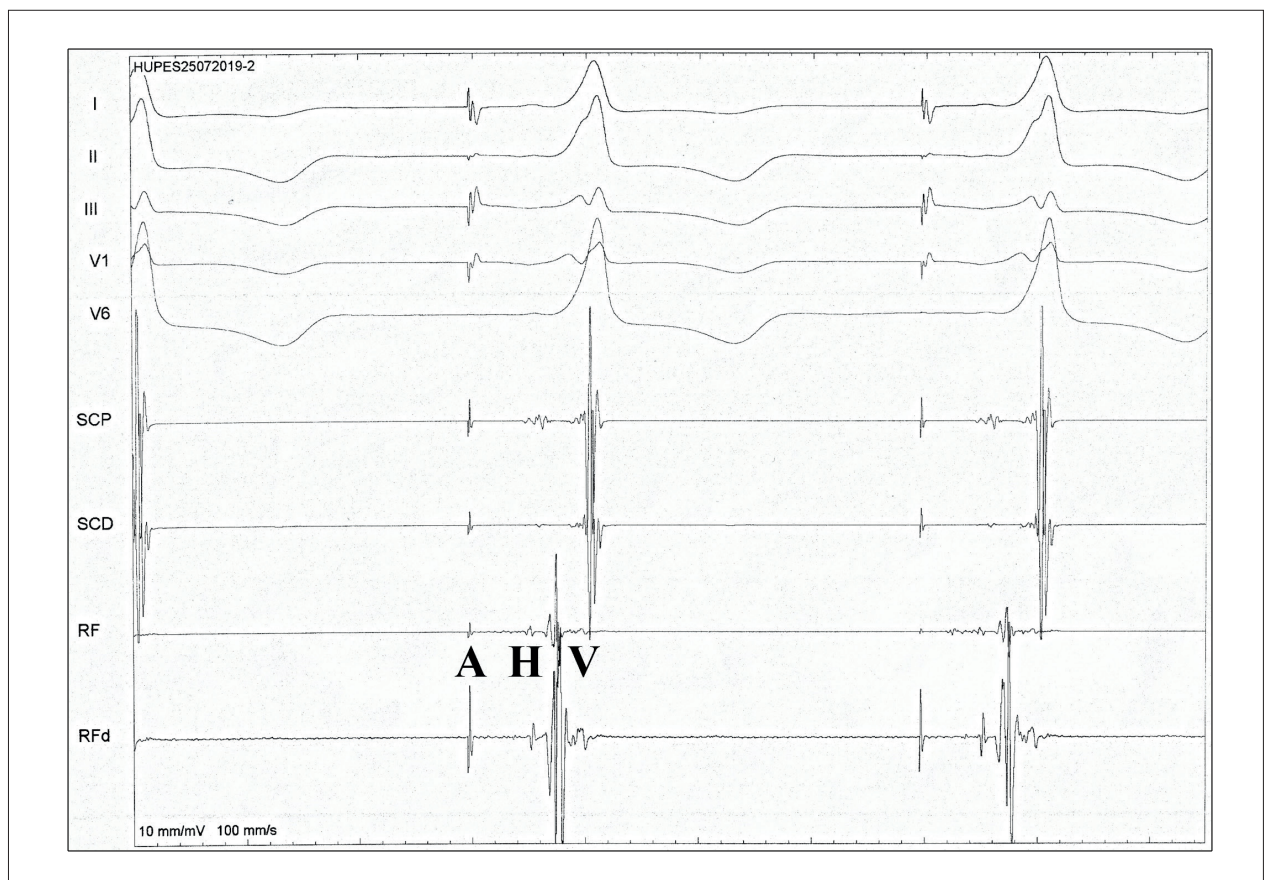


Figure 3 – Tracing of the electrophysiological study of patient II:10. 5-lead electrocardiogram and basic intervals during atrial stimulation, demonstrating HV = 33 ms. AV: atrium-ventricular; A: atrial electrogram; H: His electrogram; V: ventricular electrogram.

block and sinus bradycardia. On the other hand, only 8% of patients in group B had conduction disorder. The sinus bradycardia in *PRKAG2* mutation is typically progressive and can lead to chronotropic incompetence and the need for pacemaker implantation. Analysis from an experimental study suggests that AMPK determines cardiac physiological adaptation to exercise through modulation of ion channels and calcium release in sinoatrial cells.²⁴ In our study, another peculiar aspect was the early evolution of the electrical conduction disorder in four patients in group A, requiring pacemaker implantation.

Another aspect of interest is the approach to atrial flutter in *PRKAG2* syndrome. During the electrophysiological study, we observed the presence of a fasciculoventricular accessory pathway in the four patients of group A, without evidence of atrioventricular tachycardia or induction of ventricular tachycardia. Sternick et al. showed no inducibility of malignant ventricular arrhythmias in the electrophysiological study,¹⁴ suggesting that this is not an important mechanism of sudden death in *PRKAG2* syndrome. Patients with *PRKAG2* mutation in our study were symptomatic, and the chosen strategy was rhythm control through catheter ablation of the cavotricuspid isthmus, which prevented further recurrence. Therefore, atrial flutter ablation seems effective in patients with

PRKAG2 syndrome. Future studies should analyze a possible role for prophylactic cavotricuspid isthmus ablation in patients with *PRKAG2* syndrome undergoing diagnostic electrophysiological study.

Study limitations

Since *PRKAG2* syndrome is a rare disease, we consider as potential limitations of this study: the retrospective analysis involving only the Arg302Gln mutation of the *PRKAG2* gene and a limited number of patients, which may compromise the statistical power and extrapolation capacity of the data. Group B was composed of patients who presented atrial flutter without the phenotype of *PRKAG2* syndrome, but genotyping was not performed in these patients to exclude the presence of the mutation. Since *PRKAG2* mutation carriers have a very distinct phenotype with high penetrance, the probability of finding the mutation in individuals without *PRKAG2* syndrome phenotype is low; thus, it does not represent a significant limitation for the study.

Conclusion

Compared to patients with atrial flutter without a genetic mutation phenotype, patients with *PRKAG2* syndrome

Table 2 – Comparative result of the two groups' clinical, electro and echocardiographic characteristics

Characteristics	Group A n = 5	Group B n = 25	p
Age (years)	54 ± 6.7	60 ± 17.2	0.422
Age at diagnosis (years)	39.0 ± 5.4	58.6 ± 17.6	0.021
Male	4 (80)	19 (76)	0.999
Syncope	3 (60)	1 (4)	0.009
Hypertension	3 (60)	16 (64)	0.999
DM	0 (0)	3 (12)	0.999
Sleep apnea	0 (0)	1 (4)	0.999
Obesity, BMI > 30 kg/m ²	0 (0)	8 (32)	0.287
CAD	0 (0)	4 (16)	0.999
Creatinine clearance (mL/min/1,73m ²)	77.2 (60.7-81.5)	84.4 (66.0-102.8)	0.275
LA (mm)	42 (38-47)	40 (38-42)	0.435
SW (mm)	18 (14-26)	10 (9-11)	<0.001
PW (mm)	14 (11-15)	10 (9-11)	0.001
LVDD (mm)	46 (44-50)	50 (47-55)	0.124
EF (%)	71 (60-76)	66 (59-69)	0.223
LVH	4 (80)	1 (4)	0.009
HR (bpm)	52 (44-57)	62 (56-75)	0.007
PR interval (ms)	100 (100-110)	160 (140-188)	<0.001
QRS (ms)	120 (100-140)	90 (90-93)	0.001
RBB	3 (60)	2 (8)	0.022
CAVB	3 (60)	0 (0)	0.002
Pacemaker	4 (80)	1 (4)	0.001

*Continuous variables were expressed as mean ±, or median (interquartile interval). Categorical variables were expressed as n (%). DM: diabetes mellitus; CAD: coronary artery disease; BMI: body mass index; HR: heart rate; RBB: right branch block; CAVB: complete atrioventricular block; LA: left atrium; SW: septal wall; PW: posterior wall; LVDD: left ventricular diastolic diameter; EF: ejection fraction; LVH: left ventricular hypertrophy.

caused by Arg302Gln mutation presented atrial flutter at an earlier age, associated with a high prevalence of cardiac conduction disorder and need for pacemaker implantation. The typical atrial flutter electrophysiological circuit, dependent on the cavotricuspid isthmus, was amenable to treatment through catheter ablation.

Thus, we propose that the presence of atrial flutter in a young individual without other comorbidities should alert to the possibility of genetically determined heart disease, such as PRKAG2 syndrome, especially in the presence of ventricular pre-excitation and familial left ventricular hypertrophy. Confirmation with genetic testing and family screening should be part of the management strategy.

Author Contributions

Conception and design of the research and Statistical analysis: Magalhães EFS, Magalhães LP; Acquisition of data: Magalhães EFS, Magalhães LP, Pinheiro JO, Guabiru

AT; Analysis and interpretation of the data and Writing of the manuscript: Magalhães EFS, Magalhães LP, Aras R; Critical revision of the manuscript for important intellectual content: Magalhães EFS, Magalhães LP, Pinheiro JO, Guabiru AT, Aras R.

Potential Conflict of Interest

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

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Study Association

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PRKAG2 Cardiomyopathy

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Short Editorial related to the article: Atrial Flutter in PRKAG2 Syndrome: Clinical and Electrophysiological Characteristics

Magalhães et al.¹ assessed atrial flutter's clinical, electrocardiographic, and electrophysiologic characteristics in patients with and without PRKAG2 cardiomyopathy.¹ Although genetic sequencing was not carried out in their control patients, the absence of clinical features of this pathology is acceptable evidence of a non-carrier state. In humans, mutations in the PRKAG2 gene result in a highly penetrant phenotype. It is dominated by the cardiac features of left ventricular hypertrophy, ventricular pre-excitation, atrial tachyarrhythmia, cardiac conduction disease, and myocardial glycogen storage. It would be very unlikely to find a patient with a positive genotype for PRKAG2 in the setting of a negative phenotype.

Our group pioneered the study of PRKAG2 cardiomyopathy in Brazil. The first patient was assessed in 1994, a 36-years old male, with mild hypertension, with recurrent episodes of common atrial flutter. The electrocardiogram showed ventricular pre-excitation, enlarged P waves, a significant increase in the QRS voltage, and sinus bradycardia.² Of 8 brothers, six had very similar electrocardiographic findings. Their mother had had a pacemaker implanted at the age of 42. The echocardiogram showed a non-obstructive form of asymmetric left ventricular hypertrophy and mild left atrial enlargement. There were sufficient elements to allow a presumptive diagnosis of a phenocopy of hypertrophic cardiomyopathy! In 1994, however, we were not able to make the diagnosis. The mutations of the PRKAG2 gene had yet to be reported in 1994, but it would be 7 years later.³ Then, in 2004, we undertook genetic sequencing of the patients. We presented our experience during the NASPE Congress of 2005. Our research received the first prize in clinical arrhythmia during the Brazilian Congress of Cardiac Arrhythmias of 2004.²

After the presentation, some colleagues from Bahia and Campinas told me they had similar cases. With the help of the geneticist Dr Ramon Brugada who at that time worked at Masonic Medical Research Laboratory in New York, we obtained genetic sequencing from some of our patients. The mutation found in most cases was Arg302Gln (R301Q),

responsible for half of all cases reported worldwide, which now number around 300.⁴ Recently we reported a new pathogenic variant, H401Q.⁵ Another new variant, K290I, was reported in a family from Bahia.⁶ Over the last 5 years, genetic sequencing has been carried out at the Molecular Biology Laboratory of Dr. Fernando Eugenio Cruz at the Instituto de Cardiologia, Rio de Janeiro. We have also been collaborating with the team of Prof. Campos de Carvalho at the Federal University of Rio de Janeiro, aiming to induce pluripotent stem cell cardiomyocytes with the objective of better understanding the electrophysiologic changes and developing gene editing techniques.⁷

The work of Magalhães et al.¹ serves to increase our awareness of PRKAG2 cardiomyopathy. We now follow up a cohort of 60 individuals from 7 families from different places. Many of these young patients, aged 20 to 30, have an atrial flutter and have been appropriately referred for catheter ablation. Despite being treated in hospitals with a high standard of care, even University Hospitals, the diagnosis of PRKAG2 cardiomyopathy is usually missed. Another feature worthy of comment is ventricular pre-excitation, which is very common in this syndrome. If present, this arrhythmia should properly be identified to avoid being targeted for ablation. An attempt at ablation could result in the inadvertent production of atrioventricular block.⁴

It is of utmost significance to distinguish PRKAG2 cardiomyopathy from sarcomeric hypertrophic cardiomyopathy. This is because not only the clinical presentation but also the long-term outcomes are different. Sudden death is more prevalent in the PRKAG2 variant. Even the mechanism of sudden death is distinct. In young patients, atrial flutter, or fibrillation with a fast ventricular rate, is the common trigger for sudden cardiac death. In those reaching the fourth decade, atrioventricular conduction block is the major cause, and insertion of a pacemaker is life-saving. Fast ventricular rates during atrial tachyarrhythmias are linked to a fast-conducting fasciculo-ventricular pathway, one variant that produces pre-excitation. We have recently reported that such accessory pathways are ubiquitous in humans.⁸ In those with PRKAG2 mutations, the pathways probably manifest because of the glycogen storage in their cardiomyocytes.⁹

Another interesting characteristic of PRKAG2 cardiomyopathy is the lack of ventricular fibrosis.¹⁰ Using cardiac magnetic resonance imaging, we have identified late gadolinium enhancement in one-sixth of our cohort of 30 patients, as compared to an anticipated incidence in half of the individuals with sarcomeric hypertrophic cardiomyopathy.¹¹ We have seen patients over 50 years of age, usually with significant hypertrophy, who develop fibrosis as shown on gadolinium enhancement, and who have malignant

Keywords

Arrhythmias, Cardiac; Atrial Flutter; Hypertrophy, Left Ventricular; Cardiomyopathy, Hypertrophic; Atrioventricular Block; Glycogen Storage Disease

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arrhythmias (unpublished observations). In contrast, older individuals with the sarcomeric variant of hypertrophic cardiomyopathy seem to have a better prognosis.

The PRKAG2 syndrome should always be considered as a differential diagnosis in young patients with atrial flutter or fibrillation. This is particularly the case in the presence of additional abnormalities, such as persistent sinus bradycardia, intra-atrial or atrioventricular conduction abnormalities, ventricular pre-excitation, or unexplained cardiac hypertrophy.^{12,13} As the condition has a high penetrance and prevalence, other affected individuals are usually found in the family. Occasionally, there will be relatives with a pacemaker and others who died suddenly.

Being 100% sensitive, genetic sequencing is the gold standard for diagnosis. If not available, percutaneous endomyocardial biopsy samples from the ventricular septum, assessed using transmission electron microscopy, are diagnostic in most cases. The key findings will be the presence of large deposits of glycogen granules in the cytosol, the absence of inflammation and fibrosis, and a normal cardiomyocytic architecture.^{3,14}

To summarize, the PRKAG2 syndrome presents as an isolated cardiomyopathy, although some rare variants were associated with mild skeletal myopathies. Systemic arterial hypertension is common, and insulin resistance has been reported, along with increased levels of triglycerides. Obesity has been reported in transgenic murine models.¹⁵

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Pharmaco-invasive Strategy in Myocardial Infarction: Descriptive Analysis, Presentation of Ischemic Symptoms and Mortality Predictors

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Abstract

Background: ST-segment elevation myocardial infarction (STEMI) is defined by symptoms accompanied by typical electrocardiogram changes. However, the characterization of ischemic symptoms is unclear, especially in subgroups such as women and the elderly.

Objectives: To analyze the typification of ischemic symptoms, temporal metrics and observe the occurrence of in-hospital outcomes, in the analysis of predictive scores, in patients with STEMI, in a drug-invasive strategy.

Methods: Study involving 2,290 patients. Types of predefined clinical presentations: typical pain, atypical pain, dyspnea, syncope. We measured the time between the onset of symptoms and demand for care and the interval between arrival at the medical unit and thrombolysis. Odds-ratios (OR; CI-95%) were estimated in a regression model. ROC curves were constructed for mortality predictors. The adopted significance level (alpha) was 5%.

Results: Women had a high prevalence of atypical symptoms; longer time between the onset of symptoms and seeking care; delay between arrival at the emergency room and fibrinolysis. Hospital mortality was 5.6%. Risk prediction by Killip-Kimball classification: AUC: [0.77 (0.73-0.81)] in class $\geq$ II. Subgroups studied [OR (CI-95%)]: women [2.06 (1.42-2.99); $p=0.01$]; chronic renal failure [3.39 (2.13-5.42); $p<0.001$]; elderly [2.09 (1.37-3.19) $p<0.001$]; diabetics [1.55 (1.04-2.29); $p=0.02$]; obese 1.56 [(1.01-2.40); $p=0.04$]; previous stroke [2.01 (1.02-3.96); $p=0.04$] correlated with higher mortality rates.

Conclusion: Despite higher mortality rates in some subgroups, significant disparity persists in women, with delays in symptom recognition and prompt thrombolysis. We highlight the applicability of the Killip-Kimball score in prediction, regardless of the clinical presentation.

Keywords: ST Elevation Myocardial Infarction; Acute Coronary Syndrome; Percutaneous Coronary Intervention/methods; Thrombolytic, Therapy/methods; Angina Pectoris; Hospitalization; Mortality.

Introduction

Despite advances in reperfusion approaches, acute myocardial infarction continues to be the leading cause of death worldwide. Its diagnosis is considered when typical electrocardiographic (ECG) changes and/or the elevation of markers can be detected, notably troponins, which have received increasing attention as highly specific markers of myocardial injury. ST-segment elevation myocardial infarction (STEMI) is usually caused by acute coronary occlusion, secondary to plaque rupture and thrombosis, requiring

early intervention.¹ Therefore, the management of STEMI must be performed as quickly as possible to prevent further damage to the myocardium and decrease the risk of complications and mortality. Although primary percutaneous coronary intervention (PCI) is considered a “gold standard” treatment, it is not sufficiently available, especially in developing countries. The STREAM study values a reperfusion strategy combining fibrinolytic therapy and immediate transfer to a tertiary center for rescue PCI in non-responders to fibrinolysis, as well as early diagnostic angiography and secondary PCI within 24 h after thrombolysis.² However, some factors can influence the delay in seeking emergency assistance, such as the perception and recognition of acute ischemic symptoms. The interpretation of warning signs is the trigger that leads patients to seek medical attention, due to the severity of this potentially fatal condition. By contrast, pain must be seen as a multidimensional phenomenon involving physiological, sensory, and sociocultural aspects, and can be impacted by expectations within a cultural context.

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Risk stratification enables providers to identify the right level of care and services for distinct subgroups of patients. It is the process of assigning a risk status, then using this report to guide what care is provided and to improve overall health outcomes. Nevertheless, during the diagnostic process of myocardial infarction, based on clinical reports and ECG criteria, differences may appear regarding how the symptoms are referred to, particularly in specific subgroups, such as women or older age groups, presenting evidence and relevance of early recanalization, whose benefits become more discreet or even non-existent in late reperfusion.^{3,4} Additionally, there are still controversies and special interests regarding the performance of early mortality predictors in patients undergoing thrombolytic treatment in a pharmacoinvasive approach. Therefore, the present study considers the stratified assessment of ischemic symptoms, fundamentally associated with temporal metrics, including the time between the onset of symptoms and the search for medical care, the patients' medical needs between arrival at the emergency unit and the recognition of the acute condition, with the prompt installation of the reperfusion protocols. In the scenario of the pharmacoinvasive strategy, possible differences can also be speculated concerning the manner in which the symptoms appeared and pivotal times in some subgroups, considering the impact of late reperfusion on relevant clinical outcomes.

Thus, our study aimed to examine the associations between the clinical presentation of ischemic symptoms and risk factors with cardiovascular outcomes in a cohort of STEMI patients during the hospitalization period, as well as perform an accurate analysis of risk prediction scores.

Methods

Study design and ethical statements

Prospective and observational study, with a sample size defined by convenience, involving 2,290 STEMI patients who were consecutively admitted to a university hospital in the city of Sao Paulo, Brazil. All patients were initially submitted to thrombolytic therapy with tenecteplase (TNK) in hospital units or primary care centers and were then referred for coronary angiography. When appropriate, percutaneous coronary interventions were performed within 24 hours post-fibrinolysis, or immediately if rescue therapy was needed. This study complies with the Declaration of Helsinki; the local ethics committee approved the research protocol; and informed consent was obtained from all patients or their legal guardians. The study is registered in ClinicalTrials.gov (NCT02090712).

Pharmacoinvasive strategy

The pharmacoinvasive strategy is defined by fibrinolysis treatment with a bolus injection of TNK, with a weight-adjusted dose, followed by cardiac catheterization within 24 hours, even in stable patients with successful reperfusion, with the intention to treat the culprit lesion. After the STREAM trial results in June 2013, patients over 75 years of age received a half dose of tenecteplase (1/2 TNK). Upon diagnosis, the patients received acetylsalicylic acid

and clopidogrel, as recommended by guidelines.⁵ Rescue angioplasties were recommended by the local medical team due to ineffective thrombolysis in the treatment of an infarct-related artery (IRA). The term *culprit lesion* was used to designate the artery vessel responsible for the symptoms of the STEMI patient. In most cases, only culprit lesions were treated, that is, only IRA lesions were addressed directly through angioplasty and stent delivery. The present study counted on a centralized database, containing a demographic profile, clinical data, ECGs, treatments, time intervals, and in-hospital events. Thus, all relevant outcomes were systematically recorded and mortality rates were analyzed by independent observers.

Definitions of clinical presentations

The clinical presentation of acute ischemic symptoms was reported by the patients, and trained staff reviewed the data during the in-hospital period.

1) Typical Chest Pain: oppressive chest pain on the left side, which can be irradiated to the left upper limb, of great intensity and prolonged (longer than 20 minutes), which did not improve or had only partial relief with rest or sublingual nitrates. Irradiation to the mandible, right upper limb, back, shoulders, and epigastrium was also considered for this presentation. This group included patients with a concomitant presentation of dyspnea, or syncopal episode.

2) Atypical Pain: pain in the right upper quadrant or epigastric region of the abdomen, dorsal, mandibular region, or another non-thoracic region, referred to as a twinge or burning of variable intensity, with prolonged duration (greater than 20 minutes). Included in this group were patients with a concomitant presentation of dyspnea or syncopal episodes.

3) Dyspnea: this group included those patients who did not report chest pain but who complained of acute fatigue or worsening of this symptom within the last couple of hours. The subjective experience of respiratory distress, comprised of qualitatively different sensations with varying intensity was considered.

4) Syncope: This symptom was considered for those patients who did not report chest pain but did report fainting or a sudden and transient loss of consciousness or any worsening within the last couple of hours.

Measured pivotal times

1) Time interval between the onset of persistent chest pain, or another representative complaint of ischemic symptoms, and the patient's arrival at the primary health unit;

2) Time interval between the patient's arrival at the health unit and thrombolysis;

3) Time interval between thrombolysis and coronary angiography.

Prediction scores

Risk predictors used during first medical contact:

- 1) Killip-Kimball Classification (KK);⁶
- 2) TIMI-Risk;⁷
- 3) GRACE score⁸

Angiographic variables

Experienced interventional cardiologists performed angiographic analyses according to TIMI-flow score (epicardial coronary perfusion);⁹ and Myocardial Blush Grade (MBG)¹⁰ (myocardial tissue-level perfusion), thus obtaining TIMI-flow and MBG before and after the percutaneous intervention when applicable (named as initial and final scores). Complications inherent to the procedure have also been reported. The procedural strategy (thrombus aspiration, balloon dilatation, stent selection, and anticoagulation regimen) was left up to the discretion of the operator.

Statistical analysis

This study sought to achieve a prospective and consecutive data collection from a large population, in which current standard medical practice is applied in an organized network. Continuous variables were described as mean $\pm$ standard deviation (SD) or median and interquartile range [IQR (25th–75th percentiles)], according to the normality of the data. To assess the assumptions of normality, our study used the D'Agostino-Pearson test, developed to evaluate a large sample, and was confirmed through the visual inspection of scatter plots. Categorical variables were described as absolute and relative frequencies, and were examined by Pearson's Chi-squared test. For comparisons of numerical variables between groups, the unpaired Student's t-test or the Mann-Whitney U test was used when non-Gaussian distribution was assumed. A simple analysis of variance using the "t" test, or its non-parametric equivalents, were performed to observe the distribution and homoscedasticity of the values. To compare proportions between the groups, the χ^2 (chi-square) test was used for independent samples. To assume an equality of variance between groups, adjustments were made using Levene's test. The relative risk was determined by the ratio between carriers of a given variable and non-carriers. To analyze the relationship of some categorical variables and the outcomes, these were transformed into dichotomies. Thus, the proportions test (chi-square) was used to observe the independence between the univariates in order to obtain the odds ratios (ORs) in a correlation model between potentially predictive univariates and the outcomes. In multivariate statistics, the relationships of multiple variables were only verified for those deemed to be significant upon entry (variables with $p < 0.10$) so as to observe their degree of independence. The binary logistic regression model, by means of the maximum likelihood technique, was used, in which the dependent variable was dichotomous and the predictor variables were inserted by the stepwise model, considering the absence of collinearity by the VIF index (variance inflation factor), with the goodness of fit evaluated by the Hosmer-Lemeshow diagram. The predictor variables were analyzed simultaneously in such a way that the effect of each variable was adjusted in order to have an effect on the others. This regression model systematically adds the most significant variable or removes the least significant variable during each step. The standardized Crombach's α index was used to calculate the reliability of the TIMI-flow and MBG angiographic scores estimated by medical operators.

Receiver Operating Characteristic (ROC) curves were constructed in order to determine the sensitivity and specificity of the in-hospital outcome prediction scores. The shape of a ROC curve and the area under the curve (AUC) aided in estimating how high the discriminative power of a test was. A perfect diagnostic test has an AUC of 1.0, whereas a non-discriminatory test has an area of 0.5. Other analyses were also applied, considering the likelihood ratios in the prediction of events. Thus, based on the likelihood ratios, the diagnostic odds ratio (DOR), a global measure of diagnostic accuracy, was calculated, that is, the ratio of the odds of positivity in subjects with the outcome to the odds in subjects without the outcome. Our study considered a p -value < 0.05 to be statistically significant in two-tailed tests. All analyses were performed using the SPSS, version 20 (IBM-SPSS Statistics, USA)®

Results

Clinical and epidemiological characteristics

Table 1 shows that patients had a median (IQR) of 58 (50-65) years, and approximately 70% were male. Most patients were hypertensive and smokers, and nearly a third had diabetes. There was a small proportion of patients who presented prior events, such as myocardial infarction, surgical or percutaneous revascularization, and prior stroke. The elderly group were those aged ≥ 60 years. The risk predictors included data on the patient's medical history and risk factors, which were reviewed during hospital admission. This study also provides data on hemodynamic variables obtained in the emergency room, such as laboratory data (necrosis and biochemical markers) (Table.2).

Prediction scores, clinical presentation and pivotal times

In the analysis of ischemic symptoms, most patients reported chest pain defined as typical, which may or may not be associated with dyspnea or syncope. Angina prior to the event was present in 28%, which was more prevalent in patients with prior myocardial infarction. Women showed a high frequency of atypical symptoms, such as dyspnea and syncope, as shown in Table 3.

Women presented a delay between the patient's arrival at the emergency unit and the beginning of treatment: [women (2 h:17 min.) vs men (1 h:58 min.), $p=0.021$]. The stratified time (≥ 240 min.) to receive treatment was favorable to the males: [OR 0.73; 95% CI (0.55-0.98), $p=0.03$]. Another relevant finding was the longer time interval between the onset of symptoms and the search for medical care among women: [women: (3 h:14 min.) vs men (2 h:48 min.), $p=0.008$]. During this period, diabetic women presented a longer time interval between the onset of symptoms and thrombolysis, including the arrival at the emergency unit at the beginning of treatment (pain-thrombolysis time), especially when compared to non-diabetic men (Figure1).

Most patients were in a low functional class, according to the KK score: [I (73%), II (16.3%), III (2.2%), and IV (8.6%)]; low-risk profile in the TIMI-Risk predictions score: [3, IQR (2-5)]; and GRACE: [136, IQR (117-161)]. Approximately 24% of the patients were referred for rescue angioplasty, as

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Table 1 – Baseline characteristics of the studied cohort

Variables	
Epidemiological	
Age; md (IQR) - years	58 (50-65)
Women; md (IQR) - years	60 (52-68)
Men; md (IQR) - years	57 (49-64)
Elderly (≥ 60 years), n (%)	998 (43.6)
Gender; n (%)	Male: 1607 (70.2)
	Female: 683 (29.8)
Habits – Addictions	
Smoking, n (%)	1472 (64.3)
Alcoholism, n (%)	304 (13.3)
Illicit drugs, n (%)	97 (4.2)
Clinics	
Obesity, n (%)	481 (21.0)
*BMI, Kg/m ² ; md (IQR)	26 (23.8-29.3)
Arterial Hypertension, n (%)	1405 (61.4)
Diabetes mellitus, n (%)	661 (28.9)
Dyslipidemia, n (%)	1133 (49.5)
Hypothyroidism, n (%)	145 (6.3)
Chronic kidney disease, n (%)	187 (8.2)
Peripheral arterial disease, n (%)	117 (5.1)
Prior Stroke, n (%)	99 (4.3)
Chronic coronary syndrome	
Prior myocardial infarction, n (%)	242 (10.6)
Prior coronary angioplasty, n (%)	129 (5.6)
Prior surgical myocardial revascularization, n (%)	45 (2)

Notes: Data on medical history and comorbidities were derived from physician interviews. Demographic information and risk factor profiles were reported by patients, and trained staff reviewed the data during hospitalization. Data are expressed as median (md) and interquartile range (IQR), and categorical variables as frequency (%). For age comparison between genders, the Mann-Whitney non-parametric test was used. Chronic kidney disease (CKD) was estimated by the Modification of Diet in Renal Disease (MDRD) equation and defined when the estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m²; obesity when BMI ≥ 30 ; hypertension defined by the use of antihypertensive drugs or systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg. Smoking was defined for both ex-smoker and current smokers; dyslipidemia was defined by the use of specific drugs or total cholesterol ≥ 200 mg/dL, or triglycerides ≥ 150 mg/dL; diabetes was defined as specific treatment or glycated hemoglobin (HbA1c) $\geq 6.5\%$. *BMI: Body mass index.

judged by the local medical team, for not achieving criteria for successful initial reperfusion therapy.

Angiographic findings (culprit artery)

1) left anterior descending artery (LAD): 46.3%; 2) right coronary artery (RCA): 32.1%; 3) left circumflex artery (LCX): 6.1%; 4) left main coronary artery (LMCA): 0.4%; 5) posterior descending artery (PDA): 0.3%; 6) posterior ventricular branch

(PV): 0.9%; 7) left marginal branch: 1.0%; 8) diagonal branch: 0.7%; 9) unidentified artery: 12.1%. The subgroup analysis found no significant associations between the culprit artery and prior risk factors, nor with the initial clinical presentation of ischemic symptoms.

The TIMI-flow and MBG (initial and final) scores were recorded, ranked from 0 to 3: [TIMI-initial flow: (3)] and [MBG-initial: (3)] in approximately 60% and 42%, respectively. When these post-percutaneous procedure scores were analyzed, the [TIMI-final flow: (3)] and the [MBG-final: (3)] rates were: 78% and 58%, respectively, with a high level of reliability: Cronbach's $\alpha = 0.88$.

Outcomes associated with complications in the hemodynamics laboratory and by the index event

The average length of hospital stay was 2.0 ± 1.3 days, from admission to tertiary hospital up to discharge or transference to a counter-referenced hospital to continue the treatment. A longer hospital stay was observed in the elderly group: [1.9 days (non-elderly) vs. 2.3 days (elderly), $p = 0.004$] and notably in the group of patients who required replacement blood products due to bleeding: [1.9 days (without bleeding) vs. 3.4 days (major bleeding), $p = 0.004$].

The present study recorded the frequency of complications during the angiographic procedure, as well as those observed during the hospitalization period. These complications included important events, such as coronary dissection or rupture, among others, such as clinical complications, arrhythmias, and bleeding at the puncture site. Although infrequent, major bleeding was independently associated with in-hospital mortality. Higher bleeding rates were observed in the elderly group: [OR: 1.86; 95% CI (1.04-3.16), $p = 0.023$].

Predictors and variables associated with mortality rates

The in-hospital mortality rate was 5.6%, with 128 deaths; of these, 23 (17.9%) occurred in the hemodynamics laboratory, with electrical instability or mechanical complications being the most prevalent and with a higher incidence occurring in the rescue group (11.5% vs. 2.4%). Regarding epidemiological characteristics and risk factors, a similar distribution of the analyzed variables was observed among surviving patients, when compared with those who died during the hospital period, except for the GRACE score, which showed higher values in patients who died: [134 (115-157) vs. 202 (155-233), $p < 0.001$]. The GRACE score (median score 136) showed good sensitivity but low specificity [sensitivity: 0.86%; specificity: 0.53%]. The TIMI-Risk Prediction Score (median score 3) presented the following: sensitivity: 0.87%; specificity: 0.57% (Table 4).

The KK functional classification showed good performance in predicting in-hospital mortality: AUC: [0.77 95% CI (0.73-0.81), $p < 0.001$] in the group with a score $\geq II$, showing better accuracy than the reperfusion angiographic scores: TIMI-Flow (3) and MBG (3), AUC: [0.69; 95% CI (0.64-0.75), $p < 0.001$], as well as a better performance when we stratified the patients, according to left ventricular ejection fraction, AUC: [0.52; 95% CI (0.47-0.58), $p = 0.34$].

Table 2 – Clinical and hemodynamic characteristics, prediction scores, and pivotal times were obtained during the first medical contact and during the period of hospital stay

Variables obtained during the first medical contact	Measures
Hemodynamic variables	
Systolic blood pressure, mmHg; md (IQR)	130 (115-150)
Diastolic blood pressure, mmHg; md (IQR)	80 (70-93)
Heart rate, md (IQR)	76 (66-90)
Killip-Kimball classification, n (%)	Killip-Kimball – I: 1670 (72.0)
	Killip-Kimball – II: 362 (15.8)
	Killip-Kimball – III: 52 (2.3)
	Killip-Kimball – IV: 203 (8.0)
Clinical presentation (main symptom), n (%)	Typical Pain: 1939 (88.5)
	Atypical Pain: 166 (7.6)
	Dyspnea: 38 (1.7)
	Syncope: 26 (1.2)
	* Some patients (4%) with more than 1 reported symptom
Risk Scores	
TIMI-Risk, (0-14); md (IQR)	3 (2-5)
Grace-score; md (IQR)	135 (115-160)
Pivot Times	
Pain-Health Unit, min; md (IQR)	120 (60-220)
Pain-Needle, min; md (IQR)	222 (140-345)
Door-Needle, min; md (IQR)	71 (42-135)
Lysis-Angiography, hours; md (IQR)	12 (5,67-23)
Variables obtained during the hospital period	Measures
Necrosis biomarkers	
Initial troponin, mg/L; md (IQR)	2655 (538-7967)
Maximum troponin, mg/L; md (IQR)	4718 (1481-9842)
Laboratory variables	
Hemoglobin / Hematocrit, g/dL / %; m ± SD	14.37 ± 2.09 / 42.92 ± 12.56
Blood glucose / Glycated hemoglobin, mg/dL / %; md (IQR)	122 (102-160) / 6 (5.6-6.8)
Total Cholesterol, mg/dL; md (IQR)	191 (157-225)
HDL-C, mg/dL; md (IQR)	37 (25-46)
LDL-C, mg/dL; md (IQR)	110 (60-142)
Triglycerides, mg/dL; md (IQR)	118 (77-175)
*AST, u/L; md (IQR)	144 (63-280)
†ALT, u/L; md (IQR)	43 (27-72)
Creatinine, mg/dL; md (IQR)	0,9 (0.74-1.10)
Estimated Glomerular Filtration Rate, (MDRD); md (IQR)	85 (64-107)

Notes: Data are expressed as median (md) and interquartile range (IQR), or mean and standard deviation (m ± sd), and categorical variables are presented as frequency (%). Time metrics are expressed in minutes (min). Estimated Glomerular Filtration Rate by Modification of Diet in Renal Disease (MDRD); *AST: aspartate aminotransferase; †ALT: alanine aminotransferase.

Our study was careful to evaluate the performance of the prediction scores: TIMI-Risk, AUC: [0.79; 95% CI (0.75-0.84)], $p < 0.001$; GRACE, AUC: [0.82; 95% CI (0.78-0.86)], $p < 0.001$; Killip-Kimball AUC: [0.82; 95% CI (0.78-0.87)], $p < 0.001$, (Figure 2). For the Killip-Kimball categories, the following scores were obtained: positive

likelihood ratio: 3.76; negative likelihood ratio: 0.33; and DOR (Diagnostic Odds Ratio): 11.39 for in-hospital mortality prediction rates, defined as the probability of patients in the functional class $\geq$ II (II, III, IV) who died, relative to the probability of patients in the functional group $\geq$ II who survived.

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Table 3 – Variables associated with the type of clinical presentation in a univariate model and after multivariate adjustments in multinomial logistic regression

Model without adjustments	Typical Pain	Atypical Pain	Dyspnea	Syncope
Variables	Odds-ratio (95% CI), p-value	Odds-ratio (95% CI), p-value	Odds-ratio (95% CI), p-value	Odds-ratio (95% CI), p-value
	n = 1939	n = 166	n = 38	n = 26
Male	0.95 (0.71-1.27), p=0.74	1.05 (0.79-1.40), p=0.73	0.51 (0.27-0.96), p=0.026	0.39 (0.18-0.83), p=0.018
Obesity	1.07 (0.78-1.50), p=0.65	0.92 (0.67-1.28), p=0.65	0.30 (0.09-0.98), p=0.02	0.29 (0.07-1.26), p=0.09
Alcoholism	0.80 (0.56-1.15), p=0.24	1.24 (0.86-1.78), p=0.24	1.15 (0.48-2.77), p=0.44	1.49 (0.56-3.97), p=0.39
Hypertension	0.96 (0.73-1.26), p=0.78	1.03 (0.79-1.35), p=0.79	1.31 (0.67-2.56), p=0.26	0.67 (0.31-1.44), p=0.32
Dyslipidemia	1.39 (1.07-1.81), p=0.013	0.71 (0.55-0.93), p=0.013	1.25 (0.66-2.35), p=0.52	0.35 (0.15-0.84), p=0.019
Prior myocardial infarction	1.05 (0.68-1.61), p=0.81	0.95 (0.62-1.46), p=0.82	3.31 (1.63-6.72), p=0.002	0.67 (0.16-2.86), p=0.59
Prior Stroke	0.75 (0.42-1.34), p=0.34	1.32 (0.74-2.37), p=0.34	1.82 (0.55-6.00), p=0.24	0.85 (0.11-6.32), p=0.87
Peripheral artery disease	0.78 (0.45-1.35), p=0.30	1.27 (0.74-2.20), p=0.38	1.52 (0.46-5.00), p=0.45	0.71 (0.09-5.29), p=0.74
Chronic kidney disease	0.53 (0.35-0.79), p=0.002	1.88 (1.26-2.80), p=0.002	4.47 (2.19-9.10), p<0.001	1.97 (0.67-5.77), p=0.27
Smoking	1.17 (0.90-1.53), p=0.23	0.85 (0.65-1.11), p=0.23	1.15 (0.59-2.25), p=0.74	0.59 (0.27-1.27), p=0.22
Diabetes	0.95 (0.72-1.27), p=0.76	1.04 (0.78-1.39), p=0.75	2.26 (1.21-4.24), p=0.013	0.70 (0.28-1.74), p=0.52
Elderly	0.87 (0.67-1.13), p=0.32	1.14 (0.88-1.48), p=0.32	1.77 (0.94-3.33), p=0.07	0.76 (0.34-1.66), p=0.56
Adjusted model	Typical Pain	Atypical Pain	Dyspnea	Syncope
Variable	Odds-ratio (95% CI), p-value	Odds-ratio (95% CI), p-value	Odds-ratio (95% CI), p-value	Odds-ratio (95% CI), p-value
Males	NA	NA	0.51 (0.26-0.97), p=0.04	0.32 (0.15-0.70), p=0.005
Obesity	NA	NA	0.29 (0.08-0.95), p=0.04	NA
Dyslipidemia	1.44 (1.10-1.87), p=0.007	0.69 (0.53-0.90), p=0.007	NA	0.36 (0.15-0.87), p=0.02
Prior myocardial infarction	NA	NA	2.68 (1.28-5.58), p=0.008	NA
Chronic kidney disease	0.50 (0.34-0.75), p=0.001	1.97 (1.32-2.94), p=0.001	3.33 (1.59-6.98), p=0.001	NA
Diabetes Mellitus	NA	NA	1.93 (1.01-3.71), p=0.04	NA

Notes: Data are expressed for (OR; 95% CI, p-value). In the multivariate analysis the predictor variables were analyzed simultaneously, so that the effect of each variable was adjusted for the effect of the others. Bold indicates statistical significance. Chronic kidney disease (CKD) was estimated by Modification of Diet in Renal Disease (MDRD); elderly: age ≥60 years. Bold indicates statistical significance. NA: not applicable.

In a logistic regression model with covariance analyses, obesity, women, patients with diabetes mellitus, chronic renal failure, previous stroke, and the elderly were associated with the highest rates of fatal events (Figure 3). The model fit presented a good predictive performance.

Discussion

Even with the existence of many effective therapies, qualitative information is still lacking for stratification, notably in the pharmacoinvasive strategy, where the initial health assessment seems closely related to the prognosis.

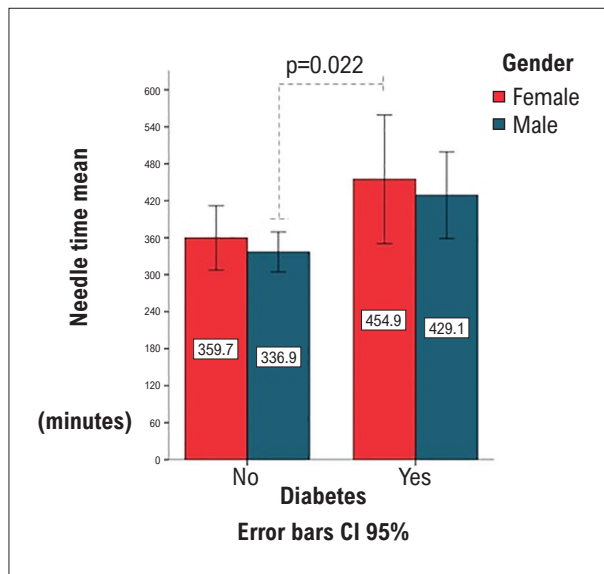


Figure 1 – Time metrics related to gender and presence or absence of diabetes. Note. Pain-needle time expressed as mean (minutes). * Significant *p*-value when comparing non-diabetic men versus women with diabetes.

There are many approaches to risk stratification. Some are very complex and costly, but simple procedures can also be effective. In this light, the present study sought to provide descriptive epidemiological data on the different forms of acute ischemic symptoms, as well as show the applicability of some prediction scores in patients who received medical care mainly in basic health units and were subsequently referred to a tertiary university hospital for angiographic study and invasive procedures.

Not every acute coronary syndrome shows classic signs or symptoms, such as the typical precordial or retrosternal pain, in turn delaying the diagnosis and therapeutic approaches, and impacting the prognosis. Thus, there is great interest in the major determinants of mortality and short-term complications after an acute myocardial infarction.¹¹ In recent years, major advances in diagnosis and treatment have contributed to the decline in mortality due to coronary heart disease. In fact, efforts have been made for more active primary prevention, through a better control of risk factors, lifestyles, and pharmacological resources. Nevertheless, challenges regarding the prevention and treatment of cardiovascular diseases need to be widely available and applied without distinction.

Clinical presentation and events in subgroups

There is evidence of differences among genders in the application of technological advances.¹²⁻¹⁵ In our analysis, symptoms referred to as dyspnea or syncopal episodes were significantly more prevalent in women, and were particularly relevant for this group, presenting higher mortality rates. Several multifactorial mechanisms have been proposed for the greater cardiac mortality of women. The explanations often include a smaller coronary diameter in females, lower collateral flow, predisposition to plaque erosion and distal embolization, and other phenotypic characteristics of

atherosclerotic plaques.¹⁶⁻¹⁸ Women generally present events approximately a decade later than men, notably in post-menopause, possibly due to an estrogenic decrease and a loss of protective effects, with a consequent worsening of risk factors, weight gain, and insulin resistance.¹⁹⁻²¹ In our cohort, the delay in recognizing symptoms, possibly due to their atypical appearance, had an impact on temporal metrics for thrombolysis, such as those recorded in the group of women and diabetics.

Diabetes is a potential risk factor in women. A meta-analysis to estimate the relative risk of fatal coronary heart disease associated with diabetes, involving approximately 450,000 patients, revealed a 50% higher relative risk in women.²² The higher coronary risk associated with diabetes in women may reflect a treatment bias favorable to men. Studies show that men with diabetes or established cardiovascular disease are more likely to receive antiplatelet drugs, statins, or antihypertensive drugs than women.^{23,24} Additionally, there are reports of poor adherence to guideline recommendations in women, such as a longer door-to-balloon time.²⁵⁻²⁸ It was also observed that males received fibrinolytic therapy earlier, possibly due to the clearer presentation of ischemic symptoms.

The clinical appearance, defined above as dyspnea, was more prevalent in patients with previous infarctions, possibly due to additional myocardial impairment. The report of dyspnea was also noted in patients with diabetes. This may have had a significant impact on the mortality rate due to the absence of typical symptoms or warning signs.

Risk scores

Although there is no ideal stratification model, it should contain the following characteristics: easy implementation, objectivity, accuracy, and widespread use. Killip-Kimball, a functional classification method applied during first medical contact, was an important predictor for fatal outcomes during the hospital period, with a good negative predictive value. The index of the severity of cardiac insufficiency in patients with acute myocardial infarction was proposed by Thomas Killip and John Kimball in an attempt to measure the risk of in-hospital events and the potential benefit of the specific management of medical care provided in coronary care units. Our analysis highlights the clinical use of a physical examination as a simple tool without sophisticated technological requirements in order to identify signs of heart failure upon hospital admission, which played a relevant prognostic role in mortality rates for the hospital period, since the proportions of deaths and the distributions of survival data were significantly different within Killip-Kimball class > 1.

Hospital mortality rates

The mortality rate, including events during the angiographic procedure and those related to the index event, was associated with mechanical complications and severe and irreversible electrical disturbances. It has been reported that delays in recanalization time are associated with a greater impairment of ventricular function, microcirculation disturbances, and higher mortality rates.²⁹ It is interesting to note that our study found no association of mortality rates among patients in the

Table 4 – Clinical and epidemiological variables between the “survivor” and the “death” groups

	Survivor group	Death group	p-value
Variables	2162 (94.4%)	128 (5.6%)	
Epidemiological			
Age, years:	58 (50-66)	56 (48-65)	0.047
Male gender:	Homens: 71.1%	Homens: 53.2%	0.02
Risk Scores			
Killip-Kimball, (%):	Killip-Kimball - I: 75.6%	Killip-Kimball- I: 20.6%	0.09
	Killip-Kimball - II: 16.4%	Killip-Kimball- II: 7.9%	0.42
	Killip-Kimball - III: 2.2%	Killip-Kimball- III: 4.8%	0.96
	Killip-Kimball - IV: 5.7%	Killip-Kimball- IV: 66.5%	0.08
TIMI-Risk:	3 (2-5)	6 (5-8.2)	0.26
GRACE-score:	134 (115-157)	202 (155-233)	p <0.001
ECG-variables			
ECG wall	anterior wall	anterior wall	anterior wall
	inferior wall	inferior wall	inferior wall
	lateral wall	lateral wall	lateral wall
Hemodynamic Variables			
Infarct-related artery:	ADA: 45.5%	ADA: 38.9%	0.84
	ACD: 32.5%	ACD: 36.5%	
	ACX: 6%	ACX: 10.3%	
	Others: 22.4%	Others: 14.3%	
†Left ventricular ejection fraction (LVEF):	50 (40-59)	49 (40-60)	0.17
Initial TIMI-flow:	TIMI-0: 19.6%	TIMI-0: 36.8%	0.97
	TIMI-1: 3.3%	TIMI-1: 11.3%	
	TIMI-2: 15.4%	TIMI-2: 17%	
	TIMI-3: 61.7%	TIMI-3: 34.9%	
Final TIMI-flow:	TIMI-0: 4.6%	TIMI-0: 19.8%	0.10
	TIMI-1: 1.2%	TIMI-1: 4.7%	
	TIMI-2: 14.1%	TIMI-2: 24.5%	
	TIMI-3: 80.1%	TIMI-3: 50.9%	
Initial myocardial Blush-grade:	Blush-0: 40.8%	Blush-0: 71.7%	0.77
	Blush-1: 3.8%	Blush-1: 2.8%	
	Blush-2: 2.6%	Blush-2: 1.9%	
	Blush-3: 52.8%	Blush-3: 23.6%	
Final myocardial Blush-grade:	Blush-0: 24.7%	Blush-0: 61%	0.39
	Blush-1: 8.8%	Blush-1: 9.5%	
	Blush-2: 6.1%	Blush-2: 5.7%	
	Blush-3: 60.4%	Blush-3: 23.8%	
Laboratory Variables			
Initial troponin (at baseline):	2704 (618-7889)	3413 (280-11506)	0.83
Maximum troponin:	4820 (1661-9796)	7925 (1145-1774)	0.80
*eGFR, (MDRD):	86 (67-107)	91 (66-111)	0.62
Hemoglobin:	14.5 (13.3-15.7)	13.7 (12.5-15.1)	0.05
Hematocrit:	42.9 (39.6-46.2)	41 (37.9-45.5)	0.14

Pivot Times			
Pain-Needle Time, (min):	220 (140-345)	245 (150-516)	0.08
Door to Needle Time, (min):	75 (45-135)	78.5 (45-163.7)	0.12
‡Lyse-CATHETERISM TIME, (hours):	11 (5-22)	11 (5-21.7)	0.43

Notes: Data are expressed as median (md) and interquartile range (IQR), and categorical variables are expressed as frequency (%). The χ^2 (chi-squared) test was used for the independent samples. *eGFR: estimated glomerular filtration rate by Modification of Diet in Renal Disease (MDRD). †LVEF: Left Ventricular Ejection Fraction. ‡Lyse-CATHE (fibrinolysis-catheterization); ECG: electrocardiographic. Bold indicates statistical significance.

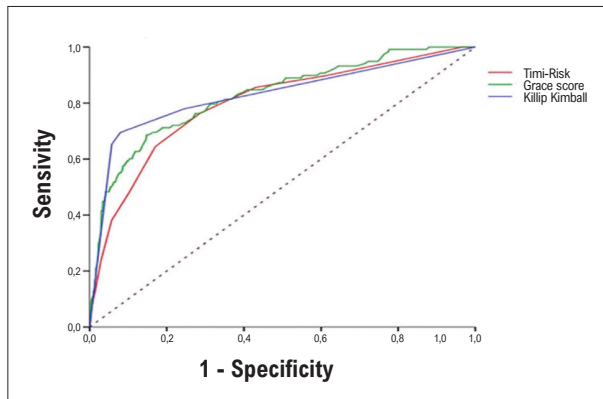


Figure 2 – Prediction scores for in-hospital mortality. Note. The C-Statistics, ROC and AUC. TIMI-Risk, AUC: [0.79; 95% CI (0.75-0.84), $p < 0.001$]; GRACE-score, AUC: [0.82; 95% CI (0.78-0.86), $p < 0.001$]; Killip-Kimball, AUC: [0.82; 95% CI (0.78-0.87), $p < 0.001$].

group with lower left ventricular ejection fraction (LVEF) nor with the angiographic scores. In fact, totally occluded culprit lesion (TIMI-flow=0) proved to be unassociated with higher in-hospital mortality rates after STEMI treated with TNK, when compared to TIMI-flow ≥ 1 . Moreover, malignant ventricular arrhythmias can appear earlier in ischemic processes and continue to be an expected cause of death in myocardial infarctions.^{30,31} In our cohort, in-hospital mortality rates were higher among patients with sustained malignant ventricular arrhythmias than among patients without sustained ventricular arrhythmias, defined as ventricular tachycardia or fibrillation. However, due to the observational characteristic of our study, several difficulties were encountered in characterizing the ventricular arrhythmias, especially in the post-angioplasty period, as the occurrence of these events was difficult to predict. Thus, it can be speculated that severe electrical disturbances could be a strong marker of in-hospital outcomes, despite the success of percutaneous coronary intervention and their respective angiographic scores, and they may not be correlated with LVEF as well. Presumably, it seems to be a better marker when applied to measure outcomes in the medium and long terms.

Some subgroups of special interest were examined in their associations with mortality rates, such as women, obese patients, diabetics, and elderly individuals. In this sense, after myocardial infarction, women appear to be at a higher risk of reinfarction and death, which can be partially explained by the more advanced age, as observed in our study.

By contrast, chronic kidney disease (CKD) represents an independent risk factor for the development of ischemic heart disease, increasing mortality with the advancement of renal impairment. Previous kidney damage to or as a consequence of infarction is associated with worse outcomes.^{32,33} It is likely that there is a reciprocal relationship between the coronary atherosclerotic process and the renal function, and that the presence of coronary disease would be associated with a worsening of the renal function. CKD and cardiovascular disease are closely related, and the presence of one condition synergistically affects the prognosis of the other.³⁴ Our data express the highest mortality rates for these patients.

Patients who had suffered a prior stroke also showed higher rates of fatal events, highlighting the need for prevention and adequate care for this subgroup.^{35,36} The same concept may be applicable for elderly individuals, possibly due to the greater biological frailty in this group. The mechanisms for this relation seem to be multiple, involving anatomical, biochemical, and immunological characteristics, or even longer exposure to classic risk factors. Another finding in our cohort was the higher mortality rates in patients with diabetes mellitus, which is in agreement with previous studies.³⁷⁻³⁹ Diabetes mellitus is often associated with multiple mechanisms for cardiovascular disease, such as obesity, hypertension, renal failure, subclinical inflammation, endothelial dysfunction, and microvascular impairment. Nonetheless, no significant differences were found in either the TIMI-flow or the MBG reperfusion angiographic scores when comparing the groups of patients with and without diabetes.

Strengths and limitations

The present study has limitations. First, it was an observational study, with correction of known or measured confounding factors. Thus, we cannot conclude that the observed associations are causal. Furthermore, our records included only patients who underwent pharmacoinvasive intervention, disregarding those who were referred for primary percutaneous treatment or those who had formal contraindications for fibrinolysis. Given that the study was performed at a single university center, these standards of practice and results should be interpreted with caution. Another limitation of our study was the analysis of outcomes for the in-hospital period only. In an important sense, our internal validation indicated that the model fit was good and the diagnostic prediction models performed well in independently predicting the prognosis.

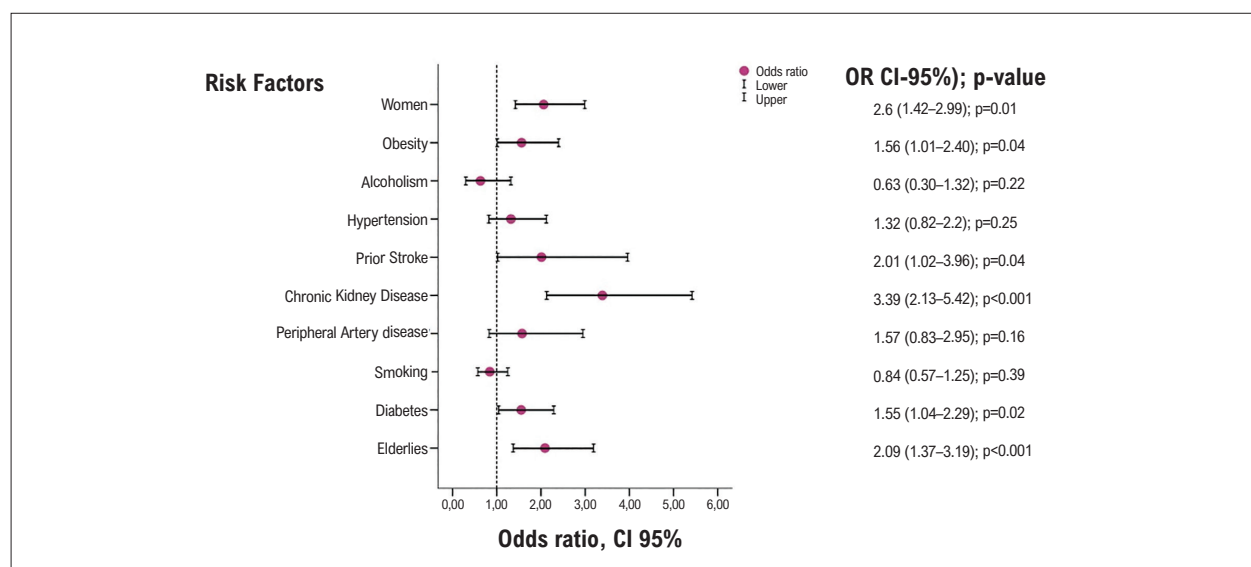


Figure 3 – In-hospital mortality predictors. Note. Prediction variables in a binary logistic regression model, with OR-95% CI; and p-value.

Conclusions

Our data revealed higher in-hospital mortality rates in women; in patients with diabetes mellitus, obesity, CKD, and prior strokes; as well as in the elderly. The significant gender-related disparity persists in women, with delays in the recognition of symptoms of ischemia, and the immediate initiation of fibrinolytic therapy, thus favoring worse clinical results. The applicability of the Killip-Kimball score in accurately predicting fatal events should be highlighted, regardless of the clinical presentation of the acute ischemic event, measured upon the first medical contact, especially in the pharmaco-invasive strategy.

Author Contributions

Conception and design of the research: Bianco HT, Gonçalves Jr. I, Stefanini E, Fonseca FAH; Acquisition of data: Bianco HT, Alves CMR, Barbosa AHP, Gonçalves Jr. I, Aguirre AC, Moraes PIM, Povia FF, Stefanini E, Caixeta AM, Bacchin AS, Moisés VA, Fonseca FAH; Analysis and interpretation of the data: Bianco HT, Povia R, Izar MC, Alves CMR, Barbosa AHP, Moraes PIM, Almeida D, Povia FF, Bacchin AS, Fonseca FAH; Statistical analysis: Bianco HT, Povia R, Izar MC, Luna Filho B, Moreira FT, Caixeta AM; Writing of the manuscript: Bianco HT, Bombig MTN, Aguirre AC, Moreira FT; Critical revision of

the manuscript for important intellectual content: Bianco HT, Povia R, Izar MC, Barbosa AHP, Bombig MTN, Luna Filho B, Almeida D, Stefanini E, Caixeta AM, Moisés VA, Fonseca FAH.

Potential Conflict of Interest

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

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Study Association

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

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Universidade Federal de São Paulo under the protocol number CAAE: 38692514.1.1001.5505. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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Pharmacoinvasive Strategy in ST-Elevation Myocardial Infarction in Brazil: Female Sex as a Prognostic Factor

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Short Editorial related to the article: Pharmacoinvasive Strategy in Myocardial Infarction: Descriptive Analysis, Presentation of Ischemic Symptoms and Mortality Predictors

Primary percutaneous coronary intervention (PCI) is the recommended therapy in patients with acute ST-elevation myocardial infarction (STEMI). In locations without immediate PCI capability or in the presence of an anticipated delay from hospital presentation to primary PCI >120 minutes, fibrinolysis is indicated. In these cases, invasive angiography and PCI 3 to 24 hours after fibrinolysis may improve the prognosis and are recommended as class 2a by the recent ACC/AHA/SCAI Guideline for Coronary Artery Revascularization.¹ The rationale for early routine PCI after fibrinolysis, the so-called pharmacoinvasive strategy, is that lytic therapy provides adequate (TIMI 3 grade) blood flow in only 50-60% of the cases. PCI can then relieve residual stenosis and restore normal flow, which is related to the benefit of reperfusion in reducing mortality. Importantly, early invasive angiography should follow fibrinolysis independently of the resolution of the ST-segment elevation since electrocardiogram changes have poor accuracy in identifying adequate reperfusion.²

The recommendation for the pharmacoinvasive strategy is supported by several randomized controlled trials (RCTs) and meta-analyses demonstrating clinical benefits over previous standard therapy.³ Moreover, the STREAM trial provided evidence that pre-hospital fibrinolysis followed by PCI after 6 to 24 hours is as efficacious as primary PCI in STEMI patients who cannot undergo primary PCI within 1 hour after the diagnosis.^{4,5}

The *Arquivos Brasileiros de Cardiologia* publishes an article thoroughly reporting the experience of a Brazilian university hospital with the pharmacoinvasive approach in STEMI.⁶ Although this observational work is completely different from previous RCTs concerning design, purpose, and study population, it is tempting to make some comparisons.

In-hospital mortality in the Brazilian study was 5.6%, which is higher than the 3.3% 30-day mortality reported in a metaanalysis of RCTs³ but not so higher than the 4.6% 30-day mortality in the pharmacoinvasive arm of the STREAM trial.⁴ Notably, the time from the symptom onset to the fibrinolytic treatment was longer in the Brazilian study (median 222 minutes) than in the STREAM trial (median 100 minutes)⁴ or in the RCTs of the metaanalysis by

Borgia et al. (median or average from 113 to 192 minutes in most of them).³ The time from the lytic therapy to the coronary angiography was also higher in the Brazilian study (median 12 hours) than in the RCTs of the metaanalysis above (typically <5 hours).³ Finally, the remarkable delay of 71 (interquartile range: 42-135) minutes from the arrival in the medical unit to the start of fibrinolysis in the Brazilian experience is much longer than the 20 minutes recommended by guidelines.⁷ Taken together, these numbers provide insights to identify targets for improvement in the quality of care of STEMI patients in Brazil.

A highlight of the article published in the *Arquivos Brasileiros de Cardiologia* refers to sex differences in treatment and prognosis in the setting of the pharmacoinvasive strategy in STEMI. In a multivariable analysis, female sex remained a predictive factor for in-hospital mortality. Also, the study showed a high prevalence of atypical symptoms and longer delays for seeking medical care and initiating fibrinolysis after admission to the medical center in women,⁶ favoring an adverse outcome. These results align with large evidence of worse prognosis after acute myocardial infarction and PCI in women.⁸⁻¹⁰ Moreover, in patients admitted for STEMI in hospitals with PCI capacity in the Brazilian state of Sergipe, striking sex disparities were observed regarding the rate of primary PCI (44% in women and 54.5% in men) and in-hospital mortality (16.1% in women and 6.7% in men).¹¹ Considering that ischemic heart disease is the main cause of death in Brazil, comprising 12% of fatal events in women,^{12,13} these findings justify initiatives such as the Brazilian Society of Cardiology Women's Letter¹⁴ in a movement to increase patient and physician awareness of the importance of cardiovascular disease in women. Similarly, the American Heart Association has recently issued the Call to Action for Cardiovascular Disease in Women, aiming to promote equity for women in the context of cardiovascular health.¹⁵

Therefore, several diagnoses can be retrieved from the comprehensive article on the dynamics of the pharmacoinvasive strategy in STEMI in a Brazilian center. The challenge now is to transform this rich information into better medical care.

Keywords

ST Elevation Myocardial Infarction; Thrombolytic Therapy; Percutaneous Coronary Intervention; Sex Differences.

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Adjusting RFR by Predictors of Disagreement, “The Adjusted RFR”: An Alternative Methodology to Improve the Diagnostic Capacity of Coronary Indices

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Abstract

Background: Cutoff thresholds for the “resting full-cycle ratio” (RFR) oscillate in different series, suggesting that population characteristics may influence them. Likewise, predictors of discordance between the RFR and fractional flow reserve (FFR) have been documented. The RECOPA Study showed that diagnostic capacity is reduced in the RFR “grey zone”, requiring the performance of FFR to rule out or confirm ischemia.

Objectives: To determine predictors of discordance, integrate the information they provide in a clinical-physiological index, the “Adjusted RFR”, and compare its agreement with the FFR.

Methods: Using data from the RECOPA Study, predictors of discordance with respect to FFR were determined in the RFR “grey zone” (0.86 to 0.92) to construct an index (“Adjusted RFR”) that would weigh RFR together with predictors of discordance and evaluate its agreement with FFR.

Results: A total of 156 lesions were evaluated in 141 patients. Predictors of discordance were: chronic kidney disease, previous ischemic heart disease, lesions not involving the anterior descending artery, and acute coronary syndrome. Though limited, the “Adjusted RFR” improved the diagnostic capacity compared to the RFR in the “grey zone” (AUC-RFR = 0.651 versus AUC-“Adjusted RFR” = 0.749), also showing an improvement in all diagnostic indices when optimal cutoff thresholds were established (sensitivity: 59% to 68%; specificity: 62% to 75%; diagnostic accuracy: 60% to 71%; positive likelihood ratio: 1.51 to 2.34; negative likelihood ratio: 0.64 to 0.37).

Conclusions: Adjusting the RFR by integrating the information provided by predictors of discordance to obtain the “Adjusted RFR” improved the diagnostic capacity in our population. Further studies are required to evaluate whether clinical-physiological indices improve the diagnostic capacity of RFR or other coronary indices.

Keywords: Angina; Fractional Flow Reserve; Resting Full-cycle Ratio; Sensitivity; Specificity.

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Introduction

Coronary physiological indices are an essential tool in decision making in ischemic heart disease.^{1,2} In clinical practice, they are used dichotomously to determine the functional significance of coronary lesions.^{3,4} However, the choice of cutoff thresholds (CoTs) using receiver operating characteristic (ROC) curve analysis means that minimal changes in CoT

may lead to relevant changes in sensitivity and specificity.⁵⁻⁷ Furthermore, the optimal CoTs vary between series, suggesting that the heterogeneity of the study populations may influence the diagnostic capacity of these indices.⁵⁻⁷

The concept of the "grey zone" in the coronary flow reserve or fractional flow reserve (FFR)^{8,9} refers to a range of values close to the CoT whose extremes have high predictive values to confirm or rule out ischemia. This concept has also been studied with non-hyperemic resting indices (NHRI).^{10,11} The RECOPA Study¹¹ was a validation study of the "resting full-cycle ratio" (RFR) against FFR in "real life" which also evaluated the usefulness of a hybrid strategy of RFR and FFR for the functional assessment of "grey zone" stenosis.¹¹

On the other hand, there is growing interest in determining predictors of discordance between NHRI and FFR. Recent studies^{12,13} have identified some of them for RFR. However, to the best of our knowledge, the information from these predictors has not been used to improve the diagnostic capacity of coronary indices in general, or of NHRI in particular.

Therefore, the objective of this study was to determine predictors of discordance between RFR and FFR and to integrate this information to construct a modified index of RFR, the "Adjusted RFR", which allows for improving the diagnostic capacity with respect to RFR in the "grey zone".

Material and methods

Study population

The population of this study was selected using data from the RECOPA Study, the details and results of which have previously been published.¹¹ This study was approved by the Ethics Committee of each site, meeting the requirements and standards of the Declaration of Helsinki and its subsequent amendments, as well as applicable data protection regulations.

To summarize, the RECOPA Study¹¹ was a validation study of RFR versus FFR in standard practice, where 380 coronary lesions in 311 patients were functionally evaluated by pressure guidance, obtaining RFR and FFR values. The thresholds for detecting ischemia were $RFR \leq 0.89$ and $FFR \leq 0.80$, with correlation levels ($R^2 = 0.81$; $p < 0.001$), sensitivity (76%) and specificity (80%), similar to those reported by other "real life" studies. However, their application to the study population showed limited predictive values (positive predictive value [PPV] = 68%; negative predictive value [NPV] = 80%). Therefore, a "grey zone" (RFR from 0.86 to 0.92) was determined in which to assess the functional impact of stenoses using both techniques (hybrid RFR-FFR strategy), making it possible to obtain high predictive values (PPV = 91%; NPV = 92%) and to reduce the administration of vasodilators by 58%.

Since the extreme values of the RFR make it possible to obtain a very high agreement, concentrating the discrepancy between both techniques in the "grey zone", only lesions with RFR of 0.86 to 0.92 were selected, ultimately including a total of 156 lesions, corresponding to 141 patients.

Determination of the Predictors of Discordance and Establishment of the "Adjusted RFR"

RFR¹⁴ is an NHRI that evaluates the hemodynamic significance of coronary stenoses, identifying the minimum ratio between blood pressure distal to the coronary stenosis (Pd) and aortic blood pressure (Pa) throughout the cardiac cycle. A CoT of $RFR \leq 0.89$ is considered the most adequate for determining the presence of ischemia, despite variations in the optimal CoTs reported in the different series.¹¹⁻¹⁷ In an attempt to fine-tune the agreement with the FFR in the "grey zone" (RFR from 0.86 to 0.92).¹¹ an analysis was performed to determine the predictors of discordance between both techniques, and information provided by them was then included in the construction of a new index: "Adjusted RFR".

First, lesions were grouped into 4 groups according to the functional study result: RFR-/FFR- (true negative), RFR+/FFR- (false positive [FP]), RFR-/FFR+ (false negative [FN]), and RFR+/FFR+ (true positive), comparing the clinical and angiographic characteristics between each group. Subsequently, the groups with discordant results were selected: RFR+/FFR- (FP) and RFR-/FFR+ (FN); independent predictors of discordance were then determined for each group. Finally, the "Adjusted RFR" was constructed including the RFR and the predictors of discordance, assigning them their corresponding weighting coefficients.

Statistical analysis

The statistical analyses were performed using SPSS version 20.0 software (IBM Corp., Armonk, NY, USA), with two-tailed values of $p < 0.05$ considered statistically significant. Categorical variables were presented as numbers and relative frequencies (percentages), and continuous variables as mean (standard deviation) or median with range or interquartile range depending on their distribution. Continuous variables were compared using Student's t test for unpaired samples, and categorical variables were compared using the chi-squared test or Fisher's exact test, as appropriate. Mann-Whitney U tests were used for non-parametric data.

To identify predictors of discordance, for both FP and FN, binary logistic regression models were used, including in the final multivariate analysis those predictors with values ≤ 0.10 in the univariate analysis. Results were given as odds ratio (OR) with 95% confidence interval (95% CI). Once the predictors of discordance were obtained, the "Adjusted RFR" was constructed using linear regression to establish a predictive model of FFR that contemplates the value of the RFR and the predictors of discordance, assigning them a coefficient that weighed their relevance using the following algorithm:

"Adjusted RFR":

$$p(y = FFR) = RFR \text{ Adjusted} = \beta_{cte} + \beta_{RFR} * RFR + \dots + \beta_n * X_n$$

*Weighted coefficients (β_i) could be positive or negative depending on whether predictors were protective or risk factors for being FN or FP.

Finally, sensitivity and specificity analyses were performed, also estimating the optimal CoT of the "Adjusted RFR" to obtain an FFR value ≤ 0.80 , using ROC

curve analysis. Positive and negative likelihood ratios (LR+ and LR-) were also calculated for RFR and "Adjusted RFR", considering the test utility as follows:¹⁴

– LR+: < 2 (not useful); 2 to 5 (fair); 5 to 10 (good); > 10 (excellent).

– LR-: > 0.5 (not useful); 0.5 to 0.2 (fair); 0.2 to 0.1 (good); < 0.1 (excellent).

Results

In this study, 141 patients, with a total of 156 lesions, were included. A single lesion was explored in most patients, with 4 being the maximum number of lesions evaluated in 1 patient.

Clinical and angiographic characteristics

Baseline characteristics per patient are shown in Table 1. Table 2 shows, per lesion, the baseline characteristics of the 4 comparison groups, observing that FPs (RFR+/FFR-) were older, and they had a greater prevalence of chronic kidney disease and a greater percentage of previous chronic ischemic heart disease. As regards FNs (RFR-/FFR+), a greater prevalence of active smoking and acute coronary syndrome was found. Table 3 also shows, per lesion, the angiographic and physiological characteristics of the comparison groups, noting that FNs (RFR-/FFR+) had a higher percentage of lesions not involving the left anterior descending artery compared to all other groups. The specifically affected coronary segment is presented in the Supplementary Material. In addition, a gradient in RFR and Pd/Pa values was observed between the 4 comparison arms.

Determination of predictors of discordance

Table 4 shows the independent predictors of discordance for FP and FN. As regards FP (RFR+/FFR-), chronic kidney disease was identified as an independent risk factor for discordance (OR 3.224; 1.386 to 7.501; $p = 0.007$). In contrast, a history of chronic ischemic heart disease was shown to be a protective factor against discordance (OR 0.296; 0.102 to 0.858; $p = 0.025$). As regards FN (RFR-/FFR+), the clinical context of acute coronary syndrome (OR 3.687; 1.247 to 10.899; $p = 0.018$) and lesions in a location other than the left anterior descending artery (OR 3.529; 1.231 to 10.118; $p = 0.019$) were finally identified as independent risk factors for discordance.

Generation of the "Adjusted RFR"

Finally, the RFR value and independent predictors were included in the model to generate the "Adjusted RFR". The algorithm with the coefficients corresponding to each predictor is shown below:

"Adjusted RFR":

Adjusted RFR = $0.009 + 0.912 \cdot \text{RFR} + 0.023 \cdot \text{CKD} - 0.019 \cdot \text{non-LAD} - 0.017 \cdot \text{ACS} - 0.005 \cdot \text{previous CIHD}$

Abbreviations: RFR: "resting full-cycle ratio"; CKD: chronic kidney disease (glomerular filtration rate < 60 ml/min/1.73 m²); non-LAD: lesions not affecting the left anterior descending artery; ACS: acute coronary syndrome; previous CIHD: history of chronic ischemic heart disease.

This algorithm shows that chronic kidney disease (risk factor for FP) is entered with a positive sign. Lesions not affecting the left anterior descending artery and indication for acute coronary syndrome (both risk factors for FN), as well as history of chronic ischemic heart disease (protective factor for FP), are entered with a negative sign.

Sensitivity and specificity analysis

Figure 1 shows the comparative ROC curves for RFR and the "Adjusted RFR". An increase was seen in the area under the curve (AUC) of the "Adjusted RFR" with respect to the RFR, from 0.651 to 0.749, determining as optimal CoT an "Adjusted RFR" of ≤ 0.8172 to detect FFR values ≤ 0.80 . Likewise, Figure 2 compares the contingency

Table 1 – Baseline characteristics per patient

	Patients (n=141)
Age, (years), mean (SD)	65.82 (12.3)
Female sex, n (%)	39 (27.7%)
BMI, (kg/m ²), mean (SD)	28.0 (4.8%)
Hypertension, n (%)	104 (73.8%)
Dyslipidemia, n (%)	93 (66%)
Diabetes mellitus, n (%)	50 (35.5%)
Current smoker, n (%)	26 (18.4%)
Previous chronic ischemic heart disease, n (%)	40 (28.4%)
Cerebrovascular disease, n (%)	13 (9.2%)
Atrial fibrillation, n (%)	15 (10.6%)
Peripheral vascular disease, n (%)	13 (9.2%)
COPD, n (%)	9 (6.4%)
Glomerular filtration rate, (mL/min/1.73 m ²), mean (SD)	74.0 (31.2)
Chronic kidney disease, (glomerular filtration rate < 60 ml/min/1.73 m ²), n (%)	51 (36.7%)
Clinical indication, n (%)	
– Stable angina	102 (72.3%)
– Non ST-segment elevation ACS: culprit lesion	21 (14.9%)
– Non ST-segment elevation ACS: non-culprit lesion	10 (7.1%)
– ST-segment elevation ACS: non-culprit lesion	8 (5.7%)
Lesions/patient, (n), median (minimum-maximum)	1 (1-4)

ACS: acute coronary syndrome; BMI: body mass index; COPD: chronic obstructive pulmonary disease; SD: standard deviation.

Table 2 – Baseline characteristics per lesion

	TN: RFR-/FFR- (n=60)	FP: RFR+/FFR- (n=41)	FN: RFR-/FFR+ (n=21)	TP: RFR+/FFR+ (n=34)	p value
Age, (years), mean (SD)	63.0 (14.0)	71.5 (10.3)	62.1 (8.7)	66.2 (10.9)	0.002
Female sex, n (%)	18 (30.0%)	13 (31.7%)	5 (23.8%)	4 (11.8%)	0.182
BMI, (Kg/m ²), mean (SD)	27.8 (4.6)	27.7 (4.8)	29.2 (5.5)	27.8 (4.2)	0.647
Hypertension, n (%)	43 (71.7%)	30 (73.2%)	18 (85.7%)	24 (70.6%)	0.600
Dyslipidemia, n (%)	38 (63.3%)	25 (61.0%)	13 (61.9%)	22 (64.7%)	0.989
Diabetes mellitus, n (%)	20 (33.3%)	18 (43.9%)	4 (19.0%)	14 (41.2%)	0.229
Current smoker, n (%)	14 (23.3%)	3 (7.3%)	9 (42.9%)	7 (20.6%)	0.013
Previous chronic ischemic heart disease, n (%)	26 (43.3%)	5 (12.2%)	8 (38.1%)	7 (20.6%)	0.004
Cerebrovascular disease, n (%)	5 (8.3%)	5 (12.2%)	2 (9.5%)	2 (5.9%)	0.862
Atrial fibrillation, n (%)	4 (6.7%)	6 (14.6%)	1 (4.8%)	4 (11.8%)	0.468
Peripheral vascular disease, n (%)	5 (8.3%)	4 (9.8%)	0 (0%)	6 (17.6%)	0.181
COPD, n (%)	6 (10.0%)	0 (0%)	0 (0%)	4 (11.8%)	0.061
Glomerular filtration rate, (mL/min/1.73 m ²), mean (SD)	78.4 (33.0)	57.5 (26.0)	90.1 (20.4)	74.4 (29.5)	< 0.001
Chronic kidney disease, (glomerular filtration rate < 60 mL/min/1.73 m ²), n (%)	19 (31.7%)	26 (63.4%)	2 (9.5%)	9 (26.5%)	< 0.001
Clinical indication, n (%)					0.012
– Stable angina	46 (76.7%)	33 (80.5%)	9 (42.9%)	24 (70.6%)	
– Acute coronary syndrome	14 (23.3%)	8 (19.5%)	12 (57.1%)	10 (29.4%)	

BMI: body mass index; COPD: chronic obstructive pulmonary disease; FFR: fractional flow reserve; FN: false negative; FP: false positive; RFR: resting full-cycle ratio; SD: standard deviation; TN: true negative; TP: true positive.

tables of both indices according to the established CoTs, with improvements in sensitivity ranging from 59% to 68%, specificity ranging from 62% to 75%, diagnostic accuracy ranging from 60% to 71%, PPV ranging from 45% to 56%, and NPV ranging from 74% to 83%. Of particular interest is the improvement in LR_s, where we found that, with the new index, LR₊ increased from 1.51 to 2.34 and LR₋ decreased from 0.64 to 0.37. Thus, the “Adjusted RFR” has satisfactory utility compared to RFR, which is not useful for discriminating patients in the “grey zone”.

Discussion

The main findings of the study were: a) chronic kidney disease, involvement of arteries other than the left anterior descending artery, indication for acute coronary syndrome, and history of chronic ischemic heart disease were shown as independent predictors of discordance in the “grey zone” of the RFR with respect to FFR; and b) the modification of the RFR by including independent predictors of discordance (“Adjusted RFR”) made it possible to improve the diagnostic capacity of the test for “grey zone” values.

Selection of the target population: Why the “grey zone”?

Any continuous quantitative index used dichotomously involves some degree of diagnostic uncertainty in values

close to the established CoT.¹⁸ The concept of “grey zone” for coronary physiological indices arises from validation studies of the FFR for the detection of ischemia induced by epicardial coronary stenosis.^{8,9,19,20} This concept was subsequently extended to other NHRI_s such as the instantaneous wave-free ratio and the RFR, showing that extreme NHRI values showed very high agreement with FFR, and, in values close to CoT (“grey zone”), the diagnostic capacity decreased.^{10,11} Since it is plausible that the few discordant results between RFR and FFR in case of extreme RFR values are mainly related to errors in the measurement technique, it was decided to restrict the determination of predictors of discordance to the “grey zone” of RFR.

In addition, the proportion of patients assessed by invasive physiological study located in the “grey zone” is relevant, showing in data on RFR and instantaneous wave-free ratio that the proportion of patients may exceed 40%.^{10,11} Therefore, we consider it essential to develop diagnostic tools that make it possible to refine the diagnosis of NHRI and eventually other invasive physiological indices, of either epicardial circulation or coronary microcirculation, for this range of values.

Assessment of predictors of discordance: Does the affected coronary territory predict false positives or false negatives?

Table 3 – Angiographic and physiological characteristics per lesion

	TN: RFR-/FFR- (n=60)	FP: RFR+/FFR- (n=41)	FN: RFR-/FFR+ (n=21)	TP: RFR+/FFR+ (n=34)	p value
Adenosine administration, n (%)					0.343
– Adenosine intravenous	18 (30.0%)	17 (51.5%)	10 (47.6%)	10 (29.4%)	
– Adenosine intracoronary	42 (70.0%)	24 (58.5%)	11 (52.4%)	24 (70.6%)	
Guide catheter size, n (%)					0.574
– 5 French	2 (3.3%)	2 (4.9%)	0 (0%)	1 (2.9%)	
– 6 French	58 (96.7%)	39 (95.1%)	21 (100%)	32 (94.1%)	
– 7 French	0 (0%)	0 (0%)	0 (0%)	1 (2.9%)	
Affected vessel, n (%)					0.019
– LAD	43 (71.7%)	33 (80.5%)	11 (52.4%)	30 (88.2%)	
– Non-LAD	17 (28.3%)	8 (19.5%)	10 (47.6%)	4 (11.8%)	
Percentage of stenosis, (%), mean (SD)	57 (11)	57 (10)	61 (10)	61 (9)	0.136
Length of the lesion, n (%)					0.716
– <12 mm	30 (50.0%)	17 (41.5%)	11 (52.4%)	13 (38.2%)	
– 12 to 25 mm	23 (38.3%)	20 (48.8%)	9 (42.9%)	14 (44.1%)	
– >25 mm	7 (11.7%)	4 (9.8%)	1 (4.8%)	6 (17.6%)	
Vessel diameter, (mm), mean (SD)	3.01 (0.53)	2.89 (0.37)	2.93 (0.53)	2.92 (0.45)	0.636
Coronary indices, mean (SD)					
– RFR	0.91 (0.01)	0.88 (0.01)	0.91 (0.01)	0.87 (0.01)	<0.001
– Pd/Pa	0.93 (0.02)	0.92 (0.02)	0.92 (0.02)	0.90 (0.03)	<0.001
– FFR	0.86 (0.03)	0.85 (0.03)	0.76 (0.04)	0.76 (0.03)	<0.001

FFR: "fractional flow reserve"; FN: false negative; FP: false positive; LAD: affection of the left anterior descending artery; non-LAD: not affecting the left anterior descending artery; Pd/Pa: ratio distal coronary pressure/aortic pressure; RFR: "resting full-cycle ratio"; SD: standard deviation; TN: true negative; TP: true positive.

Table 4 – Independent predictors of discordance

RFR+/FFR- (false positives)							
Univariate analysis	OR	CI (95%)	P value	Multivariate analysis	OR	CI (95%)	p value
CKD	4.911	2.298-10.498	<0.001	DRC	3.224	1.386-7.501	0.007
Age ≥ 75 years	3.981	1.862-8.511	<0.001	CIC prévia	0.296	0.102-0.858	0.025
Non-LAD lesions	0.657	0.274-1.576	0.345				
ACS	0.532	0.224-1.266	0.150				
Previous CIHD	0.251	0.091-0.688	0.005				
Current smoking	0.224	0.064-0.688	0.005				
RFR-/FFR+ (false negatives)							
Univariate analysis	OR	CI (95%)	P value	Multivariate analysis	OR	CI (95%)	p value
ACS	4.292	1.658-11.107	0.002	SCA	3.687	1.247-10.899	0.018
Current smoking	3.469	1.314-9.154	0.009	Lesões não DAE	3.529	1.231-10.118	0.019
Non-LAD lesions	3.323	1.285-8.594	0.010				
Previous CIHD	1.157	0.603-4.091	0.352				
CKD	0.158	0.035-0.706	0.003				
Age ≥ 75 years	0.103	0.013-0.796	0.003				

ACS: acute coronary syndrome; CI: confidence interval; CIHD: chronic ischemic heart disease; CKD: chronic kidney disease; FFR: "fractional flow reserve"; non-LAD lesions: lesions not involving the left anterior descending artery; OR: odds ratio; RFR: "resting full-cycle ratio".

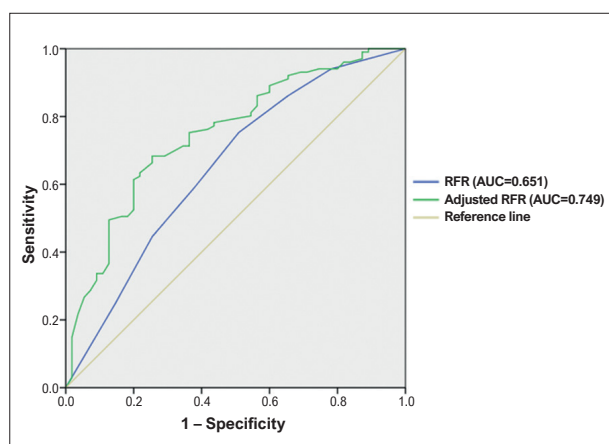


Figure 1 – ROC curves of RFR versus $FFR \leq 0.80$ and "Adjusted RFR" and $FFR \leq 0.80$. AUC: area under the curve; FFR: fractional flow reserve; ROC: receiver operating characteristic; RFR: resting full-cycle ratio. The ROC curve showed an AUC for the RFR of 0.651 (0.559 to 0.744; $p = 0.002$), improving the AUC for "Adjusted RFR" to 0.749 (0.669 to 0.828; $p < 0.001$) and establishing as optimum cutoff threshold for "Adjusted RFR" a value of 0.8172.

Given the limited sample size and the heterogeneity of the study populations assessed by the predictors of discordance between RFR and FFR, it is reasonable that exactly the same predictors are not observed.^{12,13} Our findings show results similar to those already reported by Goto¹² and Kato¹³ regarding chronic kidney disease as a risk factor for FP. We also found acute coronary syndrome to be a risk factor for FN and a history of chronic ischemic heart disease to be a protective factor for FP, and we did not find peripheral arterial disease, sex, or body dimensions, assessed as body surface area or as body mass index in our case, to be predictors of discordance as in previous studies.

However, one of the most striking findings of both previous studies was that left anterior descending artery lesions behaved as a risk factor for FP.^{12,13} Specifically, Kato's study¹³ found that lesions not affecting the left anterior descending artery behaved as a risk factor for FN, in a similar way to our own results. In this study, in the case of complementary variables (e.g., presence or absence of chronic kidney disease), we decided to assess the behavior of the least common variable as a predictor of discordance. Considering this approach regarding the location of coronary lesions (involvement versus non-involvement of the left anterior descending artery), we found that, in previous research,^{12,13} the majority of evaluated stenoses involved the left anterior descending artery, in line with standard practice.^{11,15-17} Thus, we hypothesized that the condition of risk factor for FP or FN according to the location of coronary stenoses would show complementary aspects, and since most lesions correspond to the left anterior descending artery, it seemed more appropriate to assess, as a predictor of discordance, that of lower prevalence in standard practice, which for coronary lesions is the involvement of territories other than the left anterior descending artery.

Generation of the "Adjusted RFR": Why adjust for discordance factors?

To date, studies on invasive coronary physiological indices have not considered integrating the information provided by clinical parameters, and *our work is the first to attempt this*. However, the development of clinical-physiological indices presents the question of which parameters to include to reinforce the results of coronary indices. Since the predictors of discordance are those that contain information about the specific characteristics of FPs and FNs, we chose to only include these parameters in a

		FFR		
		>0.80 (Healthy)	≤0.80 (Diseased)	
RFR	>0.89 (Negative)	60 (TN)	21 (FN)	81
	≤0.89 (Positive)	41 (FP)	34 (TP)	75
		101	55	156
Sensitivity: 59% Specificity: 62% Diagnostic accuracy: 60% PPV: 45% NPV: 74% LR+: 1.51 LR-: 0.64				
		FFR		
		>0.80 (Healthy)	≤0.80 (Diseased)	
Adjusted RFR	>0.8172 (Negative)	69 (TN)	14 (FN)	83
	≤0.8172 (Positive)	32 (FP)	41 (TP)	73
		101	55	156
Sensitivity: 68% Specificity: 75% Diagnostic accuracy: 71% PPV: 56% NPV: 83% LR+: 2.34 LR-: 0.37				

Figure 2 – Comparison of diagnostic parameters according to 2×2 Tables for the cutoff thresholds of RFR (≤ 0.89) and "Adjusted RFR" (≤ 0.8172) versus FFR (≤ 0.80). FFR: fractional flow reserve; FN: false negative; FP: false positive; NPV: negative predictive value; LR+: positive likelihood ratio; LR-: negative likelihood ratio; PPV: positive predictive value; RFR: resting full-cycle ratio; TN: true negative; TP: true positive.

global index that would make it possible to reduce errors in the diagnostic classification of patients.

In the proposed algorithm, the information provided by the independent predictors of discordance, together with the RFR, was integrated using a regression model. The model subsequently assigned a constant for the algorithm and the coefficients with their corresponding sign (positive or negative) for each variable. Finally, the model was evaluated, establishing as optimal CoT a value of "Adjusted RFR" ≤ 0.8172 to detect FFR values ≤ 0.80 .

Based on the above, the algorithm should be interpreted as follows. For "Adjusted RFR", the variable with the greatest weight is RFR since it has the highest coefficient (+0.912), which may be modified incrementally or decrementally depending on whether the patient has any or all predictors of discordance. The presence of chronic kidney disease (risk factor for FP) increases the final value of the "Adjusted RFR", making it easier to reclassify the patient as negative, while previous chronic ischemic heart disease (FP protective factor) decreases it, making it difficult to reclassify the negative patient. Similarly, lesions in territories other than the left anterior descending artery and acute coronary syndrome (both risk factors for FN) reduce the final value of the "Adjusted RFR", making it easier to reclassify the patient as positive. In addition, the algorithm guides not only the direction in which to reclassify patients but also to weigh the influence of the predictors, according to the weight of their coefficients.

Utility of the "Adjusted RFR": Can the development of clinical-physiological indices be clinically relevant?

The integration of the result of a test with the clinical characteristics of the patient is common in multiple settings. As an example, the most precise estimate of renal function is obtained by combining serum creatinine values with other parameters such as age, weight, and sex.²¹ The "Adjusted RFR" allows for an improved diagnostic capacity compared to the use of RFR alone. Although such improvement was limited in our population, the results suggest that a clinical-physiological index improves all diagnostic parameters. This is particularly visible in the improvement of LRs, where we found that "Adjusted RFR" allows for improvement of test utility compared to the RFR in the "grey zone".

Limitations

First, the RECOPA Study¹¹ was a single-country study (Spain), which may limit its extrapolation to other populations. However, its multicenter nature attenuates this limitation. Second, the inclusion criteria of the RECOPA Study¹¹ also allowed the recruitment of patients with acute coronary syndrome, despite the fact that invasive assessment of coronary lesions is mainly recommended in patients with stable angina. However, in standard practice, coronary indices are also used in acute coronary syndrome, which has been supported in the literature,²² and this scenario may also influence its results. Third, the limited sample

size of our study could be extended, and the methodology used could be modified in subsequent studies to further refine the construction of combined indices. However, our research found an improvement in all diagnostic parameters. Finally, it should be noted that, in addition to studies allowing for the derivation of new clinical-physiological indices, validation studies are required in external populations.

Conclusions

Adjusting the RFR by integrating the information provided by the predictors of discordance to obtain the "Adjusted RFR" improved the diagnostic capacity in our population. The development of clinical-physiological indices, including RFR or other indices, could improve the diagnostic capacity of coronary physiological indices. Future studies in large populations are required to assess the utility of similar methodologies in refining coronary physiology studies.

What is known about the topic?

Minimal changes in CoTs of coronary physiology tests lead to significant changes in sensitivity, specificity, and predictive values. In addition, variability exists between the CoTs of RFR in the different series, suggesting an influence of population characteristics on the diagnostic capacity of this index. Predictors of discordance have already been documented between the results offered by the RFR and the diagnostic "gold standard" for coronary physiology tests, namely, the FFR. These predictors seem useful to complement the information offered by the RFR for values in the "grey zone".

What's new?

Chronic kidney disease, involvement of arteries other than the left anterior descending artery, indication for acute coronary syndrome, and a history of chronic ischemic heart disease have been shown to be independent predictors of discordance in the "grey zone" of RFR as compared to FFR. The construction of a modified clinical-physiological index (the "Adjusted RFR") that includes information on the RFR and predictors of discordance improved the diagnostic capacity in the "grey zone". The development of clinical-physiological indices could be useful to improve both the diagnostic capacity of RFR and other coronary physiological indices.

Author contributions

Conception and design of the research: Fernández-Rodríguez D, Casanova-Sandoval J, Barriuso I, Rivera K, Otaegui I, del Blanco BG, Jiménez TG, López-Pérez M, Rodríguez-Esteban M, Torres-Saura F, Díaz VJ, Ocaranza-Sánchez R, Disdier VP, Elvira GS, Worner F;

Acquisition of data: Fernández-Rodríguez D, Casanova-Sandoval J, Rivera K, Otaegui I, del Blanco BG, Jiménez TG, López-Pérez M, Rodríguez-Esteban M, Torres-Saura F, Díaz VJ, Ocaranza-Sánchez R, Disdier VP, Elvira GS; analysis

and interpretation of the data; statistical analysis, writing of the manuscript and critical revision of the manuscript for intellectual content: Fernández-Rodríguez D.

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 CEIm Hospital Universitari Arnau de Vilanova de Lleida under the protocol number CEIC 2019. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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***Supplemental Materials**

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Positive Association between Autoantibodies Against Oxidized LDL and HDL-C: A Novel Mechanism for HDL Cardioprotection?

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Abstract

Background: In the atherosclerotic plaque microenvironment, oxidized phospholipids expressed in the oxidized low-density lipoprotein (oxLDL) surface bind to scavenger receptors of macrophages eliciting foam cell formation and plaque progression. Auto-antibodies against oxLDL (oxLDL-Ab) interact with oxidative epitopes leading to the formation of immune complexes that are unable to interact with macrophage receptors, thus abrogating atherogenesis. Release of oxLDL-Ab by B cells involves interleukin 5 and Th2 response, which in turn are potentiated by HDL. Thereby, we hypothesized that individuals with higher levels of HDL-C may plausibly display elevated titers of oxLDL-Ab.

Objective: To evaluate the relationship between HDL-C and oxLDL-Ab levels.

Methods: Asymptomatic individuals (n = 193) were grouped according to their HDL-C concentration to one of three categories: low (< 68 mg/dL), intermediate (68 to 80 mg/dL) or high (> 80 mg/dL). P values < 0.05 were considered statistically significant.

Results: Our analysis included 193 individuals (mean age: 47 years; male: 26.3%). Compared to individuals in the lowest HDL-C tertile, those in the highest tertile were older (36 versus 53 years; p = 0.001) and less frequently male (42.6% versus 20.9%; p = 0.001). Mean values of oxLDL-Ab increased as the HDL-C group escalated (0.31, 0.33 and 0.43 units, respectively; p = 0.001 for trend). Simple linear regression found a significant, positive relationship between the independent variable, HDL-C, and the dependent variable, oxLDL-Ab (R = 0.293; p = 0.009). This relation remained significant (R = 0.30; p = 0.044), after adjustment by covariates. Apolipoprotein AI levels were also related to oxLDL-Ab in both simple and adjusted linear regression models.

Conclusion: HDL-C and oxLDL-Ab are independently related.

Keywords: Cholesterol, HDL; Lipoproteins, IDL; Atherosclerosis.

Introduction

Accumulation of apolipoprotein B (ApoB)-containing lipoproteins, chiefly low density lipoprotein (LDL), in arterial intima has been pursued as the initial step of atherogenesis.¹ In this arterial microenvironment, oxidative modification generates several new epitopes in LDL, which are recognized by immune cells and lead to the activation of Th1 and Th2 inflammatory response eliciting the release of autoantibodies against oxidized LDL (oxLDL-Ab).^{2,3}

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The protective role of oxLDL-Ab in atherogenesis is supported by a growing body of evidence. In fact, treatment with oxLDL-Ab diminished atherosclerotic plaque progression, and significantly mitigated oxidized LDL (oxLDL) uptake by macrophages in apolipoprotein E (ApoE)-deficient mice.⁴⁻⁷ Moreover, observational studies have found that oxLDL-Ab levels are inversely related to carotid intima media thickness and to oxLDL levels in healthy individuals.⁸ Accordingly, a large systematic review concluded that oxLDL-Ab levels are inversely related to coronary artery disease severity and incidence of cardiovascular events.⁹

The beneficial properties of oxLDL-Ab have sparked an intense search for modulators of its release. In this matter, Chou et al.¹⁰ found that stimulation of B cells with interleukin 5 (IL5) elicited generation of oxLDL-Ab. Importantly, IL5 is related to Th2 response, which in turn is proven to be inhibited by oxLDL but enhanced by high-density lipoprotein (HDL).^{11,12} This considered, we designed the present study hypothesizing

that plasma HDL may be independently associated with plasma levels of oxLDL-Ab. To address this, our study evaluated whether oxLDL-Ab and high-density lipoprotein cholesterol (HDL-C) levels are related in individuals with a large range of plasma HDL-C concentrations.

Methods

Research design

The study was conducted as cross-sectional analysis of data from healthy individuals consecutively enrolled in a large pool of asymptomatic patients attended at the University of Campinas Teaching Hospital, in the city of Campinas, São Paulo, Brazil. Eligible patients were 18 years or older, from both sexes. After signing the informed consent form, participants answered a detailed eligibility questionnaire.

Exclusion criteria were any previous coronary artery disease or stroke; secondary causes of low or high plasma HDL-C; regular use of medical treatments (especially those interfering in lipid metabolism, such as statins, hormonal replacement therapy, and contraceptives); liver, renal, lung, and endocrine diseases (such as diabetes); chronic use of alcohol and tobacco; and women who were pregnant or lactating due to the possible hormone influence. Eligible participants then underwent a detailed physical examination, blood pressure measurements, and carotid ultrasound examination, and their peripheral blood sample was collected for biochemical analysis.

Participants were grouped according to their HDL-C levels tertiles as follows: 1) low HDL-C concentrations (HDL-C below 68 mg/dL: $n = 59$); 2) intermediate concentrations (HDL-C 68 to 80 mg/dL: $n = 71$) and high HDL-C concentrations (HDL-C > 80 mg/dL: $n = 63$).

The Research Ethics Committee of the State University of Campinas approved all procedures under opinion number 790/2006. All participants signed a consent declaration to participate in the study.

Sample collection and analytical methods

Venous blood samples were drawn after a 12-hour fasting period in individuals selected to participate in the study. The samples were centrifuged (4 °C, 1000 g, 10 minutes) for serum and EDTA plasma separation, and stored at -80 °C until analysis. Another 12-hour fasting blood sample was collected during a second visit 15 minutes after intravenous administration of heparin (Liquemine® Roche, 100 U/kg body weight).

Total cholesterol, triglycerides, and phospholipids in serum and the first two analytes in lipoproteins were analyzed by enzymatic-colorimetric methods (BM Hitachi 917 Roche, Mannheim, Germany). Apolipoprotein B100 and apolipoprotein AI (ApoAI) were measured in an automated BN II system (Siemens Healthcare Diagnostics, Marburg, Germany), using commercially available assays (Dade-Boehringer®, Deerfield, Illinois, USA). HDL-C was analyzed by a direct homogenous method. Low-density lipoprotein cholesterol (LDL-C) was calculated by Friedewald's¹³ formula.

To obtain HDL sub-fractions, lipoproteins that contained ApoB were precipitated by dextran sulfate, and the

supernatant substance was submitted to sequential micro-ultracentrifugation using the Airfuge/75B (Beckman Instruments, Palo Alto, California, USA).

Plasma activities of cholesteryl ester transfer protein (CETP) and phospholipid transfer protein (PLTP) were determined through radiometric assays using exogenous substrates as previously described.^{14,15} Hepatic lipase (HL) and lipoprotein lipase (LPL) activities were measured in post-heparin plasma samples, collected 15 minutes after intravenous administration of heparin (100 U/kg of body weight). The assay was based on the fatty acid release, using a radiolabeled triolein emulsion as substrate, and NaCl 1M as LPL inhibitor.¹⁶

High-sensitivity C-reactive protein (hsCRP) was measured by immunoturbidimetry utilizing the Tina-quant® CRP (latex) high sensitivity assay (Roche Diagnostics®, Mannheim, Germany) in the Hitachi-Roche analytical platform. A commercial ELISA kit manufactured by R&D was used for tumor necrosis factor alpha (TNF-α) measurement.

The ELISA method was used to measure oxLDL-Ab in the plasma of all participants.^{17,18} Briefly, polystyrene microtiter plates (Costar, Cambridge, Massachusetts, USA) were coated with 1 µg/ml of human oxLDL (20 mM Cu²⁺, 24 hours) in carbonate/bicarbonate buffer (20 µL/well), pH 9.4, and kept overnight at 4 °C. The plates were blocked with a 5% solution of fat-free milk (Molico/Nestlé, São Paulo, Brazil), and then incubated for 2 hours at room temperature followed by washing 4 times with PBS (100 µL). Plasma samples (20 µL) were added, and the plates were incubated overnight at 4 °C followed by washing with 1% Tween 20 in PBS. The peroxidase-conjugated rabbit anti-mouse IgG antibody (20 µL; 1:1.500) was then added, and after 1 hour at room temperature, the plates were washed. Subsequently, 75 µL of substrate solution (250 mg of tetramethylbenzidine diluted in 50 mL of DMSO, 10 µL of 30% H₂O₂, 12 mL of citrate buffer, pH 5.5) were incorporated to the mixture and, after incubation at room temperature for 15 minutes, the reaction was stopped by adding 25 µL of 2.0 M sulfuric acid. The optical density was read in a microplate reader (Titertek Multiskan MCC/340P, model 2.20, Labsystems, Finland) at 450 nm.

For all measured variables, i.e., lipid, inflammatory markers, and enzyme activities, the accepted intra/inter-assay coefficients of variation varied from 3% to 10%, and from 10% to 15%, respectively.

Statistical analysis

Data are mean ± standard deviation for normally distributed data and median (interquartile range) for non-parametric data, whereas categorical variables are presented as number of cases (percentages). The normality of the continuous variables was assessed by the Kolmogorov-Smirnov test. One-way ANOVA with Bonferroni post-hoc test and Kruskal-Wallis with Dunn-Bonferroni post hoc were used to compare the distribution of parametric and nonparametric continuous data across groups, respectively. Chi-square test with Bonferroni adjustment was employed to compare the frequency across groups of categorical data.

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Linear regression was utilized to assess the relationship between the independent variable, oxLDL-Ab, and the dependent variable, HDL-C. This test was performed after assumptions of normality, linearity, homoscedasticity, and independence were ascertained. Adjusted linear regression analysis was utilized to assess the relationship between the independent variables, HDL-C, ApoAI, and HDL3-C, and the dependent variable, oxLDL-Ab, after adjustment by covariates. The results shown as coefficients of determination (R^2) represent the percentage of variation in the dependent variable explained

by the independent variables. Probability values (p) less than 0.05 were considered statistically significant. All analyses were performed using the software SPSS version 20.0 for Mac.

Results

Table 1 shows the comparisons of clinical, anthropometric, and biochemical characteristics among all HDL subgroups. The participants were assigned, according to their HDL-C concentrations to one of three statistically different categories

Table 1 – Clinical, anthropometric, and biochemical characteristics of individuals with different concentrations of HDL-C

Parameters	Low (< 68 mg/dL)	Intermediate (68 to 80 mg/dL)	High (> 80 mg/dL)	p values
n	59	71	63	
Age (years)	36 $\pm$ 14	52 $\pm$ 12	53 $\pm$ 13	0.001 ^{1,2}
Male (%)	42.6	11.7	20.9	0.001
BMI (kg/m ²)	24 $\pm$ 5	25 $\pm$ 5	25 $\pm$ 5	0.158
SBP (mmHg)	119 $\pm$ 13	124 $\pm$ 14	130 $\pm$ 18	0.001 ^{1,3}
DBP (mmHg)	77 $\pm$ 9.2	79 $\pm$ 10	83 $\pm$ 11	0.006 ¹
Cholesterol (mg/dL)	170 $\pm$ 45	224 $\pm$ 37	231 $\pm$ 38	0.001 ^{1,2}
TG (mg/dL)	77 (38)	98 (39)	87 (40)	0.008 ²
Phospholipids (mg/dL)	206 $\pm$ 54	225 $\pm$ 41	228 $\pm$ 48	0.023 ¹
HDL-C (mg/dL)	51 $\pm$ 5.6	73 $\pm$ 3.9	86 $\pm$ 4.7	0.001 ^{1,2,3}
HDL2-C (mg/dL)	11 $\pm$ 2.9	17 $\pm$ 4.6	19 $\pm$ 4.7	0.001 ^{1,2,3}
HDL3-C (mg/dL)	36 $\pm$ 6	55 $\pm$ 7.6	64 $\pm$ 6.7	0.001 ^{1,2,3}
HDL2TG (mg/dL)	6.8 $\pm$ 4.8	8.6 $\pm$ 4.7	24 $\pm$ 9.8	0.022 ¹
HDL3TG (mg/dL)	51 $\pm$ 5.5	73 $\pm$ 4	86 $\pm$ 4.7	0.001 ^{1,2}
LDL-C (mg/dL)	105 $\pm$ 37	130 $\pm$ 35	127 $\pm$ 35	0.001 ^{1,2}
VLDL (mg/dL)	15 $\pm$ 7.9	19 $\pm$ 7.9	17 $\pm$ 8.0	0.020 ²
ApoAI (mg/dL)	140 $\pm$ 27	180 $\pm$ 24	195 $\pm$ 31	0.001 ^{1,2,3}
ApoB100 (mg/dL)	82 $\pm$ 30	104 $\pm$ 25	101 $\pm$ 26	0.001 ^{1,2}
HL (nmol/FFA/mL/h)	2529 (1361)	1539 (973)	1561 (1018)	0.001 ^{1,2}
LPL (nmol/FFA/mL/h)	2313 (1012)	2497 (1690)	2880 (1522)	0.091
CETP (%)	15.8 $\pm$ 8.3	10.4 $\pm$ 6.9	10.7 $\pm$ 7.6	0.001 ^{1,2}
PLTP (%)	14.4 $\pm$ 10.4	19.5 $\pm$ 11.4	18.3 $\pm$ 16.1	0.020 ²
hsCRP (mg/L)	0.38 $\pm$ 0.63	0.44 $\pm$ 0.54	0.32 $\pm$ 0.41	0.451
TNF- α (pg/mL)	9.8 $\pm$ 9.3	11 $\pm$ 12.3	12 $\pm$ 12.1	0.756
oxLDL-Ab (OD)	0.31 $\pm$ 0.17	0.33 $\pm$ 0.16	0.43 $\pm$ 0.17	0.001 ¹
Mean CIMT (mm)	0.62 $\pm$ 0.12	0.90 $\pm$ 0.24	0.86 $\pm$ 0.22	0.001 ^{1,2}
Alcohol use % (n)	16.1	24.7	28.4	0.265
CAD % (n)	9.4	6.8	9.0	0.866

Data are represented as mean $\pm$ standard deviation and median (interquartile range) when normally and non-normally distributed, respectively, and as number (%) when categorical. Low: HDL-C < 68 ; intermediate: HDL-C 68 to 80 mg/dL; high: HDL-C > 80 mg/dL. ApoAI: apolipoprotein AI; ApoB100: apolipoprotein B100; BMI: body mass index; C: cholesterol; CAD: coronary artery disease; CETP: cholesterol ester transfer protein; CIMT: carotid intima-media thickness; DBP: diastolic blood pressure; FFA: free fatty acids; HDL: high-density lipoprotein; HL: hepatic lipase; hsCRP: high-sensitivity C-reactive protein; LDL: low-density lipoprotein; LPL: lipoprotein lipase; oxLDL-Ab: autoantibodies against oxidized low-density lipoprotein; PLTP: phospholipid transfer protein; SBP: systolic blood pressure; TG: triglycerides; TNF- α : tumor necrosis factor alpha; VLDL: very low-density lipoprotein. The p values were obtained by one-way ANOVA and Kruskal-Wallis test for continuous variables with normal and non-normal distribution, and by chi-square test for categorical data. Differences among groups are represented by ¹(low $\neq$ high), ²(low $\neq$ intermediate), ³(intermediate $\neq$ high).

Table 2 – Simple linear regression using oxLDL-Ab as dependent variable

Independent variables	B (SE)	p values	R	R ²
Age	0.002 (.001)	0.027	0.216	0.047
Male	8.66 (.029)	0.998	0.000	0.000
HDL-C	0.002 (.001)	0.004	0.293	0.086
HDL tertiles	0.042 (.015)	0.006	0.276	0.076
HDL-2C	0.004 (.002)	0.054	0.191	0.036
HDL-3C	0.002 (.001)	0.016	0.237	0.056
ApoAI	0.001 (.000)	0.002	0.308	0.095
LDL	0.000 (.000)	0.179	0.132	0.017
ApoB	0.001 (.000)	0.204	0.126	0.016
hsCRP	0.052 (.032)	0.105	0.177	0.031
TNF- α	0.002 (.001)	0.086	0.225	0.051
CIMT	0.146 (.085)	0.093	-0.25	0.316

Simple linear regression. ApoAI: apolipoprotein AI; ApoB: apolipoprotein B; C: cholesterol; CIMT: carotid intima-media thickness; HDL: high-density lipoprotein; hsCRP: high-sensitivity C-reactive protein; LDL: low-density lipoprotein; oxLDL-Ab: autoantibodies against oxidized low-density lipoprotein; TNF- α : tumor necrosis factor alpha.

Table 3 – Linear regression adjusted by covariates

Independent variables	Models	B (SE)	p values	R	R ²
HDL-C	HDL-C				
	Age	0.002 (.001)	0.044	0.30	0.090
HDL-3C	HDL-C				
	ApoB	0.002 (.001)	0.011	0.279	0.078
ApoAI	HDL-3C				
	Age	0.001 (.001)	0.166	0.272	0.074
	HDL-3C				
	ApoB	0.002 (.001)	0.054	0.234	0.055
	ApoAI				
	Age	0.153 (.059)	0.019	0.318	0.101
	ApoAI				
	ApoB	0.001 (.00)	0.004	0.310	0.096

Adjusted linear regression. ApoAI: apolipoprotein AI; ApoB: apolipoprotein B; HDL-C: high-density lipoprotein cholesterol.

($p \leq 0.006$): low (< 60 mg/dL), intermediate (68 to 80 mg/dL) or high (> 80 mg/dL).

When compared to the lowest tertile of HDL-C, the highest tertile had more women, older ages, and, as expected, higher concentration of cholesterol. HL and CETP activities were reduced, and HL and PLTP increased in the upper tertile of HDL-C as compared to those in the lowest tertile. No differences were found in hsCRP and TNF- α . It is noteworthy that oxLDL-Ab levels were significantly higher in the high HDL-C group, in comparison to the low HDL-C group.

To explore the influence of the independent variables, HDL-C concentration, HDL-C tertiles, sex, ApoAI, ApoB, inflammatory markers and age, on the dependent variable, oxLDL-Ab, a linear regression analysis was performed, as

shown in Table 2. OxLDL-Ab levels were influenced by age, HDL-C, HDL-C tertiles, HDL-3C, and ApoAI.

In the adjusted regression analysis, only HDL-C and ApoAI were independently related to oxLDL-Ab levels in the model adjusted by the covariates of age and ApoB, as shown in Table 3.

Linear regression curve models of HDL and ApoAI relationships to oxLDL-Ab are shown in Figures 1 and 2, respectively.

Discussion

Retention of oxLDL in the subendothelial layer of the arterial wall is an initiating step of atherosclerosis.¹⁹ OxLDL binds to scavenger receptors, such as Lox1 and SR-B1, to

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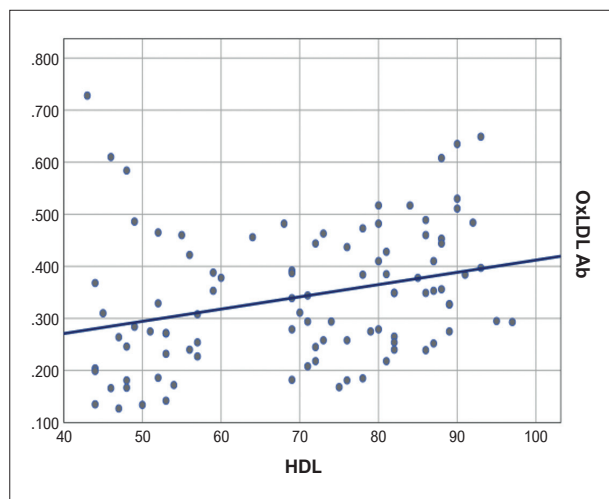


Figure 1 – Curve model: oxLDL-Ab versus HDL. HDL: high-density lipoprotein; oxLDL-Ab: autoantibodies against oxidized low-density lipoprotein.

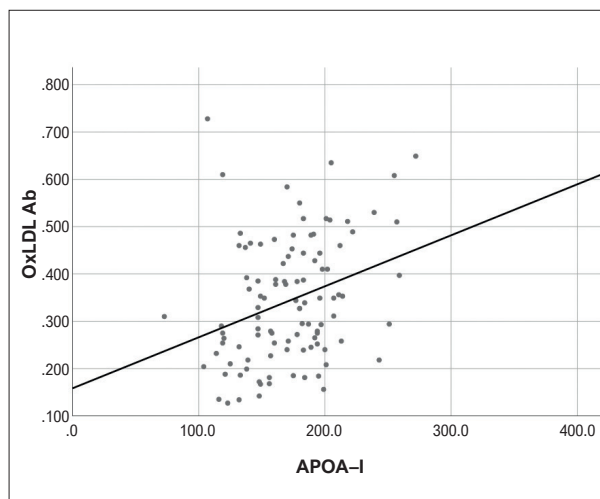


Figure 2 – Curve model: oxLDL-Ab versus ApoA-I. ApoA-I: apolipoprotein A-I; oxLDL-Ab: autoantibodies against oxidized low-density lipoprotein.

prompt downstream deleterious pathways that culminate in plaque progression.²⁰ Beyond reverse cholesterol transport, HDL modulates humoral immunity of atherosclerotic plaque, upregulating IL5 and Th2 response, which are involved in B cell activation and release of oxLDL-Ab.²¹ Correspondingly, our study, for the first time, found an independent positive correlation between serum levels of HDL-C and oxLDL-Ab.

Prior experimental data have consistently demonstrated an atheroprotective role for oxLDL-Ab. From a mechanistic perspective, oxLDL-Ab colocalizes in the atherosclerotic plaque, where it binds to oxLDL epitopes forming immune complexes that cannot interact with macrophage Fcγ receptors.^{13,22} As a result, neutralization of oxLDL epitopes by oxLDL-Ab prevents macrophage activation, interrupting an imperative pathway of plaque progression.¹³ In line with this, Dai et al²² demonstrated that pretreatment of macrophages with oxLDL-Ab prevented oxLDL-induced cell death and NF-κB activation. Accordingly, treatment with oxLDL-Ab significantly reduced cross-sectional atherosclerotic plaque area and vascular cell adhesion molecule 1, and it mitigated macrophage uptake in LDLr^{-/-} mice.^{22,24}

Cumulative data from clinical studies have also supported a role for oxLDL-Ab as a marker of cardiovascular disease. In this matter, serum levels of oxLDL-Ab have consistently shown an independent inverse correlation with common carotid artery intima-media thickness and progression of carotid atherosclerosis.^{16,25-30} For example, in a cohort of 226 patients with hypertension prospectively enrolled in carotid ultrasound analysis, those with the lowest value of oxLDL-Ab showed a 3-fold reduced risk of any 4-year progression of intima-media thickness of the carotid arteries.³¹ Similarly, among individuals undergoing clinically indicated coronary angiography, those in the highest tertiles of oxLDL-Ab had a 37% lower risk of angiographically significant coronary atherosclerosis, and displayed a lower number of diseased arteries when compared to those with

the lowest titers of antibodies.^{32,33} Consistently, Shoji et al.³⁴ observed a 2-fold increased 5-year cardiovascular mortality among individuals with end-stage renal disease and low oxLDL-Ab, when compared to patients with end-stage renal disease with higher levels of oxLDL-Ab.

In addition to the aforesaid, we found a positive independent correlation between serum levels of HDL-C and oxLDL-Ab. From a mechanistic perspective, this finding may derive from immunomodulatory effects of HDL on Th2 response, which reasonably potentiates oxLDL-Ab release. This hypothesis still warrants further examination. Other potential reasons for the verified correlation may be highlighted, for example, experimentally, HDL attenuated uptake of oxLDL by macrophages. This may result in accumulation of oxLDL in the plaque microenvironment, favoring local humoral response.³⁵

This study had some limitations. More importantly, we assumed that HDL induces oxLDL-Ab by modulating IL5-related Th2 response. Nevertheless, measurement of IL5 were not performed. Furthermore, oxLDL levels, which are closely related to oxLDL-Ab release, were also not assessed and would have been a reasonable adjustment variable in our models. Finally, sample size was relatively small, which may have jeopardized statistical power to claim correlation.

Conclusion

Serum levels of oxLDL-Ab and HDL-C are positively related.

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Author Contributions

Conception and design of the research: Sposito AC, Faria EC; Acquisition of data: Nunez CEC, Zago VHS, Kaplan DB, Gomes EIL; Analysis and interpretation of the data: Oliveira JB, Barros-Mazon S, Cazita PM, Nakandakare E, Carmo HR, Sposito AC, Faria EC; Statistical analysis: Oliveira JB; Obtaining financing: Faria EC; Writing of the manuscript: Nunez CEC, Oliveira JB, Zago VHS; Critical revision of the manuscript for important intellectual content: Oliveira JB, Barros-Mazon S, Cazita PM, Nakandakare E, Carmo HR, Sposito AC, Faria EC; Performed all carotid intima-media thickness (cIMT) measurements: Nakamura RT; Performed the assays to quantify the titers of anti-oxLDL Ab: Gidlund MA; Assisted in sample collection, performed the experiments: Gomes EIL.

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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Antiinflammatory and Cardioprotective Effects of HDL-C: Association With Autoantibodies Against Oxidized LDL?

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Short Editorial related to the article: Positive Association between Autoantibodies Against Oxidized LDL and HDL-C: A Novel Mechanism for HDL Cardioprotection?

The accumulation of lipoproteins containing apolipoprotein B (ApoB), mainly low-density lipoprotein (LDL), in the arterial intima has been attributed to one of the initial steps of atherogenesis.¹ In other studies, oxidized LDL and macrophages are the main pathogenic factors for the development of atherosclerosis.^{2,3} In turn, there is increasing evidence of the protective role of autoantibodies against oxidized LDL (oxLDL-AboxLDL-Ab in atherogenesis, a fact that can be potentiated by high-density lipoprotein (HDL).^{4,5}

In this volume of *Arquivos Brasileiros de Cardiologia*, Nunez et al.⁶ evaluated the hypothesis that individuals with higher levels of HDL-C would have elevated levels of oxLDL-Ab. This is a cross-sectional study that included 193 consecutive healthy individuals aged ≥ 18 years and excluded patients with coronary artery disease (CAD), stroke, secondary causes of HDL elevation or reduction, use of lipid-lowering drugs, alcoholism, and smoking. The subjects underwent a detailed physical examination, blood pressure measurements and carotid ultrasound, in addition to biochemical analyzes of peripheral blood. Participants were divided into tertiles, according to HDL-C levels: low (< 68 mg/dL: $n = 59$); intermediate ($68-80$ mg/dL: $n=71$) and high (>80 mg/dL: $n=63$).

Compared to the lowest HDL-C tertile, the highest tertile had more women, older ages, and higher cholesterol concentrations. Hepatic lipase (LH) and cholesterol ester transfer protein (CETP) activities were reduced, and LH and phospholipid transfer protein (PLTP) increased in the highest tertile of HDL-C compared to the lowest tertile. There were no

significant differences in the levels of high-sensitivity C-reactive protein (hsCRP) and tumor necrosis factor (TNF α). However, oxLDL-Ab levels were significantly higher in the high HDL-C group compared to the low HDL-C group. Linear regression analysis revealed that OxLDL-Ab levels were influenced by age, HDL-C, HDL-C, HDL-3C and ApoAI tertiles. In the adjusted regression analysis, only HDL-C and ApoAI were independently related to oxLDL-Ab levels.⁶

Atherosclerosis is a chronic inflammatory disease of the arterial wall, characterized by the formation of plaques containing lipids, connective tissue and immune cells in the intima of the arteries. Oxidized LDL would be a trigger to activate this immune response.⁷ The CANTOS study proved, for the first time, that antiinflammatory treatment (in this case, with the antibody against interleukin IL-1 β) reduced clinical outcomes in patients with acute myocardial infarction (AMI).⁸ Subsequently, the antiinflammatory effects of colchicine reduced events in patients with AMI⁹ or CAD.¹⁰

In the study by Nunez et al.,⁶ the authors observed a positive and independent correlation between serum levels of HDL-C and ox-LDL-Ab. This agrees with the hypothesis that HDL would modulate humoral immunity of the atherosclerotic plaque and shows the role of oxLDL-Ab as a potential marker of cardiovascular disease. One of the study's limitations is that they did not measure interleukins (especially IL5, which would induce the HDL-C-induced release of ox-LDL-Ab). In addition, this study was carried out in a single center with a relatively small sample ($n = 193$). In any case, it is a very elegant study and opens the way for future research.

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Keywords

Atherosclerosis; Cholesterol, HDL; Lipoproteins, HDL.

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Cardiovascular Health and Atrial Fibrillation or Flutter: A Cross-Sectional Study from ELSA-Brasil

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Abstract

Background: The association between ideal cardiovascular health (ICVH) status and atrial fibrillation or flutter (AFF) diagnosis has been less studied compared to other cardiovascular diseases.

Objective: To analyze the association between AFF diagnosis and ICVH metrics and scores in the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil).

Methods: This study analyzed data from 13,141 participants with complete data. Electrocardiographic tracings were coded according to the Minnesota Coding System, in a centralized reading center. ICVH metrics (diet, physical activity, body mass index, smoking, blood pressure, fasting plasma glucose, and total cholesterol) and scores were calculated as proposed by the American Heart Association. Crude and adjusted binary logistic regression models were built to analyze the association of ICVH metrics and scores with AFF diagnosis. Significance level was set at 0.05.

Results: The sample had a median age of 55 years and 54.4% were women. In adjusted models, ICVH scores were not significantly associated with prevalent AFF diagnosis (odds ratio [OR]:0.96; 95% confidence interval [95% CI]:0.80–1.16; $p=0.70$). Ideal blood pressure (OR:0.33; 95% CI:0.15–0.74; $p=0.007$) and total cholesterol (OR:1.88; 95% CI:1.19–2.98; $p=0.007$) profiles were significantly associated with AFF diagnosis.

Conclusions: No significant associations were identified between global ICVH scores and AFF diagnosis after multivariable adjustment in our analyses, at least partially due to the antagonistic associations of AFF with blood pressure and total cholesterol ICVH metrics. Our results suggest that estimating the prevention of AFF burden using global ICVH scores may not be adequate, and ICVH metrics should be considered in separate.

Keywords: Atrial Fibrillation; Atrial Flutter; Epidemiology; Stroke.

Introduction

In 2010, the American Heart Association (AHA) set a decade-long goal to decrease cardiovascular disease (CVD) and stroke mortality by 20%.¹ The main strategy to achieve this goal included raising the prevalence of ideal cardiovascular

profiles, measured by seven ideal cardiovascular health (ICVH) metrics: diet, physical activity, smoking, body mass index (BMI), blood pressure, fasting plasma glucose, and total cholesterol. The AHA established specific definitions for each of these metrics, as well as a ICVH score for an individual as the sum of the ideal profiles.

The effectiveness of such a strategy is subject to the strength of the associations between each ICVH metric and occurrence of fatal or non-fatal CVD. Some authors evaluated the association of the ICVH score and its components with subclinical CVD,² clinical CVD³ and cardiovascular mortality.⁴ A less studied cardiovascular

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condition in this context is atrial fibrillation or flutter (AFF). AFF has a lifetime risk of 25%,⁵ is associated with multiple cardiovascular risk factors, and is a major risk factor for stroke, with population attributable fractions of stroke estimated between 2% and 6%.⁶⁻⁸ Ogunmoroti et al.⁹ analyzed data from 6,506 participants from the Multi-Ethnic Study of Atherosclerosis (MESA) and found that individuals with an optimum ICVH score at the baseline had a 27% lower risk of AFF after a median follow-up of 11.2 years as compared to those with inadequate ICVH scores. Garg et al.¹⁰ analyzed data from 13,182 Atherosclerosis Risk in Communities (ARIC) participants and found that, after a follow-up of 25.1 years, each ideal component increase was associated with a 17% lower risk for AFF. Similar analyses were also performed by Garg et al. in the Reasons for Geographic and Racial Differences in Stroke Study (REGARDS),¹¹ resulting in a smaller (7%) although significant reduction in the risk for AFF for each ideal component increase. Recently, Lee et al.¹² analyzed 208,598 individuals who underwent national health check-up examinations in South Korea and found, after a median follow-up of 7.2 years, that ICVH scores were significantly associated with incident AFF.

Most information about the association between AFF and ICVH metrics and score come from large cohorts in the United States; however, 72% of global disability-adjusted life-years and 67% of deaths due to stroke were estimated to occur in countries with middle or low sociodemographic index in 2016.¹³ AFF is also common in Brazil, with a frequency of about 2% in primary care-based studies,¹⁴ with higher frequencies associated with advancing age.

The aim of the present study is to report the associations between AFF diagnosis and ICVH metrics and score in the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil), a Brazilian multicenter cohort study of individuals of 35-74 years of age at the baseline.

Methods

The ELSA-Brasil design¹⁵ and cohort profile¹⁶ are detailed elsewhere. ELSA-Brasil is an ongoing multicenter cohort study in Brazil which enrolled 15,105 active or retired civil servants, from 35 to 74 years of age at baseline, from six institutions in six Brazilian cities. Baseline assessment occurred between August 2008 and December 2010. During this period, trained staff conducted in-person interviews, as well as clinical, laboratory, and imaging exams. After the baseline, all participants received a yearly telephone follow-up contact. From August 2012 to December 2014, all participants were invited to a second visit, during new questionnaires were administered, together with clinical and laboratory evaluations. A total of 14,014 (92.8%) individuals were reassessed. In the present article, information was obtained from the second visit, unless stated otherwise. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the Institutional Review Boards of all institutions where ELSA-Brasil investigation centers are located. Informed consent was obtained from each participant.

Study sample

From 14,014 individuals who were present in the second onsite assessment, 505 individuals were excluded due to a lack of electrocardiographic (ECG) information and 368 participants due to missing information on ICVH metrics. Therefore, our main sample consisted of 13,141 individuals. For some sensitivity analyses, the sample was restricted to 12,307 individuals without previous self-reported myocardial infarction, stroke, or heart failure.

Data collection

ELSA-Brasil protocols^{17,18} for anthropometric, clinical and laboratory exams did not change between the first and second assessments. Age, sex, race, education level, and monthly family income were self-reported and stratified accordingly. Monthly income was analyzed as multiples of the Brazilian minimum wage (one Brazilian minimum wage during data collection averaged approximately 310 US dollars). Systolic and diastolic blood pressure (SBP and DBP, respectively) measurements were taken using a validated oscillometric device (Omron HEM 705CPINT). Three measurements were taken at one-minute intervals after a five-minute rest with the subject in the sitting position, and the average of the second and third measurements was considered to define SBP and DBP. Fasting plasma glucose was determined using the hexokinase method and total cholesterol using the cholesterol oxidase method, conducted in an ADVIA 1200 Siemens® equipment.

AFF diagnosis

ECG recordings in ELSA-Brasil were obtained as described elsewhere.^{19,20} Electrocardiography in onsite assessments was performed using a Burdick Atria 6100 device, calibrated at 10 mm/mV and a speed of 25 mm/second. The recordings were transmitted to the reading center in the Minas Gerais Investigation Center. Analyses followed the Glasgow system and were coded according to the Minnesota Coding System. Selected codes (including AFF) were manually reviewed by trained staff. These methods have been adopted in all ELSA-Brasil assessments to date. AFF diagnosis in this article was defined as its presence in ECG tracing at the baseline or on the second visit.

ICVH score

Detailed information about the ideal ICVH scoring in ELSA-Brasil can be found elsewhere.²¹ The following definitions were used for the seven ICVH metrics, based on the AHA guidelines:¹

1. Diet: Four adequate components from (a) ≥ 4 servings of fruit and vegetables per day, (b) ≥ 7 ounces of fish per week, (c) ≥ 2 servings of fiber-rich whole grains per day, (d) ≤ 450 kcal of sugar-sweetened beverages per week, and (e) sodium consumption ≤ 1500 mg/day;
2. Physical activity: ≥ 75 minutes/week of vigorous physical activity, or ≥ 150 minutes/week of moderate physical activity, or ≥ 150 minutes/week of moderate + vigorous physical activity;

3. Smoking: never smoked or former smoker age upon quitting of at least two years less than the age at onsite assessment;
4. BMI < 25 kg/m²;
5. Blood pressure: SBP < 120 mmHg and DBP < 80 mmHg, without antihypertensive medication;
6. Fasting plasma glucose: < 100 mg/dL, without hypoglycemic medication;
7. Total cholesterol: < 200 mg/dL, without lipid-lowering medication.

All information for ICVH scoring was obtained from the second visit, except for the diet ICVH metric. The diet ICVH metric was evaluated using information from the complete food frequency questionnaire, which was applied in the ELSA-Brasil baseline. The global ICVH score was calculated as the sum of the ideal profiles (range: 0 to 7 points). Scores of participants' lifestyle (diet, physical activity, smoking, and BMI; range 0-4) and health (blood pressure, fasting plasma glucose, and total cholesterol; range 0-3) were evaluated separately.

Statistical analysis

Categorical variables were presented as counts and proportions, and continuous variables were presented as medians and interquartile ranges. Normality of data was evaluated using density plots and the Anderson-Darling test. We calculated the sensitivity and specificity of different cutoffs for global ICVH score to classify individuals with and without AFF in the sample. We plotted a receiver-operating characteristic (ROC) curve using these values and calculated the area under the ROC curve (AUROC) to estimate the discriminative capacity of the global ICVH scores to identify individuals with AFF in this setting. Binary logistic regression models were built to analyze the association of ICVH metrics and global, lifestyle, and health scores with AFF diagnosis. These models are presented in their crude form and adjusted for age, sex, and race. Sensitivity analyses were performed, restricting the sample to the individuals without previous self-reported myocardial infarction, stroke, or heart failure. After observing a paradoxical association between the total cholesterol ICVH metric and AFF, we ran some analyses *a posteriori*, (1) excluding individuals under statin use, as some authors pointed a potential benefit of statins on incident atrial fibrillation;^{22,23} (2) excluding the total cholesterol ICVH metric from the global and health ICVH scores. The crude and adjusted binary logistic regression models were also presented in order to analyze the association between these modified scores and AFF diagnosis. Analyses were performed using R software, version 4.0.0. The significance level was set at 5%.

Results

Table 1 summarizes the characteristics of the sample. Median age was 55 years and 7,147 (54.4%) were women. Most participants were of white race, had a college education and a family income between six and 15 Brazilian minimum wages (approximately 1,860 to 4,650 US dollars/month). AFF in ECG tracings was detected in 80 (0.6%) participants. The most frequent ICVH metric was smoking, present in 11,548 (87.9%)

participants. Supplemental Table 1 shows the characteristics of study participants after excluding those with previous self-reported myocardial infarction, stroke, or heart failure.

Supplemental Figure 1 shows the ROC curve addressing the accuracy of global ICVH scores in identifying individuals with AFF in the sample. The AUROC is 0.59, indicating a relatively low discriminatory power of global ICVH scores in this scenario. More details are shown in the Supplemental Table 2, which displays sensitivity and specificity values for different global ICVH score cutoffs.

Table 2 shows the odds ratios (OR) and respective 95% confidence intervals (95%CI) for the association of ICVH scores and metrics with prevalent AFF. In the entire sample, ICVH scores were inversely associated with AFF diagnosis in crude models ($p=0.012$), although this association disappeared vanished after adjustment for age, sex, and race ($p=0.70$). No lifestyle ICVH metric nor the lifestyle ICVH score was significantly associated with AFF. The blood pressure ICVH metric was inversely associated with AFF in both crude ($p<0.001$) and adjusted ($p=0.007$) models. There was a paradoxical positive association between the total cholesterol ICVH profile and AFF in the adjusted models ($p=0.007$). The exclusion of individuals under statin use from analyses led to a loss of significance for the association between the total cholesterol ICVH profile and AFF in the adjusted models (OR: 2.22; 95%CI: 0.86 - 5.70; $p=0.098$). However, this loss of significance seems to be primarily due to a lack of statistical power, as 46.2% of participants with AFF and 51.0% of participants without AFF were under statins.

As the associations of AFF with blood pressure and total cholesterol ICVH metrics were antagonistic, AFF was not associated with an overall health ICVH score in adjusted models ($p=0.76$). After excluding individuals with self-reported myocardial infarction, stroke, or heart failure, the associations between AFF and blood pressure ($p=0.023$) and total cholesterol ICVH metrics ($p=0.007$) in adjusted models remained.

We also verified whether the global and/or health ICVH scores were associated with AFF after the exclusion of the total cholesterol ICVH metric. The global ICVH score was shown to be inversely associated with an AFF diagnosis in crude models (OR: 0.70; 95% CI: 0.57 - 0.86; $p=0.001$) with a non-significant trend towards an inverse association in adjusted models (OR: 0.84; 95% CI: 0.67 - 1.04; $p=0.11$). Health ICVH scores were inversely associated with an AFF diagnosis in both crude (OR: 0.41; 95% CI: 0.28 - 0.59; $p<0.001$) and adjusted (OR: 0.63; 95% CI: 0.42 - 0.93; $p=0.020$) models.

Discussion

In the ELSA-Brasil sample, global ICVH scores were associated with prevalent AFF in crude models. However, they were associated with low AUROC values and statistical significance disappeared in models adjusted for age, sex, and race. Analyzing ICVH metrics separately, a strong inverse association was found between the blood pressure ICVH metric and AFF. A positive but paradoxical association was observed between the total cholesterol ICVH metric and AFF: an ideal total cholesterol ICVH metric was associated with AFF

Table 1 – Characteristics of the study sample

	No atrial fibrillation or flutter (N=13,061)	Atrial fibrillation or flutter (N=80)	Total (N=13141)
Age (years; mean $\pm$ SD)	55.0 [49.0 - 62.0]	64.5 [57.0 - 73.2]	55.0 [49.0 - 62.0]
Female sex (N (%))	7117 (54.5%)	30 (37.5%)	7147 (54.4%)
Race (N (%))			
White	6750 (52.3%)	46 (60.5%)	6796 (52.3%)
Brown	3625 (28.1%)	21 (27.6%)	3646 (28.1%)
Black	2071 (16.0%)	9 (11.8%)	2080 (16.0%)
Other	471 (3.6%)	0 (0.0%)	471 (3.6%)
Educational level (N (%))			
Incomplete high school	1472 (11.3%)	13 (16.2%)	1485 (11.3%)
High school	4110 (31.5%)	25 (31.2%)	4135 (31.5%)
College or above	7476 (57.3%)	42 (52.5%)	7518 (57.2%)
Monthly family income (N (%))			
< 6 BMW	2816 (21.7%)	16 (20.0%)	2832 (21.6%)
6 to 15 BMW	6112 (47.0%)	29 (36.2%)	6141 (46.9%)
> 15 BMW	4073 (31.3%)	35 (43.8%)	4108 (31.4%)
Use of antihypertensive medication (N (%))	5800 (44.4%)	61 (76.2%)	5861 (44.6%)
Use of hypoglycemic medication (N (%))	2577 (20.9%)	30 (39.5%)	2607 (21.0%)
Use of lipid-lowering medication (N (%))	6658 (51.0%)	37 (46.2%)	6695 (51.0%)
ICVH metrics (N (%))			
Diet	177 (1.4%)	0 (0.0%)	177 (1.3%)
Physical activity	3488 (26.7%)	15 (18.8%)	3503 (26.7%)
Body-mass index	4229 (32.4%)	27 (33.8%)	4256 (32.4%)
Smoking	11474 (87.8%)	74 (92.5%)	11548 (87.9%)
Blood pressure	4499 (34.4%)	7 (8.8%)	4506 (34.3%)
Fasting plasma glucose	5927 (45.4%)	23 (28.7%)	5950 (45.3%)
Total cholesterol	5213 (39.9%)	38 (47.5%)	5251 (40.0%)
ICVH score (mean $\pm$ SD)			
Global	3.0 [2.0 - 4.0]	2.0 [1.0 - 3.0]	3.0 [2.0 - 4.0]
Lifestyle	1.0 [1.0 - 2.0]	1.0 [1.0 - 2.0]	1.0 [1.0 - 2.0]
Health	1.0 [0.0 - 2.0]	1.0 [0.0 - 1.0]	1.0 [0.0 - 2.0]

BMW: Brazilian minimum wage; one Brazilian minimum wage during data collection averaged approximately 310 US dollars. ICVH: Ideal cardiovascular health. Source: The authors.

diagnosis. The restriction of the sample to individuals with no self-reported myocardial infarction, stroke, or heart failure yielded similar results. The exclusion of the total cholesterol ICVH metric led to a significant inverse association between health ICVH scores and AFF.

The importance of hypertension as a risk factor for AFF is well defined in the literature. In a systematic review of risk factors for incident AFF, Allan et al.²⁴ reviewed data from 32 population-based cohorts, including more than 20 million subjects. The authors found that the diagnosis of hypertension and high systolic blood pressure were consistently associated with incident AFF. Recently, Rattani et al.²⁵ used data from

the ARIC study to calculate the population attributable risk of hypertension for AFF. The authors defined hypertension according to the criteria from the 7th Report of the Joint National Committee ($\geq 140/90$ mmHg) and the 2017 American Heart Association/American College of Cardiology guidelines ($\geq 130/80$ mmHg), and found population attributed fraction values of 11% and 13%, respectively. Expectedly, the presence of an ideal blood pressure profile was also inversely associated with AFF in the ARIC,¹⁰ REGARDS,¹¹ and MESA⁹ cohort studies.

Although total cholesterol (mainly due to its main subfraction, LDL-c) is a major risk factor for atherosclerotic

Table 2 – Odds ratios (95% CI) for the association between ICVH scores and metrics and atrial fibrillation or flutter diagnosis

	All sample		Excluding patients with self-reported myocardial infarction, stroke or heart failure	
	Crude	Adjusted for age, sex and race	Crude	Adjusted for age, sex and race
Global ICVH score	0.80 (0.67 - 0.95)*	0.96 (0.80 - 1.16)	0.87 (0.71 - 1.08)	1.01 (0.81 - 1.26)
Lifestyle ICVH score	0.95 (0.71 - 1.26)	0.96 (0.70 - 1.30)	1.00 (0.70 - 1.42)	0.96 (0.67 - 1.38)
Diet	†	†	†	†
Physical activity	0.63 (0.36 - 1.11)	0.65 (0.37 - 1.15)	0.71 (0.36 - 1.38)	0.67 (0.34 - 1.31)
Body mass index	1.06 (0.67 - 1.69)	1.19 (0.74 - 1.92)	1.33 (0.77 - 2.32)	1.38 (0.79 - 2.40)
Smoking	1.71 (0.74 - 3.93)	1.40 (0.60 - 3.23)	1.08 (0.46 - 2.52)	0.92 (0.39 - 2.18)
Health ICVH score	0.66 (0.51 - 0.85)*	0.96 (0.73 - 1.26)	0.77 (0.57 - 1.03)	1.06 (0.77 - 1.46)
Blood pressure	0.18 (0.08 - 0.40)*	0.33 (0.15 - 0.74)*	0.23 (0.10 - 0.53)*	0.36 (0.15 - 0.87)*
Glucose	0.49 (0.30 - 0.79)*	0.79 (0.48 - 1.31)	0.65 (0.37 - 1.13)	0.97 (0.54 - 1.74)
Total cholesterol	1.36 (0.88 - 2.12)	1.88 (1.19 - 2.98)*	1.62 (0.95 - 2.79)	2.14 (1.23 - 3.72)*

ICVH: Ideal cardiovascular health. † Odds ratio estimates for the association between the diet ICVH metric and atrial fibrillation or flutter could not be obtained due to the lack of individuals with an optimal profile of diet and a diagnosis of atrial fibrillation or flutter; * $p < 0.05$. Source: The authors.

cardiovascular disease, its association with AFF is much less clear. Other authors have pointed to the cholesterol paradox in AFF, describing lower cholesterol levels in individuals with AFF, upon comparing controls in diverse scenarios, such as individuals treated in referral centers for other cardiovascular diseases, those treated in primary care units,^{26,27} or even those from community samples.²⁸ In a recent systematic review, Guan et al.²⁹ found that high levels of total cholesterol (defined at cutoffs between 220 and 260 mg/dL across studies, or based on the empirical distribution within the sample) were associated with a pooled hazard ratio for AFF of 0.81 (95% CI: 0.72-0.92), which was consistent with our findings. In the same systematic review, analyses using LDL-C instead of total cholesterol levels yielded similar results.

There is some evidence that statins may have a potential benefit on incident atrial fibrillation.^{22,23} However, the ICVH metric considers as a non-ideal profile if the individual is under lipid-lowering medications, regardless of his/her total cholesterol levels. Therefore, it could be argued that the paradoxical association between total cholesterol ICVH profile and AFF is explained by statin use. Our data suggest this is not the case. The proportion of individuals in our sample using lipid-lowering medication is similar. Moreover, although the exclusion of individuals under statins led to a loss of statistical significance, this was probably due to the high number of exclusions from this sensitivity analysis (51.0% of our sample), as the OR point estimates were also similar (1.88 for the whole sample; 2.22 after excluding those using lipid-lowering medication).

The criterion used as the total cholesterol ICVH metric (<200 mg/dL without lipid-lowering medication use) is stricter than those in the studies included in this systematic review. The cohort studies⁹⁻¹¹ that evaluated

ICVH scores and their relationship with AFF diagnosis have also studied the total cholesterol ICVH metric separately. In all cases, the hazard point estimates suggested higher odds for AFF in individuals with ideal total cholesterol, but without statistical significance. Their non-significant results contrast to our finding of a significant, positive, but paradoxical association between the total cholesterol ICVH metric and AFF diagnosis in adjusted models. This significant association in our study was evident even with less AFF cases in the sample, when compared to these previous publications. Differences in study populations and design may be partly responsible for this discrepancy. Similar to the United States, black Brazilians have a higher prevalence of hypertension³⁰ and a lower prevalence of dyslipidemia,³¹ when compared to white Brazilians. It could be argued, given the strong inverse association between blood pressure and AFF, that race could be a confounder in the positive association between a total cholesterol ICVH profile and AFF diagnosis. However, it is important to note that our results were maintained even after adjustment for race. Future longitudinal analyses from the ELSA-Brasil, including the occurrence of more AFF cases, will clarify if the cholesterol paradox in individuals with AFF is particularly strong in the Brazilian population.

In 2018, Isakadze et al.³² proposed that the use of the ICVH score to improve overall cardiovascular health may substantially reduce AFF prevalence. Although current evidence suggests this is probably true, our results and previous data also point out that individual ICVH metrics may have different (and even antagonistic) effects on AFF prevalence. Therefore, it is arguable that the progress in AFF prevention resulting from improvements in ICVH scores must be estimated considering not only the impact of all ICVH metrics together but also of each metric separately.

The present study has strengths. First, it evaluated data from a large sample in Brazil. To our knowledge, this is the first study to analyze the association between AFF and ICVH metrics in a South American sample with different characteristics compared to the samples analyzed in previous studies. ECG tracings were also analyzed in a centralized reading center, using a standardized protocol,¹⁹ and the ICVH score criteria could be applied with minimal adaptations.

This study also needs to be interpreted in the context of its limitations. The sample of this study included a small number of AFF participants. This is most probably due to its high proportion of individuals of less than 60 years of age. As time progresses, incident AFF cases may increase the power of our analyses. This may have influenced our finding of non-association between AFF diagnosis and ICVH scores. The food frequency questionnaire was not applied in the second visit of patients in the ELSA-Brasil; therefore, it was considered that participants maintained their diet ICVH status after the baseline. The prevalence of an ICVH diet was very low in the ELSA-Brasil baseline (1.3%),²¹ which is consistent with the findings from other populations.³³ Therefore, it is unlikely that a large proportion of participants would have adopted an ideal diet between the baseline and the second onsite assessment. The AFF was defined based only on ECG tracings of the ELSA-Brasil and, although this ensures high specificity, paroxysmal AFF may be underrepresented in our analyses.

Conclusions

In conclusion, no significant associations were observed between global ICVH scores and AFF diagnosis in our analyses, at least partially due to antagonistic associations of AFF with blood pressure and total cholesterol. Our results suggest that estimating the AFF prevention effect using global ICVH scores may not be adequate, and ICVH metrics should be considered in separate.

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Conception and design of the research: Santos IS, Lotufo PA, Goulart AC, Barreto SM, Ribeiro ALP, Bensenor IM; Acquisition of data: Brant LCC, Pinto Filho MM, Barreto SM, Ribeiro ALP; Analysis and interpretation of the data: Santos IS, Lotufo PA, Goulart AC, Brant LCC, Pinto Filho MM, Pereira AC, Barreto SM, Ribeiro ALP, Thomas GN, Lip GYH, Bensenor IM; Statistical analysis: Santos IS; Obtaining financing: Lotufo PA, Barreto SM, Ribeiro ALP, Thomas GN, Lip GYH, Bensenor IM; Writing of the manuscript: Santos IS, Bensenor IM; Critical revision of the manuscript for important intellectual content: Lotufo PA, Goulart AC, Brant LCC, Pinto Filho MM, Pereira AC, Barreto SM, Ribeiro ALP, Thomas GN, Lip GYH.

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 Hospital Universitário da USP under the protocol number 659/06. 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.

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*Supplemental Materials

For additional information Supplemental Figure 1, please click here.

For additional information Supplemental Tables, please click here.



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Analysis of Atrial Fibrillation Prevalence and Cardiovascular Health in Cohort Derived from the ELSA-Brasil Project

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Short Editorial related to the article: Cardiovascular Health and Atrial Fibrillation or Flutter: A Cross-Sectional Study from ELSA-Brasil

This interesting study¹ of prevalence analyzed the association between atrial fibrillation (AF) and atrial flutter (AFL) with cardiovascular health status, in a cohort derived from the ELSA-BRASIL project, in an observational, cross-sectional design. A total of 13,141 participants were included in this analysis. Biomarker metrics and epidemiological data were entered with subsequent association analysis in an adjusted model and logistic regression for the variables of interest.

The mechanisms of association between AF and cerebrovascular accident (CVA) risk are well known. AF is associated with abnormal blood stasis that involves atrial hypocontractility, atrial structural remodeling, platelet activation and the coagulation cascade, promoting thrombus formation and ischemia.^{2,3} Thus, AF is an independent predictor of ischemic diseases, notably stroke. The estimated lifetime risk of AF is between 22% and 26%.^{4,5} Metrics to assess the impact of this association are constantly published in documents, such as the recommendations of the American Heart Association Strategic Planning Task Force Goals and Metrics Committee, which developed continuous and long-term monitoring strategies.⁶ Within a general concept, cardiovascular health must contain clinical and behavioral aspects, such as an adequate lifestyle (no smoking, avoiding obesity), concomitant with the correction and adequacy of metabolic biomarkers, such as cholesterol and triglyceride levels; blood glucose; and adequate blood pressure control. Thus, this committee proposed a challenge to reach these goals: “By 2020, improve the cardiovascular health of all Americans by 20%, reducing deaths from cardiovascular disease and stroke by 20%”. So, identifying individuals at risk for developing AF is a clinical imperative, as modifying some variables can reduce the incidence of this condition.^{7,8}

In a recently published study, it was demonstrated that, in a model using “machine learning”, using the electrocardiogram (ECG) to estimate the risk of AF, they were robust and validated

in several populations using rigorous epidemiological metrics. AF can be predicted by assessing clinical risk factors or analyzing ECGs based on artificial intelligence. However, the combination of both provides greater predictive accuracy.⁹

In the study entitled: Cardiovascular health and atrial fibrillation or flutter: A cross-sectional study from ELSA-Brasil,¹ no significant associations were observed between global scores (ideal cardiovascular health) and the diagnosis of AF, at least partially due to antagonistic correlations with blood pressure and total cholesterol, data which are extensively discussed in this manuscript. This paradox between cholesterol and AF was consistent with previously published data. In a systematic review, Guan et al. pointed out that high levels of total cholesterol (defined in studies with cut-off points between 220 and 260 mg/dL) were associated with AF [HR 0.81 (95% CI: 0.72-0.92)]. In the same systematic review, analyses using LDL-C rather than total cholesterol levels produced similar results.¹⁰ However, there is robust evidence that statins have a potential health benefit in the incidence of AF or AFL.^{11,12} Therefore, metrics should consider a non-ideal cardiovascular health profile if patients were on lipid-lowering medication, regardless of their total cholesterol levels.

Regarding arterial hypertension, the present manuscript from the ELSA-BRASIL cohort analyzed the metrics of global health scores separately. The authors of this study found a strong and inverse association between blood pressure with the presence of AF. Thus, highlighting the relevance of control and adequate treatment of this important risk factor, in line with data in the literature.¹³⁻¹⁵

The authors state some limitations that could impact the results obtained, such as the small number of participants and, above all, the high proportion of individuals under 60 years, with a possible influence of the findings of “non-association” between the AF diagnosis and the assessed global health scores.

Keywords

Atrial Fibrillation, Atrial Flutter, Risk Factors.

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Clinical Features and Survival Analysis of Patients after Mechanical Heart Valve Replacement, with an Emphasis on Prosthetic Valve Thrombosis

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Abstract

Background: Valvular heart diseases are highly prevalent in the world, and surgical valve replacement has improved patients' survival.

Objectives: To describe clinical and laboratory data of patients undergoing mechanical valve replacement, and to determine the incidence of prosthetic valve thrombosis (PVT).

Methods: Retrospective cohort study with a follow-up of up to nine years. The study variables were collected from conventional and electronic medical charts. Statistical calculations were performed using the Jamovi software version 1.2.2.; a $p < 0.05$ was considered statistically significant. Kaplan Meier curves were constructed, and Cox regression analysis was performed for analysis of factors related to mortality.

Results: A total of 473 patients were included, mean age of 46.9 ± 11.3 years. Rheumatic disease was the most common etiology. In a mean follow-up period of 4.43 years, mortality rate was 16.1%. Patients with aortic prosthesis showed higher survival than patients with double implant (mitral and aortic) ($p = 0.026$). Of the factors adjusted for mortality, only functional class and chronic renal failure showed statistically significant association. The incidence of PVT was 0.24/100 patients/year, and the first event occurred more than 1000 days after the implant. Smoking and pannus formation were significantly associated with PVT. No differences were found in INR variability between patients with and without thrombosis by prosthetic position, but significant differences were found in INR before thrombosis as compared with patients without thrombosis (INR = 2.20 [1.80-2.20] vs. 2.80 [2.20-3.40]; $p = 0.040$). The incidence of stroke and bleeding was 4.4% and 5.2% respectively.

Conclusions: The study population was young, and rheumatic valve disease was common in this group. The prevalence of PVT was similar to that described in the literature, despite the low income and low educational level of our sample.

Keywords: Anticoagulants; Survival Analysis; Brazil; Heart Valve Prosthesis Implantation; Thrombosis.

Introduction

Valvular heart diseases (VHD) are highly prevalent, affecting more than 100 million people in the world.¹ In developing countries, like Brazil, VHD account for a large proportion of hospitalizations for cardiovascular diseases. In these countries, rheumatic valve diseases are preponderant² and represent a public health problem, with a greater impact on poorer and younger populations.³

Despite effective pharmacotherapy in most cases, more severe cases of VHD may be absolute indication for surgical therapy. Surgical procedures involve valve repair or replacement by implantation of a mechanical or a biological prosthetic valve. Due to their higher durability, mechanical prostheses have been widely preferred in younger patients.^{4,5} However, as compared with biological prosthesis, mechanical valve prostheses have been associated with a higher probability of thrombus formation and thromboembolic events due to their physical properties, with an overall incidence of mechanical valve thrombosis of 0.4 per 100 patients per year. It is of note that the incidence of thrombosis of mitral valve prosthesis is 0.5 per 100 patients per year, approximately five times more frequent than in the aortic position (0.1 per 100 patients per year).⁶

Thus, a careful postoperative follow-up of patients undergoing surgical valve replacement should be performed, since inadequate

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anticoagulation may lead to PVT and consequent dysfunction, with or without thromboembolism.⁷ Therefore, the choice for a mechanical prosthesis should be individualized even in younger patients, considering the variables: risk of bleeding, patient's level of education and understanding, place of residence and distance from health facilities, patient's preference and desire to become pregnant in women.⁴

There are few studies describing prosthetic thrombosis and its management in Brazil.^{8,9} Thus, the present study aimed to describe demographic, clinical, surgical characteristics and outcomes of patients undergoing mechanical heart valve replacement in a public tertiary hospital referral for cardiovascular care for users of the Brazilian Unified Health System, with emphasis on the incidence of mechanical prosthesis thrombosis.

Methods

Study design

This was a retrospective cohort study. Patients were identified in the database of the Department of VHD and in the Registry of the Department of Surgery of a tertiary hospital. The variables of interest were collected from electronic and conventional medical records. All patients that underwent surgery and were followed in the institution were monitored for INR (international normalized ratio) every 4-6 weeks at the anticoagulation outpatient center. Patients who had been regularly followed-up and were lost to follow-up for 12 consecutive months were checked for death at the website for out-of-court services of Rio de Janeiro state, since all patients with mechanical valve prosthesis had scheduled visits in the outpatient clinic every six months.

Study population

All adult patients who underwent mechanical valve prosthesis replacement in Instituto Nacional de Cardiologia, Rio de Janeiro. Between January 2011 and December 2017 were studied.

Study variables

The study variables were: sex, age, socioeconomic status, comorbidities, medications, presence of atrial fibrillation, region of residence (in the state of Rio de Janeiro), etiology and type of the original lesion, NYHA functional class in the last visit, echocardiogram functional and hemodynamic data after valve implantation and current ones, valve position and prosthesis brand, level of anticoagulation by measurement of prothrombin time and consecutive INR measurements in the last six months, or before the diagnosis of valve thrombosis or death. The incidence of valvular thrombosis, stroke and bleeding was calculated, and the type of intervention and presence or not of pannus associated with thrombosis was assessed.

Operational definitions

Prosthetic valve thrombosis (PVT) was defined as any thrombus attached to or near a functioning valve, in the

absence of infection, which occludes part of the blood flow or interferes with valvular function.

A new PVT was defined as an episode of PVT occurring more than three months after therapeutic intervention in which thrombus resolution was documented, confirmed by clinical assessment and complementary tests.

Severe bleeding was considered in case of an immediate risk of death, regardless of emergency surgical intervention or use of blood derivatives; major bleeding was defined as potentially severe bleeding, with mandatory hospitalization but predominantly conservative management, with or without the use of blood derivatives.

Data analysis

Data were expressed as frequency (categorical variables), mean and standard deviation (continuous variables with normal distribution) or median and interquartile range (continuous variables without normal distribution). Statistical analysis was performed using the Jamovi software, version 1.2.2. Categorical variables were analyzed by the chi-square test and the Fisher's exact test. The unpaired t-test was used for comparison of continuous variables with normal distribution, and the Mann-Whitney test for continuous variables without normal distribution. Comparison of means between more than two time points was made by analysis of variance (ANOVA) for repeated measures. Analysis of events (death and prosthetic thrombosis) was made using Kaplan-Meier curves. A $p < 0.05$ was considered statistically significant. Adjusted hazard ratios (aHR) and their respective 95% confidence interval (CI) were estimated by Cox proportional hazard regression for analysis of the effects of variables on survival after valve replacement surgery. The assumptions of proportional hazards for the adjustments of the Cox regression model were tested by correlation analysis and the chi-square test based on scaled Schoenfeld residuals and transformed survival times.

Ethical issues

The study was approved by the Instituto Nacional de Cardiologia ethics committee on August 01, 2018 (CAAE: 87442918.3.0000.5272, approval number 2.793.851).

Results

In the study period, the total of 1,901 valve replacements were performed in the institution, including both biological and mechanical prostheses. A total of 473 (24.9%) patients received metallic prostheses (Figure 1), and 456 of these were followed-up until December 2019, with a mean follow-up of 4.4 years per patient. Seventeen patients lost follow-up in the institution.

A total of 609 mechanical prostheses were implanted, 49.9% of them in the aortic position, 30.2% in the mitral and aortic positions, and 19.9% in the mitral position. Prostheses' brands were St. Jude[®] (Minneapolis, USA), (n=465, 74,2%), ATS Medical[®] (Minnesota, USA) (n=159, 25,4%), Carbomedics[®] (Austin, USA) (n=1, 0,2%). The models were not specified in 0.3% of the cases (n=2).

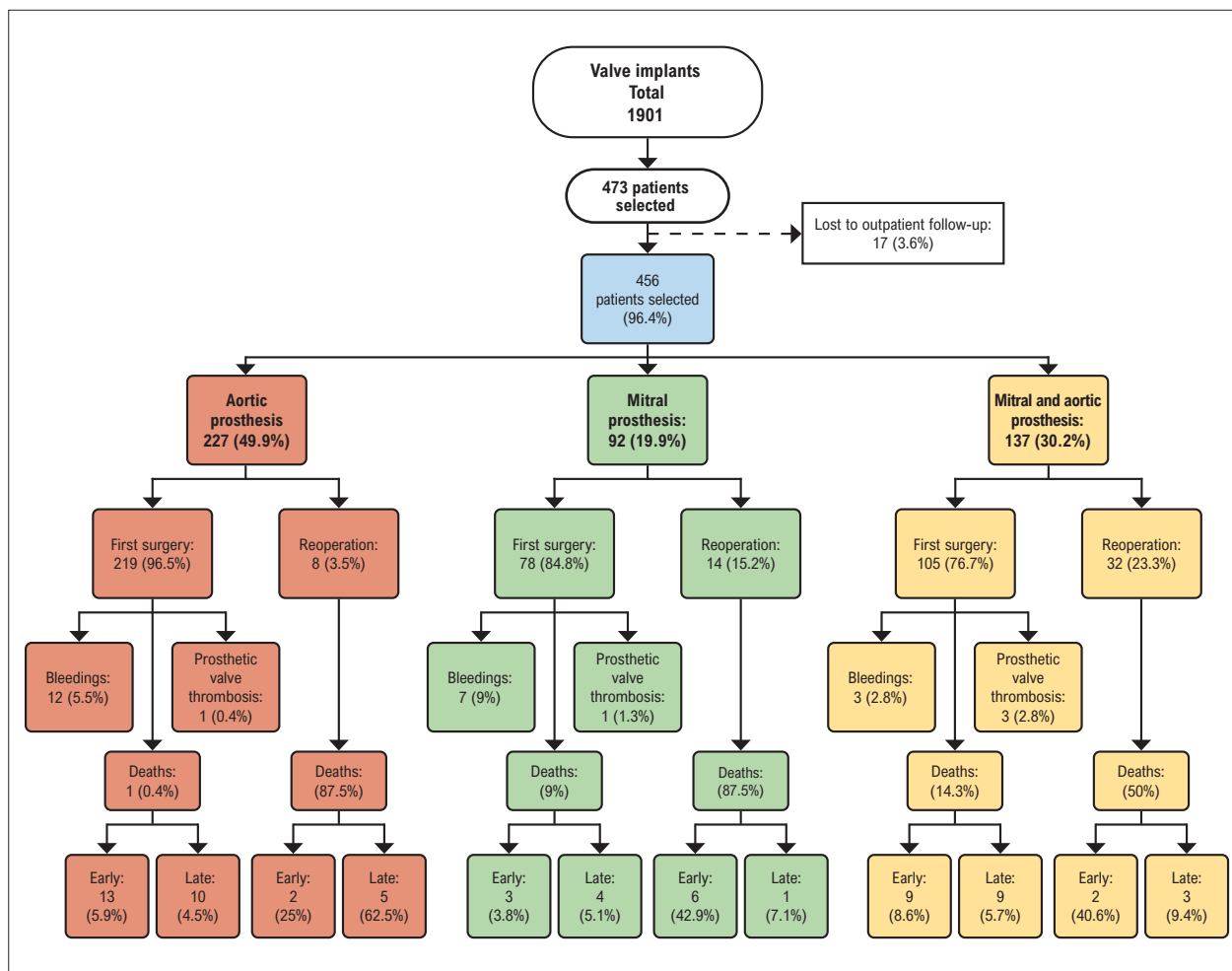


Figure 1 – Flowchart of inclusion of patients with valve prostheses and outcomes according to the location of the valve prosthesis.

Table 1 presents clinical and demographic characteristics of the 473 study patients according to prosthetic position. Mean age was 46.9 ± 11.3 years. Most patients had (some or completed) elementary school, and family income until three minimum wages. Among the comorbidities, essential systemic arterial hypertension was the most common, detected in more than 50% of patients, followed by dyslipidemia in approximately one fourth, and type 2 diabetes mellitus. Of all patients, 46.5% were from Rio de Janeiro, and 37.3% were from Baixada Fluminense region.

Rheumatic valvular disease was the most common etiology (57.7%), followed by degenerative valve disease (12.9%) and bicuspid aortic valve (12.1%). Infective endocarditis was the main secondary etiology, leading to a second valve replacement surgery in 24 (5.1%) of the cases. Figure 2 shows the etiologies by categories (mitral, aortic and double valve replacement, i.e., mitral and aortic).

The following severe lesions were found: 107 aortic stenosis (45.9%), 93 (39.9%) aortic insufficiency and 16 (6.8%) double aortic arch; severe mitral stenosis in 41 (44%), mitral insufficiency in 30 (32.2%) and double valve in 8 (8.6%).

The New York Heart Association (NYHA) functional class (FC) of 422 patients reported in the last visit at the outpatient was FC I in 323 (76,5%); FC II in 85 (20,1%), FC III in 12 (2,8%), and FC IV in only two (0.5%).

Table 2 describes echocardiographic data post-valve replacement and recent data obtained during patients' follow-up. As compared with the echocardiogram performed right after surgical implantation, more recent tests revealed that aortic prostheses showed improvement of the hemodynamic parameters ($p < 0.001$). In mitral position and double replacement (mitral and aortic positions), there was an improvement in the mean ejection fraction and mean pressure gradient between the left atrium and left ventricle.

Figure 3 shows the survival curve for the implanted prosthesis by position. Patients with aortic prosthesis showed higher survival than patients with prosthesis in the mitral and aortic position ($p = 0.026$). No other differences were seen in the other comparisons. In the survival curve, no statistical difference was seen between age groups or sex (Supplementary Figures 1 and 2). When we analyzed survival rates in patients with rheumatic valvular disease only, no difference was observed between valve positions. However,

Table 1 – Demographic and clinical characteristics of patients undergoing mechanical valve replacement from January 2011 to December 2017

Variables		Aortic (n=236)	Mitral (n=96)	Mitral-aortic (n=141)	p value
(n = 473)	Male	148(62.7%)	31 (32.3%)	51 (36.2%)	p<0.01
	Female	88 (37.3%)	65 (67.7%)	90 (63.8%)	
Age (years) (n = 473)	< 20	0	0	0	p=0.015
	20-29	6 (2.5%)	2 (2.1%)	3 (2.1%)	
	30-39	26 (11.0%)	7 (7.3%)	14 (9.9%)	
	40-49	35 (14.8%)	19 (19.8%)	43 (30.5%)	
	50-59	70 (29.6%)	36 (37.5%)	46 (32.6%)	
	60-69	82 (34.7%)	25 (26.0%)	32 (22.7%)	
	≥ 70	17 (7.2%)	6 (6.2%)	3 (2.1%)	
Educational attainment (n = 382)	Illiterate	1 (0.42%)	0	1 (0.7%)	p=0.003
	Elementary school	95 (40.2%)	55 (57.3%)	77 (54.6%)	
	High school	73 (30.9%)	16 (16.6%)	32 (22.7%)	
	Higher education	22 (9.3%)	1 (1.0%)	9 (6.3%)	
Family income (minimum salaries) (n = 153)	< 1	23	1	15	p=0.697
	1 - 2	19	2	19	
	2 - 3	17	0	12	
	> 3	29	1	15	
Comorbidities	SAH	Yes	143(60.6%)	48 (50.5%)	p=0.017
		No	93 (39.4%)	47 (49.5%)	
	DLP	Yes	78 (33.6%)	25 (26.6%)	p<0.001
		No	154(66.4%)	69 (73.4%)	
	DM2	Yes	31 (13.6%)	16 (17.2%)	p=0.020
		No	197(86.4%)	77 (82.8%)	
	Smoking	Yes	19 (8.0%)	3(3.1%)	p=0.273
		No	217(92%)	92 (96.9%)	
	Previous stroke	Yes	5 (2.1%)	9(9.5%)	p=0.006
		No	229(97.9%)	86 (90.5%)	
	TIA	Yes	2 (0.8%)	0	p=0.672
		No	232(99.2%)	95 (100%)	
	CRF	Yes	4 (1.7%)	7 (7.3%)	p=0.038
		No	232(98.3%)	89 (92.7%)	
	COPD	Yes	12 (5.1%)	2 (2.1%)	p=0.224
		No	223(94.9%)	93 (97.9%)	
	Alcohol consumption	Yes	1 (0.4%)	0	p=0.605
		No	233(99.6%)	95 (100%)	
	Hepatopathies	Yes	0	0	p=0.029
		No	233 (100%)	94 (100%)	
Atrial fibrillation (n = 473)	Present	19 (8.0%)	52 (54.2%)	62 (44%)	p<0.001
	Absent	217 (92%)	44 (45.8%)	79 (56%)	

SAH: systemic arterial hypertension; DLP: dyslipidemia; DM2: type 2 Diabetes Mellitus; TIA: transient ischemic attack; CRF: chronic renal failure; COPD: chronic obstructive pulmonary disease. Note: Numbers in educational attainment, family income, and comorbidities correspond to those with data available in the medical charts, as this was a retrospective study.

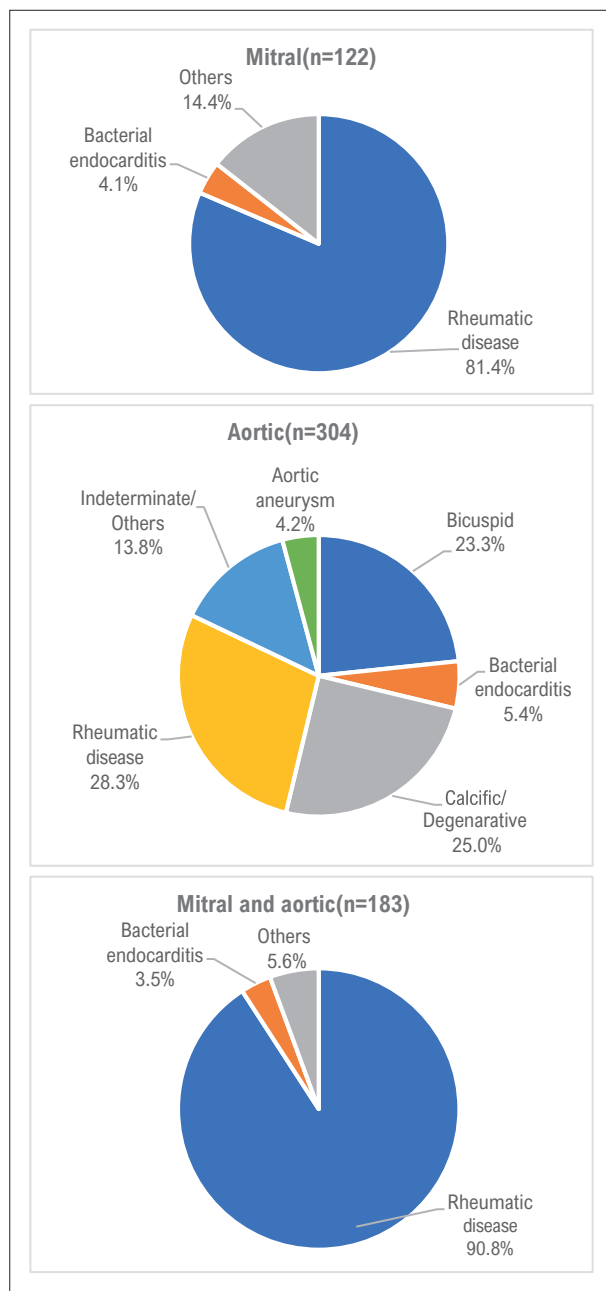


Figure 2 – Etiology of heart valve disease by position of the mechanical valve prosthesis implanted.

in non-rheumatic patients, a difference was observed between valve positions, although the number of individuals undergoing mitral valve surgery or both mitral and aortic valve surgery was very small. Most non-rheumatic patients had undergone aortic valve replacement (n=127) (Supplementary Figures 3 and 4). No difference was found in survival between rheumatic and non-rheumatic patients with aortic valve prosthesis.

Cox regression for the variables associated with survival revealed that the main factor related to death was functional class after valve implantation. For FC II, aHR was 5.18 (2.17-12.39; $p<0.001$), for FC III, aHR was 41.13 (14.95-113.15;

$p<0.001$) and for FC IV, aHR was 200.48 (21.60-1861.12; $p<0.001$). Another associated factor was the presence of chronic renal failure, with an aHR of 3.52 (1.12-11.09, $p=0.032$). The positions of mechanical valve prosthesis did not show statistically significant difference after HR adjustment. These results are presented in Supplementary Figure 6.

Seventy-six (16.1%) all-cause deaths occurred, 36 (7.4%) within 30 days. Considering the number of deaths by prosthesis position, mortality rate among patients with aortic prosthesis was 6%, mitral prosthesis 8.2%, and mitral and aortic position 14.2%. The most frequent causes of death were cardiogenic shock (R57.0), hypovolemic shock and disseminated intravascular coagulation (R57.1 and D65). Of the 17 patients who were lost to follow-up, one patient died according to the website for out-of-court services of Rio de Janeiro state, but the cause of death was not specified.

The overall incidence of thrombosis per patient was 1.1% (0.24 per 100 patients per year), with seven thrombotic events in five patients. Mechanical PVT occurred in the late post-implantation period, with the first being registered only five years after surgery. Details of the patients who had PVT are described in Chart 1.

Table 3 shows the comparison of monthly variation in INR, from the most recent (INR6) to the earliest (INR1), between patients with and without PVT. There was no significant variation between these groups over time. The absence of values between parentheses indicates the absence of standard deviation values, since there was only one patient with thrombosis in the sample. Similarly, no difference was found in variability of INR between patients with bleeding as compared with those without bleeding.

Table 4 describes INR values obtained from six collections before the thrombotic event of the patients who had PVT, and from six collections before the last visit in those who did not have PVT. No significant difference was found in INR values between patients with and without thrombosis regarding the position of the prosthetic valve. Values of INR of some months of patients with mitral and aortic position were missing, which made comparisons difficult. INR of patients who had thrombosis was significantly lower than of patients who did not have thrombosis (median 2.20 [1.80-2.20] and 2.80 [2.20-3.40], respectively, $p=0.04$) in the month prior to the event (INR6), independently of the valve prosthesis position. In the analysis of each prosthesis position, no statistically significant difference was found in INR between patients with PVT and those without PVT (Table 4). We found an association between smoking habit and PVT (2 of 5 patients with PVT vs. 27 of 441 patients without PVT). The presence of pannus was detected at surgery in 11 patients, four of them associated with thrombosis ($p<0.001$). Of seven events of PVT detected in five patients, one death occurred in the immediate postoperative period of valve replacement surgery (Chart 1).

Regarding hemorrhagic events, 23 patients with bleeding were found, eight (1.7%) with severe bleeding and 15 (3.5%) with major bleeding. Bleeding rate was 1.02 per 100 patients per year. There were two deaths among patients with severe bleeding, one caused by cardiac tamponade and caused by

Table 2 – Comparison of echocardiographic parameters between after implant and recent parameters by mechanical prosthesis position

	PRIOR TO HOSPITAL DISCHARGE (mean [SD] or median [IQR])	RECENT RESULTS (mean (SD) or median [IQR])	p-values
Aortic valve prosthesis (n= 233)			
LVEF (%)	54.1 (14.7)	62.6 (12.0)	< 0.001
Maximum gradient LV/AO (mmHg)	32.0 [25.0 - 41.8]	26.0 [20.0 - 34.0]	< 0.001
Mean gradient LV/AO (mmHg)	18.0 [13.0 - 23.0]	14.0 [11.5 - 15.8]	< 0.001
Mitral valve prosthesis (n= 93)			
LVEF (%)	54.2 (2.7)	56.8 (13.4)	0.028
Maximum gradient LV/AO (mmHg)	13.3 (4.55)	26.6 (4.04)	0.837
Mean gradient LV/AO (mmHg)	5.0 [4.0 - 6.0]	4.0 [4.0 - 5.0]	0.036
Mitral and aortic prosthesis (n= 141)			
LVEF (%)	55.5 (14.2)	61.2 (12.7)	<0.001
Maximum gradient LV/AO (mmHg)	30.0 [23.0 - 39.5]	29.0 [21.0 -40.5]	0.477
Mean gradient LV/AO (mmHg)	17.0 [11.0 -23.0]	16.0 [11.0 -22.3]	0.642
Maximum gradient LV/AO (mmHg)	12.4 (5.05)	12.4 (5.1)	0.749
Mean gradient LV/AO (mmHg)	5.0 [3.0 - 6.0]	4.0 [3.0 - 5.0]	0.003

LVEF: left ventricular ejection fraction; gradient LV/AO: pressure gradient between the left ventricle (LV) and the aorta; unpaired t-test and Mann-Whitney test.

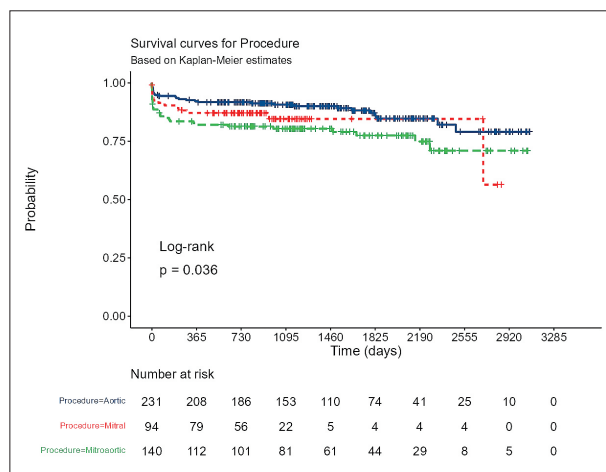


Figure 3 – Survival curve according to valve position in patients who had surgery with mechanical valve prosthesis , Instituto Nacional de Cardiologia, Rio de Janeiro, January 2011 to December 2017.

hemorrhagic stroke. Ischemic stroke occurred in 4.4% of the sample, with an incidence of 0.86 per 100 patients per year.

Five patients with periprosthetic leak were identified. Two of them had had infective endocarditis as the cause of mechanical valve replacement, two patients developed periprosthetic leak after valve replacement, and one had rheumatic mitral and aortic valve disease. Only one patient

required surgery and died; percutaneous occlusion was performed in two patients.

Discussion

The present study evaluated demographic, clinical, surgical characteristics, and the outcomes of patients undergoing implantation of mechanical valve prosthesis in a public tertiary hospital referral for cardiovascular care for users of the Brazilian Unified Health System, with emphasis on the incidence of mechanical prosthesis thrombosis. In this sample of 473 patients, we found a similar proportion of men and women, which is in accordance with recent literature,^{10,11} but different from the study by Brandão et al.⁹ conducted in the state of São Paulo and published three decades ago, in which male sex corresponded to 64.3%. Most patients had a low socioeconomic status, with a monthly income up to three minimum wages, and some or completed elementary school. Mean age of our patients was 47 years, lower than that described in the international literature,¹²⁻¹⁴ but similar to Brazilian studies,^{10,11} explained by the fact that rheumatic disease was the main cause of heart valve replacement in the Brazilian public health system. Most patients were from the city of Rio de Janeiro, followed by the metropolitan area I (Baixada Fluminense). The importance of the place of residence is related to the possibility of better access to a good follow-up in the outpatient anticoagulation clinic.

Original Article

Chart 1 – Clinical and echocardiographic characteristics, and outcomes of five patients (and seven events) diagnosed with mechanical prosthetic valve thrombosis

Patient	1	2	3	4	5
Age	43	44	52	38	54
Sex	Male	Female	Male	Female	Female
Educational level	Elementary school	Elementary school	Elementary school	Superior	Elementary school
Family income	2 MSs	1 MS	5MSs	5MSs	4MSs
Rio de Janeiro	Yes	Yes	Yes	No	Yes
Primary etiology	Rheumatic	Rheumatic	Rheumatic	Rheumatic	Congenital - bicuspid
Prosthesis	Mitral 27	Aortic 18 Mitral 27	Aortic 21 Mitral 27	Aortic 21 Mitral 29	Aortic 19
Prosthesis brand	ATS	ATS	St Jude ATS	St Jude St Jude	St Jude
Atrial fibrillation	Yes	No	Yes	No	No
Time of implant x thrombotic event	8 years	A – 5 years B – 7 years	A – 5 years B – 2 years	6 years	5 years
Smoking	No	No	Yes	Yes	No
NYHA functional class	III	A – I B – III	A – II B – IV	III	II
Follow-up	Current	Current	Current	Current	Not current (death)
LV dysfunction	Yes	Yes	No	No	No
Pannus	No	Yes	Yes	Yes	Yes
Treatment	UH + TT	A – UH + TT B – Surgery	A – UH + TT B – Surgery	Surgery	Surgery

A and B refer to the first and second episodes of prosthetic valve thrombosis, respectively, in the same patient; NYHA: New York Heart Association; ATS: Medtronic's bileaflet mechanical prosthesis; St. Jude: Abbott's bileaflet mechanical prosthesis; UH: unfractionated heparin; TT: thrombolytic therapy; LV (left ventricular) dysfunction: degree of left ventricular failure characterized by ejection fraction $\leq 52\%$ (Teichholz method), according to the American Society of Echocardiography; MS: minimum salary.

Table 3 – Variability of international normalized ratio (INR) between patients with and without prosthetic valve thrombosis

Thrombosis	INR month 1 (n=52)	INR month 2 (n=144)	INR month 3 (n=256)	INR month 4 (n=335)	INR month 5 (n=381)	INR month 6 (n=407)	p-value
Yes (n=5)	4.70 (-)	1.50 (-)	2.37 (0.61)	3.00 (2.02)	2.30 (0.673)	2.06 (0.42)	0.392
No (n=451)	3.09 (1.45)	3.15 (1.30)	2.97 (1.12)	2.97 (1.23)	2.82 (1.00)	2.94 (1.26)	

Values expressed as mean ($\pm$ SD); INR: international normalized ratio; ANOVA with repeated measures.

Rheumatic valve disease was the most common primary etiology, affecting more than half of patients. This is in accordance with national data, such as the study carried out in the city of Salvador, and a article on data of valve replacement surgery among users of the public health system, which is in contrast with studies in developed countries.^{1,2,7} Data from the Brazilian literature, of populations with characteristics similar to our sample, show a predominance of mitral valve surgery, which is different from our study that revealed a predominance of aortic valve surgery. We believe that many factors are responsible for this difference, including i) rheumatic valvular

disease frequently results in mitral stenosis, specially in female patients; in this group, there is a preference for bioprosthesis implantation in reproductive-age women; ii) although percutaneous balloon mitral valvuloplasty or commissurotomy (without valve replacement) is a possible therapeutic procedure in case of mitral valve disease, the approach is not feasible in rheumatic aortic valve disease. In fact, in our sample, there were cases of mechanical mitral valve replacement prior to the study, but during the study, only aortic valve replacement was performed. Of the 67 rheumatic patients that underwent aortic valve replacement, mitral commissurotomy associated with

Table 4 – Comparative analysis of monthly INR between patients with and without thrombosis by position of the mechanical valve prosthesis

Prosthesis /Position	Mitral (target INR=2.5 – 3.5)*		Mitral and aortic (target INR=3)*		Aortic (target 2.5 – 3.5)*	
	Yes	No	Yes	No	Yes	No
INR month 1	-----	-----	4.70 [4.70 - 4.70]	2.80 [2.55 - 4.00]	-----	-----
p value	-----	-----	0.193		-----	-----
INR month 2	-----	-----	1.50 [1.50 - 1.50]	3.15 [2.32 - 3.60]	-----	-----
p value	-----	-----	0.163		-----	-----
INR month 3	-----	-----	2.70 [2.60 - 2.80]	3.00 [2.30 - 3.50]	1.70 [1.70-1.70]	2.70 [2.10-3.30]
p value	-----	-----	0.600		0.161	
INR month 4	-----	-----	1.85 [1.68 - 2.03]	2.95 [2.40 - 3.73]	5.30 [5.30-5.30]	2.60 [2.20-3.20]
p value	-----	-----	0.063		0.098	
INR month 5	1.30 (-)	2.94 (0.981)	2.60 (0.141)	3.05 (1.10)	2.70 [2.70-2.70]	2.60 [2.00-3.10]
p value	0.100		0.565		0.865	
INR month 6	2.60 [2.60-2.60]	3.00 [2.2-3.70]	2.20 [1.85 - 2.2]	2.90 [2.20 - 3.50]	1.80 [1.80-1.80]	2.60 [2.10-3.30]
p value	0.71		0.073		0.211	

INR reference range as proposed by Nishimura et al.²⁷; unpaired t-test and Mann-Whitney test. INR: international normalized ratio.

mechanical aortic valve replacement was performed in seven (10.4%) patients. There were mild rheumatic mitral lesions associated with the aortic valve replacement in 34 patients (50.7%), and two patients had concomitant moderate mitral valve disease, who did not undergo intervention at surgery. The ATS and St. Jude prostheses were the almost exclusive brands used. Patients with aortic valve implantation showed higher survival than patients undergoing double (aortic and mitral) valve replacement ($p=0.026$), which corroborates previous studies.^{13,15} No differences were found in survival between sex and age groups, although there were only 10 patients (17.1%) older than 65 years in our sample. Our results were different from a Brazilian study¹⁰ that reported a higher survival among female than male patients in the first and fifth year of follow-up.¹⁰ According to the multivariate analysis, the factors strongly correlated with death after valve replacement was cardiac function in the outpatient follow-up and presence of chronic renal failure as comorbidity.

In our study, overall mortality and 30-day mortality were 16% and 7.4%, respectively, with the highest rates among patients with double valve replacement of the aortic and mitral valves. In the Japanese study by Tominaga et al.,¹⁶ published in 2005, in a 10-year follow-up of patients who underwent valve replacement with the Carbomedics bileaflet mechanical prosthesis, the authors reported an early mortality rate for the total population of 2.8% (1.2% for the aortic position, 3.6% for the mitral position, and

3.8% for double valve implants). A Swiss article published in the '90s¹³ and a Belgian study¹⁴ described an in-hospital mortality of 5.7% and 5.2%, respectively, which were lower than ours. It is worth mentioning that the populations of these studies were very different, with a predominance of older patients. A Brazilian study¹¹ of hospitals of the public health system reported a mortality rate of 22.1%, higher than that found in our study. In a two-year period, the authors found a mortality rate of 12.3%, 8.5% of them among patients with aortic valve prosthesis, 12.2% among patients with mitral valve prosthesis, and 18.4% in patients with double valve implants. In our study, the five-year follow-up survival rate was 83.4% versus 74.5% in this Brazilian study.¹¹

Considering the occurrence of PVT, our data are in accordance with the international literature, of 0.1 – 5.7% and 0.3-1.3%, respectively.^{7,17} Put in a different way, the incidence of thrombosis in our in the study was slightly lower than that reported by Van Nooten et al. (0.31 per 100 patients per year), indicating the low incidence of this event in our institution. The mean time to the first thrombosis event in our study was longer than that in the Canadian study (39 months).¹⁸ Considering the low socioeconomic status of our population, the low incidence of thrombosis is a positive result, which encourages us to consider the recommendation of mechanical prosthesis for younger patients with less fear.

Smoking habit, which was shown to be significantly associated with PVT in our study, was identified from patients' medical charts, and is known to be a risk factor for a secondary hypercoagulable state, as it contributes to a pro-thrombotic mechanism, as described in the literature.⁷

The diagnosis of mechanical PVT was made based on clinical assumptions and use of complementary tests available at the institution. Among these tests, in our opinion, transesophageal echocardiography is the most important tests. Radioscopy has been shown to be useful as a complementary diagnostic method to echocardiography. Anticoagulation strategies after mechanical valve replacement have not been well established, with differences between European and American guidelines. The American guidelines report complications related to fluctuations in INR with warfarin, suggesting the adoption of a unique INR target.¹⁹ For aortic valve prosthesis, a target INR of 2.5 was suggested; for mitral or aortic prosthesis and presence of risk factors (atrial fibrillation, previous thromboembolism, left ventricular dysfunction, hypercoagulable state), target INR of 3.0 combined with aspirin at a dose of 75-100 mg (class IA). The European guidelines determine INR values according to thrombogenicity of the prosthesis and presence of risk factors, and combination of aspirin in case of concomitant atherosclerotic disease and/or thromboembolism despite inadequate INR.²⁰ Considering the target INR in the guidelines, not only considering the antithrombotic effect but also the bleeding factor, only 40.6% of our patients with mitral and/or aortic valve prosthesis had INR within the target range, based on laboratory results in the six months prior to the last medical visit. There are several articles discussing the challenge of maintaining the anticoagulation target ranges.²¹⁻²³ Variability in INR values in the last six months were not statistically different between patients with and without PVT, or between prosthesis position. Nevertheless, when all patients with PVT were compared with those without PVT, we observed a significant difference in the last INR. Although expected, further differences between these groups may have not been possible due to the small number of events in the sample.

Pannus formation was significantly associated with the presence of thrombus. This finding corroborated the literature, as many studies have suggested that thrombosis occurs concomitantly with other causes of valve prosthesis dysfunction, such as pannus growth. The presence of pannus is a pro-thrombotic factor.⁷

With respect to treatment and outcomes of patients with PVT, three of the five patients received pharmacotherapeutic treatment with unfractionated heparin followed by thrombolytic therapy. There are articles reporting the effectiveness of long-term oral anticoagulation therapy combined with unfractionated heparin in preventing early thromboembolic events in obstructive and small (<5mm) thrombi after mitral valve replacement.²⁴ There is a consensus for this therapy for non-obstructive small thrombi in the left side of the heart, still with reduced effectiveness and recurrence of thrombosis in 16%.²⁵ Heparin seems ineffective for treatment of obstructive thrombus.²⁶ In

our study, three patients underwent thrombolytic therapy with recombinant tissue plasminogen activator (rT-PA). All patients showed a good response, with recurrence of thrombosis in two patients in a time interval of seven months and two years, respectively. Our small sample precludes a more accurate comparison with literature data. In addition, unfractionated heparin was ineffective in our patients. American and European guidelines state that surgical treatment is the first option for patients with mechanical PVT and NYHA III/IV functional class except for those at high surgical risk (class IIa). Data from the literature have supported the use of thrombolytic therapy for PVT, including the TROIA and PROMETEE,²⁷ using, respectively, slow-infusion and ultra-slow infusion of rT-PA. The surgical approach for thrombosis of mechanical valve prosthesis is a procedure of valve replacement and its risks cannot be underestimated; there are reports of mean mortality rates of 12% in these circumstances.²⁸ Surgery in emergency or urgent care has been the strategy of choice, although associated with high mortality (7.1-69%), depending on patients' functional status.²⁹ For two patients in our study surgery was the first option, and in one patient, pregnancy and infective endocarditis were detected.

The rate of bleeding in our study was similar to that reported in an Italian study published in 2018.²⁰ All patients required hospitalization and specific treatment and follow-up. In a Brazilian study, patients undergoing mechanical valve prosthesis replacement were followed-up for 40.6 months, and the incidence of bleeding was 0.95%/patient-year.⁹ Another study reported that in patients with INR of > 2.5 to 4.5 taking warfarin, the likelihood of bleeding is 3%/patient-year.²⁹

Regarding ischemic stroke, the incidence was similar to that in the literature, 0.9-3.6 per 100 patients per year.²¹

Limitations of the study include the fact that this was a single-center study, conducted with public health users, so that the conclusions may not be applicable to other centers. Due to the retrospective nature of the study, some data could not be obtained. Besides, the number of events observed was small, including PVT and bleeding, which limit the analysis of variables possibly associated with these events. Another possible limitation is missing events (PVT or bleeding) that may have occurred in other hospitals.

Conclusions

Our patient population was young, with history of surgical valve replacement, and rheumatic heart disease as its main cause.

The incidence of PVT was 1.1%, which is in accordance with the international literature, with late events after the implant. Due to the low educational level and income of our patients, this was a positive result, which encourages us to recommend implantation of mechanical valve prosthesis for these patients.

Factors associated with PVT in all valve positions assessed together were INRs are out of the target range, smoking and presence of pannus. The factors strongly correlated with death after valve replacement was cardiac

function in the outpatient follow-up and presence of chronic renal failure as comorbidity.

Author Contributions

Conception and design of the research: Tagliari F, Lamas C; Acquisition of data: Tagliari F, Amorim GD; Analysis and interpretation of the data: Tagliari F, Correia MG, Colafranceschi AS, Pedrosa JM, Rodrigues Junior LF, Tagliari TR, Lamas C; Statistical analysis: Correia MG; Writing of the manuscript: Tagliari F, Correia MG, Rodrigues Junior LF, Tagliari TR, Lamas C; Critical revision of the manuscript for important intellectual content: Colafranceschi AS, Pedrosa JM, Weksler C, Lamas C.

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*Supplemental Materials

For additional information Supplemental Material 1, please click here.
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For additional information Supplemental Material 5, please click here.
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Prognosis and Characteristics Associated with Prosthetic Valve Thrombosis: Insights from a Brazilian Study

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Short Editorial related to the article: *Clinical Features and Survival Analysis of Patients after Mechanical Heart Valve Replacement, with an Emphasis on Prosthetic Valve Thrombosis*

Since the 1960s, heart valve disease has undergone critical changes in its therapeutic strategy. The beginning of valve replacement surgeries using prostheses changed the prognosis of patients with valve disease worldwide. Annually, more than 280 thousand valve prostheses are implanted.¹

The incidence of valvular disease of degenerative etiology has increased in industrialized countries while, unfortunately, rheumatic heart disease is still often observed in many parts of the world, being the most prevalent etiology of valvular heart disease in Brazil. The mechanical valve prosthesis is the most indicated for younger patients, often affected by the rheumatic disease, which explains its relevance in our country.²⁻⁴

A prosthetic valve thrombosis is an uncommon event that is more frequent in mechanical prostheses, especially in the mitral position.⁵ This event is one of the most serious complications in the postoperative period of valve replacement, with an annual incidence that varies between 0.5 and 6%⁶ and a high mortality rate, which, in some studies, can exceed 30%.⁷

The study “Clinical Features and Survival Analysis of Patients after Mechanical Heart Valve Replacement, with an Emphasis on Prosthetic Valve Thrombosis” brought important insight into this topic.⁸ This is a large retrospective cohort in which 473 mechanical prosthesis surgeries were identified from 2011 to 2017. To a study conducted in Brazil, the rheumatic disease was the main cause of valve replacement, justifying the younger age profile of this population. In contrast, aortic valve replacement was more prevalent (49.9%), followed by mitral-aortic valve replacement (30.2%) and mitral valve replacement (19.9%). The authors justified these findings based on two hypotheses: (1) preference for bioprosthesis in young women and/or (2) the possibility of intervention by percutaneous valvuloplasty in mitral valve disease.

The overall mortality observed in this study was slightly higher than in other studies, despite the great heterogeneity in the studied populations. In any case, overall mortality was lower than that observed nationally. Some studies have already shown that mechanical prostheses lead to greater survival in younger populations,⁹ with a mortality rate of 26.4% in 15 years. Tagliari's study found a mortality of 16% at a mean follow-up of 4.4 years. Notably, the functional class after surgery and chronic renal failure were the main variables associated with mortality.

Prosthetic valve thrombosis was a rare event, similar to the data available in the literature. In addition, we observed that it is a generally late event, with a mean time of occurrence of 39 months. Warfarin is the anticoagulant of choice in patients with mechanical prostheses. However, its pharmacological profile, which promotes fluctuations in the therapeutic level, may expose the patient to a greater risk of thrombosis. In this study, the RNI of patients with thrombosis showed no difference from those who did not have thrombosis, showing that other factors may be involved. The formation of pannus, a known prothrombotic factor, was associated with a higher occurrence of prosthesis thrombosis. Finally, smoking, another known prothrombotic factor, was also associated. Thus, these patients should routinely evaluate identifying factors that increase the risk of thrombosis.

Bleeding is a feared complication in patients with prosthetic valves. We know that the risk of bleeding is higher in this population compared to patients with bioprosthesis.¹⁰ In Tagliari's study, this complication occurred in 23 patients (4.86%), all of whom required hospitalization. Bleeding was responsible for the death of 2 patients. In a study by Labaf et al., age and previous bleeding were important predictors of bleeding.¹¹ Chronic kidney failure was also an important predictor in patients with mechanical mitral valve prosthesis.

Tagliari's study is an interesting record of valve disease in our population. Especially for showing the young population affected by the rheumatic disease with a high frequency of mechanical valve replacement and its complications. The mortality of the studied population was high, in agreement with the variations observed in the world literature. Functional status and chronic renal failure were associated with higher mortality. Smoking and pannus were highlighted as factors to be carefully observed in this group of patients, considering the hypothesis raised by this article of its relationship with prosthesis thrombosis. Such findings reinforce the importance of the correct indication of valve replacement and adequate follow-up of this population.

Keywords

Thrombosis; Prosthetic Valve; Prognosis

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Does Myocardial Injury Occur After an Acute Aerobic Exercise Session in Patients with Refractory Angina?

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Abstract

Background: It is unclear whether exercise is safe in patients with more advanced forms of coronary artery disease, such as those with refractory angina (RA).

Objective: We aimed to determine the effect of an acute aerobic exercise session (AAES) on high-sensitivity cardiac troponin T (hs-cTnT) levels in patients with RA.

Methods: This was a longitudinal, non-randomized, and non-controlled clinical study. Participants were recruited from April 2015 to January 2019. On a visual pain scale from 0 to 10, pain rated up to 3 was considered as the top level allowed to continue exercising. We assessed hs-cTnT at baseline and 3 hours after the AAES. The protocol consisted of 5 minutes of warm-up, 30 minutes of continuous aerobic exercise at heart rate corresponding to the anaerobic threshold or angina threshold obtained in the cardiopulmonary exercise testing, and 5 minutes of cooling down. P values less than 0.05 were considered statistically significant.

Results: Thirty-two patients with RA were included (61 ± 9 years, 59.4% male). The baseline hs-cTnT concentration was 10.9 ng/L (95% confidence interval: 9.1 to 13.0 ng/L). The hs-cTnT collected 3 hours after the AAES was 11.1 ng/L (95% confidence interval: 9.1 to 13.5 ng/L). No difference occurred in hs-cTnT before and after AAES ($p = 0.657$).

Conclusions: A single AAES performed at the angina threshold with corresponding visual pain scale did not alter hs-cTnT in patients with RA, suggesting that no significant myocardial injury was elicited by exercising and that this exercise protocol can be considered safe.

Keywords: Angina Pectoris; Exercise; Troponin; Biomarkers.

Introduction

Refractory angina (RA) is a chronic and debilitating condition characterized by angina pectoris lasting > 3 months, with an important impairment of quality of life, as a result of coronary insufficiency in the setting of artery disease that cannot be controlled by medical therapy in patients who are not eligible for coronary revascularization (surgery or angioplasty). Despite the complexity of the disease, these patients present low incidence of combined events, including an approximately 2% to 3% per year incidence of death and a 3.5% per year incidence of myocardial infarction.¹

Growing evidence shows that exercise is an important strategy in the treatment of patients with coronary artery

disease (CAD).² Exercise has been shown to increase coronary and peripheral blood flow.² Likewise, exercise training improves neurovascular control in patients with CAD,³ which seems to be associated with improvement in arterial baroreflex control. Moreover, exercise training improves exercise tolerance and quality of life⁴ and reduces mortality in this group of patients.⁵ It is still unclear whether exercise is safe in patients with more advanced forms of CAD, such as those with RA, because, at least theoretically, exercise could provoke severe and/or prolonged ischemia, leading to myocardial damage.

High-sensitivity cardiac troponin T (hs-cTnT) is a specific myocardial injury (MI) marker.⁶ Also, this protein is related to the prognosis of patients with RA. Previous studies have shown that hs-cTnT is a significant predictor of mortality and nonfatal myocardial infarction.⁷ Some investigators have suggested that elevation of hs-cTnT after physical exercise is a sign of exercise-induced ischemia,⁸⁻¹⁰ which depends upon exercise intensity and duration.¹⁰

In this study, we report the levels of hs-cTnT after an acute aerobic exercise session (AAES) in patients with RA. We hypothesized that moderate-intensity exercise done at the anaerobic threshold or angina threshold confirmed by a

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subjective visual pain scale would not alter the levels of hs-cTnT in this group of patients.

Methods

This was a longitudinal, non-randomized, and non-controlled clinical study performed to evaluate the responses to programmed AAES in patients with RA followed in a tertiary university hospital. This analysis was part of the study entitled “Cardiac Rehabilitation in Patients with Refractory Angina”. The sample size was defined by convenience. The study was approved by the ethics and research committee of the Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (CAAE: 24308213.7.0000.0068), submitted to and approved in Clinical Trials (NCT03218891). Investigations followed the Declaration of Helsinki. All patients provided written informed consent.

Patient selection

From April 2015 to January 2019, we enrolled patients of both sexes, aged 45 to 75 years, with symptomatic angina (Canadian Cardiovascular Society [CCS] angina functional class II to IV) with at least 3 months of duration on optimal medical therapy, in whom myocardial ischemia could be documented by physical stress echocardiography, and who were not eligible for surgical or percutaneous myocardial revascularization procedures.

Exclusion criteria

Exclusion criteria were as follows: 1) permanent pacemakers or implantable cardiac defibrillators; 2) patients with nonsinus rhythm; 3) history of recent (< 3 months) acute coronary syndrome or myocardial revascularization (percutaneous or surgical); 4) functional impairment caused by any clinical condition preventing exercise; and 5) activity restriction (class D) according to the American Heart Association criteria for risk stratification of events during exercise.⁷

Cardiopulmonary exercise testing

The cardiopulmonary exercise test (CPET) was performed on a motorized treadmill (T2100 model, GE Healthcare, USA) using a graded exercise protocol (Balke 2.5 mph). Heart rate (HR) was continuously recorded using a 12-lead electrocardiogram (Ergo PC, Micromed, Brazil). The oxygen and carbon dioxide outputs were measured by breath-by-breath analysis (SensorMedics, VmaxAnalyzer Assembly, Encore 29S, USA). CPET was performed following the guidelines, as well as the criteria for defining maximal effort and determination of the anaerobic threshold. The angina threshold was determined at the exact HR at which the patient complained of angina symptoms.

High-sensitivity cardiac troponin T analysis

A commercially available high-sensitivity assay for cTnT (Troponin T, Elisa kit, Roche Diagnostics, Germany), with a detection limit of 3 ng/L and a 99th percentile cut-off from an apparently healthy reference population of < 14 ng/mL was utilized. Because exercise-induced hs-cTnT peak release

occurs within the first 1 to 4 hours,¹¹ we measured the hs-cTnT level at 3 hours post-AAES.

Pain scale

A visual numeric pain scale was adopted and used either to determine exercise interruption or to reduce its intensity. The scale was graded from 0 (no pain) to 10 (severe pain). Pain rated up to 3 (mild to moderate) was considered as the top level allowed to continue aerobic exercise. When the pain reached an intensity higher than 3 (moderate), exercise was interrupted, or its intensity was reduced.

Acute aerobic exercise session protocol

The protocol consisted of a total of 40 minutes exercising: 5 minutes of warm-up, 30 minutes of continuous aerobic exercise on a motorized treadmill at HR corresponding to the anaerobic threshold or angina threshold obtained in the CPET, and 5 minutes of cool-down. Continuous exercise was recommended; however, brief interruptions or reduction in intensity were allowed if the patient experienced moderate angina or moderate effort perception. The exercise was restarted when the symptoms were no longer observed. Patients were continuously monitored by telemetry. Administration of 5 mg of sublingual isosorbide dinitrate was administered as needed.

Statistical analysis

Continuous variables are expressed as mean $\pm$ standard deviation or median and interquartile range (IQR) as appropriate, and categorical variables are expressed as absolute and relative frequencies. The distributions of numerical variables were studied using histograms and boxplots, as well as by Shapiro-Wilk normality tests. Generalized estimating equation models were adjusted to investigate variations between the assessments before and after a physical exercise session to compare groups with and without RA, nitrate use during the physical exercise session, and CCS functional class, in relation to the dosage of ultrasensitive troponin. Adjustments were performed with gamma distribution and logarithmic linkage function, considering the correlation between the measurements of the same patient in both evaluation moments. To compare the presence of angina in relation to the variations observed in troponin dosages, the non-parametric Mann-Whitney test was used. Correlations between numerical measures were investigated using Spearman's correlation coefficient. A generalized linear model with gamma distribution and logarithmic link function was fitted to compare groups with and without angina during the physical exercise session in relation to HR during that session. The analyses were performed using the SPSS statistical package for Windows, version 20.0 (IBM Corp), considering a significance level of 5%.

Results

Baseline measures

A total of 92 patients were recruited, and 60 of them were excluded for not meeting the inclusion criteria. The study

included 32 patients with RA (61 ± 9 years, 59.4% male), 40.6% with CCS II angina functional class, 21.9% with CCS III, and 37.5% with CCS IV. The clinical characteristics of the patients and antianginal medications used by patients are shown in Table 1. Most patients (90.6%) were on a combination of at least 3 antianginal drugs, 93.8% aspirin, 100% statin, and 34.4% insulin. The CPET analysis demonstrated a mean total exercise time of 344.5 ± 139.5 seconds. HR of angina threshold and anaerobic threshold were 88.5 ± 15.9 beats per minute (bpm) and 84.6 ± 11.9 bpm, respectively. Peak oxygen consumption was 16.1 ± 3.4 mL/kg/min.

The analysis of ischemia documented by the stress echocardiogram demonstrated that 62.5% of the patients had ischemia in the left anterior descending artery, 41% in the circumflex artery, and 37% in the right coronary artery territories. Most (66%) patients had ischemia in only 1 coronary territory, 28% in 2 territories, and 6% in 3 territories.

Responses to exercise

The baseline hs-cTnT concentration was 10.9 ng/L (95% confidence interval [CI]: 9.1 to 13.0 ng/L), and 3 hours after the exercise session it was 11.1 ng/L (95% CI: 9.1 to 13.5 ng/L). No significant differences were found in hs-cTnT dosages before and after the session ($p = 0.657$, Table 2). The hs-cTnT levels decreased in 21.9% of patients, did not change in 31.2%, and increased in 46.9%.

The mean HR maintained during AAES was 82.8 ± 7.8 bpm, with 37.5% of patients achieving the HR of anaerobic threshold. During the session, 53.1% of patients experienced angina at the mean of 81.2 ± 8.5 bpm, and, of these, 52.9% did not achieve CPET angina threshold. On the other hand, of the patients who did not have angina during AAES, 40% achieved a CPET angina threshold. Patients who experienced angina during AAES had a significantly higher AAES HR (mean difference: 6.3 bpm) than those who did not ($p = 0.018$; 95% CI, 1.1 to 11.5 bpm). However, no correlation was noted between AAES HR and delta hs-cTnT levels ($R = -0.25$; $p = 0.176$) (Figure 1). The delta hs-cTnT concentrations did not differ between patients who experienced angina during the session and those who did not (medians of 0.0 [IQR: 0.0 to 2.0] and 1.0 [IQR: -1.0 to 1.0], respectively [$p = 0.941$]).

Only 12.5% of all patients required short-term sublingual nitrate for relief of angina during AAES, and of these, only 1 (25%) had reached the CPET angina threshold during the session. No significant differences occurred between hs-cTnT levels and nitrate use during AAES ($p = 0.077$) or between hs-cTnT levels and CCS functional class of angina of patients ($p = 0.395$). No adverse events occurred during AAES throughout the study.

Discussion

To the best of our knowledge, this is the first study to specifically investigate MI by hs-cTnT after a single exercise session in patients with RA. Our results demonstrate that an AAES performed up to the angina threshold corresponding to 3 on the visual pain scale from 0 to 10 did not alter hs-cTnT concentration or cause clinical complications in patients with RA. Therefore, physical exercise may be more

Table 1 – Baseline demographic and clinical characteristics of patients

Clinical data	(N=32)
Age, years (mean $\pm$ SD)	61 $\pm$ 9
Male (%)	59.4
BMI, kg/m ² (mean $\pm$ SD)	29.1 $\pm$ 4.0
AC, cm (mean $\pm$ SD)	100.6 $\pm$ 10.0
Resting HR, bpm (mean $\pm$ SD)	61 $\pm$ 7
SBP, mmHg (mean $\pm$ SD)	124 $\pm$ 16
DBP, mmHg (mean $\pm$ SD)	77 $\pm$ 11
Past medical history (%)	
Hypertension	75.0
Diabetes mellitus	71.9
Hyperlipidemia	93.8
Previous smoking	71.9
Obesity	34.4
Family history of CAD	56.3
Previous acute myocardial infarction	75.0
CAD diagnostic time, years (mean $\pm$ SD)	12 $\pm$ 9
Echocardiographic LVEF, % (mean $\pm$ SD)	54 $\pm$ 9
CAD obstructive pattern (%)	
One-vessel disease	6.3
Two-vessel disease	12.5
Three-vessel disease	81.3
Laboratory findings (mean$\pm$SD)	
LDL-cholesterol, mg/dL	78.0 $\pm$ 26.5
HDL-cholesterol, mg/dL	44.3 $\pm$ 12.9
Triglycerides, mg/dL	129.6 $\pm$ 54.3
HBA1C, %	7.2 $\pm$ 1.7
Antianginal drugs in use (%)	
β -blockers	100
Calcium channel blockers	84.4
Long-acting nitrates	93.8
Trimetazidine	96.9
Ivabradine	15.6

AC: abdominal circumference; BMI: body mass index; CAD: coronary artery disease; DBP: diastolic blood pressure; HR: heart rate; LVEF: left ventricular ejection fraction; SBP: systolic blood pressure; SD: standard deviation.

comprehensively indicated as part of nonpharmacological treatment of these patients.

These results are an important step in clinical practice, because one of the most important clinical characteristics of patients with RA is low exercise tolerance, limiting their daily activities and worsening their quality of life.¹² In this context, physical exercise could be included as part of safe clinical treatment of RA. Habitually, these patients are restricted in physical activities because of the fear that exercise may exacerbate symptoms or trigger recurrent cardiovascular

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events. Cardiac rehabilitation, an established treatment for CAD patients^{13,14} (class I, level of evidence A), is not clearly recommended for patients with RA, because of the lack of evidence regarding the safety and beneficial effects.^{15,16}

Hs-cTnT is a recognized biomarker for diagnosis of myocardial infarction and MI.^{17,18} Troponin concentrations, even below the 99th percentile, predict adverse outcomes in patients and the general population.¹⁹ In patients with CAD, including those with RA,¹ hs-cTnT is an important prognostic marker of cardiovascular events.^{1,20,21} Low circulating hs-cTnT was identified as the strongest predictor of death and nonfatal MI. A possible explanation is due to the occurrence of silent ruptures of vulnerable atherosclerotic plaques, which lead to microembolization and subsequent microinfarction in areas of myocardium not supplied by sufficient collateral circulation, elevating hs-cTnT plasma levels before MI and cardiovascular death occurrence.⁷

Cardiac troponins can also be released with exercise; however, the underlying mechanisms and the real clinical value of this increase are not completely understood.^{8,10,22} Several theories have been proposed to explain the mechanism underlying troponin release, followed in many cases by documented echocardiographic ejection fraction abnormalities.²³ MI is the most concerning proposed mechanism, because it could result in a negative clinical outcome. Another well accepted mechanism is the release of an unbound troponin that exists in cardiomyocyte cytosol through the increased membrane permeability of cardiomyocytes (triggered by the shear stress of exercise). This could explain the short duration (< 1 week) of hs-cTnT increase after exercise.

The magnitude of the hs-cTnT response depends on the duration and, principally, intensity of physical activity, and the long-term prognostic significance of repetitive, exercise-induced troponin release is not completely known.^{10,22} Many authors consider these exercise-induced increases in troponin concentrations benign, because they occur frequently, are present even in (apparently) healthy individuals, and are not accompanied by clinical symptoms.²⁴⁻²⁶ On the other hand, a recent study observed that baseline and postexercise hs-cTnT were independent predictors of mortality and major adverse cardiovascular events in a cohort of older long-distance walkers, calling attention to the fact that high troponin levels may not be only a benign physiological response, but an early prognostic marker of cardiovascular events.¹⁹

Considering the lack of consensus about the clinical relevance of postexercise hs-cTnT on prognosis, the interpretation of these studies must take the following into account: 1) population evaluated, 2) intensity and volume of exercise applied, 3) hs-cTnT measurement assays, 4) training experience, 5) blood sample timing, and 6) presence of symptoms during exercise.^{10,22}

In view of these controversial points and our findings, it seems that physical activity, especially in patients with CAD, may be safely practiced when it is not followed by an increase in postexercise hs-cTnT, guiding the prescription of an "optimal target dose." Accordingly, it minimizes the possible harmful

Table 2 – Estimated mean values and 95% confidence intervals for ultrasensitive troponin dosage before and after an exercise session (n=32)

Assessment	Ultrasensitive troponin dosage (ng/L)
Before EX	10.9 (9.1; 13.0)
After EX	11.1 (9.1; 13.5)
Variation (after EX –before EX)	0.2 (–0.8; 1.2)
p value	0.657

Values expressed as estimated averages (95% confidence interval); EX: exercise session. Statistical test: generalized estimating equation models.

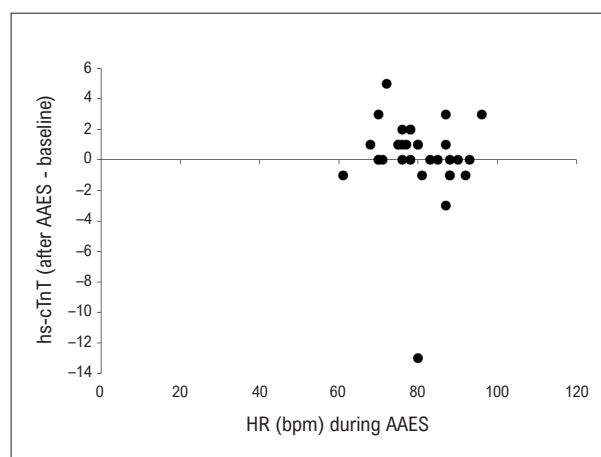


Figure 1 – Relationship between AAES HR and delta hs-cTnT. AAES: acute aerobic exercise session; bpm: beats per minute; HR: heart rate; hs-cTnT: high-sensitivity cardiac troponin T.

effects of exercising, achieving maximal health benefits, and additionally changing paradigms of limiting exercise prescription below ischemia or angina threshold.

Physical training based on the pain threshold associated with the visual pain scale is widely used and accepted in patients with peripheral arterial disease.²⁷ In these patients, this type of training is considered a form of treatment.²⁷ In patients with CAD, exercise is actually recommended at the intensity below inducible ischemia. The aerobic exercise intensity should be prescribed 10 beats below the ischemia threshold, usually controlled by electrocardiographic changes.⁷ In patients with RA, who are extremely limited in performing daily tasks due to angina and whose symptoms are triggered by both physical and emotional stressors, it is a challenge to define exercise-based HR.

In our patients with RA, 25% had hs-cTnT above the 99th percentile of normality (> 14 ng/L), that is, at a higher risk of cardiovascular events. In spite of this and the presence of moderate angina (up to 3 of 10 on visual pain scale), in more than a half of the patients, we did not observe a significant increase in hs-cTnT after AAES or clinical events during the session. Angina, like other chronic pain,

is a subjective and very individual symptom and it should, of course, be taken into consideration for the safety of these patients. It is essential to highlight that our patients did not experience electrocardiographic alterations during the exercise session, even though they experienced angina. Therefore, an exercise intensity prescription based on electrocardiographic modifications does not appear to be an appropriate strategy in patients with RA.

We have to emphasize that patients who experienced angina during the exercise session had higher HR than patients without angina. However, the patients without angina trained to the anaerobic threshold or moderate effort, which is the recommended exercise intensity for CAD patients. These results reinforce that our proposed exercise prescription may be considered safe to apply in patients with RA.

Limitations

The hs-cTnT analysis was made based on 2-point samples: before and 3 hours after an AAES. The last one was defined based on evidence that any change in hs-cTnT level is already detectable at that time;^{17,28} therefore, we do not believe that it interfered with our results.

Conclusion

A single AAES performed at the angina threshold and corresponding visual pain scale (up to 3 of 10) did not alter hs-cTnT in patients with RA, suggesting that no significant MI was elicited by exercising. Therefore, we conclude that this exercise protocol can be considered safe for patients with RA.

What is known about the topic and what does this study add?

Exercise training improves exercise tolerance and quality of life and reduces mortality in this group of patients; however, the safety of physical activity is still questioned for patients with refractory angina and is often an impediment to performing

cardiac rehabilitation, thus impacting this population's quality of life. This manuscript creates a paradigm for future studies of rehabilitation in patients with refractory angina.

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Author Contributions

Conception and design of the research and Acquisition of data: Montenegro CSP, Dourado LOC, Jordão CP, Vieira MLC, Assumpção CRA, Gowdak LHW, Pereira AC, Negrão CE, Matos LDNJ; Analysis and interpretation of the data: Montenegro CSP, Dourado LOC, Negrão CE, Matos LDNJ; Statistical analysis: Montenegro CSP, Dourado LOC, Matos LDNJ; Obtaining financing: Dourado LOC, Assumpção CRA, Gowdak LHW, Matos LDNJ; Writing of the manuscript: Montenegro CSP; Critical revision of the manuscript for important intellectual content: Montenegro CSP, Dourado LOC, Jordão CP, Vieira MLC, Gowdak LHW, Pereira AC, Negrão CE, Matos LDNJ.

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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Refractory Angina Referral to Cardiovascular Rehabilitation: A Neglected Patient

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Short Editorial related to the article: Does Myocardial Injury Occur After an Acute Aerobic Exercise Session in Patients with Refractory Angina?

Cardiovascular rehabilitation (CR) is an effective and safe treatment for stable coronary artery disease (CAD) patients,¹ with established benefits to improving quality of life and reducing cardiovascular mortality and hospital admission.² The effects of CR on reducing myocardial ischemia have been documented,³⁻⁵ justifying the CR Class IA recommendation.¹ However, CR is still neglected and underused worldwide.⁶

Refractory angina (RA) is a disabling condition affecting CAD patients under optimized medical therapy with a residual ischemic burden for more than three months who are ineligible for revascularization interventions. RA is associated with reduced quality of life, exercise limitation, and biopsychosocial disorders. Ideally, clinical management should be guided by specialized centers aiming to optimize multiple pharmacologic therapies and evaluated interventional options.⁷ In this context, comprehensive CR is a valuable treatment for RA considering its multi-component approach, including risk factor management, psychological support, and exercise training,⁸ although the latter possess limited evidence.¹

A decade ago, Asbury et al.⁹ demonstrated in a randomized controlled pilot study the benefits of a CR in improving physical ability without compromising comorbid pain, angina, or risk of a severe adverse event in 42 RA patients. However, in this study, the physical capacity was assessed by the Shuttle Walk test, and the exercise intensity prescription (60-75% of age-predicted heart rate reserve or 40-60% if heart failure) was different from the current guidelines recommendation,^{1,10} stressing the necessity for studies in the area.

Despite the potential benefits, patients with RA are generally not referred to CR due to apprehension of adverse events during physical exercises,¹ mainly related to myocardial ischemia triggering during exercise training. Conversely, Noel et al.¹¹ demonstrated that prolonged and repeated ischemic training could be well tolerated without evidence of myocardial injury, significant arrhythmias, or left ventricular dysfunction. However, this study focused not on

RA but 22 CAD patients. Likewise, the actual prevalence of myocardial ischemia triggering during a CR session might be underestimated since some studies have already demonstrated a 54 to 81% prevalence of silent scintigraphic ischemia during exercise training in CAD patients with residual ischemia burden, although with no secondary adverse events.^{5,12,13}

In this context, it is important to highlight the findings from the study entitled “Does myocardial injury occur after an acute aerobic exercise session in patients with refractory angina?”.¹⁴ This study aimed to assess the effect of an acute aerobic exercise session on high-sensitivity cardiac Troponin T (hs-cTnT) levels in 32 patients with RA with functional class (CCS) above II and myocardial ischemia documented by stress echocardiography. In this study, the exercise intensity was determined according to a previous cardiopulmonary exercise testing (CPET), a gold-standard method for exercise prescription.¹⁰ The exercise session was performed on a treadmill with exercise intensity monitored by heart rate according to the first ventilatory threshold or the angina threshold. An angina pain up to 3 on a 0-10 scale (mild to moderate) was allowed during the acute exercise training, and the levels of hs-cTnT were determined 3 hours after the session.¹⁴

The study's main finding was that hs-cTnT dosages did not reveal significant differences before and after an exercise session, although 53.1% of the patients had experienced angina symptoms during the exercise without electrocardiographic changes. Also, there were no adverse events throughout the study, and the authors concluded that exercise protocol was safe for patients with RA.¹⁴

Although exciting and extremely promising, the conclusion was based on a single exercise session of a non-randomized and non-controlled clinical study,¹⁴ once again highlighting the demand for further research on this topic. The authors may have additional data to be published in the future, as the study is registered in clinical trials (NCT03218891) as interventional. We are looking forward to these upcoming results to allow the increase of the recommendation and the level of evidence of CR in RA patients in future guidelines.¹

Until then, the safety of CR demonstrated by this study¹⁴ and the preliminary safety and efficacy shown by Asbury et al.⁹ must be reinforced, stimulating the indication of CR to refractory angina patients by targeting the potential benefits already demonstrated in the broad spectrum of CAD, reversing the previously neglected referral.

Keywords

Coronary Artery Disease; Cardiac Rehabilitation; Exercise; Myocardial Ischemia/drug therapy; Angina, Stable.

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Assessment of the Impact of the Implementation of a Pre-Hospital Ambulance System on Acute Myocardial Infarction Mortality in a Developing Country

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Abstract

Background: The effective management of patients with acute myocardial infarction (AMI) is time-dependent.

Objectives: To assess the impacts of the implementation of prehospital care on admission rates and mortality associated with AMI.

Methods: Retrospective, ecological study, which assessed data from the Brazilian Universal Health System, from all 853 municipalities of Minas Gerais, from 2008 to 2016. Excessive skewness of general and in-hospital mortality rates was smoothed using the empirical Bayes method. This study assessed the relationship between Mobile Emergency Care Service (SAMU) in each municipality and the following 3 outcomes: mortality rate due to AMI, AMI in-hospital mortality, and AMI hospitalization rate, using the Poisson hierarchical model. Rates were corrected by age structure and detrended by seasonality and temporal influences. A confidence interval of 95% was adopted.

Results: AMI mortality rates decreased throughout the study, on average 2% per year, with seasonal variation. AMI in-hospital mortality also showed a decreasing trend, from 13.81% in 2008 to 11.43% in 2016. SAMU implementation was associated with decreased AMI mortality (odds ratio [OR] = 0.967, 95% confidence interval [CI] 0.936 to 0.998) and AMI in-hospital mortality (OR = 0.914, 95% CI 0.845 to 0.986), with no relation with hospitalizations (OR = 1.003, 95% CI 0.927 to 1.083).

Conclusion: SAMU implementation was associated with a modest but significant decrease in AMI in-hospital mortality. This finding reinforces the key role of prehospital care in AMI care and the need for investments on this service to improve clinical outcomes in low- and middle-income countries.

Keywords: Acute Myocardial Infarction, Emergency Medical Services, Hospital Mortality.

Introduction

Acute myocardial infarction (AMI) remains a leading cause of morbidity and mortality worldwide.^{1,2} The effective management of patients with AMI is directly linked to time to medical assistance, and approximately one half of the deaths attributed to AMI result from out-of-hospital cardiac arrest, reinforcing the importance of prehospital care and, ultimately, the development of evidence-based AMI systems of care.

Specifically, in relation to ST-elevation myocardial infarction, early diagnosis and appropriate reperfusion therapy are of the utmost importance for mortality reduction.

Primary percutaneous coronary intervention (PCI), the first choice for reperfusion, when available, is more effective than thrombolytic therapy, but it should ideally be performed up to 120 minutes after the first medical contact, or within 90 minutes if the patient presents at a primary PCI-capable unit. Thrombolysis is more effective when delivered within 3 hours of symptom onset. Either strategy should be delivered no later than 12 hours after symptom onset.³ In clinical practice, a significant proportion of patients do not receive care that meets those time targets, and the situation is even worse in rural communities and under-resourced areas.³⁻⁷

There is still a lack of contemporary data about the impact of the use of prehospital care in the setting of AMI, especially in low- and middle-income countries, particularly from the more generalizable perspective of a community-based investigation, as well as information about hospital outcomes of patients transported by ambulance. However, it is known that the first minutes after AMI onset are crucial to the patient's prognosis and survival, and, considering that, it is important to objectively evaluate the possible impacts of emergency prehospital services on AMI management and outcomes.⁸

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Nonetheless, it is difficult to obtain this type of information from observational studies, as there is no control over the classification of the studied variables, and it is often difficult to isolate the dependent variable.

Therefore, we aimed to assess the impacts of the implementation of a nationwide ambulance service (*Serviço de Atendimento Médico de Urgência*, SAMU) on hospitalization rates and general and AMI in-hospital mortality in the state of Minas Gerais (MG), in the Southeast Region of Brazil.

Methods

This is an observational, retrospective, ecological study, which assessed data from the Brazilian Universal Health System (SUS, DataSUS TabNET),⁹ from all 853 municipalities of the Brazilian state of MG, from 2008 to 2016. It follows the RECORD statement for studies that use routinely collected health data.¹⁰

MG is the Brazilian state with the largest number of municipalities (853), and it is located in the Southeast Region of Brazil. It is the second most populous state in Brazil, with 21 million inhabitants distributed across an area comparable to France. The average Human Development Index (HDI) is 0.731, and 14.46% of the population is considered poor or very poor, according to the Brazilian Institute of Geography and Statistics (IBGE).¹¹ MG can be considered representative of the country, as age distribution, percentage of urbanization, and social inequality are similar to the overall national pattern. The north and the northeast of MG have the lowest HDI, similar to the North and Northeast regions of Brazil, while the west and south of the state have HDI similar to the areas with the highest HDI in the country.¹⁰⁻¹²

The Brazilian nationwide ambulance service, called SAMU, was implemented in the state of MG in 2003 by a national program called “*Política Nacional das Urgências*” (National Emergency Policy). The program started in some selected municipalities, which were responsible for managing their own system. Since 2009 regionalized prehospital care systems were created, called “consortiums”, which currently correspond to the main model of care and cover various regions of the state. In the period analyzed, there were five consortia in the state: Consórcio Intermunicipal de Saúde da Macrorregião do Sul de Minas (CISSUL), Consórcio Intermunicipal de Saúde da Região Sudeste (CISDESTE), Consórcio Intermunicipal de Saúde da Rede de Urgência Centro Sul (CISRU), Urgência do Norte de Minas (CISRUN) and Consórcio Intermunicipal de Saúde Rede de Urgência Macro Nordeste/ Jequitinhonha (CISNORJE), covering 469 municipalities in the south, southeast, center-south, north, and northeast regions, respectively (Figure 1).

SAMU implementation dates were obtained from the state government and local SAMU coordinators. The first inter-city consortium was implemented in 2009, one in 2011, two in 2012, and one in 2015. Some services were implemented before the analyzed time period, while others were implemented during the study period. At the same time, some municipalities had already implemented SAMU consortiums at the beginning of the analysis, while others

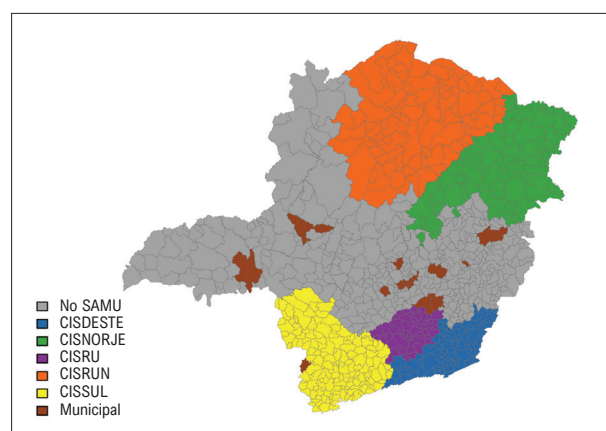


Figure 1 – Distribution of municipal SAMUs and SAMU consortia in Minas Gerais. Acronyms: CISDESTE: Consórcio Intermunicipal de Saúde da Região Sudeste; CISNORJE: Consórcio Intermunicipal de Saúde Rede de Urgência Macro Nordeste/Jequitinhonha; CISRU: Consórcio Intermunicipal de Saúde da Rede de Urgência Centro-Sul; CISRUN: Consórcio Intermunicipal de Saúde da Rede de Urgência do Norte de Minas; CISSUL: Consórcio Intermunicipal de Saúde da Macrorregião do Sul de Minas; SAMU: Mobile Emergency Care Service. Source: SES-MH 2016.

implemented SAMU during the study period and others did not have SAMU within this time frame. Fourteen municipalities had SAMU during the analysis period (municipal SAMUs). SAMU was implemented in 86 municipalities in January 2009 (CISRUN), in 94 municipalities in November 2014 (CISDESTE), in 86 municipalities in April 2012 (CISNORJE), in 51 municipalities in June 2012 (CISRU), and in 152 municipalities in July 2015 (CISSUL). The remaining municipalities of the state ($n = 370$) remained without SAMU throughout the study period. Supplementary Figure 1 shows the evolution of SAMU coverage in the state, as each regional consortium was implemented.

The outcomes of interest were AMI general and in-hospital mortality rates and rate of admissions due to AMI, assessed from 2008 to 2016. The choice of those outcomes is justified by the fact that they have the greatest clinical and epidemiological relevance and greatest potential for association with SAMU implementation, in addition to high completion rates, as mandatory variables.

Data on the population of each municipality was obtained from IBGE, the official demographic and statistical institute of Brazil.¹³ For deaths and hospitalizations, data were extracted from DATASUS TabNET,⁹ an electronic database that collects patient-level information from the SUS. We used information of monthly occurrences of those outcomes, from the Mortality Information System (SIM) and the Hospital Information System (SIH) databases, respectively, for the population of the 853 municipalities of MG, from 2008 to 2016.¹⁴

Deaths were considered AMI deaths when the main cause of death had the following ICD-10 codes (I21 to I24): I21 “acute myocardial infarction”, I22 “recurrent myocardial infarction”, I23 “some current complications subsequent to acute myocardial infarction”, I24 “other acute ischemic heart diseases”. Data from the SIH was used to obtain data on hospital admissions due to AMI: procedure “treatment

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of AMI", SIH/DATASUS code 03.03.06.019-0 and "primary coronary angioplasty", code 040.603.004-9. In this study, AMI in-hospital mortality was calculated from the number of deaths with the aforementioned codes, divided by the number of hospitalizations with these same codes in each municipality per month of analysis.

As the study used public data available through the DATASUS platform, approval by a research ethics committee was not necessary.

Data analysis

The software R version 3.3.4 was used for statistical analysis.¹⁵ The unit of analysis was the municipality. A monthly analysis of the outcomes, from January 2008 to December 2016, for each of the 853 municipalities in MG was performed, considering the population by estimates of each year.¹⁵

The 3 outcomes were adjusted for the age structure, based on the population of 2010.¹¹ The rates were estimated for each municipality and month considering the adjustment for age. The municipalities were indexed by $i = 1, \dots, n$, where $n = 853$ is the total number of municipalities, while the months were indexed by $t = 1, \dots, T$, where T is the number of months in the period analyzed.

Excessive skewness of AMI mortality and in-hospital mortality rates were smoothed using the empirical Bayes method.¹⁶ The method was used to estimate the rates instead of the classic rate estimate approach. In the classical approach, the rate is calculated as the ratio of the number of events (deaths, hospitalizations) per the population at risk. Therefore, the variability of the estimated rates is strongly affected by small changes in the number of events (deaths) when they are computed for small areas where the expected value for events is low. The empirical Bayes method aims to minimize the variations of the estimated rates through a weighted average between the municipal rate and the regional rate. In the present study, the region was defined as the state of MG. The weights were interpreted by the population size; the higher a population was, the lesser the weight of the region rate. The AMI mortality and hospitalization rates were modeled using Poisson distribution, while AMI in-hospital mortality was using binomial distribution, and then estimated them through the empirical Bayes method (Supplementary Figures 2 and 3). Hospital admissions with the aforementioned SIH/DATASUS hospital admission codes from 2008 to 2016 in all municipalities of MG were assessed and, as this variable is also subject to significant variations in municipalities with small populations, the global empirical Bayes method was used for adjustment, as explained for mortality rate analysis.

Seasonality and temporal trends of decrease in the general and hospital mortality rates were observed, with semiannual tendency in the oscillation between the lowest and highest rates and gradual reduction of the same over the analyzed period. Thus, seasonality and temporality were included in the statistical analysis models. This study assessed the relationship between the availability of SAMU care in each municipality and the following 3 outcomes: the mortality due to AMI in the general population, AMI in-hospital mortality, and number of hospitalizations due to AMI, using the Poisson hierarchical

model, and the analyzed rates were corrected by the age structure and detrended by temporal and seasonal influences. A 95% confidence interval (CI) was used for all outcomes.

Results

AMI mortality rates, adjusted by age distribution, showed a decreasing trend throughout the study, ranging from 35.7 deaths per 100,000 inhabitants in 2008 to 30.4 deaths per 100,000 inhabitants in 2016, i.e., about 2% per year on average (Table 1). Seasonal variation in AMI mortality rates was also observed, and it was higher during the winter season and lower during the summer season (Figure 2).

Age-corrected AMI in-hospital mortality also showed a decreasing trend, from 13.81% in 2008 to 11.43% in 2016 (Table 1), with wide monthly variations and a seasonal pattern, although this was less evident when compared to AMI mortality rate (Figure 3).

SAMU implementation was associated with decreased AMI mortality (odds ratio [OR] = 0.967, 95% CI 0.936 to 0.998) and AMI in-hospital mortality (OR = 0.914, 95% CI 0.845 to 0.986) with no significant association with the number of hospitalizations (OR 1.003, 95% CI 0.927 to 1.083). There was no seasonal variation in the number of AMI hospitalizations during the study period.

Discussion

In the present study, it was observed that the implementation of SAMU in the Brazilian state of MG was associated with a reduction in general AMI mortality rates. Age-corrected AMI in-hospital mortality also showed a decreasing trend over time, with a seasonal pattern. However, no significant association was found with AMI hospitalization rates during the analyzed period.

Despite the lack of evidence in developing countries, these results are in line with studies developed in high-income countries, and they are likely related to increased patient access to some type of AMI treatment and decreased time between

Table 1 – Annual AMI mortality, hospitalization, and in-hospital mortality rates, adjusted by age, in the state of Minas Gerais from 2008 to 2016

Year	Mortality (per 100,000)	In-hospital mortality (%)*	Hospitalization (per 100,000)
2008	35.7 (35.3 – 36.1)	13.81	152 (146 – 158)
2009	34.1 (33.8 – 34.5)	13.65	150 (144 – 156)
2010	35.0 (34.6 – 35.3)	13.78	140 (134 – 145)
2011	33.8 (33.4 – 34.1)	11.82	147 (142 – 152)
2012	32.4 (32.1 – 32.6)	11.29	146 (141 – 151)
2013	31.9 (31.7 – 32.2)	11.99	142 (137 – 146)
2014	30.9 (30.6 – 31.1)	12.15	137 (132 – 141)
2015	29.9 (29.7 – 30.2)	10.82	138 (133 – 142)
2016	30.4 (30.1 – 30.6)	11.43	147 (142 – 151)

*Rates are expressed with 95% confidence

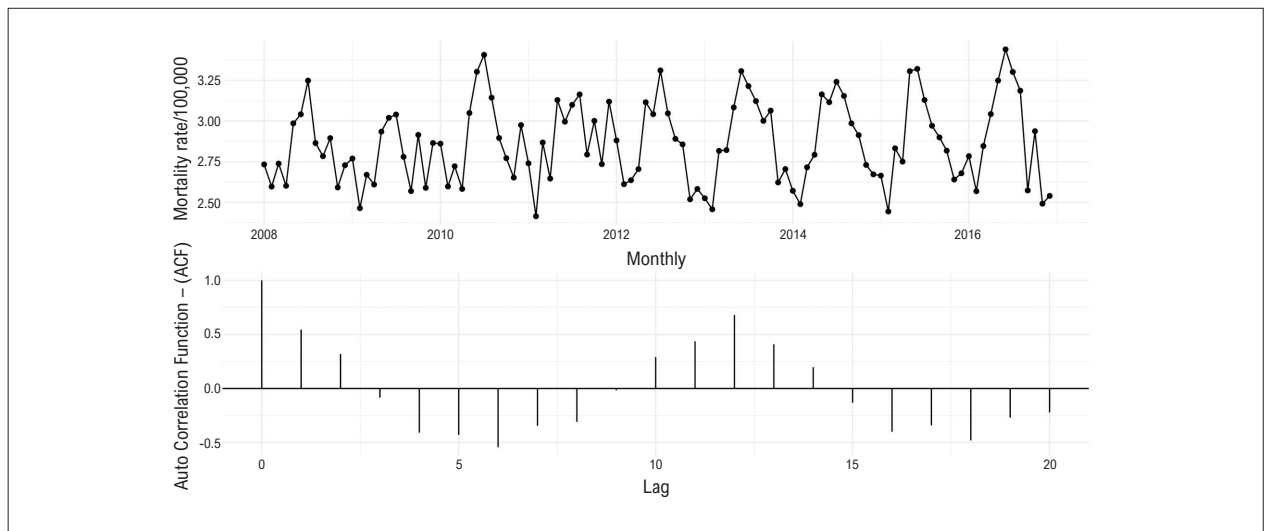


Figure 2 – Occurrence of seasonal variation in mortality rates from 2008 to 2016. A higher mortality rate is observed during winter, and lower rates are observed during summer.

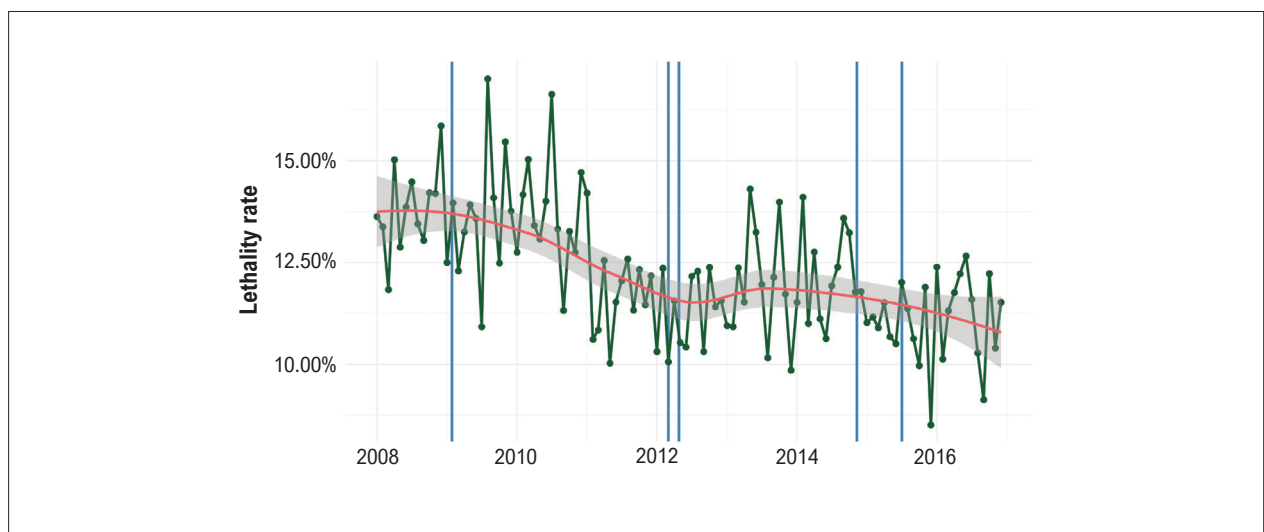


Figure 3 – Lethality and mortality monthly rates for the municipalities of Minas Gerais, from 2008 to 2016. Green dots represent monthly lethality rates for the whole analyzed population, which presents considerable monthly variation with no defined seasonal pattern. The red line represents the rate trend through time, with an accentuated reduction from 2008 to 2012, stagnation at 2013 and a new slower decrease from 2014 to 2016. We observed that the implementation of Mobile Emergency Care Service (SAMU), represented by the vertical blue lines, did not have any clear influence on lethality on the descriptive analysis.

symptom onset and initiation of specific therapy, including reperfusion when indicated.^{3,8,17,18} On the other hand, some studies have failed to demonstrate an association between the implementation of AMI systems of care and decreased mortality, despite the improvement in quality of healthcare, adherence to guideline-driven recommendations, and shortened treatment times.^{3-5,8,12,19,20} This has occurred even with the use of protocols designed with multiple interventions other than prehospital care only. Among these studies, the Reperfusion of Acute myocardial infarction in North Carolina Emergency departments (RACE) stands out. It was conducted in the state of North Carolina, USA, leading to a reduction in consultation time and the delays for reperfusion treatment administration

following the implementation and systematization of protocols for AMI patient care.²⁰

Differently from previous reports, our study was conducted in a middle-income country, a fact that can help to explain our positive results in terms of hard endpoints. In studies conducted in developed countries, the baseline quality of AMI care is generally superior to that observed in our country.^{6,8,20} Thus, demonstrating the magnitude of the incremental benefit of any intervention is more difficult to obtain in this situation, while in places where there is poor quality and care delivery, less complex interventions may have a greater impact on outcomes. A previous evaluation of adherence to AMI quality of care

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criteria in MG illustrates this care gap in the region.²¹⁻²³ Despite the fact that the implementation of prehospital care was not part of the implementation of AMI systems of care, interventional facilities or dedicated cardiac care units in those regions, it may have influenced the improvement of the quality of care during the study period, since a higher proportion of patients might have received accurate diagnosis and appropriate treatment.

Outcomes associated with AMI are related to multiple variables, especially the structure for the care of patients.²²⁻²⁴ It is worth highlighting some relevant elements in the formulation of a high complexity network in cardiology: 1) the inverse relationship between the size and volume of procedures performed in referral hospitals and AMI mortality; 2) benefit of the “pharmaco-invasive” strategy, which consists of prehospital or early in-hospital fibrinolysis followed by routine PCI between 3 and 24 hours, comparable to primary PCI in patients with short-term AMI-related symptoms, whenever a timely transfer to a PCI-capable units is possible;¹⁹ 3) the cost-effectiveness of prehospital care expansion in relation to the construction of new interventional cardiology services, which was demonstrated in the USA, where the distance to hemodynamic services is around 70 km in the vast majority of sites.^{1,2,20}

As expected, there was greater variation of rates in places with smaller populations, such as in the eastern and central-southern regions of the state, which have the lower HDIs of the state, respectively covered by the CISDESTE and CISRU consortia. This finding is possibly associated with the lower quality of the death certificate filling, with a higher proportion of deaths from undefined causes and “garbage codes” (health conditions that cannot be directly attributable to mortality), associated with the influence of other causes of mortality in those populations, such as infectious diseases, consistent with that observed in other low HDI regions in Brazil and worldwide

(WHO, 2017).²⁴⁻²⁶ This finding reiterates the importance of using analytical adjustment methods for extreme variations. In this sense, the methodological analysis applying the global empirical Bayes method was effective in reducing the variation of rates in small populations, without changing the values in places with larger populations, as shown in Figure 4. The use of the rates observed in the state of MG as a reference for smoothing allowed this process to be done with a reference population similar to the analyzed municipalities, but with a larger population.

With regards to seasonal variation in AMI mortality rates, this variation was not expected in a region with much lower temperature variation compared to North American or European countries, or even cooler regions of Brazil, such as São Paulo and the South Region. It raises the possibility of explanations other than the temperature, or temperature-related physiological changes, such as changes in blood viscosity, platelet volume, and blood pressure.²⁷ Other diseases that are more common during the winter, especially respiratory infections by viruses and community-acquired pneumonia have shown to affect the cardiovascular system in various ways and to precipitate adverse cardiac outcomes, such as heart failure, myocardial infarction, and cardiac arrhythmias.²⁸ As coronary artery disease is essentially an inflammatory disease, it has been shown that inflammation related to respiratory pathogens can trigger it.²⁹ In a self-controlled case series using national infection surveillance data linked to the Scottish Morbidity Record, AMI and stroke rates substantially increased in the week following a respiratory infection.³⁰ In addition, a recent meta-analysis has shown the impact of the 23-valent polysaccharide pneumococcal vaccine in providing protection from any cardiovascular event (risk ratio [RR]: 0.91; 95% CI: 0.84 to 0.99), myocardial infarction (RR: 0.88; 95% CI: 0.79 to 0.98), and all-cause mortality (RR: 0.78;

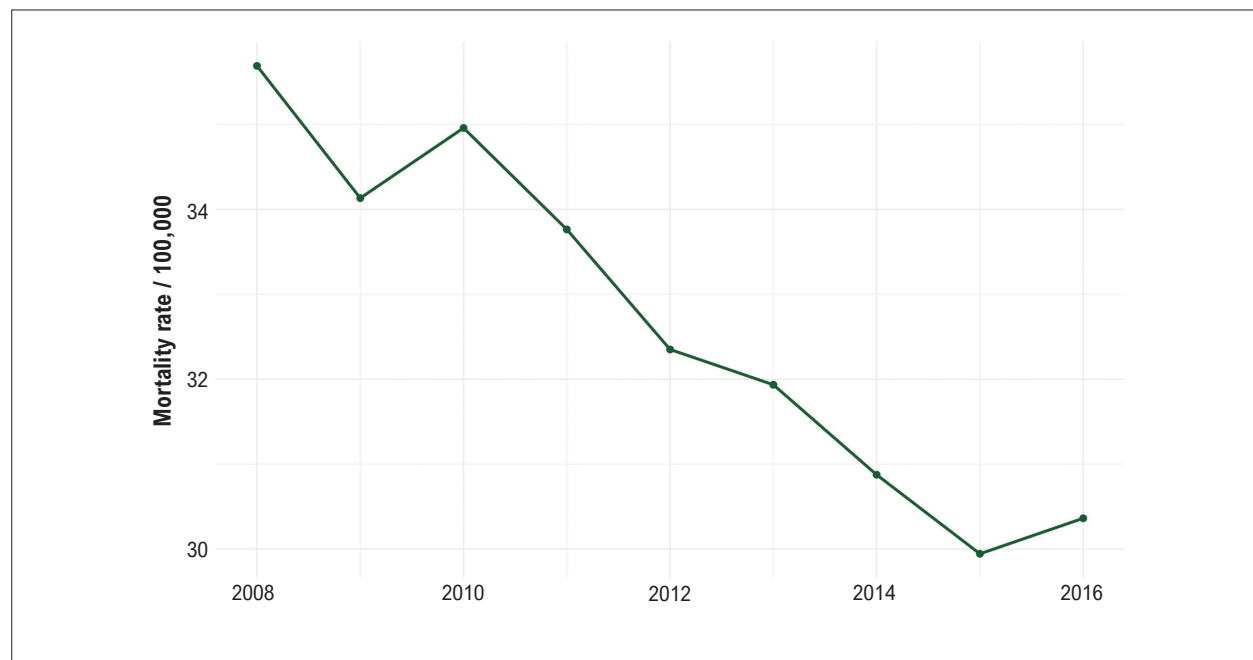


Figure 4 – Annual crude mortality rates in the state of Minas Gerais from 2008 to 2016. A temporal reduction trend.

95% CI: 0.68 to 0.88) in individuals of all age groups.³¹ On the other hand, an ongoing clinical trial conducted in Brazil comparing single- to double-dose influenza vaccine after an acute coronary event was interrupted early due to apparent lack of benefit in interim analyses.³²

Air pollution, especially exposure to particulate matter, has also been associated with a higher risk of cardiovascular diseases, including AMI.^{33,34} A recent study has observed that an increase of around 10 micrograms per m³ of air was associated with an increase of 16% of AMI mortality.³³ Meanwhile, another study using a global atmospheric chemistry model has shown that over 60% of cardiovascular deaths worldwide have been related to air pollution, and short-term increases in air pollution are associated to AMI.³⁴ Sunyer et al., observed that the increase in sulfur dioxide levels in the air of seven European cities increased hospital admissions for cardiovascular diseases on the previous day and on the day of higher pollutant levels.³⁵ This association remained significant even after adjusting for particles with size lower than 10 μm among subjects younger than 65 years. Air pollution tends to be higher in months in which rain levels are lower. Therefore, in Brazil, where the summers are rainy while winters have predominantly drier weather, seasonality may play an important role in AMI mortality indeed.

Our study has some limitations that should be addressed. The implementation of prehospital care is accompanied by co-interventions, such as articulation of the linkage of healthcare institutions of the AMI care system and increased local emergency services, which were not systematically studied in this study, and may have influenced the findings. Through public information available from the Ministry of Health, Minas Gerais State Health Secretariat, Municipal Health Secretariats and SAMUs' databases, it is possible to affirm that the available networks were incipient and that there was a lack of infrastructure, supplies, human resources, and organizational and management processes in the majority of the state and the country.^{11,13,14} Examples include the low availability of interventional cardiology services and the concentration of health resources in regions with better sociodemographic profiles; the low utilization of telehealth services by prehospital teams; the absence of fibrinolytics in SAMU ambulances; the lack of clinical protocols and standardization of evidence-based care; the poor infrastructure of most emergency departments in the state, mostly prehospital emergency units and small hospitals; and the suboptimal training of health personnel involved in emergency care. Finally, these factors add to the difficulty of implementing the health care networks due to financial and political reasons.

This study did not address the impact of other levels of attention on the outcomes studied, such as primary health care (PHC). Although there are consistent data in the literature showing the key role of PHC in the prevention, promotion, and treatment of health conditions that are risk factors for AMI, with its ability to reduce the incidence rates of AMI, the focus of this study was acute events, which occur, albeit to a lesser extent, in well-established PHC systems.^{1,2,6,8,20} As the health effects associated with PHC are typically observed over the long term, no adjustment was made for this variable, given the technical difficulties inherent in this process and the scarcity of databases to perform it.

Another limitation is related to the fact that the ecological model does not include relevant individual clinical variables; therefore, it is not possible to establish relationships between such characteristics and the outcomes studied or to establish a definitive causal relationship between the implementation of SAMU and these outcomes. Finally, like all observational studies, the risk of bias has been minimized but cannot be completely excluded, in particular residual confounding bias.

Nevertheless, the major strength of our study is its methodological contribution, i.e., presenting a method that can take into account the seasonality and temporal trends to observe the effect of an intervention. The temporal trend of mortality reduction was taken into account in the analysis, and mortality reduction with SAMU implementation was observed regardless of this temporal trend.

Conclusion

In the present study, a small reduction in general and in-hospital mortality rates attributable to AMI was observed following the implementation of SAMU in the Brazilian state of MG in the time frame analyzed, with no significant changes in hospital admission rates. Results suggest that prehospital care plays an important role in the healthcare system, especially considering the growing burden of cardiovascular diseases, especially acute coronary syndromes.

Author Contributions

Conception and design of the research: Vieira RCP, Marcolino MS, Nascimento BR, Ribeiro ALP; Acquisition of data and Statistical analysis: Vieira RCP, Marcolino MS, Silva LGS; Analysis and interpretation of the data: Vieira RCP, Marcolino MS, Silva LGS, Ribeiro ALP; Obtaining financing: Vieira RCP, Marcolino MS, Ribeiro ALP; Writing of the manuscript: Vieira RCP, Marcolino MS, Pereira DN, Jorge AO, Ribeiro ALP; Critical revision of the manuscript for important intellectual content: Vieira RCP, Marcolino MS, Silva LGS, Pereira DN, Nascimento BR, Jorge AO, Ribeiro ALP.

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 Master thesis submitted by Rodrigo Costa Pereira Vieira, from Universidade Federal de Minas Gerais.

Ethics approval and consent to participate

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

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***Supplemental Materials**

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Having Symptoms of an Acute Myocardial Infarction? Call Your Emergency Medical Service Immediately!

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Short Editorial related to the article: Assessment of the Impact of the Implementation of a Pre-Hospital Ambulance System on Acute Myocardial Infarction Mortality in a Developing Country

Timely reperfusion of the occluded coronary arteries is critical to saving at-risk ischemic myocardial cells in acute ST-elevation myocardial infarction (STEMI). This fact led to the concept of “Time is Muscle” related to acute myocardial infarction (AMI) management.¹

Independently of what reperfusion strategy is chosen (lytics or percutaneous coronary intervention (PCI)), the time from symptom onset to successful reperfusion is critical to the patient’s short- and long-term prognosis.^{2,3}

Total ischemic time is the major determinant of infarct size in STEMI. It has been divided, since Terkelsen et al.⁴ paper, into ‘patient delay’ and ‘system delay,’ suggesting that the latter, but not the former, can be influenced by the healthcare systems and providers.

The patient delay (defined as the time between the initiation of symptoms and the first medical contact (FMC), can be attributed to several individual, but also societal characteristics of the patients presenting with STEMI and has been the subject of many studies in the past. It largely depends on the patient’s knowledge of coronary disease-related symptoms and presentation.^{5,6}

On the other hand, hospital organizations have made large efforts in the last decades to achieve timely reperfusion of the occluded coronary arteries by reducing the door-to-needle or door-to-balloon times and looking for better and safer modalities of reperfusion therapies.

However, there is another crucial fraction of the total ischemic time whenever the FMC occurs in the pre-hospital setting. The so-called Emergency Medical System (EMS) delay can play a major role in the reduction of the interval from first medical contact (FMC) to reperfusion, either by starting lytic therapy in the pre-hospital phase or by redirecting the patients to the nearest hospital with available PCI facilities, thus bypassing the regional hospitals that might not have those facilities available.

Keywords

Myocardial Infarction; Hospitalization; Mortality; Emergency Medical Services

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The 2017 European Society of Cardiology STEMI guidelines⁷ indicate that all components of the system delay (including the EMS delay) represent the quality of care, and it is recommended to measure them as quality indicators.⁷

The EMS delay largely depends on the local, regional, or national authorities’ policies regarding the organization of the ambulance services and the implemented protocols regarding acute coronary syndrome’s pre-hospital care.

In this issue of *Arquivos Brasileiros de Cardiologia*, Vieira et al.⁸ present a very thorough evaluation of the implementation of a pre-hospital ambulance system on AMI mortality in the state of Minas Gerais in southeastern Brazil.⁸

This study’s main outcomes were total and in-hospital mortality rates due to AMI and hospitalization rates AMI-related. As the authors mention, these outcomes were chosen due to their high epidemiological and clinical relevance and the highest association potential with the ambulance system implementation.

After a very comprehensive study of the multiple factors that might influence the AMI outcomes during the 2008-2016 period, a modest (as assumed by the authors) but significant reduction in mortality attributable to AMI was found, and one of the major factors of this outcome could be explained by the implementation of a pre-hospital ambulance first-response system.

These results are in line with the ones reported by Ferreira et al.⁹ They published an analysis of the mortality due to AMI in the different regions of Brazil over 21 years. Their findings have shown an impressive 68% reduction in AMI mortality rates in the Southeast region of Brazil, which can be, at least partially, explained by the Minas Gerais state results in the overlapping period of the Vieira et al.⁸ study.

The good coordination between the emergency medical services and the local/regional hospitals, with the adoption of common protocols regarding AMI care and the implementation of coronary fast-track systems, are good examples of health policies and public health initiatives that translate into better outcomes after an AMI.^{10,11}

However, not even the better-implemented ambulance system or the best pre-hospital care protocols will give the desired outcomes if the patients do not timely activate the EMS response.

Large efforts should then be put into educating patients presenting with symptoms that might raise the suspicion of having an AMI to immediately call their EMS emergency number and ask for assistance (that might include the dispatch of an ambulance with the proper crew and equipment) rather than going to the health services by their own means of transportation.

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Body Surface Potential Mapping during Ventricular Depolarization in Rats after Acute Exhaustive Exercise

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Abstract

Background: Exhaustive physical exercise can cause substantial changes in the electrical properties of the myocardium.

Objective: To evaluate, using body surface potential mapping, the electrical activity of the heart in rats during ventricular depolarization after acute exhaustive exercise.

Methods: Twelve-week-old male rats were submitted to acute treadmill exercise at 36 m/min until exhaustion. Unipolar electrocardiograms (ECGs) from the torso surface were recorded in zoletil-anesthetized rats three to five days before (Pre-Ex), 5 and 10 minutes after exhaustive exercise (Post-Ex 5 and Post-Ex 10, respectively) simultaneously with ECGs in limb leads. The instantaneous body surface potential maps (BSPMs) were analyzed during ventricular depolarization. P values <0.05 were considered statistically significant.

Results: Compared with Pre-Ex, an early completion of the second inversion of potential distributions, an early completion of ventricular depolarization, as well as a decrease in the duration of the middle phase and the total duration of ventricular depolarization on BSPMs were revealed at Post-Ex 5. Also, compared with Pre-Ex, an increase in the amplitude of negative BSPM extremum at the R-wave peak on the ECG in lead II (R_{II}-peak) and a decrease in the amplitude of negative BSPM extremum at 3 and 4 ms after R_{II}-peak were showed at Post-Ex 5. At Post-Ex 10, parameters of BSPMs did not differ from those at Pre-Ex.

Conclusion: In rats, acute exhaustive exercise causes reversible changes in the temporal and amplitude characteristics of BSPMs during ventricular depolarization, most likely related to alterations in the excitation of the main mass of the ventricular myocardium.

Keywords: Rats; Heart Ventricles; Myocardium; Exercises; Acute; Body Surface Potential Mapping.

Introduction

The beneficial effects of regular physical exercise on public health, including reduced risk of cardiovascular diseases, have been well established.^{1,2} However, excessive exercise can cause damage to the body, especially the heart. A number of studies have demonstrated a transient deterioration in cardiac function after acute bouts of prolonged endurance exercise in apparently healthy individuals.^{3,4} Excessive physical exercise may be a trigger for malignant ventricular arrhythmias, acute myocardial infarction and sudden cardiac death in susceptible persons.⁵

Research on the impact of exhaustive exercise on the cardiovascular system is essential. But, in humans,

it is difficult to objectively determine exhaustion under laboratory conditions, since it is measured by the inability of the subject to maintain the exercise regimen by volitional effort.^{6,7} In this regard, the advantage of model animals (e.g., rats, mice) in evaluating physiological responses to exhaustive exercises is that there are objective criteria for the definition of exhaustion, such as the inability of an animal to continue running despite the external stimuli during a treadmill running test^{8,9} or sinking to the bottom of the pool during a forced swimming test.¹⁰

Numerous studies in laboratory animals have shown myocardial tissue damage and cardiac function impairment associated with cardiomyocyte apoptosis, oxidative stress and inflammatory responses after acute bouts of exhaustive exercise.¹¹⁻¹³ It has been reported that acute exhaustive exercise causes changes in electrocardiographic patterns in rats, suggesting ventricular depolarization alterations.^{14,15}

Body surface potential mapping based on a simultaneous register of cardiac-generated potentials, from multiple sites, over the entire torso surface, provides more physiological and diagnostic information about electrical events in the myocardium, compared with conventional

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electrocardiography.¹⁶⁻¹⁸ By using body surface potential mapping, the present study aimed to evaluate the electrical activity of the heart in laboratory rats during ventricular depolarization after acute exhaustive exercise.

Methods

Experimental animals

Twelve-week-old male outbred albino rats ($n=24$), weighing between 200 and 300 g, were purchased from the Stolbovaya Branch of the Scientific Center for Biomedical Technologies of the Federal Medical-Biological Agency (Russian Federation). The rats were housed in group cages in a temperature-controlled room ($22 \pm 2^\circ\text{C}$) under a 12-h light/dark cycle and fed standard commercial rodent chow and water *ad libitum*. All experimental procedures and protocols were carried out in accordance with the Guide for the Care and Use of Laboratory Animals published by the National Institutes of Health (NIH Publication No. 85-23, revised 1996) and approved by the Ethics Committee of the Komi Science Centre of the Ural Branch of the Russian Academy of Sciences (Syktyvkar, Russian Federation).

Exercise protocol

A motorized rodent treadmill (Panlab / Harvard Apparatus, Spain) was used to create acute exhaustive exercise for rats. Mild electrical pulses (0.5 mA) from the electrified grid on the rear of the treadmill motivated the animals to exercise. Before experimentation, the rats were accustomed to treadmill exercise for three consecutive days (10 min/day, 12-36 m/min, 0° incline). Only certain rats, capable of running in an adaptive mode, were selected for further study. On the day of the exercise test, the rats were running at a speed of 36 m/min and 0° incline until exhaustion. Exhaustion was defined as the point at which the rat could not run anymore, despite being pushed against the shock grid by the moving treadmill belt.⁸ The running time to exhaustion was computed using Sedacom version 2.0 software (Panlab / Harvard Apparatus, Spain).

Conventional electrocardiography and body surface potential mapping

The registration of heart electrical activity was performed three to five days before (Pre-Ex), 5 and 10 minutes after (Post-Ex 5 and Post-Ex 10, respectively) acute exhaustive exercise. The rats were anesthetized with Zoletil (tiletamine / zolazepam combination, Virbac, France) at a dose of 3.5 mg / 100 g, i.m. and placed in the supine position on a heating pad to maintain body temperature approximately at 37°C . Unipolar electrocardiograms (ECGs) were recorded from subcutaneous needle electrodes, evenly distributed around the torso from the level of the cervicothoracic junction to the inferior rib margins (Figure 1). A total of 64 electrodes at Pre-Ex and 32 ones at Post-Ex 5 and Post-Ex 10 were used. Simultaneously with unipolar ECGs from the surface of the torso, ECGs were recorded in bipolar limb leads. The Wilson central terminal served as a reference for the unipolar torso leads. The data were acquired using a multichannel computer

system (bandwidth of 0.05-1000 Hz, sampling rate of 4000 Hz, and accuracy of 16 bits). The rats had a period of three to five days to recover from anesthesia prior to exhaustive exercise. To register post-exercise cardiac potentials, the rats were anesthetized immediately after exhaustion.

The duration of R-R intervals and ventricular depolarization parameters (QRS duration, R- and S-wave duration and amplitude, the sum of R- and S-wave amplitudes) were analyzed on the ECG in the limb lead II (ECG_{II}). The R-R intervals were used to compute the heart rate (HR). Based on unipolar ECGs, instantaneous body surface equipotential (isopotential) maps were constructed, reflecting the distribution of cardiac potentials in each instant of ventricular depolarization on a flat pattern of the chest surface aligned to a rectangular plane. The body surface potential maps (BSPMs) analyzed the spatial location and shifting trajectories of the areas and extrema of positive and negative potentials on the thorax surface, the amplitudes of extrema in sequential time instants during ventricular depolarization, the maximum amplitudes of extrema for the whole ventricular depolarization, and the time when the extrema reached maximum amplitudes. Temporal characteristics of the BSPMs were presented in ms, relative to the peak of R_{II} -wave (up to the R_{II} -peak – with a minus sign).

According to the spatial-temporal dynamics of body surface potential distribution, the following phases of ventricular depolarization were differentiated:¹⁹

1. Initial phase – from the formation of a cardiac potential distribution pattern, corresponding to ventricular depolarization, to the completion of the first inversion of positive and negative potential areas.
2. Middle phase – from completion of the first inversion to completion of the second inversion of potential areas.
3. Terminal phase – from the completion of the second inversion of potential areas to the disappearance of potential distribution pattern corresponding to ventricular depolarization.

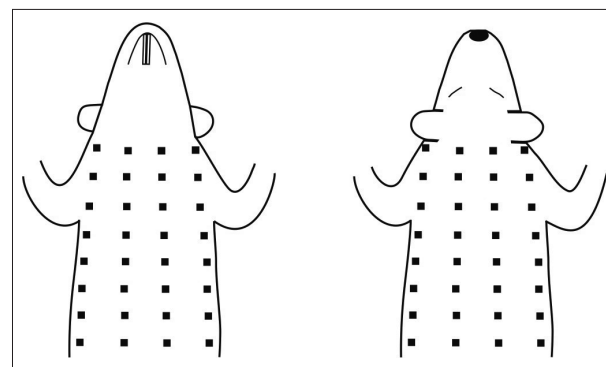


Figure 1 – Positions of electrodes on the rat's body surface using 64 unipolar torso leads. Four rows of needle electrodes were placed on the ventral, and four rows on the dorsal surface of the body (eight electrodes in each row). When using 32 unipolar torso leads, the number of electrode rows on the ventral and dorsal body surfaces decreased twice.

For each rat, characteristics of ECG_{II} and BSPMs were determined from the three to five beats at Pre-Ex, Post-Ex 5, and Post-Ex 10.

Statistical analysis

The statistical analysis was performed using a Statistica software package (version 10.0, StatSoft, Tulsa, OK, USA). Continuous data normality was checked using the Shapiro-Wilk test. Normally distributed variables were expressed as mean $\pm$ standard deviation, and non-normally distributed variables were presented as median, first and third quartiles. For the data with normal distribution, the repeated measures analysis of variance (ANOVA) was used, followed by Dunnett's multiple comparison test as a *post-hoc* analysis. When the data were non-normally distributed, the non-parametric Friedman test, followed by Wilcoxon's test with Bonferroni adjustment, was performed. A statistical significance was established at an alpha level of 0.05, except for Wilcoxon's test, in which the alpha level was adjusted to 0.025 (according to the number of pairwise comparisons) to avoid a type I error. The sample size was determined by convenience. Data²⁰ have been taken into account that up to 10% of rats from commercial vendors refuse to run on a treadmill and should be eliminated from exercise studies.

Results

Exercise performance

Of 24 rats used to get familiarized with running sessions, 20 were selected for the acute exhaustive exercise according to their running ability. In these rats, the running time to exhaustion was 19.5 ± 5.6 min.

Table 1 – ECGII parameters before and after acute exhaustive treadmill exercise

	Pre-Ex	Post-Ex 5	Post-Ex 10
HR, bpm	480.3 $\pm$ 23.3	484.5 $\pm$ 25.2	490.7 $\pm$ 28.8
QRS _{II} duration, ms	16.0 $\pm$ 1.1	15.3 $\pm$ 1.2*	15.8 $\pm$ 1.7
R _{II} -wave duration, ms	9.7 $\pm$ 1.0	9.1 $\pm$ 0.9*	9.4 $\pm$ 1.0
S _{II} -wave duration, ms	6.3 $\pm$ 1.4	6.2 $\pm$ 1.5	6.3 $\pm$ 1.7
R _{II} -wave amplitude, mV	0.62 $\pm$ 0.16	0.65 $\pm$ 0.15	0.63 $\pm$ 0.14
S _{II} -wave amplitude, mV	-0.28 $\pm$ 0.15	-0.35 $\pm$ 0.18*	-0.35 $\pm$ 0.19*
Sum of RII- and SII-wave amplitudes, mV	0.90 $\pm$ 0.19	0.99 $\pm$ 0.20*	0.98 $\pm$ 0.20*

Data are expressed as mean $\pm$ standard deviation ($n = 20$). Pre-Ex: before exhaustive exercise; Post-Ex 5: 5 minutes after exhaustive exercise; Post-Ex 10: 10 minutes after exhaustive exercise. HR: heart rate. Repeated measures ANOVA and Dunnett's *post-hoc* test; * $p < 0.05$ vs. Pre-Ex.

Conventional ECG parameters

Table 1 shows the ECG_{II} findings. There were no statistically significant changes in HR values after exhaustive treadmill exercise. Compared with those at Pre-Ex, the QRS_{II} duration and R_{II}-wave duration were lower at Post-Ex 5. Compared with those at Pre-Ex, the S_{II}-wave amplitude and the sum of R_{II}- and S_{II}-wave amplitudes were higher at Post-Ex 5 and Post-Ex 10. There were no significant changes in either the S_{II}-wave duration or the R_{II}-wave amplitude after exhaustive treadmill running.

Spatial pattern of BSPMs

Before exhaustive exercise, the body surface potential distribution pattern, corresponding to the onset of ventricular depolarization, was observed prior to the appearance of the QRS complex on ECG_{II} (Figure 2, Pre-Ex, instant -9 ms). In this case, the area of the positive cardiac potentials covered the cranial part of the ventral chest and the entire dorsal chest, with the positive extremum being located mainly in the cranial third of the left-lateral chest. The area of negative potentials, and the negative extremum, were located in the caudal part of the ventral chest. During the upslope of R_{II}-wave, the first inversion of potential distributions occurred on BSPMs, and as a result, the positive and negative areas changed their relative positions (Figure 2, Pre-Ex, instant -5.5 ms). By the completion of the first inversion, the positive extremum was located caudally on the ventral chest, and the negative extremum was located cranially, more frequently on the back. In the instant of the R_{II}-wave peak, the location of areas and extrema on BSPMs remained essentially unchanged (Figure 2, Pre-Ex, instant 0 ms). During the downslope of R_{II}- and S_{II}-waves, the second inversion of potential distributions was observed on the BSPMs, and as a consequence, the area of negative potentials was located in the caudal part of the chest, left laterally or ventrally, while the area of positive potentials occupied the remaining chest surface (Figure 2, Pre-Ex, instant 4.0 ms). By the completion of the second inversion, the positive extremum shifted cranially and right laterally, with the negative extremum being located caudally on the left lateral chest. During the transition from S_{II}-wave to T_{II}-wave, a pattern was recorded on the BSPMs of an unstable position of the positive and negative areas, which indicated the completion of the ventricular depolarization (Figure 2, Pre-Ex, instant 5.5 ms). After exhaustive exercise, spatial potential distributions during ventricular depolarization were quite similar to those at Pre-Ex (Figure 2, Post-Ex 5 and Post-Ex 10).

Temporal characteristics of BSPMs

There were no significant changes in either the time of ventricular depolarization onset or the time of the first inversion completion of potential distributions on BSPMs after exhaustive treadmill exercise (Figure 3). Compared with that at Pre-Ex, the second inversion of potential distributions on BSPMs was completed significantly earlier at Post-Ex 5 (Figure 3). In addition, compared with that at Pre-Ex, ventricular depolarization on BSPMs was completed significantly earlier at Post-Ex 5 (Figure 3).

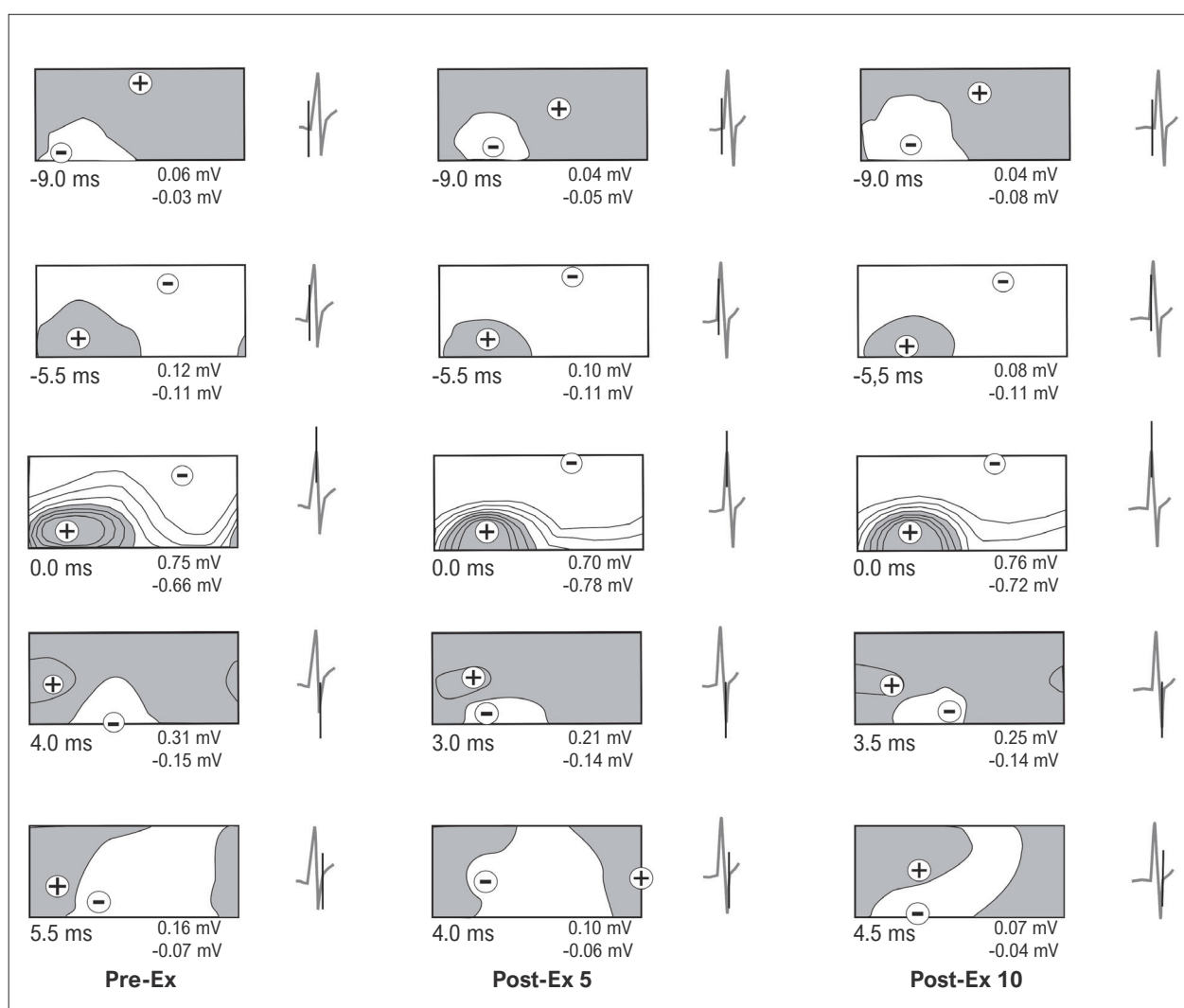


Figure 2 – Body surface equipotential maps during ventricular depolarization before and after acute exhaustive treadmill exercise in the same rat. The areas of positive (filled) and negative potentials are shown. The signs, plus and minus, show the location of the positive and negative extrema, respectively. Below each map, the time relative to the RII-wave peak and the amplitudes of the positive and negative extrema are shown. Near to each map, ECGII is shown with a time marker (vertical line). The isopotential contour spacing is 0.2 mV. In each map, the left part represents the ventral body surface, and the right represents the dorsal body surface. Pre-Ex: before exhaustive exercise; Post-Ex 5: 5 minutes after exhaustive exercise; Post-Ex 10: 10 minutes after exhaustive exercise.

No significant changes in the duration of the initial and the terminal phases of ventricular depolarization were observed on the BSPMs after exhaustive treadmill running (Figure 4). Compared with those at Pre-Ex, the duration of the middle phase and the total duration of ventricular depolarization decreased at Post-Ex 5 (Figure 4).

Characteristics of BSPM extrema

During ventricular depolarization, the amplitudes of positive and negative BSPM extrema pre- and post-exhaustive treadmill exercise progressively increased, reaching maximum values near the peak of the R_{II}-wave, then decreased (Figure 2, Table 2). There were no significant changes in either the maximum amplitudes of

BSPM extrema during ventricular depolarization, or the time when extrema reached maximum amplitudes after acute exhaustive exercise (Figure 5).

The amplitudes of BSPM extrema at different moments during ventricular depolarization are shown in Table 2. Due to the individual variations in the onset and completion times of ventricular depolarization on BSPMs, the time range corresponding to the depolarization of ventricles in all studied animals (i.e. from -5 to 4 ms relative to R_{II}-peak) was analyzed. At each analyzed moment of the chosen time range, no significant changes in the amplitude of positive BSPM extremum were observed after exhaustive treadmill exercise. At the R_{II}-peak, the amplitude of negative BSPM extremum at Post-Ex 5 was higher compared with that at Pre-Ex (Table 2, instant 0 ms). Additionally, 3 and 4 ms

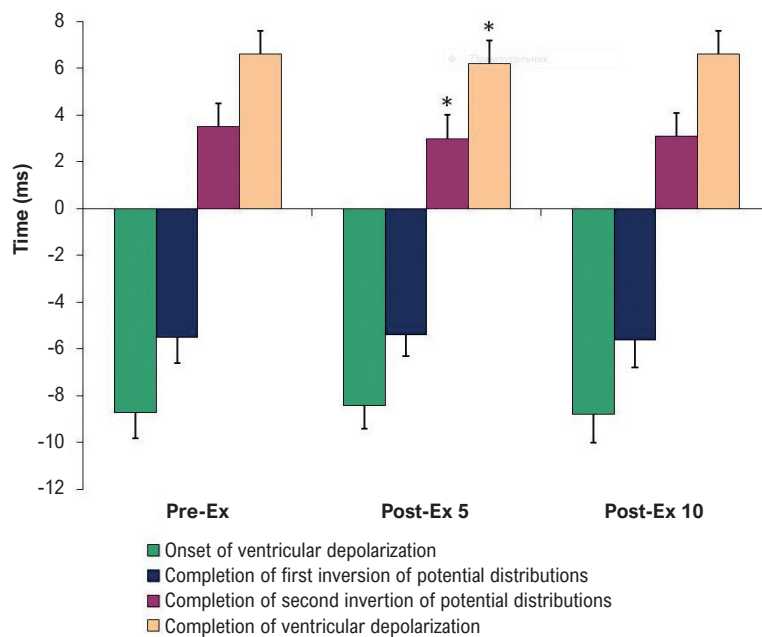


Figure 3 – Temporal parameters of BSPMs during ventricular depolarization, before and after acute exhaustive treadmill exercise. The time is shown relative to the RII-wave peak. Data are expressed as mean $\pm$ standard deviation ($n = 20$). Pre-Ex: before exhaustive exercise; Post-Ex 5: 5 minutes after exhaustive exercise; Post-Ex 10: 10 minutes after exhaustive exercise. Repeated measures ANOVA and Dunnett's post-hoc test; * $p < 0.05$ vs. Pre-Ex.

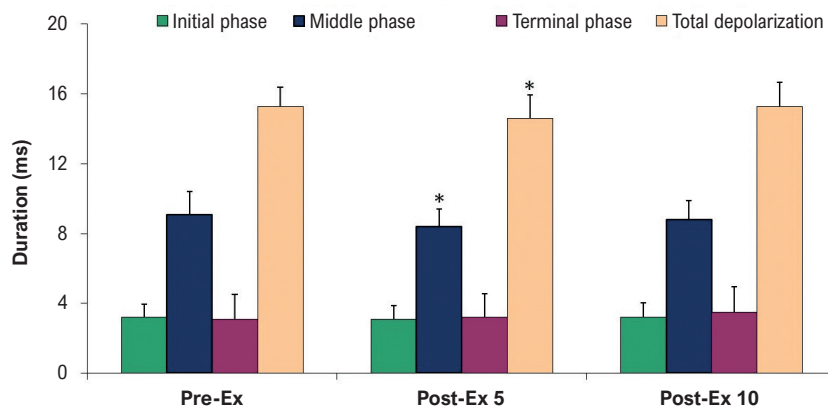


Figure 4 – Duration of individual phases and total duration of ventricular depolarization on BSPMs before and after acute exhaustive treadmill exercise. Data are expressed as mean $\pm$ standard deviation ($n = 20$). PreEx: before exhaustive exercise; Post-Ex 5: 5 minutes after exhaustive exercise; Post-Ex 10: 10 minutes after exhaustive exercise. Repeated measures ANOVA and Dunnett's post-hoc test; * $p < 0.05$ vs. Pre-Ex.

after R_{II}-peak, the amplitudes of negative BSPM extremum at Post-Ex 5 were lower compared with those at Pre-Ex (Table 2, moments 3 and 4 ms).

Discussion

In the present study, the electrical activity of the heart was evaluated during ventricular depolarization after acute exhaustive treadmill exercise in previously untrained rats,

by using body surface potential mapping in combination with conventional electrocardiography.

The immediate cardiovascular response to forced treadmill exercise in rodents is an increase in HR,^{21,22} ensuring an increase in cardiac output. In Wistar rats, the HR acceleration, during treadmill exercise, is predominantly determined by the cardiac autonomic nerve activity, especially by an augmentation in sympathetic

Table 2 – Amplitudes of BSPM extrema at different time moments during ventricular depolarization before and after acute exhaustive treadmill exercise

	Time moment, ms										
	-5	-4	-3	-2	-1	0	1	2	3	4	
Positive extremum, mV											
	Pre-Ex	0.19 (0.06; 0.31)	0.44 (0.19; 0.54)	0.67 (0.41; 0.81)	0.89 (0.80; 1.09)	1.06 (0.90; 1.20)	0.92 (0.79; 1.16)	0.74 (0.54; 0.91)	0.45 (0.17; 0.79)	0.41 (0.29; 0.63)	0.4 (0.33; 0.52)
	Post-Ex 5	0.14 (0.05; 0.24)	0.34 (0.19; 0.46)	0.57 (0.43; 0.73)	0.88 (0.67; 1.05)	1.02 (0.78; 1.20)	0.95 (0.77; 1.15)	0.76 (0.39; 0.9)	0.33 (0.22; 0.59)	0.44 (0.19; 0.59)	0.34 (0.20; 0.46)
Post-Ex 10	0.19 (0.06; 0.28)	0.41 (0.19; 0.50)	0.67 (0.44; 0.77)	0.84 (0.56; 1.02)	0.95 (0.75; 1.16)	0.95 (0.76; 1.15)	0.61 (0.28; 0.91)	0.39 (0.18; 0.57)	0.41 (0.21; 0.58)	0.4 (0.2; 0.53)	
Negative extremum, mV											
	Pre-Ex	-0.14 (-0.11; -0.21)	-0.28 (-0.16; -0.35)	-0.40 (-0.26; -0.52)	-0.58 (-0.38; -0.64)	-0.64 (-0.51; -0.73)	-0.71 (-0.62; -0.85)	-0.58 (-0.49; -0.74)	-0.42 (-0.29; -0.56)	-0.28 (-0.20; -0.40)	-0.16 (-0.09; -0.27)
	Post-Ex 5	-0.14 (-0.07; -0.19)	-0.26 (-0.18; -0.35)	-0.42 (-0.27; -0.50)	-0.57 (-0.41; -0.67)	-0.65 (-0.58; -0.78)	-0.77 (-0.68; -0.92)*	-0.65 (-0.44; -0.78)	-0.39 (-0.22; -0.44)	-0.21 (-0.14; -0.30)*	-0.08 (-0.05; -0.189)*
Post-Ex 10	-0.16 (-0.08; -0.20)	-0.29 (-0.17; -0.35)	-0.45 (-0.30; -0.53)	-0.60 (-0.40; -0.69)	-0.66 (-0.55; -0.75)	-0.75 (-0.60; -0.90)	-0.67 (-0.45; -0.73)	-0.39 (-0.20; -0.46)	-0.23 (-0.13; -0.36)	-0.12 (-0.06; -0.23)	

The time is shown relative to the RII-wave peak. Data are expressed as median, first and third quartiles (n = 20). Pre-Ex: before exhaustive exercise; Post-Ex 5: 5 minutes after exhaustive exercise; Post-Ex 10: 10 minutes after exhaustive exercise. Wilcoxon test with Bonferroni adjustment; *p < 0.025 vs. Pre-Ex at the same time.

outflow.²³ The decrease in HR, after physical exercise cessation, is likely the manifestation of vagal reactivation.²⁴ Previous studies on untrained rats have demonstrated the decline in HR to the initial level at 10 minutes after acute exhaustive treadmill running.²⁵ In the present study, in both situations after exhaustive exercise (Post-Ex 5 and Post-Ex 10), HR values were nearly equal to that at baseline (Pre-Ex). In our opinion, these results could be explained by a decrease in HR to the pre-exercise level within the first 5 minutes following running until exhaustion.

In healthy human subjects, the ECG response to physical exercise consists of either a decrease in the QRS duration or no changes in QRS duration.^{26,27} The shortening of the QRS duration with exercise in healthy individuals is attributed to enhanced intraventricular conduction velocity, due to increased adrenergic tone.²⁶ Meanwhile, QRS prolongation with exercise is considered an abnormal ECG finding and might be used as a marker of myocardial ischemia.²⁸ The significant prolongation of the duration of QRS, accompanied by the impairment of the cardiac functional capacity, was observed in healthy Sprague-Dawley rats, which were submitted to acute exhaustive treadmill exercise, compared with their sedentary control.¹⁵ We found a decrease in the QRS_{II} duration and R_{II}-wave duration at Post-Ex compared with those at Pre-Ex, while at Post-Ex 10 these parameters returned to near Pre-Ex level. It is generally accepted that, in humans, the R-wave in limb leads of ECG represents the depolarization of the left and right ventricles, and S-wave reflects predominantly the excitation of the basal parts of ventricles.²⁹ The genesis of R- and S-waves on ECGs in rats is similar to that in humans.³⁰ Thus, our results suggested that the changes in QRS duration after acute exhaustive exercise in rats were related to a transient decrease in the excitation duration in most of the ventricular myocardium.

In apparently healthy humans, a decrease in the R-wave amplitude, with or without an increase in the S-wave amplitude, is observed on ECGs at maximal exercise.^{31,32} The reduction in the R-wave amplitude, with strenuous exercise, is attributed to a decrease in the ventricular end-diastolic volume,²⁷ as well as to changes in cardiac electrical activation,³¹ while the increase in S-wave amplitude is assumed to be related to electrical axis shifts or ventricular conduction alterations.³³ In this study, the R_{II}-wave amplitude did not alter after exhaustive treadmill running. However, compared with Pre-Ex, the amplitude of S_{II}-wave increased at Post-Ex 5 and Post-Ex 10. Since the sum of the R_{II}- and S_{II}-wave amplitudes also increased at Post-Ex 5 and Post-Ex 10, variations in S_{II}-wave amplitude following exhaustive exercise were probably not the result of a QRS axis deviation. Because of the lack of an isoelectric ST-segment in rats, the increase in the S-wave amplitude on rat ECGs is regarded as the ST-segment depression and is interpreted as a sign of myocardial ischemia.^{34,35} So, in the present study, the increase in the amplitude of S_{II}-wave in exhausted rats may be caused by exercise-induced ischemic alterations in heart ventricles. Nonetheless, further studies are needed to confirm this assumption.

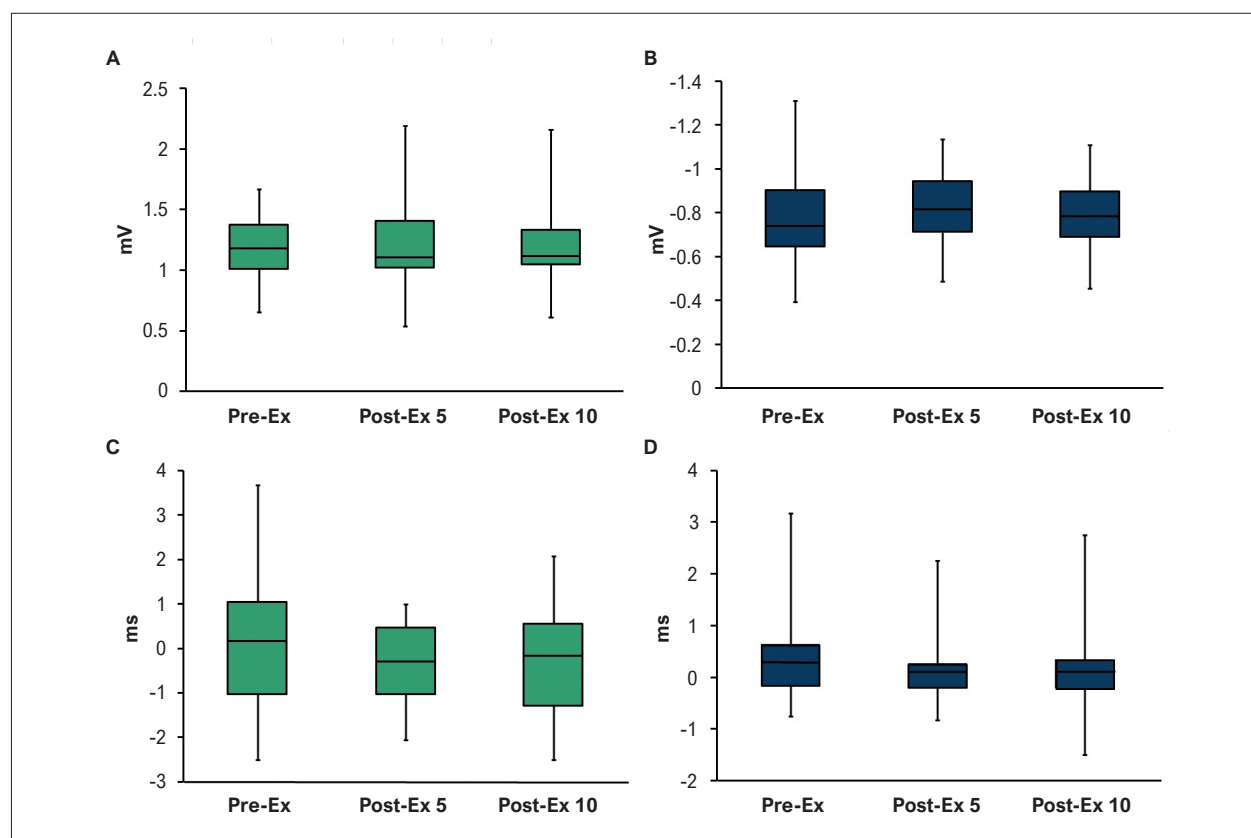


Figure 5 – Maximum amplitudes of positive (A) and negative (B) extrema on BSPMs during ventricular depolarization, and the time when positive and negative extrema reached maximum amplitudes (C and D, respectively) before and after acute exhaustive treadmill exercise. The time is shown relative to the RII wave peak. Data are expressed as median, first and third quartiles, minimum and maximum (n = 20). Pre-Ex: before exhaustive exercise; Post-Ex 5: 5 minutes after exhaustive exercise; Post-Ex 10: 10 minutes after exhaustive exercise. Friedman test, $p > 0.05$.

Changes in the spatial distribution of cardiac potentials on the body surface, during ventricular depolarization, are indicators of alterations in the direction of excitation wavefronts in the heart ventricles.^{16,36} Miller et al.³⁷ observed significant changes in the migration trajectory of negative extremum, as well as the appearance of additional anterior positive extrema on BSPMs during the QRS complex at maximal exercise in healthy subjects, which they considered to be due to a delay in the activation of the left ventricular free wall, relative to the onset of excitation in the right ventricle and intraventricular septum.

Takala et al.³⁸ disclosed no changes in spatial patterns of QRS-time BSPMs after maximal exercise in healthy individuals. In the present study, spatial BSPM patterns during ventricular depolarization were similar to those previously observed in healthy Wistar rats.³⁹ The locations of areas and extrema, and their dynamics on BSPMs at Post-Ex 5 and Post-Ex 10 were almost identical to those at Pre-Ex, which suggested that the main direction of the activation wave in rat ventricles did not change greatly with acute exhaustive treadmill exercise.

In rats, the first inversion of potential distributions on the BSPMs, during ventricular depolarization, is caused by a breakthrough of the excitation wave on the subepicardium of both the base of the right ventricle and the apex of the

left ventricle, and the second inversion resulted from the change in the direction of the activation wave towards the base of the left ventricle and the excretory cone of the aorta.¹⁹ During the initial phase of ventricular depolarization on BSPMs, the excitation wave, in rats, spreads through the conducting system and then moves through the myocardium in an endo-epicardial direction. During the middle and terminal phases of ventricular depolarization on BSPMs, there is an excitation of the main mass of the ventricular myocardium, and the base of the left ventricle, respectively.¹⁹ In this study, at Post-Ex 5, in comparison with Pre-Ex, an earlier completion of the second inversion of potential distributions, an earlier completion of ventricular depolarization, as well as a decrease in the duration of the middle phase and the overall duration of ventricular depolarization were demonstrated on BSPMs, which appears to have resulted from a decrease in the activation duration of the main mass of the ventricular myocardium. At Post-Ex 10, temporal parameters of BSPMs did not differ from those at Pre-Ex. Thus, in the present study, the changes in the temporal BSPM characteristics, subsequent to acute exhaustive treadmill exercise, were caused by a reversible reduction in the duration of the middle phase of ventricular depolarization, while the durations of the initial and terminal phases remained essentially unchanged.

Compared with conventional electrocardiography, body surface potential mapping allowed a more accurate identification of the stage of ventricular depolarization, the duration of which was considerably altered as a result of exhaustive treadmill exercise in rats.

Regarding the effect of strenuous exercise on the amplitude of BSPM parameters, Mirvis⁴⁰ described a reduction in the amplitude of positive extremum and an increase in the amplitude of negative extremum on isopotential maps of the anterior surface of the thorax at different points of the QRS complex during submaximal exercise in healthy subjects. Other authors³⁷ revealed the decrease in the maximum amplitude of the positive BSPM extremum during QRS, with maximal exercise in healthy volunteers, which they surmised was a result from the changes in activation wavefronts in the left ventricular wall. In our study, the maximum amplitudes of positive and negative BSPM extrema during ventricular depolarization, and the time when the extrema reached maximum amplitudes, did not alter significantly after exhaustive treadmill exercise. Meanwhile, compared with those at Pre-Ex, the amplitude of negative BSPM extremum in the instant of R_{II} -peak and 3 and 4 ms after R_{II} -peak changed at Post-Ex 5. The exact causes of these changes are unclear. As we have shown, in the moment of 3 ms after R_{II} -peak, the second inversion of potential distributions on BSPMs was still continuing at Pre-Ex, whereas it was already completed at Post-Ex 5. Therefore, the decrease in amplitude of the negative BSPM extremum 3 and 4 ms after R_{II} -peak at Post-Ex 5 as compared with those at Pre-Ex may be associated with an earlier completion of the second inversion of potential distributions on BSPMs.

In summary, according to the results, this is the first study to show the body surface potential distributions during ventricular depolarization following acute exhaustive exercise in rats. We suggest that the transient changes in temporal and amplitude characteristics of BSPMs observed in rats, after treadmill running until exhaustion, were physiological and reflected the electrical behavior of the heart at strenuous physical exercise.

The present study has limitations. First, our results are restricted only to young adult male rats and cannot be applied directly to the population of laboratory rats as a whole. Second, in the current study, the recording of the heart electrical activity was performed in zoletil-anesthetized animals. Although it has been shown that zoletil has a minimal cardiovascular effect,⁴¹ the influence of this anesthetic on the obtained data cannot be completely excluded.

Conclusion

In conclusion, our data showed that acute treadmill exercise until exhaustion did not alter the spatial pattern of body surface potential distributions during ventricular depolarization but induced the decrease in the duration of the middle phase, and the total duration of ventricular depolarization, as well as the changes in the amplitude of negative extremum of BSPMs during ventricular depolarization in rats.

Author Contributions

Conception and design of the research, Acquisition of data and Critical revision of the manuscript for important intellectual content: Ivonin AG, Smirnova SL, Roshchevskaya IM; Analysis and interpretation of the data: Ivonin AG, Roshchevskaya IM; Statistical analysis and Writing of the manuscript: Ivonin AG.

Potential Conflict of Interest

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

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Study Association

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

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Applicability of Body Surface Potential Mapping Through Exercise in Small Animals

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Short Editorial related to the article: *Body Surface Potential Mapping during Ventricular Depolarization in Rats after Acute Exhaustive Exercise*

The electrical potentials of the heart have been recorded for over a hundred years to represent the distribution of these internal electrical events on the torso surface. Such recordings that started with Waller tried to establish a resultant vector from a bipolar source, the “heart vector,” assuming that this distribution of potentials would act as if an electrical bipole was inserted inside the thorax and applied to the body surface, with a third electrode adding the sagittal component of the vector. The three would be enough to supply all the electrocardiogram (ECG) information extracted from measurements from the body surface. It was not until the 1930s and 1940s that the number of electrodes on the chest surface was tentatively increased to detect events occurring in cardiac areas near the precordial leads. Finally, after 1950 some studies demonstrated that the complexity of the electrical information generated inside the heart was far greater than that generated by a sole bipole, with multiple wavefronts in the ventricles creating currents that flow into and from the heart in several places; the potentials, therefore, would exhibit maximum and minimum distributions varying with time, usually located in areas unexplored by the conventional electrocardiogram.

New methodologies complementing the ECG and vectorcardiogram (ECG) added new electrodes (dorsal and right precordial leads), and, since Wilson, the 12-lead ECG started to have three bipolar and three unipolar modified leads in the frontal plane, in addition to six unipolar (precordial) leads on the anterior chest, which can record most of the information about electrical events in the heart. However, the myocardial electrical activity global expression cannot be captured without a larger number of simultaneously recorded leads.

The body surface potential mapping (BSPM) can provide, spatially and noninvasively, in great detail, both the electrical non-bipolar components and the bipolar component of the cardiac electrical activity. It is responsive to regional events inside the heart by capturing the distribution of potentials on the body surface and evaluating the various aspects within the cardiac field.

Keywords

Exercise; Physical Conditionning, Animal; Body Surface Potential Mapping; Myocardial; Rats; Heart Ventricle.

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Manual assessment of a large number of electrograms recorded simultaneously demands computerized processing, and for this reason, it was only in the 1960s that the BSPM became usable in medical practice. Several systems were developed in the 1970s and 1980s to deploy electrodes across the torso.

In Brazil, the experience with the BSPM methodology began early in the 1990s,¹⁻³ when we could acquire the 87-lead Fukuda Denshi 7100 equipment, the first to be manufactured in the world; we were trained for its use at the manufacturer's premises in Japan (Tokyo).

During the last three decades, thereby, we developed pioneering studies in all the specialties of Cardiology, including our partnership with colleagues developing doctoral theses at InCor HCFMUSP.⁴⁻¹³

The Biomedical Engineering Department of InCor HCFMUSP has been working on the development of a fully nationalized 64-lead BSPM equipment since 2016, with the contribution of the Electrocardiography Unit of InCor.

The first experiences with the BSPM analysis with this new equipment, including vectorcardiography, have already been approved and published.^{14,15}

The evolution of BSPM utilization has been very promising, especially from the experimental viewpoint, since it enables placing a much bigger number of electrodes than with standard ECG and forward evaluation of isopotential and isochronal maps.

In the article by the Russian group headed by Dr. Irina Roshchevskaya,¹⁶ who has deep knowledge in experimental work with Electrocardiography in small animals, we find interesting experiences, such as using BSPM in small animals with a very challenging adaptation of electrodes; this work brings us an innovative experience in this field.

The authors evaluated the electrical activity of the heart of untrained rats during ventricular depolarization after the performance of acute exhaustive exercises on a treadmill using the BSPM combined with the standard ECG.

Using isopotential maps obtained from the BSPM to assess the heart's electrical activity during ventricular depolarization is an extensively studied tool. The novelty of this study is the use of this resource in rats submitted to exhaustive physical exercise. BSPM evaluation of these animals under such conditions did not reveal any alteration of the spatial pattern of body surface potential distribution during ventricular depolarization. What could be seen was a decrease in the duration of the middle phase and in the overall duration of the ventricular depolarization, as well as in the amplitude of BSPM negative extremum.

The results showed that this activity causes reversible alterations of BSPM temporal features and amplitudes during ventricular depolarization, which are related to alterations

of the main ventricular myocardial mass excitability. These findings may contribute to the analysis of cardiac electrical activation in high-performance athletes.

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F Wave Amplitude as a Predictor of Thromboembolism and Success of Electrical Cardioversion in Patients with Persistent Atrial Fibrillation

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Abstract

Background: Atrial fibrillation (AF) is classified according to the amplitude of fibrillatory waves (f) into fine waves (fAF) and coarse waves (cAF).

Objectives: To correlate the amplitude of f waves with clinical, laboratory, electrocardiographic, and echocardiographic variables that indicate a high risk of thromboembolism and to assess their impact on the success of electrical cardioversion (ECV).

Methods: Retrospective, observational study that included 57 patients with persistent non-valvular AF who underwent ECV. The maximum amplitude of f waves was measured in lead V1. cAF was defined when $f \geq 1.0\text{mm}$ and fAF when $f < 1.0\text{mm}$. The findings were correlated with the indicated variables. Values of $p < 0.05$ were considered statistically significant.

Results: cAF ($n = 35$) was associated with greater success in ECV (94.3% vs. 72.7%, $p = 0.036$) even after adjusting for variables such as age and BMI ($p = 0.026$, OR = 11.8). Patients with fAF ($n = 22$) required more shocks and more energy to revert to sinus rhythm ($p = 0.019$ and $p = 0.027$, respectively). There was no significant association between f-wave amplitude and clinical, echocardiographic, and laboratory parameters.

Conclusions: The amplitude of f wave was not associated with echocardiographic, clinical and laboratory parameters that indicate a high risk of thromboembolism. cAF was associated with a higher chance of success reverting to sinus rhythm employing ECV. A greater number of shocks and energy were required for reversion to sinus rhythm in patients with fAF.

Keywords: Atrial Fibrillation; Electrocardiography; Thromboembolism; Electrophysiology.

Introduction

Atrial fibrillation (AF) is classified, according to the amplitude of the fibrillatory waves (f), into fine wave AF (fAF) and coarse wave AF (cAF). There is great controversy regarding the value of f-amplitude as a marker for inferring risks and contributing to the direction of therapeutic strategies in patients with AF.¹⁻⁴

The objective of this study was to evaluate the relationship between the amplitude of f waves and the risk of thromboembolism determined by the clinical, laboratory, electrocardiographic, and echocardiographic parameters, as well as to assess their impact on the outcome of electrical cardioversion (ECV) in patients with persistent non-valvular AF (NVAF).

Methods

This was a retrospective, observational study based on the analysis of medical records of 57 patients approved by the local research ethics committee.

Patients of both genders with persistent NVAF (duration > 7 days, not previously reversed) undergoing ECV with or without success and who had pre and post-ECV electrocardiogram (ECG) (performed immediately before and 1 hour after ECV, respectively) were included in the analysis.

Exclusion criteria were: atrial flutter, patients who had pharmacologic cardioversion, and non-interpretable ECG.

Electrocardiographic analysis

Pre and post ECV ECG, recorded at a speed of 25 mm/s, were digitized. F wave amplitude was measured in lead V1 using the CardioCalipers® 3.3 program. AF was classified according to the amplitude of f waves in cAF, when the maximum amplitude was $\geq 1.0\text{mm}$, and fAF when $< 1.0\text{mm}$, measured by the maximum wave deflection by the previously described technique (Figure 1).⁵ The maximum amplitude of the f (f-max) wave in V1 was calculated with signal magnification up to 10x for better accuracy (Figure 2). They were always identified within the T-QRS interval, paying attention to the correct distinction between U and

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T waves. Measurements were performed by two independent examiners who were blinded to the results of the transesophageal echocardiogram (TEE) and ECV.

The duration of the p wave in lead II and the terminal deflection of the p wave in V1 (Morris index) were analyzed on the ECG after ECV, according to the technique described by Peter et al.⁵

Conducting and analyzing the TEE

The TEE was performed with a *General Electric* echo with a transesophageal transducer. The acquisition of images followed

the guidance of the institutional echocardiography section and was based on current guidelines.⁶

Data such as left atrium (LA) size and volume, ejection fraction (LVEF), presence of thrombus/spontaneous contrast, and left atrial appendage (LAA) flow velocity were obtained. Spontaneous contrast was defined by the presence of swirling “smoke” in the atrial cavity and classified as discrete (when seen only with high signal gain) and significant (when it occupied a large part of the atrial cavity and visualized even with low signal gain). Atrial thrombus was defined as a circumscribed, uniformly consistent and echo reflective intracavitary mass, different from



Figure 1 – AF subtypes based on the amplitude of f waves in V1. At the top, cAF. On the bottom, fAF. Source: personal archive.

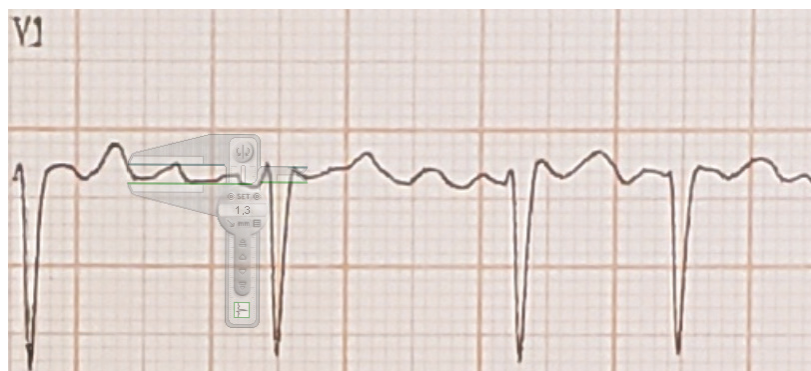


Figure 2 – Calculation of wave f amplitude from peak to valley. Source: personal archive.

the atrial endocardium and pectineal musculature and present in more than one imaging plane.

Conducting and analyzing the ECV

Prescription of antiarrhythmic drugs for at least one week before ECV was allowed. Patients could also be on adjunctive medications depending on underlying clinical conditions and control of the ventricular response.

Shocks were performed by an attending physician, blinded to the TEE result, as long as the patient had been on a direct-acting oral anticoagulant (DOAC) or vitamin K antagonist (target INR between 2-3) for at least 3 consecutive weeks. A biphasic direct current cardioverter was used with paddles placed in the anterior chest region (second right intercostal space) and left midclavicular line (sixth intercostal space). The shocks were synchronized with the peak of the R wave and performed with increasing intensities of energy. The protocol was interrupted after sinus rhythm was reestablished or after the loading applications had ended.

In case of immediate recurrence, the procedure was repeated following the same protocol. When considering failure, the control of the ventricular response was performed. Success was defined as the maintenance of sinus rhythm for at least 1 hour after the procedure. Oral anticoagulation was continued for at least 4 weeks after ECV.

Statistical analysis

Quantitative variables were expressed as mean and standard deviation or median and interquartile range (IQR), according to data normality, and categorical variables as absolute frequency and percentage.

To analyze the difference between groups, the *t*-Student test was used for independent samples or the non-parametric Mann-Whitney test for quantitative variables (depending on the assumption of normality of the data assessed by the Kolmogorov-Smirnov test). For categorical variables, Fisher's exact test was used.

A ROC curve was fitted to assess the discriminative power of the maximum amplitude of f waves measured in V1 in the success of the procedure. To determine the cutoff point, the Youden criteria were considered.

A logistic regression model was used for uni and multivariable adjustment of maximum f as a predictor of success in ECV. In the multivariable model were included explanatory variables with *p* values < 0.10 in the univariable analysis or the comparison of the cAF and fAF groups.

The correlation coefficient of agreement (CCC) and C.b (*correct bias*) were used to measure intraobserver and interobserver agreement, respectively.

The sample size was calculated based on evaluating the first 20 patients included in the study. Of these, 2 were unsuccessful in ECV (10%), and 18 were successful (90%), with average f-max in V1 respectively equal to 0.45 mm and 1.01 mm (SD $\pm$ 0.37 mm). Considering the significance level of 5%, test power of 90% and allocation of 9 to 1 (assuming that in every 10 patients, 9 are successful), to detect a difference of 0.56 mm in f-max in V1 in comparison to successful and unsuccessful cases, a total of

53 cases would be required. The calculation was performed using the Stata/SE v.14.1 program, StataCorpLP, USA.

Data were analyzed using SPSS version 19.0. The significance level adopted was 5%.

Results

Of the 92 selected patients, only 57 met the eligibility criteria. In 8 (14%; 95% CI: 5.0%-23.1%) of them, ECV was not successful (Figure 3).

Clinical features

Patients were predominantly elderly males. The most frequent comorbidity was hypertension, and more than half had CHA₂DS₂VASc $\geq$ 2. The most used anticoagulant was warfarin, and five patients were on DOACs. Most were pre-treated with amiodarone and were using β -blockers (Table 1).

Laboratory and echocardiographic features

The mean LVEF was preserved. Only 7 patients (12.3%) had LVEF < 40%. Despite anticoagulation, thrombus and/or significant spontaneous contrast in the LA were observed in 35 patients. The mean values of pre-ECV pro-BNP and C-reactive protein (CRP) were high (Table 1).

Electrocardiographic characteristics

The amplitude of the f-max waves measured in V1 ranged from 0.3 to 2.9 mm. The Morris index was altered in most patients who had restored sinus rhythm, and the mean duration of the P wave in lead II in these patients was high (Table 1).

Features based on the amplitude of f waves

There were no differences between groups regarding clinical and echocardiographic characteristics, except for weight. The fAF group consisted of patients with higher weight values than the cAF group (Table 1).

ECV success

None of the parameters interfered with the success of ECV. Only the presence of cAF favored this outcome (94.3% vs. 72.7%, *p* = 0.036; OR 6.17; 95% CI 1.21-34.5) (Table 2 and Figure 4).

An operational curve was fitted to determine the best cutoff point for maximum f in V1 associated with the success of ECV. The value of 1.0 mm was the one with the best accuracy (Figure 5).

Patients with fAF received a median of 3 (IQR 2-3.5) shocks compared with 2 (IQR 1-3) in the cAF group (*p* = 0.019). When analyzing only those with successful ECV, the fAF group required a greater number of shocks to revert to sinus rhythm [3 (IQR 1-3) vs. 2 (IQR 1-2), *p* = 0.064] (Figure 6). Likewise, the maximum and cumulative energies (sum of loads) used for reversion to sinus rhythm were higher in the fAF group [150J (IQR 150-200J) vs. 150J (IQR 100-150J), *p* = 0.027 and 320J (IQR 200-450J) vs. 200J (IQR 100-300J), *p* = 0.020; respectively] (Figure 7).

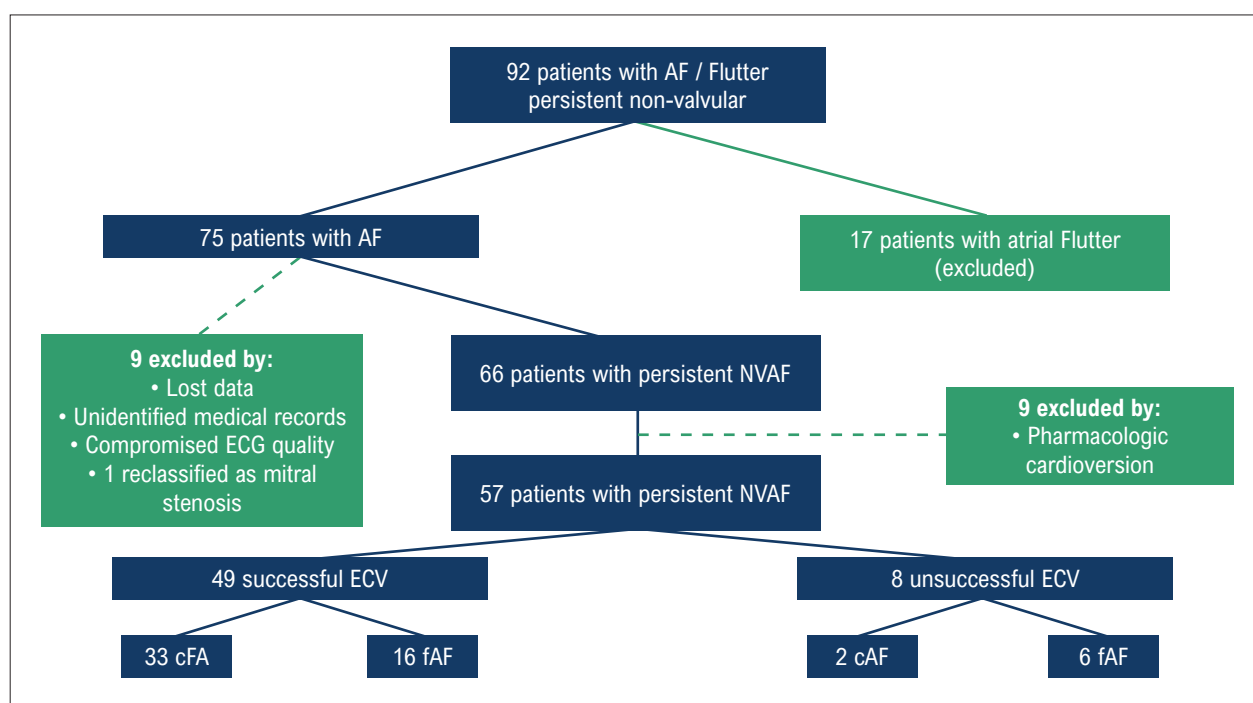


Figure 3 – Study flowchart. AF: atrial fibrillation; ECG: electrocardiogram; NVAF: non-valvular AF; cAF: coarse f-waves atrial fibrillation; fAF: fine f-waves atrial fibrillation; ECV: electrical cardioversion.

In the multivariable analysis, the presence of cAF was associated with the success of ECV ($B = 2.470$, $p = 0.026$), regardless of age and BMI, favoring reversion to sinus rhythm by 11.8 times.

Intra and interobserver variability

The calculation of intraobserver variability showed CCC and C.b of 0.90 and 0.98 for maximum f in V1, respectively. Likewise, the CCC and C.b values for interobserver variability were 0.90 and 0.98, respectively.

Discussion

In the present study, the amplitude of f waves was not associated with the clinical, laboratory, and echocardiographic parameters suggestive of increased risk of thromboembolism. However, it contributed to the prediction of reversion to sinus rhythm using ECV.

Several factors that increase the risk of thromboembolism in patients with AF are related to each other, making individual analysis difficult as independent factors. In the studied sample, all patients were on full anticoagulation (most were on warfarin and had strict pre-ECV INR control). In the publications that proposed to evaluate the correlation between f amplitude and thromboembolism, no sample consisted of 100% of patients adequately anticoagulated. In the study conducted by Icen et al.,⁷ for example, 89% of the patients were using anticoagulants and reports of thromboembolic events were described in patients outside the anticoagulation range. In the study of Nakagawa et al.,⁸ only 54% of patients were on full anticoagulation. In

the research carried out by Yamamoto et al.,⁹ only those with spontaneous contrast or thrombus were indicated for anticoagulation (75%). All these studies showed percentage differences in anticoagulant therapy between groups defined based on f amplitude.

Despite adequate anticoagulation in all patients in the sample, 56.1% had significant spontaneous contrast, and 8.8% had LA thrombus, showing that other mechanisms not treated by anticoagulation would still be present, increasing the risk of thromboembolism. Even so, there was no significant correlation between these findings and the amplitude of f waves, a fact also found by Nakagawa et al.⁸ Similarly, the presence of spontaneous contrast was not associated with f amplitude in the analysis by Yamamoto et al.;⁹ however, the authors reported a higher percentage of patients with LA thrombus and thromboembolic events in the fAF group, which can be explained by the lower percentage of patients on anticoagulation in this group during follow-up.

Contrary to these findings, Li et al.¹⁰ found a relationship between cAF and the presence of spontaneous contrast, LA thrombus and LAA dysfunction. Although both groups were more uniform concerning anticoagulant therapy, the authors did not report on differences in the CHA₂DS₂VASc score between them, which could influence the variation in thrombogenesis. In addition, there was a difference of one month between the performance of the TEE and the ECG, which may have contributed to the findings. In the present study, patients with cAF and fAF had similar values for CHA₂DS₂VASc, age, BMI and other clinical parameters. All were on anticoagulation, and the TEE and ECG were performed simultaneously.

Table 1 – General characteristics and based on the maximum f amplitude in V1

Variable	General population N=57	cAF (f-max V1 ≥ 1 mm) N=35 (61.4%)	fAF (f-max V1 < 1 mm) N=22 (38.6%)	p*
Age (years)	61.53±10.86	61.43±12.41	61.68±8.07	0.933
Male gender	40 (70.2%)	23 (65.7%)	17 (77.3%)	0.391
Weight (Kg)	86.1±22.8	81.0±18.13	94.23±27.31	0.032
Body surface (m ²)	2.79±0.28	1.90±0.25	2.05±0.30	0.054
BMI (Kg/m ²)	29.77±6.04	28.44±4.62	31.88±7.42	0.061
Hypertension	47 (82.5%)	27 (77.1%)	20 (90.9%)	0.287
Diabetes	14 (24.6%)	8 (22.9%)	6 (27.3%)	0.758
CAD	9 (15.8%)	4 (11.4%)	5 (22.7%)	0.286
HF	4 (7.0%)	4 (11.4%)	0 (0%)	0.151
Stroke	7 (12.3%)	4 (11.4%)	3 (13.6%)	1
PAD	4 (7.0%)	3 (8.6%)	1 (4.5%)	1
CHA ₂ DS ₂ VASc	2 (1–3)	2 (1–3)	2 (1–3)	0.880
0	5 (8.8%)	3 (8.6%)	2 (9.1%)	
1	17 (29.8%)	11 (31.4%)	6 (27.3%)	
≥ 2	35 (61.4%)	21 (60%)	14 (63.6%)	
AF duration (days)	210 (90–365)	210 (90–365)	225 (60–365)	0.938
Warfarin	52 (91.2%)	31 (88.6%)	21 (95.5%)	0.639
DOAC	5 (8.8%)	4 (11.4%)	1 (4.5%)	
Amiodarone	54 (94.7%)	34 (97.1%)	20 (90.9%)	0.553
Propafenone	3 (5.3%)	1 (2.9%)	2 (9.1%)	0.553
β-blocker	42 (73.7%)	26 (74.3%)	16 (72.7%)	1
LVEF (%)	55.44±11.55	54.09±13.64	57.59±6.85	0.948
LA diameter (mm)	46.91±5.14	47.20±5.31	46.45±4.94	0.599
LA indexed volume (ml/m ²)	52.38±13.73	53.57±14.57	50.38±12.28	0.405
LAA flow speed (cm/s)	30.26±9.69	28.71±8.99	32.83±10.49	0.125
Spontaneous contrast	32 (56.1%)	20 (57.1%)	12 (54.5%)	1
LA thrombus	5 (8.8%)	4 (11.4%)	1 (4.5%)	0.639
Pre-ECV pro-BNP	1090 (595–1960)	1280 (565–2450)	870 (626–1344)	0.254
Pre-ECV CRP	0.61 (0.30–1.10)	0.50 (0.25–1.00)	1.10 (0.50–1.50)	0.070
Pre-ECV INR	2.73 (2.47–3.28)	2.73 (2.50–3.29)	2.63 (2.43–3.21)	0.948
Maximum F in V1 (mm)	1.11±0.51	1.41±0.41	0.64±0.16	<0.001
Post-ECV Morris Index	29 (58%)	21 (63.6%)	8 (47.1%)	0.366
Post-ECV P wave duration in lead II (ms)	128.41±26.42	130.38±20.54	124.35±36.16	0.542

Quantitative variables described as mean ± standard deviation or median (interquartile range); categorical variables described by frequency (percentage). *Association between cAF and fAF: t-Student test for independent samples or non-parametric Mann-Whitney test (quantitative variables); Fisher's exact test (categorical variables); p < 0.05. cAF: coarse f-waves atrial fibrillation; fAF: fine f-waves atrial fibrillation; BMI: body mass index; CAD: coronary artery disease; HF: heart failure; PAD: peripheral artery disease; AF: atrial fibrillation; DOAC: direct oral anticoagulant; LVEF: left ventricular ejection fraction; LA: left atrium; LAA: left atrial appendage; ECV: electric cardioversion; BNP: brain natriuretic peptide; CRP: C reactive protein; INR: international normalized ratio.

In the present sample, patients with mitral stenosis were not included. The reason is that blood stasis caused by flow obstruction in the mitral valve predisposes to echocardiographic changes, which in this case would be more related to the obstructive factor itself than to the amplitude of the f waves. Particularly, patients with stenosis have dilated and

hypertrophic LA, with increased atrial intracavitary pressure. Since patients with mitral stenosis are mostly of rheumatic etiology and present younger age and fewer comorbidities, despite being larger, the atria are less electrically remodeled, generating larger reentrant circuits, which are expressed by a more prominent resultant vector in the ECG (cFA).^{11–13}

Table 2 – Association among echocardiographic, laboratory and electrocardiographic parameters with success in electric cardioversion

Variable	N (57)	Success N=49 (86%)	Failure N=8 (14%)	p*
Age (years)		62.55±10.40	55.25±12.22	0.088
Gender Female	17	15 (88.2%)	2 (11.8%)	
Male	40	34 (85%)	6 (15%)	0.748
Weight (Kg)		84.82±23.39	94.00±18.39	0.296
Body surface (m ²)		1.94±0.29	2.07±0.23	0.244
BMI (Kg/m ²)		29.46±6.03	31.65±6.17	0.344
Hypertension	47	42 (89.4%)	5 (10.6%)	0.126
Diabetes	14	12 (85.7%)	2 (14.3%)	0.975
CAD	9	9 (100%)	0 (0%)	0.332**
HF	4	4 (100%)	0 (0%)	1**
Stroke	7	6 (85.7%)	1 (14.3%)	0.977
PAD	4	4 (100%)	0 (0%)	1**
CHA ₂ DS ₂ VASc		2 (1–3)	1 (0.5–3)	0.200
0	5	3 (60%)	2 (40%)	
1	17	14 (82.3%)	3 (17.6%)	
≥ 2	35	32 (91.4%)	3 (8.6%)	
AF duration (days)		210 (100–370)	135 (75–270)	0.190
Amiodarone	54	48 (88.9%)	6 (11.1%)	-
Propafenone	3	1 (33.3%)	2 (66.7%)	-
B-blocker	42	37 (88.1%)	5 (11.9%)	0.443
LVEF (%)		55.67±11.68	54±11.39	0.702
LA diameter (mm)		47.24±5.11	44.88±5.19	0.229
LA indexed volume (ml/m ²)		52.67±14.12	50.29±11.32	0.665
LAA flow speed (cm/s)		29.43±8.81	35.25±13.54	0.125
Spontaneous contrast	32	29 (90.6%)	3 (9.4%)	0.262
LA thrombus	5	4 (80%)	1 (20%)	0.690
Pre-ECV pro-BNP		1195 (564–2005)	776 (649–1272)	0.607
Pre-ECV CRP		0.60 (0.25–1.10)	0.71 (0.55–1.50)	0.142
Pre-ECV INR		2.72 (2.50–3.29)	2.72 (2.24–2.95)	0.836
Maximum F in V1 (mm)		1.15±0.50	0.85±0.47	0.118
≥ 1 (cAF)	35	33 (94.3%)	2 (5.7%)	
<1 (fAF)	22	16 (72.7%)	6 (27.3%)	0.036

Quantitative variables described as mean ± standard deviation or median (interquartile range); categorical variables described by frequency (percentage). *Univariable logistic regression model and Wald test, $p < 0.05$. ** Fisher's exact test, $p < 0.05$. BMI: body mass index; CAD: coronary artery disease; HF: heart failure; PAD: peripheral artery disease; AF: atrial fibrillation; LVEF: left ventricular ejection fraction; LA: left atrium; LAA: left atrial appendage; ECV: electric cardioversion; BNP: brain natriuretic peptide; CRP: C reactive protein; INR: international normalized ratio; cAF: coarse f-waves atrial fibrillation; fAF: fine f-waves atrial fibrillation.

As for LA size, no significant differences were observed between the groups, and these findings agree with several other publications.^{8,10,14,15} This is because atrial dilation does not reliably reflect the degree of electrical, structural, and histological remodeling suffered by the atrium. In both groups, the values found for atrial diameter and volume were high, which reduced the influence of this variable on the f waves.

As for the evaluation of the LAA, we observed a reduction in the flow velocity of the LAA in both groups, however, without differences between them. The LAA contributes to atrial electrical and mechanical activity despite being a structure attached to the LA. Correlating its changes with the amplitude of f is a challenge since many factors can influence its performance, such as morphology, function (measured by flow velocity or ejection fraction), degree of fibrosis, and the area of the entry orifice.¹⁶

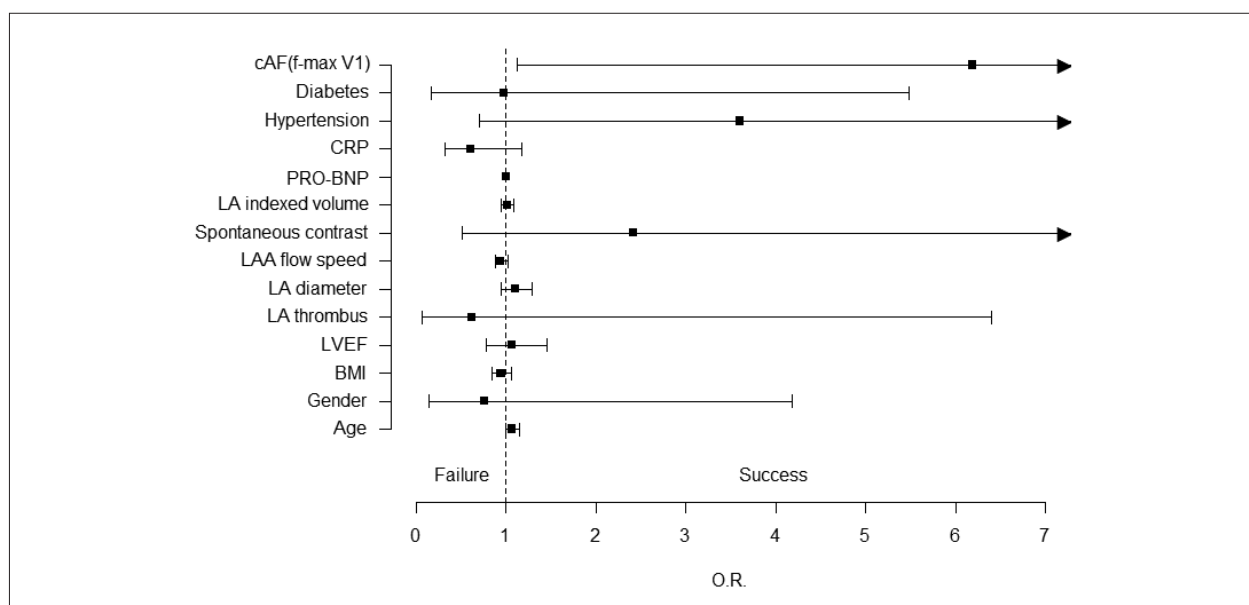


Figure 4 – Forest plot with OR and 95% CI of clinical, echocardiographic and electrocardiographic parameters related to success in electric cardioversion (univariable analysis). cAF: coarse f-waves atrial fibrillation; CRP: C reactive protein; LA: left atrium; LAA: left atrial appendage; LVEF: left ventricular ejection fraction; BMI: body mass index.

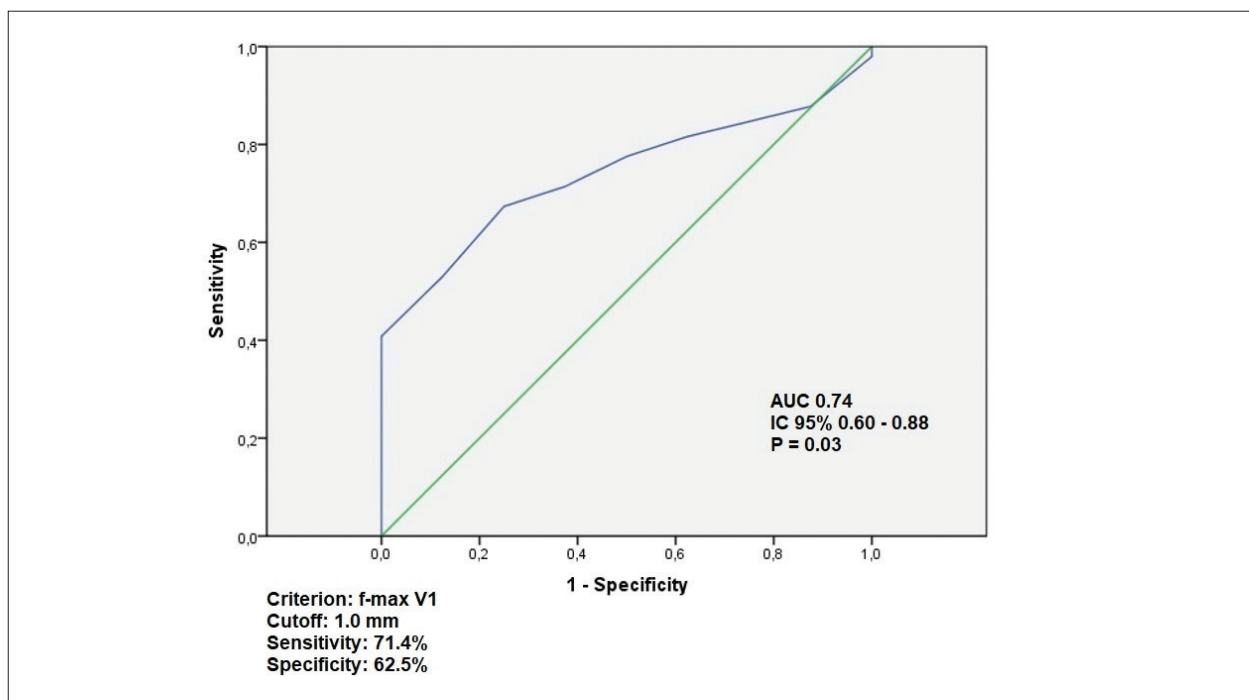


Figure 5 – ROC curve of maximum f amplitude in V1 as a successful predictor of electric cardioversion.

Li et al.¹⁰ showed a correlation between cAF in patients with NVAf, and low flow velocity in the LAA, results contradictory to those of Yamamoto et al.⁹ and Nakagawa et al.⁸ who showed an association with the fAF group. On the other hand, Blackshear et al.,¹⁴ when evaluating 53

patients involved in SPAF III, did not find a relation between the amplitude of f-waves and the flow velocity in the LAA, justifying the finding due to temporal discordance between the ECG and the TEE. In the present study, there was a satisfactory temporal correlation between these exams;

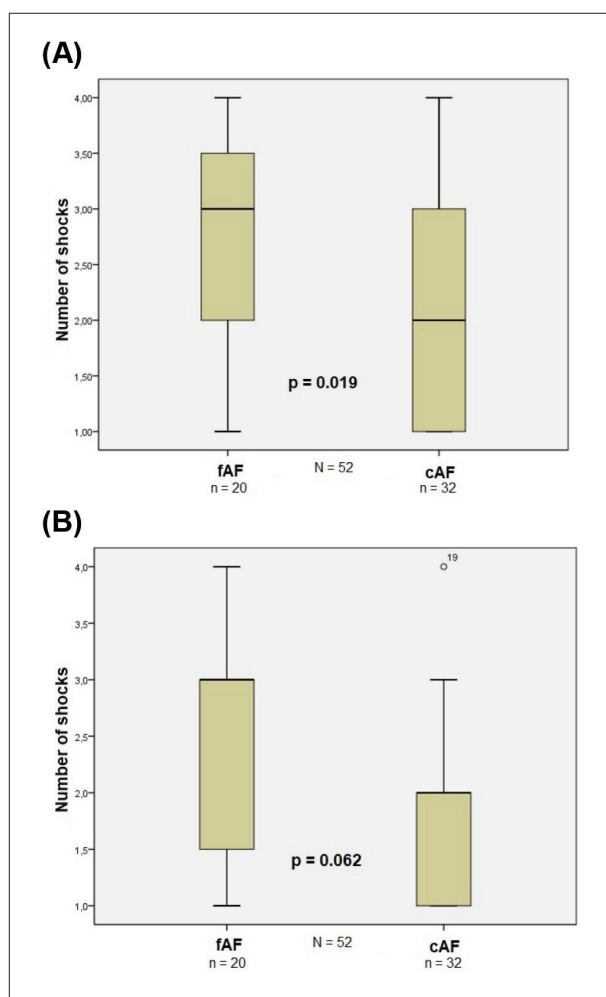


Figure 6 – Number of shocks delivered in each group (A) and number of shocks needed (B) for reversion to sinus rhythm in both groups. cAF: coarse f-waves atrial fibrillation; fAF: fine f-waves atrial fibrillation.

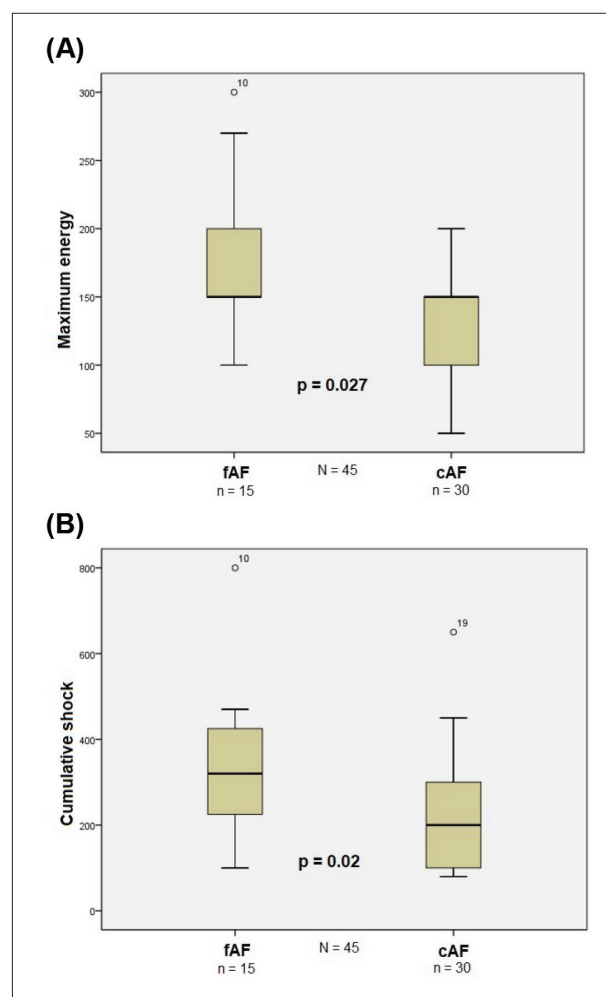


Figure 7 – Maximum (A) and cumulative (B) energies necessary for reversion to sinus rhythm in both groups. cAF: coarse f-waves atrial fibrillation; fAF: fine f-waves atrial fibrillation.

even so, no significant association was demonstrated with the amplitude of f.

Likewise, clinical variables showed no association with f-wave amplitude. The groups contained patients with similar age, sex and CHA₂DS₂VASc score, providing greater homogeneity and reducing interference with other variables. Given that the amplitude of f translates information about atrial remodeling, we would expect patients with fAF to have higher CHA₂DS₂VASc scores, duration of AF, and older ages. In this context, the sample size may have been a limiting factor.

Among the comorbidities presented, hypertension was more prevalent in the fAF group (90.9% vs. 77.1%), in agreement with the findings of Yilmaz et al.¹⁷ and Icen et al.⁷ in patients with NVAf. BMI also tended to be higher in the fAF group, which may have been a confounding factor since this relationship has not been described in the literature.

Regarding laboratory data, in the fAF group, CRP values were higher, although not statistically significant. Given

that this represents the presence of an inflammatory process and is related to the risk of stroke and prognosis in patients with AF, it is plausible to expect higher values in patients with fAF since they have more frequently remodeled atria as a result of multiple factors, including those that generate inflammation.¹⁸ On the other hand, pro-BNP levels were found to be high in both groups. This finding is frequent in patients with AF and acts as a marker of atrial heart disease, in addition to being indicative of a higher risk of stroke and death in this population.¹⁹

Similar to previous studies, the ECV success rate was 86%.²⁰⁻²² In the study conducted by Zhao et al.,²⁰ despite cAF being associated with higher rates of maintenance of sinus rhythm after 6 weeks of ECV (72% vs. 42%), there was no difference in the immediate success of the procedure between the groups (100% cAF vs. 94% fAF). However, data on mitral valve disease were not reported, which would justify the early recurrence of AF after ECV.^{23,24} In the present study, the presence of cAF was an independent predictor for immediate reversion to sinus rhythm. In

addition to higher ECV success rates, the presence of cAF resulted in the need for fewer shocks and lower maximum and cumulative energy compared to fAF. This is relevant in clinical practice as it contributes as one more factor to deciding whether or not to indicate ECV in patients with persistent AF.

It is possible that cAF is related to the presence of more viable muscle in the atria that accommodate more organized reentry circuits, facilitating the cancellation of wave fronts through cardioversion. Age, type of arrhythmia and duration of AF, factors that influence the success rates of ECV,²⁵ did not influence the discriminatory power of the amplitude of f waves because they did not differ between the groups formed.

As for the lead analyzed, we chose V1 because it is the one that most expresses changes in the atria due to proximity, for presenting higher values of the f amplitude, facilitating measurement, and for having been the lead applied by most studies published on the topic since 1966.

As for the cutoff point used to classify AF, we chose the value of 1.0 mm based on the fact that there is no significant difference between the findings when using the value of 0.5 mm and 1 mm, as demonstrated by Peter et al. and the highest value facilitates its measurement.³ Using smaller cutoff points implies more accurate measurement techniques and more measurement errors, with few gains in sensitivity and specificity.

The use of antiarrhythmic drugs as a pre-treatment before ECV was allowed for better stabilization of atrial electrical activity and to prevent early recurrence of arrhythmia.²⁴ The fact that almost all of them used amiodarone reduces the interference between the groups in the ECV result. In addition, Nault et al.²⁶ demonstrated that antiarrhythmic drugs such as amiodarone did not influence the f amplitude.

It is possible that the small sample size may have influenced the results, particularly regarding the association between echocardiographic parameters and f amplitude. Studies with a greater number of patients are needed to establish these relationships.

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Conclusions

The amplitude of f was not associated with clinical and echocardiographic changes that signal a higher risk of thromboembolism. Maximum f wave ≥ 1.0 mm measured in lead V1 was associated with a higher chance of success in restoring sinus rhythm through ECV in patients with persistent NVAf. A greater number of shocks and energy was required for reversion to sinus rhythm in patients with fAF compared with cAF.

Author Contributions

Conception and design of the research: Campelo RT, Armaganian L, Moreira DAR; Acquisition of data: Campelo RT, Scheffer MK; Analysis and interpretation of the data: Campelo RT, Armaganian L, Moreira DAR, Scheffer MK; Statistical analysis: Campelo RT, França JID; Writing of the manuscript: Campelo RT, Armaganian L, Moreira DAR, Carvalho GD; Critical revision of the manuscript for important intellectual content: Campelo RT, Armaganian L, Moreira DAR, Carvalho GD.

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 thesis of master submitted by Renan Teixeira Campelo, from Instituto Dante Pazzanese de Cardiologia.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Instituto Dante Pazzanese de Cardiologia under the protocol number CAAE: 09597319.2.0000.5462/grant: 3.244.400. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013.

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Fibrillatory Wave Amplitude: Should We Use It Routinely in Clinical Practice?

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Short Editorial related to the article: F Wave Amplitude as a Predictor of Thromboembolism and Success of Electrical Cardioversion in Patients with Persistent Atrial Fibrillation

Atrial fibrillation (AF) is the most prevalent sustained arrhythmia worldwide and is associated with an increased burden of morbidity and mortality in different clinical scenarios, even for patients with optimal anticoagulation and rate control treatment.^{1,2} Although previous studies did not show the benefit of rhythm control strategy compared to rate-control,^{3,4} recent data suggest that current rhythm control strategies, in addition to symptom control, can improve hard clinical outcomes, including mortality and stroke.^{5,6}

Rhythm control strategy refers to attempts to restore or maintain sinus rhythm and includes antiarrhythmic drugs, electrical cardioversion and atrial fibrillation ablation.⁷ Despite progressive improvement in rhythm control strategies over the years, a substantial amount of failure in maintaining sinus rhythm,⁸ mainly in patients with persistent forms of AF, underscores the importance of properly selecting patients for rhythm-control strategies.

There are well-known factors associated with increased risk of AF recurrence after cardioversion, such as older age, female sex, previous cardioversion, chronic obstructive pulmonary disease, renal impairment, structural heart disease, larger left atrial volume index, and heart failure.¹ Nevertheless, considering AF's burden on patients and the health economy, continuous efforts to improve patient selection for rhythm control remain pivotal in AF management.

In this *Arquivos Brasileiros de Cardiologia*, Campelo et al.⁹ explore fibrillatory wave amplitude as a predictor of successful electrical cardioversion and its association with multiple markers of increased thromboembolic events. They retrospectively evaluated 57 patients who had undergone electrical cardioversion. The fibrillatory wave was classified according to amplitude in lead V1. Fibrillatory wave $\geq 0,1$ mV was used to define coarse fibrillatory wave AF.

The coarse fibrillatory wave was not associated with the presence of left atrial thrombus nor spontaneous echo contrast. AF duration left atrial volume and left atrial flow velocity were similar in both groups.

Notwithstanding, the main finding of this study was the association of fibrillatory wave amplitude to electrical cardioversion success. Electrical cardioversion was performed with progressive energy increase, and acute success was defined if sinus rhythm was maintained one hour post-procedure. Although similar to many studies, this definition makes it difficult to draw broad conclusions concerning pathophysiological or clinical issues, given that immediate recurrence and absence of reversion to sinus rhythm probably have very different meanings.

In Campelo et al.⁹ population, coarse fibrillatory wave was associated to acute success cardioversion (94,3% vs. 72,7%, $p=0,036$; OR 6,17; IC 95% 1,21-34,5). In addition, maximum and cumulative energies were higher in the fine AF group. These findings are closely related to other studies showing an association of fine AF to increased prevalence of left atrial fibrosis,^{10,11} since atrial fibrosis is supposed to be an important marker of poor response to rhythm control therapies.

Concerning catheter-based ablation of AF, the most effective tool for rhythm control therapies,^{12,13} there are conflicting studies correlating fibrillatory p wave amplitude to AF ablation success. In 2009, Nault et al.¹⁴ assessed the association of fibrillatory wave amplitude with clinical, echocardiographic variables and AF recurrence in 90 patients who underwent AF ablation. An association between F-wave amplitude and AF recurrence was observed. Forty-three percent of patients with mean f wave amplitude <0.05 mV in lead V1 had AF recurrence compared to 12% of those with F-wave ≥ 0.05 mV ($p = 0.004$).

More recently, Squara et al.¹⁰ evaluated the association of fibrillatory wave amplitude to the extent of low voltage areas in 29 patients who underwent catheter ablation for AF. The fibrillatory wave amplitude was inversely correlated to the extent of left atrial endocardial low-voltage areas. However, fibrillatory wave amplitude did not predict AF recurrence after a follow-up of 23.3 ± 9.8 months.

In the context of electrical cardioversion of AF, Zhao et al.¹⁵ evaluated 94 patients stratified by fibrillatory wave amplitude and determined acute (4 h after cardioversion) and medium-term (6 weeks after cardioversion) success rates. There was no difference in acute success rate, maximal energy used or the number of shocks required. At 6 weeks, in the coarse fibrillatory wave group, 75% of patients maintained SR vs. 40% in the fine fibrillatory wave group ($p = 0.006$). Despite the difference in acute success rates, both studies show that fibrillatory waves can have a role in predicting acute or medium-term success in the rhythm control strategy.

Keywords

Atrial Fibrillation, Electric Stimulation Therapy, Practice Guideline, Heart Rate.

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Short Editorial

In summary, Campelo et al.⁹ provide further evidence in fibrillatory wave amplitude used as a marker of better response in rhythm control strategy of AF. Even with conflicting studies in this scenario, there is substantial evidence that fine fibrillatory wave is associated with the

extent of atrial fibrosis and can lead to poorer results in rhythm control therapies. However, further studies with a larger number of patients and evaluation of different strategies for rhythm control are required to be routinely used in clinical practice.

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The Electrocardiogram in the Pediatric Population in the 21st Century. How to Keep Evolving after 135 Years of the Method Discovery History

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Short Editorial related to the article: *Electrocardiographic Evaluation of Normal Newborns in the First Week of Life – Observational Study*

Knowledge of the electrocardiogram remains constantly evolving in medical practice. The new interfaces for electrocardiogram (ECG) correlation with cardiac images and heart functional changes increase the method's applicability. However, in children and adolescents, the constant change generated by these young people's body and functional development often generates doubts in the interpretation of electrocardiographic tracings, even in the most experienced professionals. Recently, important data on ECG interpretation were extensively reviewed in the IV Guidelines of the *Sociedade Brasileira de Cardiologia* on Analysis and Issuance of Electrocardiographic Reports published in 2022.¹

But what is the role of the electrocardiogram, especially applied to pediatrics, in the 21st century? What is normal for the child? What is the prevalence of electrocardiogram changes in asymptomatic patients?

A national study using the tele ECG system in the asymptomatic pediatric population aged 0 to 10 years evidences the presence of electrocardiographic alterations with the possibility of clinical repercussions. A total of 3,139 asymptomatic children aged between 0 and 10 years were evaluated, and we observed the presence of atrioventricular blocks in 0.41% and 0.44% of the ventricular pre-excitation syndrome. A prolonged QTC interval was observed in 0.35% of the population studied.² During the European Congress of Cardiology in 2022, Fuziy et al. presented data from more than 11,000 asymptomatic adolescents tracing the electrocardiographic profile of these young people. It was observed 0.5% of cardiac arrhythmias, mostly atrial arrhythmias. Electrocardiographic changes with risk of serious arrhythmias were 0.13% of ventricular pre-excitation and repolarization changes, including prolonged QT in 1.8% of the population.³

The ECG is also essential during the emergency assessment of the child in emergency care units. In these cases, correct tracing identification can allow adequate treatment and better therapeutic results.⁴ In our country, the Brazilian Guideline on Cardiac Arrhythmias in Children and Congenital Heart Diseases provides a fundamental guide for addressing rhythm disorders in this population.⁵

Data from the Davignon table, mainly on the average HR for each age group, can certainly be overestimated due to electrode fixation techniques, crying, stress from another source or adverse clinical conditions that may motivate the performance of the ECG. The use of the Davignon table as a reference for normal ECGs in children is based on a survey of 2,141 white children without symptomatic or structural alterations in Quebec City, Canada, published in 1979. Thus, tracing parameters of normality in children of other ethnicities and the result of miscegenation may show differences concerning Davignon's initial reports.

Routine electrocardiographic assessment and saturation testing in neonates could be routinely used in the first months of life with the aim of early detection of electrocardiographic alterations involved in sudden death in bed syndrome.

The use of devices (watches and cell phones) to detect changes in heart rhythm in these young people has also been gaining volume in the world's scientific production and can be applied to different age groups, including neonates. Rhythm alterations based on the analysis of the QRS complex, but not on the P wave, do not show differences concerning the ECG for rhythm analysis, with the feasibility of performing more than 94%.⁶ The different diagnostic modalities that use the ECG as a basis (Holter, exercise test, event monitor, tilt test and electrophysiological study, for example) constantly expand their indications in the pediatric population and congenital heart diseases.^{7,8}

Despite the extreme importance of the pure clinical approach, it often does not allow the physician to rule out electrical phenotypic alterations that can result in cardiovascular events in childhood and adolescence.⁹ Performing an ECG as a routine in medical practice allows the early identification of most channelopathies and also discards alterations that can worsen during sports practice and adrenergic activities that can put the lives of these individuals at risk. The ECG is a low-cost screening method and allows for the prophylaxis of sudden events, starting with early diagnosis, which strongly impacts the health of a family or community.

Keywords

Electrocardiogram; Pediatrics; Children; Arrhythmias.

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In this century, telemedicine systems allow the survey of many exams in a short period and a reliable portrait of normal electrocardiographic patterns and the density of asymptomatic electrocardiographic changes in the pediatric population. Undoubtedly, the ECG is the ideal screening method for young people to detect electrical abnormalities and structural alterations, as it has rapid feasibility, low cost, extensive technical knowledge, and accessibility in different parts of our country. Furthermore, access to centers specialized in electrocardiographic reports can detect, through telemedicine, early changes in neonates and infants, as well as risk conditions in the pre-practice

sports assessment. In a country of continental dimensions, where 65% of the most remote access municipalities are in the north and central west of the country, telemedicine represents the shortening of distance and the possibility of earlier diagnoses and more adequate therapeutic adjustments, particularly concerning channelopathies in the pediatric population.

Because of the above, we can conclude that after more than 100 years of existence, the electrocardiogram has not yet reached its peak; it has been expanding in indications and uses, changing its form of analysis and expanding its use in specific populations.

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Clinical Reasoning in Cardiology: Past, Present and Future

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Abstract

Clinical reasoning was born 2,500 years ago with Hippocrates, having evolved over the centuries, becoming a mixture of art and science. Several personalities throughout history have contributed to improving diagnostic accuracy. Nonetheless, diagnostic error is still common and causes a severe impact on healthcare systems. To face this challenge, several clinical reasoning models have emerged to systematize the clinical thinking process. This paper describes the history of clinical reasoning and current diagnostic reasoning methods, proposes a new clinical reasoning model, called Integrative Reasoning, and brings perspectives about the future of clinical reasoning.

Introduction

Clinical diagnosis was born 2,500 years ago with Hippocrates, having evolved over the centuries, and become a mixture of art and science. Many personalities throughout the history of medicine have contributed to improving diagnostic accuracy. However, diagnostic error is still very common, with previous studies in outpatient clinics in the USA showing a 5% prevalence of errors.^{1,2} Furthermore, a report from the World Health Organization (WHO) showed that about 138 million people are affected by medical errors annually, of which 2.6 million have lost their lives.³ It is known that the differential diagnostic capacity and diagnostic accuracy tend to improve with clinical experience.⁴ Recent studies however have shown that it is difficult for physicians to make assertive decisions. This phenomenon is further aggravated by the fact that clinical reasoning and cognitive processes involved in the physician's decision-making process are not well covered in medical schools' curricula.⁴ Typically, more experienced doctors will need less data to reach the same conclusion as less experienced doctors or doctors in training.⁴

Keywords

Diagnostic Errors; Cardiology; Cardiovascular System; History of Medicine.

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Teaching clinical reasoning is challenging, since it is subjective and requires multiple skills (e.g. history taking, physical examination, to order appropriate complement tests, and to think about differential diagnoses).⁵ In cardiology, the challenge is even greater, due to the overlap of symptoms between different cardiovascular diseases.⁵ Recently, many authors have suggested tools to systematize the clinical thinking process, reduce diagnostic errors and facilitate teaching to undergraduate students and less experienced physicians.⁶ Nonetheless, reviews that address clinical reasoning in cardiology in a comprehensive manner are scarce. Therefore, this paper describes the history of clinical reasoning and current diagnostic reasoning methods, and proposes a new clinical reasoning model, called Integrative Reasoning, and brings perspectives about the future of clinical reasoning.

Past

Clinical reasoning is the mental process used by physicians to generate diagnostic hypotheses for a disease. It plays an important role in the medical ability to formulate and test diagnostic hypothesis, solve problems, and make assertive decisions.⁷ Thus, it is considered the center of medical competence and an integral part of clinical practice, coupled with the experiences accumulated throughout one's career.⁸ Therefore, clinical reasoning is a continuous, non-linear, extremely complex process that requires cognitive processes, acquisition of theoretical and practical knowledge, problem-solving capacity, and metacognition.⁹

Historically, clinical diagnosis has emerged with Hippocrates (2,380 years ago, in 370 B.C.). Many physicians have made significant contributions over the history, with the discovery of diseases and their pathophysiological processes, and development of technologies to improve physical examination.¹⁰ Particularly for heart disease, the drawings of Andreas Vesalius and the description of blood circulation and cardiac physiology by William Harvey were the first steps towards the foundation of modern cardiology.¹¹⁻¹⁴ Years later, Giovanni Battista Morgagni published his great work: “*De Sedibus et Causis Morborum per Anatomen Indagatis*” (Of the sites and causes of disease, investigated by autopsy), for which he was marked as the founder of pathological anatomy, which allowed the association of autopsies with patient's clinical status.^{15,16}

The French school was another great contributor to the birth of modern cardiology. Importantly, Corvisart with the valorization of a detailed bedside anamnesis and physical examination.¹⁷ Beyond that, Corvisart reintroduced and perfected the method of chest percussion in clinical

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diagnosis, translating Leopold von Auenbrugger's manuscript "Inventum Novum" from Latin into French.¹⁷ This fact led to his recognition as the founder of clinical cardiology. Still from the French school, René Théophile Hyacinthe Laennec invented the stethoscope, an indispensable instrument to perform a thorough physical examination, capable of bringing key points for the cognitive process of formulating the diagnosis.¹⁸ Laennec coined and described several terms used until today, such as "vesicular murmur", "bronchial sounds", "crackling", "snoring", "pectoriloquy", "egophony" and "pleural friction rub".¹⁹ Another member of the French School, Marie-François-Xavier Bichat discovered the independence of the heart from the brain, the first step to understand the cardiac conduction system.^{20,21}

Moving on to the German school, Rudolf Ludwig Karl Virchow and William Osler must be acknowledged for their prominence in building medical thinking in the diagnosis of cardiovascular disease. Virchow coined terms that are still used today, such as thrombosis, embolism, agenesis, chromatin, parenchyma, myelin, leukocytosis, leukemia, endarteritis, amyloid, degeneration, and osteoid, in addition to performing the description of the mechanism of thrombus formation in blood vessels, known as Virchow's triad.^{22,23} Osler highlighted the importance of the physician-patient relationship, observation, and scientific rigor, and of assessing the patient and symptoms in detail, describing each change in the physical examination.²⁴ Another major contribution of his work was the creation of medical residency, in defense of continuous medical education.²⁵ Osler also created the so-called "Osler's Rule" - each patient should be given only one diagnosis that explains his disease - which was followed until the 20th century when patients had a low life expectancy and therefore died before they developed multiple comorbidities.²⁵

Another physician of importance was Sir Arthur Ignatius Conan Doyle, of the Edinburgh school. Sir Arthur Doyle, inspired by the art of deduction of his teacher Dr. Joseph Bell, created the character Sherlock Holmes, described as a meticulous investigator, which shows how Sir Doyle viewed the importance of constructing scripts in the formulation of diagnosis.^{26,27}

After the period of anatomopathological studies and meticulous analysis of patients' symptoms, new tools to aid diagnosis in cardiology were developed, especially the electrocardiogram (1902), by the Dutch physiologist Willem Einthoven. Then, Dr. Paul Dudley White contributed to the discovery of important electrocardiographic findings that are still part of problem lists today, with emphasis on the description of the Wolff-Parkinson-White Syndrome.^{28,29}

Another important name in the history of the development of clinical reasoning, Paul Hamilton Wood, is recognized as an icon in the transition from ancient to modern cardiology, as are Paul Dudley White and Ignacio Chávez Sánchez.^{30,31} Wood redefined the Eisenmenger Complex as a pathological state attributed to pulmonary hypertension with an inverted or bidirectional shunt, which would minimize its effects. He also described that pulmonary hypertension is capable of producing pulmonary arterial vasoconstriction,³⁰ which can be reversed by injection of acetylcholine into the pulmonary

artery, and drafted that pulmonary arterial vasoconstriction would act as a protective mechanism against acute pulmonary edema.^{31,32} Ignacio Chávez Sánchez contributed to the description of the clinical findings of pulmonary hypertension. In addition to bringing Mexican cardiology to the forefront, he laid the foundation to include humanism as the great driving force behind medical actions; this is important for the establishment of a good doctor-patient relationship and favors the collection of information in the anamnesis and physical examination.^{33,34} Finally, the cardiologist Eugene Braunwald, who developed a calculation method that later became known as the ejection fraction, which became essential to evaluate the condition of heart failure.³⁵ In 1967 Eugene Braunwald and his study group identified the main determinants of oxygen consumption: the development of tension, and the velocity and frequency of contraction.³⁶ In 1984, he created the TIMI (Thrombolysis in Myocardial Infarction) Study Group,³⁷ which involved several hospitals and compared streptokinase, an old drug, with alteplase, demonstrating the superiority of the latter, which was important for the approval of alteplase by the US Food and Drug Administration.³⁶ Important contributions to the foundation of clinical reasoning in cardiology are described in Table 1 and Figure 1.

Present

Today, clinical reasoning has been studied by researchers from various fields, such as medicine, education, clinical psychology, and cognitive psychology.³⁸⁻⁴⁰ These fields investigate the process in different ways, but are unanimous in noting that it is necessary skill for medical decision-making.³⁹ In this context, cognitive psychology studies on cognition have brought important insights into mental processes.⁴⁰ This area investigates issues such as metacognition, memory, pattern recognition, perception, attention, creativity, reasoning, and problem-solving.^{41,42} In this sense, we can state that cognitive psychology unites structural cognition with critical reasoning processes such as deductive and inductive reasoning, which generates the so-called systems thinking.

Clinical reasoning is governed by two systems of thought, known as "system 1" or general clinical reasoning, and "system 2" or clinical reasoning in particular; the interaction between these two systems determines the thinking. These systems are based on Daniel Kahneman's book, "Thinking, Fast and Slow".⁴³ System 1 is fast, automatic, impulsive, and intuitive, and often acts without voluntary control. System 2, on the other hand, is calculating, deliberate, and analytical, and is responsible for reasoning and decision making. This last system seeks to focus on the object of interest and avoid distractions to achieve a goal.⁴³

During the clinical reasoning process, pattern recognition resorts to system 1. Experienced physicians, after years of practice and case studies, tend to formulate the final diagnosis mainly through system 1, since the long journey of accumulating knowledge has allowed them to store a series of patterns, known as disease scripts. The method used by these more experienced doctors is also what Cognitive Psychology calls "heuristics", which consists in simplifying the search for solutions when faced with a problem to save the mind effort.⁴⁴

Table 1 – Centuries of work for the understanding of diagnosis in cardiology, described by physicians and their main contributions

Doctors	Contributions
Hippocrates	Pioneer in case study documentation and interpretation ¹⁰
Andreas Vesalius	Anatomical-clinical correlation is eternalized in the anatomy atlas "De Humani Corporis Fabrica". ¹¹
William Harvey	Description of the heart as a pump and of the circulatory system as a closed circuit ¹⁴
Giovanni Morgagni	Definition of mitral stenosis, angina pectoris, endocarditis in the work "De Sedibus et Causis Morborum per Anatomen Indagatis". ¹⁵
Jean-Nicolas Corvisart-Desmarets	Published the first modern treatise on cardiology and reintroduced Auenbrugger's method of chest percussion for clinical diagnosis. ^{17,19}
René Theophrile Laennec	Invented the stethoscope, described concepts of respiratory semiology (De L'auscultation médiate) and heart sounds ¹⁷
Marie François Xavier Bichat	Discovery of cardiac automatism ²⁰
Rudolf Virchow	Description of the thrombus formation mechanism, known as the "Virchow Triad". ²³
William Osler	Created the Osler's rule, founded the medical residency, and participated in the discovery of platelets. ^{24,25}
Arthur Conan Doyle	Described vasomotor changes in Tabes Dorsalis and advocated the exhaustive search for clinical data leading to diagnosis, and based on this, created the character, Sherlock Holmes. ²⁷
Paul Dudley White	Participated in the discovery of Wolff-Parkinson-White Syndrome and the creation of the American Heart Association, as well as advocated the relationship between lifestyle and coronary artery disease. ²⁹
Ignácio Chávez Sánchez	Founded the Mexican National Cardiology Institute and authored papers on syncope, essential hypertension, pulmonary hypertension, and ischemic heart disease associated with atherosclerosis. ^{33,34}
Paul Hamilton Wood	Worked with congenital heart diseases, rheumatic valve disease, and pulmonary hypertension, and wrote the book "Diseases of the heart and circulation". ³⁰
Eugene Braunwald	Described the relationship between circulating LDL level and risk of heart attack; participated in the TIMI study group that led to FDA approval of alteplase for treatment of acute coronary syndrome. ³⁷

TIMI: Thrombolysis in Myocardial Infarction; FDA: U.S. Food and Drug Administration.

On the other hand, students and doctors who have just started their careers tend to use mainly system 2, since accumulation of experience and knowledge is gradual.

Heuristics is a model of rapid, non-analytical, intuitive reasoning to unconsciously establish the relationship between patient presentation and disease patterns stored in long-term memory. Heuristics are characterized by the rapidity with which the physician raises diagnostic hypotheses.^{44,45} This activity is required in the traditional model of scientific reasoning called hypothetico-deductive reasoning, which consists of finding a solution to a problem using attempts (conjectures, hypotheses, theories) and eliminating errors.⁴⁶ This method was born in scientific epistemology, the result of discussions about inductive versus deductive methods.⁴⁷ According to this thinking, the doctor looks for a solution for a problem (disease) through possible answers, in a process of attempts, conjectures, and refutations.⁴⁷ The set of data obtained about the patient's problem is recorded and includes the first medical impression, the history, and the physical examination of the patient.⁴⁸ The hypotheses found for the case are divided into main and alternative hypotheses. The physician tests the hypotheses until finding a degree of probability that will be used to confirm the diagnosis and exclude others and guide the individualized therapeutic plan.³⁷ In this model of reasoning, the physician's experience in understanding diseases is placed as a determinant of the probability of a correct diagnosis. In this sense, researchers have begun to question how we can understand the reasoning pattern used by the experienced physician and bring it to the novice physician.⁴⁹ The intensification of research in this area began in the 1970s when studies involving clinical reasoning showed that what differentiated students from experienced physicians was not the cognitive model, but the assertiveness and quality of the hypotheses. Therefore, according to this view, the accuracy of the initial hypothesis predicts the accuracy of the diagnosis.⁵⁰

Illness scripts are the data stored in the memory, accessed when the physician is faced with a picture presented by a patient at the very beginning of the clinical reasoning process.⁵¹ The scripts are formed according to the experience lived by doctors and students, that is, they are organized based on the patterns of diseases analyzed along their trajectory. The more often the patterns are seen and discussed, the more refined the scripts become. However, the formation and establishment of illness scripts by the practitioner occur not only with the practical experience of but with studies and theoretical knowledge.^{51,52}

After learning and accumulating many scripts, when presented to a patient's disease, the physician uses of memorized diagnoses and picks the disease that quickly comes to mind because of its very similar characteristics with those seen at the occasion.⁴⁴ This quick and very intuitive process involves the so-called "cognitive bias", which is characterized by the use of shortcuts that lead in one direction to simplify thinking, i.e. a bias is a tendency or a distortion in favor or against something.⁴⁵ This may lead to an incorrect diagnosis, and consequent transmission of inappropriate information to the patient, and initiation of inadequate therapy. There are several types of biases, and in Table 2 we describe the five most

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1975	Eugene Braunwald - Estudo TIMI
1968	Paul Wood - Diseases of the heart and circulation
1954	Paul White - Coronary Heart Disease in young adults - A multidisciplinary study
1944	Ignacio S. Chavez - National Institute of Cardiology
1892	Arthur C. Doyle - The Adventures of Sherlock Holmes
1892	William Osler - The Principles and Practice of Medicine Designed for the Use of Practitioners and Students of Medicine
1884	Rudolf Virchow - Triade de Virchow
1819	René-Laennec - da l'Auscultation Médiate
1806	Jean-Nicholas Corvisart - An essay on the organic diseases and lesions
1801	Marie F. X. Bichat - General Anatomy Applied to Physiology and Medicine
1761	Giovanni B. Morgagni - De sedibus et causis morborum
1628	William Harvey - Exercitatio Anatomica de Motu Cordis et Sanguinis in Animalibus
1543	Andreas Vesalius - De Humani Corporis Fabrica
430 a.C	Hipócrates - Pai da medicina

Figure 1 – Most of these doctors have left their discoveries described in their books, which are mentioned in the figure.¹⁷

important ones in clinical practice and how to reduce their impact on diagnostic reasoning. Awareness of these biases can evoke analytic strategies to correct it, probably reducing the occurrence of diagnostic errors.^{38,56}

Similarly, the so-called “noise” is also likely to contribute to the occurrence of diagnostic errors. This concept was addressed in the book “Noise: a flaw in human judgment”, also by Daniel Kahneman, who defines this concept as “variability in judgments that should be identical.”⁴⁰ Furthermore, the book brings two main types of noise, the occasion noise, when external factors influence the decisions of an individual or a group, and the systemic noise, which describes the unwanted variability that happens when a group of experts tries to separately evaluate similar events. Having different opinions is healthy and important for medicine and knowledge building. However, when there is variability in judgments that should be identical, the diagnostic reasoning process becomes fuzzy and even more error-prone.⁴⁰ Thus, according to Kahneman, when a combination of biases and noise occurs, complex errors occur.⁴⁰

Integrative Reasoning

Based on evidence from cognitive theories, contemporary models of clinical diagnosis, and analysis of the errors mentioned in this article, we structured a proposal to approach clinical reasoning that we named Integrative Reasoning, which encompasses the steps detailed in Figure 2. The first contact with the patient consists of a detailed history and physical examination. Next, the physician must organize the most important data, formulating a symptom chart and a problem list. This step is essential to transform the complaints brought by the patients into semantic qualifiers and a case

Table 2 – The most important biases in clinical practice and how to reduce their impact on diagnostic reasoning

Cognitive biases	Description
Premature closure	Stopping to think about differential diagnoses after reaching an initial diagnosis. ⁴⁶ It is the most common type of bias in diagnostic error according to the article “Diagnostic error in internal medicine” ^{63,64}
Availability	When the diagnosis is established by the easiest hypothesis to remember, with little thought devoted to the case. ^{63,64}
Confirmation	Greater appreciation of facts that confirm the diagnostic hypothesis than those that refute it. ^{63,65}
Framing	The way data is presented to the doctor influences reasoning and can lead to error. ^{63,65}
Anchoring	The most likely diagnosis is the one that is justified by the patient's history of disease. The starting point for clinical reasoning becomes the patient's comorbidity, reducing the possibilities of other diagnoses. ^{63,64}

summary. After analyzing this last step, we proceed to the formulation of hypotheses based on previous knowledge and learned patterns, and we already think about possible differential diagnoses, considering the epidemiology. At least three differential diagnoses should be listed. If necessary, complementary exams are requested, and low, medium or

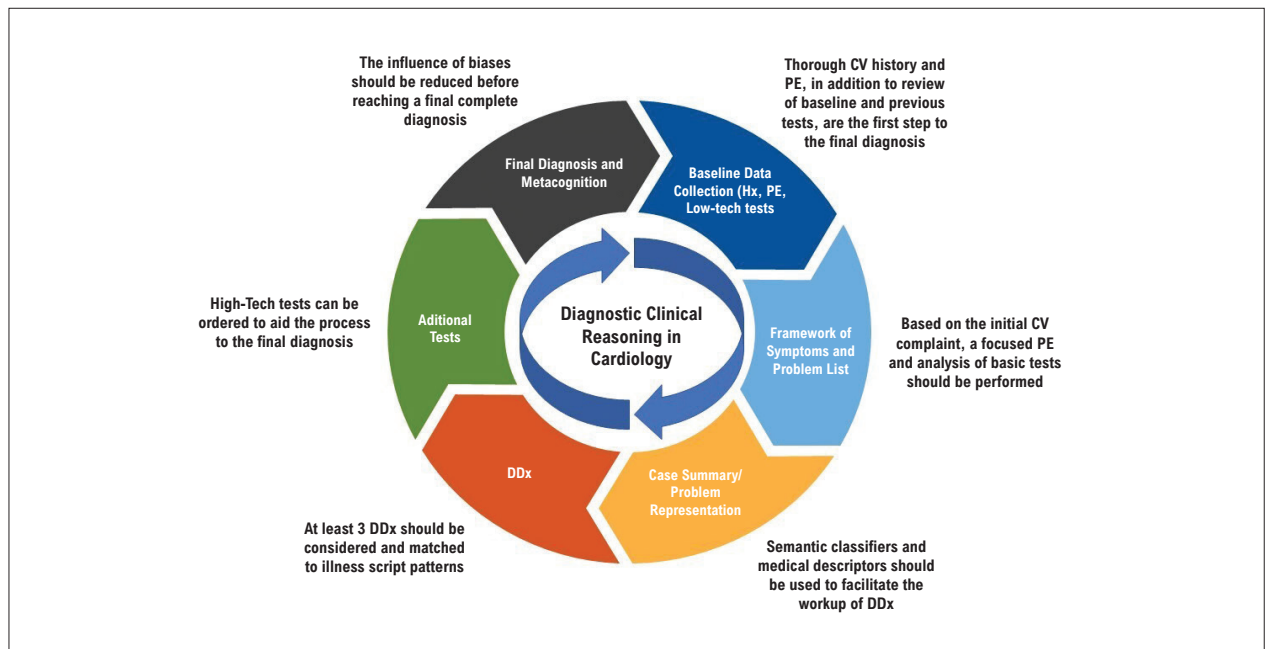


Figure 2 – Flowchart of medical reasoning in cardiology. CV: cardiovascular; Hx: history; PE: physical examination; DDx: differential diagnoses.⁶⁵

high-cost tests may be required. It is important to emphasize that, in the proposed model, when the diagnostic hypotheses are assertively made, the tests ordered will be those that are strictly necessary. After these steps, the final diagnosis is reached, but the process of metacognition must be carried out. When necessary, the physician can return to collection of data from patient's history, generate new hypotheses, and/or request new tests. In this way, the physician can add or remove new data from the problem list and generate new hypotheses and differential diagnoses. Returning to the processes already applied involves metacognition, which is defined as the human ability to monitor and self-regulate cognitive processes and is based on the human characteristic of being aware of one's actions and thoughts. Metacognition is important not only for the formulation of the final diagnosis, but also for doctors and students to recognize their limitations and difficulties, and especially to lose the fear of asking for a second opinion. This process is essential for the diagnosis of diseases, because the recurrent thinking during clinical reasoning may contain biases, noise, and lead to diagnostic error.^{40,45} Misdiagnosis is defined as the failure to establish a correct diagnosis at the appropriate time for a health problem (which may be life-threatening) or to communicate this explanation to the patient.⁵⁴ Another factor that contributes to avoiding diagnostic errors is the encouragement of learning the mental processes of clinical reasoning early on during medical training. To this end, from the beginning of medical school, students should be encouraged to establish a good doctor-patient relationship in conjunction with detailed data collection, involvement of patient and family in the diagnosis, and careful review of test results.^{54,55} A complete medical history is of paramount importance for clinical reasoning. Then, discussions of the cases should be carried out and the process proposed above be followed. It is worth emphasizing

the importance of formulating differential diagnoses, and reviewing the data collected and the proposed hypotheses. Also, students should be encouraged to practice asking for help from other professionals to discuss the case, understand the complementary exams, and formulate the final diagnosis.⁴¹ Moreover, the discussion of noise biases and diagnostic errors should be constantly promoted during training, and failure at any point of mental thinking during clinical reasoning can generate diagnostic errors.^{56,57} Furthermore, with the advance of technologies, the use of applications and websites that help in the formulation of differential diagnoses and hypotheses is inevitable and positive. However, some medical schools, especially the more traditional ones, still present a refusal to encourage these tools, and this is a barrier that must be overcome to improve the mental process of clinical reasoning of both students and physicians.^{50,57}

Future

Many tools hold promise on improving diagnostic accuracy and helping physicians to reach a final diagnosis. For example, artificial intelligence and Big Data will certainly play a role in selecting diseases with higher likelihood in each case presentation. This is the case of Isabel Healthcare,⁵⁸ a medical tool that helps doctors to come up differential diagnoses and the CHAMPION study that demonstrated the clinical effectiveness of the CardioMEMS hemodynamic monitoring system to improve clinical management of patients with symptomatic heart failure. These devices can range from simple bracelets and watches to measure oxygen saturation, blood pressure, and heartbeat, to invasive hemodynamic devices to register volume status in heart failure patients.⁵⁹ Telemedicine devices will also help to collect data and guide decision making from distance. Finally, 3D printing may one

day be used to guide cardiac surgeons to plan surgeries with precision, avoiding undesirable outcomes.^{60,61}

Conclusions

The development of clinical reasoning began centuries ago and is still in constant progression. However, this subject is not well explored by medical schools and residencies. As presented in this paper, the integrative reasoning model may serve as a simple and stepwise framework for diagnostic reasoning and removal of noise and biases, serving both experienced physicians and students in training. However, future studies are needed to validate this model.

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Physician-Researcher, Medical Practice and Research: The Importance of the Physician-Researcher in Current Medicine

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*“One does not learn, Sir, by fantasy
Dreaming, imagining, or studying
But rather by seeing, treating, and striving”*

**Luís de Camões, on military arts, in *The Lusíads*.
The same applies to the art of medicine**

Medical education and practice in Brazil suffer from countless limitations, among which lacking scientific training stands out. Recently, the physician-researcher has emerged as a figure capable of partially correcting this gap. In this paper, I will seek to evaluate the physician-researcher's role.

Conventional medicine is dedicated to the application of medical knowledge. Therefore, it deals with the general characteristics of diseases, namely, symptoms, evolution, pathophysiological impairment of organs and systems, etiology, diagnostic and therapeutic methods.

This requires conventional hospital, outpatient, and laboratory structures that make it possible to conduct diagnostic tests, such as imaging and biochemical profile. Within clinical practice, experimenting is not permitted. Practice of the medical profession is based on the judicious application of current knowledge.

One of the main difficulties in this process is that diseases do not occur as purely biological, biochemical, or physical phenomena. On the contrary, because diseases occur in people, their manifestations are dependent on the individuality of each person. Medical schools seek to show students the current state of illnesses and how they are investigated and treated. It so happens that biomedical truths change as knowledge evolves, and this is currently taking place at an amazing speed, given the evolution of research and medical knowledge. An essential aspect of medical education is the concept that we must not only teach what is known today, but also teach students to think critically in order to be able to judge published reports and to apply only well-established knowledge that is based

on high-level research. Evidently, if educators themselves do not incorporate this concept, they will not be able to transmit it to students. Therefore, the quality of medical practice depends not only on teaching, but also on the structures of the health system as a whole.

The quality of medical education in Brazil is currently inadequate. For example, the Regional Council of Medicine of the State of São Paulo (CREMESP) exam, which is taken voluntarily by students at the end of their medical course, shows an approval rate of only 50%.¹ CREMESP is limited to the state of São Paulo, which has some of the best medical schools in Brazil. It is possible to imagine what the results of a similar exam would be, were it applied to all Brazilian medical schools, many of which do not possess technical structures or qualified teaching staff. The unprecedented opening of new medical schools in the past years has been a cause of immense concern among professionals dedicated to medical education. Evidently, it is possible to expect that a large number of underqualified doctors will begin practicing the profession in the coming years. This poses a threat to the medical care of the general population.

To complicate matters further, the number of teaching hospitals is notoriously insufficient. Thus, of the 353 medical schools, only 69 (19.5%) have teaching hospitals.^{2,3} Moreover, teaching hospitals, in general, do not have structures for research training.

To summarize, it is reasonable to conclude that medical education in Brazil is, in general, of low quality. By extension, medical practice is also low-level. As there is no external control, each doctor practices the profession according to their own convictions. This results in “off-label” applications and numerous questionable procedures, such as excessive use of laboratory and imaging tests and inappropriate medication prescriptions with no proof of efficacy. This obviously overloads the health system, without any benefits for patients. It is in this context that physician-researchers are positioned, regarding both training in basic science and clinical practice.

To begin with, a researcher's training requires a special formulation. Researchers need to understand *latu sensu* scientific methodology. Specifically, they need to understand the importance of experimental models, whether benchside, animal, or clinical. Registries based on electronic medical records, with large numbers of patients, are now widely used to complement randomized studies, and they represent the so-called “real world”.⁴ Researchers need to understand the basic principles of statistics, which has become a mandatory discipline on its own. They require a deep understanding of the issue of different biases, such as sample selection and the presence of confounding factors, especially in observational studies. It is mandatory

Keywords

Physicians; Research Personnel; Schools, Medical; Education, Medical; Biomedical Research.

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Research Letter

to understand the adequacy of samples and models to answer specific questions. A very illustrative example is that of Eric Kandel,⁵ who in his magnificent book *In Search of Memory* reports that he spent fourteen months in Paris, exclusively studying the characteristics of the *Aplysia* sea slug, which proved to be the ideal model for his studies of memory. He received the Nobel Prize in Medicine or Physiology in 2000 for his discoveries on memory. In addition, modern technologies, such as molecular biology, genetics and epigenetics, Mendelian randomization, as well as various imaging techniques for organs, tissues, and intracellular structures such as molecules and paracellular and intracellular signaling have recently added powerful tools for knowledge creation.

Differently from clinical practice, research results are generally long-term, and they may take years or even a lifetime. A researcher's training is an apprenticeship in service, which involves many disciplines, whose foremost purpose is the search for the truth and the creation of new knowledge.

The physician-researcher's relevance is evident within the scope of associating clinical practice and research to create a joint, integrated view of major medical problems. This is related to efficiency, relevance, innovation, and the notion of cost/benefit. However, a certain amount of knowledge is required on the part of the physician-researcher on essential aspects of contemporary medicine: genetics and epigenetics, molecular biology, vascular biology, cellular and intracellular signaling systems, redox systems, among others. They are specifically responsible for: a) critically analyzing the results of research, whether experimental or applied, with the objective of verifying that the procedures employed are of high quality and, therefore, reliable. Recent examples of publications without a solid scientific basis are the multiple studies related to medical treatment of Covid-19; several therapeutic proposals turned out to be totally innocuous or even harmful, causing serious disorder in the treatment of this pandemic.⁶ Part of this problem is due to "pre-print" publications, which are not backed by peer review. Similar cases are those of vitamin E,⁷ hormone replacement,⁸ and antioxidants,⁹ whose hypothetical benefits have not been proven; b) interpreting and disseminating the findings of investigations to clinicians, highlighting the pros and cons of these findings; c) generating relevant protocols that can be developed in our setting; d) creating adequate means for the development of research and new technology or for the implementation of recent developments. This is perhaps the most important mission of physician-researchers. Hospitals, with the exception of teaching hospitals, are normally prepared for medical care; therefore, they do not have their own research structures. Administrative managers are usually more concerned with the finances and efficiency of

the hospital complex. However, modern concepts indicate that, when they practice clinical investigations, the quality of medical care improves. Accordingly, associating care and research is a means of learning from their own experience and maximizing the effects of their work. It is a way to avoid repetitive errors, through constant and critical evaluation of an institution's procedures. This is a trend in modern medicine.

These functions of the physician-researcher are essential in translational medicine,¹⁰ ranging from the dissemination of basic findings to the elucidation of pathophysiological mechanisms and clinical syndromes and, above all, shortening the period between discoveries of basic sciences and their clinical application. Therefore, the role of the physician-researcher is essential to qualified practice of the medical profession, as well as to the scientific development of the country.

In conclusion, physician-researchers can play a fundamental role in improving teaching and medical practice. Their knowledge of the scientific method can contribute to judicious medical practice, based on truly qualified investigations.

Fortunately, in recent years, we have observed an increasing number of physician-researchers in Brazil. However, these numbers are still insufficient. Therefore, we must encourage scientific initiation and qualified postgraduate courses in Brazil and abroad and, above all, adapt medical schools not only to exercise their traditional role, but also to create research structures.

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Heart Failure Mortality during COVID-19 Pandemic: Insights from a Cohort of Public Hospitals in Brazil

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Introduction

Brazil is one of the most hit countries by the pandemic caused by the novel coronavirus (Coronavirus Disease, COVID-19), with more than half million deaths in June, 2021, the world's second-highest number of deaths.¹ It has been reported that the COVID-19 outbreak has affected the delivery of care of patients without COVID-19 (non-COVID-19 patients), particularly patients with cardiovascular (CV) diseases, increasing the death toll from the pandemic. Studies have shown a reduction in hospitalizations in tandem with an increase mortality from CV diseases during the outbreak in many countries.²⁻⁸ However, most of these reports focused on patients with acute coronary syndrome (ACS) in developed countries, with few data on heart failure (HF) admissions, and the reasons for the worse mortality are not well understood. We evaluated the changes in severity, reasons for decompensation and 30-day mortality of patients admitted for HF in public hospitals included in the Best Practices in Cardiology (BPC) program in Brazil during the COVID-19 outbreak and compared with previous periods.

Keywords

Cardiovascular Diseases/complications; Pandemic; COVID-19; Heart Failure; Public Hospitals; Mortality; Delivery of Health Care/methods

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Methods

We performed a cohort study using data from the BPC program, which is an ongoing program adapted from the Get With The Guidelines initiative, to improve quality of cardiovascular care and patients' outcomes in Brazil. The study design, rationale and procedures have been previously published.⁹ We included consecutive patients aged 18 years or older admitted with decompensated HF in tertiary public hospitals affiliated to the Brazilian Unified Health System (SUS) during the COVID-19 outbreak from March 12th, 2020 to October 31st, 2020 (epidemiological weeks 11 to 44) and compared them with patients admitted in the same hospitals during the same epidemiological weeks in 2019 and 2018.

Baseline HF-specific characteristics were prospectively collected during hospitalization, by trained local investigators, using medical charts and structured interviews with the patient. The Acute Decompensated Heart Failure National Registry (ADHERE) algorithm score was calculated using a stepwise approach according to systolic blood pressure, creatinine and urea nitrogen blood levels to stratify HF patients into low, intermediate and high risk.^{10,11} The outcome was all-cause death in a 30-day follow up. Death and date of death were ascertained through medical records, next of kin and death certificates.

Informed consent was obtained from every patient and this study was approved by the Coordinating Center's Institutional Review Board (# 48561715.5.1001.0060).

Statistical analysis

Continuous variables were evaluated for the normal distribution using the shape, skewness, and kurtosis of distribution, and Kolmogorov-Smirnov test if needed. We compared clinical characteristics, measures of severity and treatment between study periods using the unpaired t test

for normally distributed variables, which were presented as mean $\pm$ standard deviation, and the Mann-Whitney U test for non-normally distributed variables, presented as median (25th percentile, 75th percentile). Categorical data was presented as proportions and compared using the chi-square test. To assess the association between study periods and the outcomes, we calculated Kaplan-Meier estimates and compared the probability of all-cause mortality using the log-rank test. A Cox (proportional hazards) regression analysis adjusted for age, sex, etiology of HF (ischemic, Chagas, other), left ventricular ejection fraction (LVEF), cardiac resynchronization therapy (CRT), implantable cardioverter defibrillator (ICD), and education levels, and stratified by income levels, chronic kidney disease (CKD) and previous HF was performed; the proportional hazard assumption was tested based on Schoenfeld residuals, with no violation for the proportional hazard assumption for the studied groups. P-values < 0.05 were considered statistically significant. Analyses were performed using Stata version 15.1 (Stata Corp., College Station, TX).

Results

During the epidemiological weeks 11 to 44 in the years of 2018, 2019 and 2020, 1,084 patients were admitted for HF in seven eligible centers, representing six states (*Alagoas, Bahia, Ceará, Minas Gerais, Pará* and *São Paulo*) in Brazil. From these, we excluded 218 patients due to missing systolic blood pressure ($n=86$), creatinine ($n=43$), blood urea levels ($n=20$) or loss to follow-up ($n=69$). The final analysis was performed in 866 patients admitted for HF.

Compared with the previous two years, we observed a 20% reduction in the number of patients admitted for HF during the COVID-19 outbreak, particularly in the first four months (9.2 ± 4.2 vs 11.6 ± 3.0 admissions per week during vs. before outbreak, respectively).

During COVID-19 outbreak, most baseline characteristics remained the same, but LVEF was lower than before the outbreak. Ischemic heart disease and Chagas disease were the most common etiology of HF, and history of CKD was more prevalent during the pandemic. Also, severity of HF at admission seemed to be worse during COVID-19 outbreak. Although clinical profiles did not differ between study periods, patients admitted during COVID-19 outbreak had significantly worse ADHERE risk score (Table 1).

All-cause mortality of patients hospitalized for HF significantly increased during the COVID-19 outbreak (Figure 1). In the 30-day follow-up period, 50/637 (7.8%) and 31/229 (13.5%) patients died before and during the outbreak, respectively. After adjusting for potential baseline confounders, the risk of death in 30 days was approximately two times higher in patients admitted during the COVID-19 outbreak (adjusted HR = 1.89 [95% CI 1.19, 3.03]; $p=0.007$), as compared with the two previous years.

Poor compliance to either dietary and medication treatment recommendations, and acute kidney disease were more commonly reported as factors triggering HF decompensation during the COVID-19 outbreak, as compared

with the previous period (Figure 2). Infection as reason for decompensation during the COVID-19 outbreak was not different as compared with before the outbreak.

Discussion

In this large registry of HF hospitalizations in Brazil, our main findings were: 1) the 30-day mortality increased roughly twice during the COVID-19 outbreak compared with before the pandemic; 2) patients with HF were more likely to decompensate due to poor treatment compliance and acute kidney disease; and 3) they were admitted in worse condition, as indicated by a worse ADHERE risk score. These findings help understand the impact of the pandemic in patients with HF in Brazil, affecting patients' behavior, disrupting the delivery of healthcare, and increasing the risk of dying from acute HF.

So far, there are few reports of the impact of the COVID-19 pandemic on HF patients. Similar to our findings, studies from Germany and England found that the short-term mortality significantly increased among patients admitted for HF during the beginning of the COVID pandemic, but this was not found in later studies from Denmark.^{2,4,5} This indicates that patients with CV diseases have been differently affected depending on the country-level response to the pandemic. Our study showed an increase in mortality from acute HF in a largely affected country, and that this impact has lasted longer than the first few months of the outbreak.

The reasons for the higher mortality are multifactorial. Non-adherence to dietary and drug treatment as factors triggering HF decompensation during the COVID-19 pandemic may provide insights on the mechanisms for these worse outcomes. Treatment of HF is complex, and it often requires a patient-centered multidisciplinary approach to improve long-term treatment compliance.¹² The worse outcomes from acute HF may reflect a disruption in the delivery of care in the outpatient setting. Ambulatory services were interrupted, and cardiology teams were rearranged and transitioned to the care of COVID-19 in many centers, shifting the focus from effective measures that are essential to reduce mortality of this population. Moreover, loss of social support due to social isolation may have hampered continuity of treatment, particularly among vulnerable individuals.

It should be noticed that guidance to manage CV diseases during the COVID-19 pandemic have mainly focused on ACS, but patients with HF have also been largely affected by the pandemic. Efforts should be made to continue providing adequate care for these patients.¹³ Healthcare policies targeted to this population, including strategies to maintain delivery of outpatient care, such as telemedicine and remote monitoring, may help reduce mortality during the pandemic.

Our study has limitations: we included only public hospitals, most of them university hospitals. Also, all hospitals in our study participated in the BPC program, which aims to improve quality of cardiovascular care and patients' outcomes, and this may not reflect HF admissions in all public hospitals in Brazil. Finally, our results do not represent those patients who were not admitted or who did not come to the hospital.

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Table 1 – Characteristics at admission of patients hospitalized for acute heart failure before and during COVID-19 outbreak

	Before COVID-19 Outbreak (2018 to 2019)	During COVID-19 Outbreak (2020)	p value
	n=637	n=229	
Age, years	59.83 ± 16.00	61.00 ± 14.05	0.33
Women, n(%)	275 (43.2)	93 (40.6)	0.50
BMI, Kg/m ² *	26.16 ± 5.56	27.03 ± 6.30	0.05
Etiology*			0.028
Ischemic	109 (17.1)	47 (20.5)	
Chagas	54 (8.5)	31 (13.5)	
Other	474 (74.4)	151 (65.9)	
LVEF, %	43.51 ± 17.62	37.33 ± 15.07	< 0.001
Previous HF, n(%)	395 (62.0)	153 (66.8)	0.20
CKD, n(%)	66 (10.4)	50 (21.8)	< 0.001
CRT, n(%)	3 (0.5)	3 (1.3)	0.19
ICD, n(%)	44 (6.9)	16 (7.0)	0.97
Low education, n(%)	265 (41.6)	119 (52.0)	0.007
Low income, n(%)*	469 (73.7)	170 (74.6)	0.81
Length of stay, days	19.0 [10.0. 33.0]	17.0 [9.0. 28.0]	0.17
Clinical profile			0.62
Warm-dry	56 (10.3)	13 (7.7)	
Warm-wet	368 (67.9)	114 (67.9)	
Cold-wet	92 (17.0)	34 (20.2)	
Cold-dry	26 (4.8)	7 (4.2)	
ADHERE risk, n(%)			0.009
Low	290 (45.5)	79 (34.5)	
Intermediate	319 (50.1)	134 (58.5)	
High	28 (4.4)	16 (7.0)	

BMI: body mass index; HF: heart failure; CKD: chronic kidney disease; CRT: cardiac resynchronization therapy; ICD: implantable cardioverter defibrillator; BUN: blood urea nitrogen. *Clinical profile was missing for 156 patients; BMI was missing for 56 patients; income level was missing for 2 patients; LVEF was missing for 23 patients.

Conclusion

In this large registry of patients admitted for HF in public hospitals included in the BPC program in Brazil, one of the most-affected countries by the COVID-19 pandemic, poor treatment compliance and acute kidney disease were the most common reasons for HF decompensation, and the 30-day mortality increased twice during the COVID-19 outbreak, as compared with previous periods. Public health strategies in response to the pandemic should ensure maintenance of care to HF patients, particularly in the most affected countries.

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The authors are solely responsible for the design, conduct and analyses of this study, the drafting and editing of the paper and its final contents.

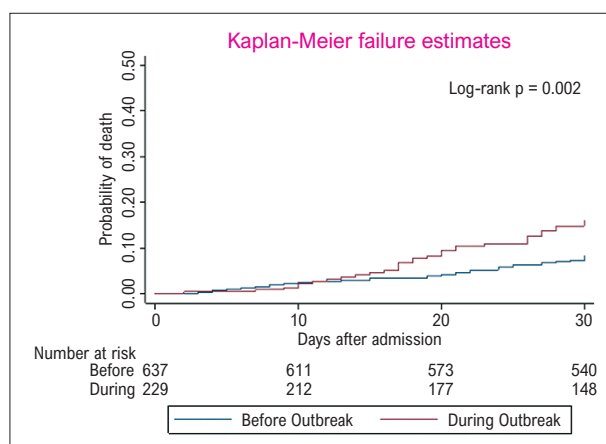


Figure 1 – Kaplan-Meier estimates of the probability of death in patients admitted for heart failure before and during the COVID-19 outbreak. Before COVID-19 outbreak: epidemiological weeks 11 to 44 in 2018 and 2019; during COVID-19 outbreak period: epidemiological weeks 11 to 44 in 2020

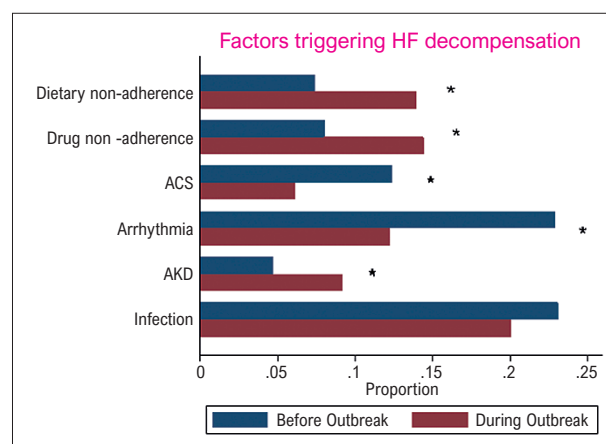


Figure 2 – Factors triggering HF decompensation according to study period; ACS: acute coronary syndrome; AKD: acute kidney disease.

* $p < 0.05$ from Chi-square tests comparing the proportions between the two periods; before COVID-19 outbreak: epidemiological weeks 11 to 44 in 2018 and 2019; during COVID-19 outbreak period: epidemiological weeks 11 to 44 in 2020

Author contributions

Conception and design of the research and analysis and interpretation of the data: Fernandes-Silva MM, Bernardes-Pereira, Silva AS; acquisition of data: Passaglia LG, Pereira KRP, Guedes MAV, Souza Neto JD, de Paola AAV, Rivera MAM; statistical analysis: Fernandes-Silva MM; obtaining financing: Bernardes-Pereira, Silva AS; writing of the manuscript: Fernandes-Silva MM, Adam EL; critical revision of the manuscript for intellectual content: Fernandes-Silva MM, Adam EL, Bernardes-Pereira, Silva AS, Passaglia LG, Pereira KRP, Guedes MAV, Souza Neto JD, de Paola AAV, Rivera MAM.

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 Comitê de Ética do Hospital do Coração under the protocol number 48561715.5.1001.0060. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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Mitral Valve Perforated Aneurysm: An Issue of Inflammation or Pressure Gradients?

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Case Report

Mitral valve aneurysms (MVA) are uncommon and usually develop acutely in the setting of infective endocarditis (IE).¹ MVA as a late complication of IE in a patient with obstructive hypertrophic cardiomyopathy (HCM) is rather unusual, raising considerations regarding the role of the infectious process and the hemodynamic conditions inherent to the cardiomyopathy.^{1,2} We present a case report of a patient with HCM and a ruptured aneurysm of the mitral valve (MV) leaflet, secondary to previously treated IE.

A 68-year-old male patient with type 2 diabetes mellitus and dyslipidemia was admitted to a hospital with a 3-week history of malaise, fever, and recent left-sided abdominal pain. His physical examination revealed a grade II/VI systolic heart murmur at the cardiac apex, fever, abdominal tenderness in the left upper quadrant, and purpuric lesions in the inferior limbs. Blood analyses showed neutrophilia and C-Reactive Protein of 211mg/L. Positive blood cultures indicated *Staphylococcus aureus* methicillin-sensitive. Abdominal Computed Tomography revealed spleen embolization, with no abscess. Transthoracic (TTE) and transesophageal echocardiography (TEE) disclosed a highly mobile polypoid mass in the atrial side of the anterior MV leaflet, suggestive of a vegetation, with mild mitral regurgitation and no evidence of abscess, aneurysm, or valve perforation; asymmetrical left ventricular (LV) hypertrophy with the presence of an increased intraventricular systolic gradient (IVSG) and systolic anterior motion (SAM) of the MV (Figure 1). The diagnosis of IE in HCM was established and treated accordingly with flucloxacillin, presenting a favorable clinical evolution. After three months of follow-up, cardiac magnetic resonance was performed, confirming the diagnosis of HCM: an increased LV mass (96g/m²) with asymmetrical left ventricular hypertrophy (maximal thickness of 20mm in the inferoseptal wall), with no perfusion defects but with evidence of intramural late gadolinium enhancement in the inferoseptal

wall, and SAM of the MV (Figure 2). Echocardiography was repeated and, in addition to evidence of obstructive HCM with a rest IVSG of 44 mmHg, an aneurysm of the anterior leaflet of the MV was identified. Two mitral regurgitant jets were observed, one due to incomplete coaptation of the leaflets and another through the perforated aneurysm, quantifying global mitral regurgitation (MR) in a moderate (grade II/IV) (figure 3). The beta-blocker dose was increased, and a strategy of close follow-up was adopted. Maintenance of the characteristics of the aneurysm was verified in outpatient follow-up after 2 years.

MVA are rare but potentially serious conditions. Published literature shows that they mostly develop in the anterior MV leaflet in the acute setting of IE of the aortic valve (AV), due to the aortic regurgitant jet direction and secondary spreading of the infectious process to the MV.^{1,3} This leads to localized inflammation, tissue weakness, abscess formation with posterior drainage, and eventually to the formation of an aneurysm.^{1,3} Echocardiographic features vary from a small saccular bulges, often difficult to identify due to the presence of vegetations, to a large leaflet protuberance towards the left atrium, which may be associated with various degrees of MR and thrombus formation.^{1,3} Clinical manifestations and surgical indications depend on the hemodynamic significance of the valvular lesions.^{1,3} In a manuscript from Reid et al.,¹ five patients with MVA of the anterior MV leaflet, in the setting of AV IE, were described, considering clinical, echocardiographic, and pathological features. Symptoms of heart failure and various degrees of valve regurgitation were reported. Four underwent AV replacement, while only two received MV intervention, as the MVA had not been previously diagnosed – these were identified in an autopsy, highlighting the importance of a detailed preoperative evaluation.¹ Autopsy studies found that MVA had necrotic material surrounded by vegetations in the anterior leaflet, with a sparing of the posterior MV leaflets.¹

Even less frequent is the finding of MVA in patients with connective tissue diseases, which has seldom been reported, suggesting a connection between tissue fragility and their development.³

The anterior MV leaflet is also the most often affected valve leaflet in IE in patients with HCM.^{2,4} Although nowadays no direct association is established between IE and HCM, this cardiomyopathy used to be considered a moderate-risk condition for IE development, in view of the published reports depicting an association of the infectious disease and HCM.² Increased leaflet susceptibility to IE seems to be primarily due to structural abnormalities in MV leaflets, such as leaflet elongation and papillary muscle displacement, along with continuous microtrauma of the valve endocardium by mitral-septal contact during SAM.^{2,4,5} LV outflow tract obstruction has also been suggested as an important contributor for SAM

Keywords

Endocarditis, Bacterial; Cardiomyopathy, Hypertrophic/complications; Mitral Valve/abnormalities; Inflammation; Aneurysm, Valvular; Diabetes Mellitus/complications; Dyslipidemia/complications; Diagnostic, Imaging

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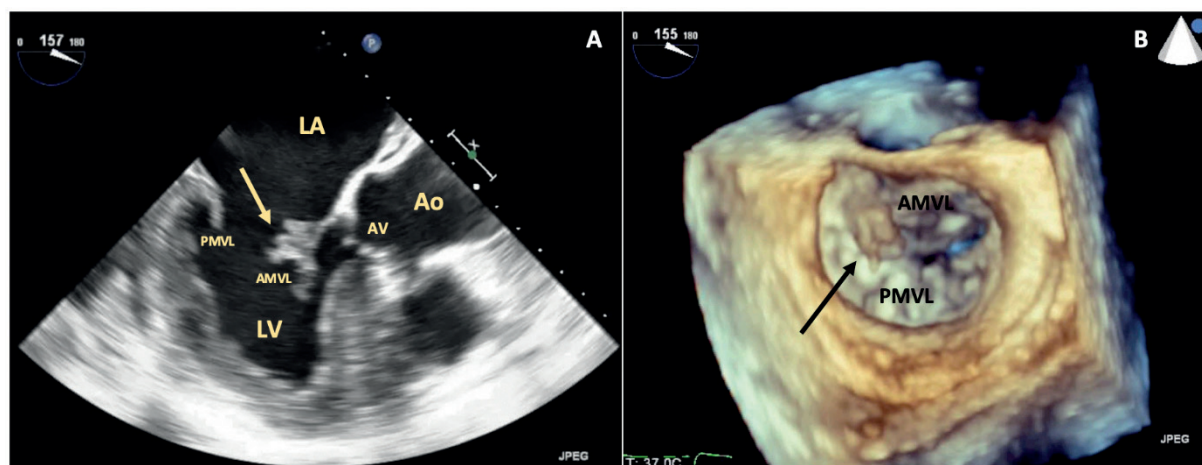


Figure 1 – A) 2-D Transesophageal echocardiographic evaluation revealing left ventricular hypertrophy and systolic anterior motion of the mitral valve, with a polypoid mobile mass in the atrial side of the anterior valve leaflet, highly suggestive of a vegetation (→); B) 3-D Transesophageal echocardiographic evaluation, "en-face" view of the mitral valve, revealing a polypoid structure adherent to its anterior leaflet (→), corresponding to a vegetation. AMVL: anterior mitral valve leaflet; Ao: aorta; AV: aortic valve; LA: left atrium; LV: left ventricle; MV: mitral valve; PMVL: posterior mitral valve leaflet.

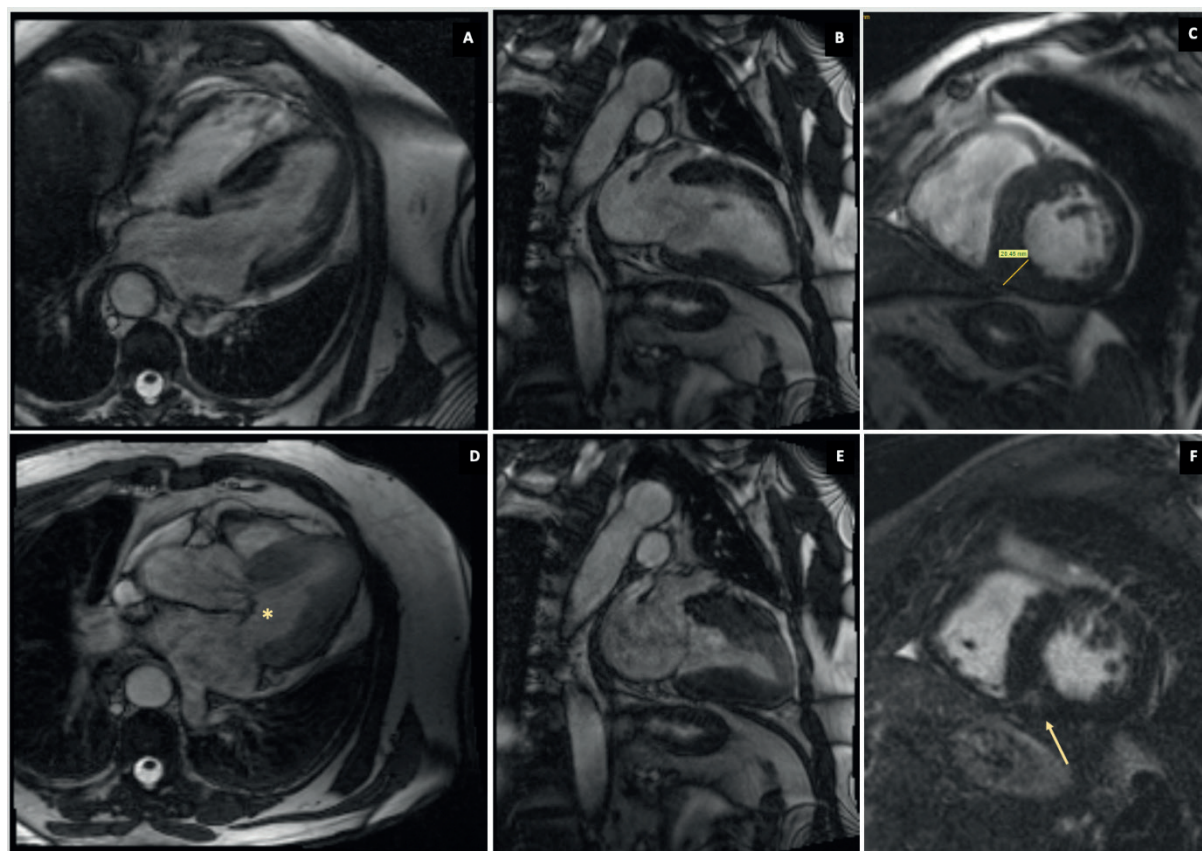


Figure 2 – A, B, C, E) Magnetic Resonance Imaging evaluation showing asymmetrical left ventricular hypertrophy, with maximal thickness of 20 mm in the inferoseptal wall (C); D) 3-Chamber view depicting systolic anterior motion of the mitral valve leaflet (*); F) Mid-ventricular short-axis view revealing the presence of intramyocardial late gadolinium enhancement located in the inferoseptal mid wall (→), suggestive of myocardial fibrosis.

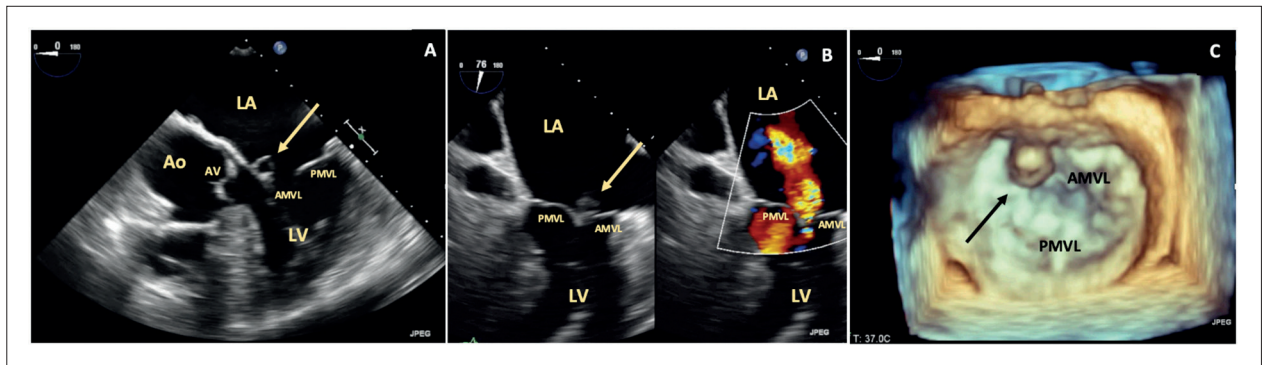


Figure 3 – A) 2-D Transesophageal echocardiographic evaluation depicting a saccular bulge in the anterior mitral valve leaflet with systolic expansion towards the left atrium, suggestive of a leaflet aneurysm (→); B) Moderate mitral regurgitation (grade II/IV) through the aneurysm of the anterior mitral valve leaflet; C) 3-D Transesophageal echocardiographic evaluation, “en-face” view showing the saccular bulge located on the anterior mitral valve leaflet corresponding to the leaflet aneurysm (→). AMVL: anterior mitral valve leaflet; Ao: aorta; AV: aortic valve; LA: left atrium; LV: left ventricle; MV: mitral valve; PMVL: posterior mitral valve leaflet.

and IE development, as the high pressure difference and the shear stress on the MV in this setting leads to SAM, and the high velocity and turbulent blood flow in obstructive HCM damages the valve endocardium.^{2,4,6}

In this case, the MVA developed as a late complication of IE of the MV itself, which is unusual, not only because it is more often found in AV IE, but also due to its subacute presentation. We believe that structural characteristics of the anterior MV leaflet, typical of HCM, formed a susceptible substrate for vegetations to develop in this leaflet. It can therefore be speculated that possible persistent latent inflammation after completing antibiotic therapy and resolving systemic inflammatory markers, coupled with the presence of the SAM of the MV and a high IVSG, have played a role in aneurysm formation in the anterior MV leaflet.

Depending on hemodynamic conditions and local environment, aneurysm size may increase and complicate, leading to clinical deterioration.^{5,7} The most dreadful complication is acute severe MR and pulmonary edema due to MVA perforation or as a result of a leaflet coaptation defect caused by its mass effect.^{1,3} In the setting of obstructive HCM, the presence of a significant IVSG seems to be a contributor to the growth of an aneurysm, increasing its propensity to bulge towards the atrium, growing and perforating.⁷ In our case, MVA size has remained reasonably stable over time. We thus hypothesize that the increase in beta blocker dose may have prevented MVA growth, decreasing the IVSG characteristic of this cardiomyopathy and the flow turbulence against the MV leaflet – a hypothesis that still requires further confirmatory studies, as data published on the issue is scarce.

Regarding the diagnosis, TTE and TEE are the methods of choice for identifying MVA and perforation of the valve leaflets.^{8,9} TEE has a higher sensitivity and specificity for aneurysmal lesions, enabling a more accurate morphologic tissue characterization.⁹ Computed tomography and magnetic resonance imaging are useful in valvular evaluation, but little data exists considering their role in the evaluation and diagnosis of valvular aneurysms.^{10,11}

An optimal approach to MVA has not yet been defined, depending on the size and hemodynamic consequences of the valvular lesion. In small aneurysms with mild or moderate MR, a conservative approach seems reasonable, as decided in this case, while in severe MR, surgery is the only reasonable option.³⁻⁷

In conclusion, MVA are rare but potentially life-threatening complications of IE. The purpose of this case is to highlight possible complications of this infectious process and to remind that certain heart conditions may have an increased propensity to develop complications and unfavorable outcomes due to the interplay between inflammation and pressure gradients.

Author Contributions

Conception and design of the research and Writing of the manuscript: Oliveira I, Cruz I, Neto A, Bragança B; Acquisition of data: Oliveira I, Cruz I; Analysis and interpretation of the data: Oliveira I, Abreu G; Critical revision of the manuscript for important intellectual content: Abreu G, Azevedo J, Andrade A.

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

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Analysis of the Neutrophil-Lymphocyte Ratio as a Marker of Atherosclerosis of the Abdominal Aorta

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Dear Editor,

We read with great interest the article: Neutrophil-Lymphocyte Ratio and Abdominal Aortic Atherosclerosis among Asymptomatic Individuals, which evaluated whether the neutrophil-lymphocyte ratio (NLR) could be associated with abdominal aortic atherosclerosis (AtAA). A positive association between the increase in NLR and AtAA was demonstrated when comparing carriers and non-carriers of the disease. However, when adjusting the statistical analysis for age and risk factors, this association did not remain true.¹

It is better established in the literature that NLR is associated with the acute phase of coronary atherosclerosis. Furthermore, it is known that the increase in the number of neutrophils present in the aortic wall is significantly greater in unstable, ruptured and/or recent plaques when compared to stable fibrotic atheromas. The latter show a reduction not only in the number of neutrophils but also in dendritic and natural killer (NK) cells.²

The adoption of conventional ultrasonography has a sensitivity of 62% for detecting arterial occlusions with a volume of less than 8mm⁴ and only 25% sensitivity for unstable carotid plaques.^{3,4} Such a technique may have influenced the study's results, given that newly growing plaques and unstable, non-calcified plaques may not have been identified. A possible solution would have been to adopt another screening method. Real-time elastography has a sensitivity of 50% for the detection of the same unstable plaques or the combination of both methods - which would have increased the sensitivity to 62.5%.⁴ Adopting a more sensitive screening method could not only identify a greater number of patients with an ongoing atherosclerotic process but also detect more

recent and/or unstable atheromas, which would significantly alter the final statistics.

Atherosclerosis can affect different vascular territories with different prevalence. Even though confounding factors are well highlighted, the high prevalence of this disease in other arteries, in addition to the aorta, in older individuals should be noted. One may question the possibility that elderly patients in the control group, whose statistics were adjusted for age, have an atherosclerotic process beyond the abdominal aorta. This confounding factor could be avoided by investigating the presence of atherosclerosis in other arteries, entering as an exclusion criterion, or approaching the LNR as a possible predictor of systemic atherosclerosis and not only of the abdominal aorta.

Finally, the proportion of males in the NLR quintiles in Table 1 is epidemiologically similar to those with/without atherosclerosis in Table 2. As the sample was not randomly selected, this may only portray greater access to preventive examination by males. This also occurs with the current smoking variable. Added to this are analytical statistics absent from multivariate modeling as indicators of the quality of the fitted models that prevent a critical interpretation by the reader regarding the reported associative validity. Risk estimation of the adjustments would also improve the interpretation of the models. In addition, in studies with the outcome (atherosclerosis) and independent (NLR) data collected at the same time (cross-sectional design), the use of logistic regressions overestimates interval estimators such as the 95%CI, which may have occurred in models 1 and 2. The best indication in these analyses is the adapted Poisson or Cox regressions.⁵

Keywords

Atherosclerosis; Biomarkers; Lymphocytes; Neutrophils; Risk Factors; Aorta.

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Letter to the Editor

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1. Marin BS, Ceseria F, Laurinavicius AG, Santos RD, Bittencourt MS. Razão Neutrófilo-Linfócito e Aterosclerose da Aorta Abdominal entre Indivíduos Assintomáticos. *Arq Bras Cardiol.* 2022;118(4):729-34. doi: <https://doi.org/10.36660/abc.20201163>
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Reply

We would like to express our gratitude for the comments regarding our article. As stated in our article, the objective was to investigate the association of the neutrophil-to-lymphocyte ratio with abdominal aortic atherosclerosis in asymptomatic patients.¹ Although this association has been more frequently described in cases of plaque instability, previous publications have reported its increase in association with stable coronary disease.

As indicated, we also recognize that abdominal ultrasound has limitations in the assessment of aortic atherosclerosis. However, due to the investigation routine for screening asymptomatic patients, especially in large databases such as that of our recent study, this was the only method that could be used on a large scale with low cost and low risk to patients.

With respect to the model proposed in the letter, we disagree with the point of view of the authors of the letter. Cox models are survival models, and they can only be used with time-to-outcome variables. In the case of simultaneous collection, there is no time to event, and the model recommended for binary outcomes is the one with logistic regression. The cited reference discusses the prevalence estimate, which was not performed in our study.

Notwithstanding the relevant points of criticism raised, we believe that our study provides innovative information that contributes to scientific knowledge in the area.

Marcio Sommer Bittencourt

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1. Marin BS, Ceseria F, Laurinavicius AG, Santos RD, Bittencourt MS. Razão Neutrófilo-Linfócito e Aterosclerose da Aorta Abdominal entre Indivíduos Assintomáticos. *Arq Bras Cardiol.* 2022;118(4):729-34. doi: <https://doi.org/10.36660/abc.20201163>.



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Position Statement on Women's Cardiovascular Health – 2022

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Note: These guidelines 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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Position Statement on Women's Cardiovascular Health – 2022

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Statement

List of Abbreviations and Acronyms

ACS	Acute Coronary Syndrome
AD	Alzheimer's Disease
AF	Atrial Fibrillation
AMI	Acute Myocardial Infarction
ARNI	Angiotensin-Receptor Neprilysin Inhibitor
ASA	Acetylsalicylic Acid
BMI	Body Mass Index
BP	Blood Pressure
CABG	Coronary Artery Bypass Grafting
CAD	Coronary Artery Disease
CC	Congenital Cardiopathy
CCaS	Coronary Calcium Score
CKD	Chronic Kidney Disease
CMRI	Cardiac Magnetic Resonance Imaging
CSD	Cardiac Sudden Death
CT	Cardiac Transplantation
CTA	Computed Tomography Angiography
CTX	Chemotherapy
CV	Cardiovascular
CVD	Cardiovascular Disease
CVP	Coronary Vasospasm
CVR	Cardiovascular Risk
CVRF	Cardiovascular Risk Factor
DALYs	Disability-Adjusted Life Years (1 DALY represents the loss of 1 year of healthy life)
DCS	Diseases of the Circulatory System
DM	Diabetes mellitus
DOACs	Direct Oral Anticoagulants
DPP-4	Dipeptidyl Peptidase-4
ECG	Electrocardiogram
ET	Exercise Test
GBD	Global Burden of Disease
GD	Gestational Diabetes
GH	Gestational Hypertension
GLS	Global Longitudinal Strain
HF	Heart Failure
HFpEF	Heart failure with preserved ejection fraction

List of Abbreviations and Acronyms

HFREF	Heart failure with reduced ejection fraction
ICD	Implantable Cardioverter Defibrillator
IHD	Ischemic Heart Disease
IMR	Index of Microcirculatory Resistance
IMT	Intimal-Media Thickness
INOCA	Ischemia with non-obstructive coronary arteries
LDL-c	Low-density-lipoprotein cholesterol
LVEF	Left Ventricular Ejection Fraction
LVH	Left Ventricular Hypertrophy
MCS	Malformations of the Circulatory System
MHT	Menopausal Hormone Therapy
MINOCA	Myocardial infarction with non-obstructive coronary arteries
MVD	Microvascular Disease
NSTEMI	Non-ST Elevation Myocardial Infarction
NT-proBNP	N-terminal fragment of pro-B-type natriuretic peptide
OECD	Organization for Economic Cooperation and Development
PAD	Peripheral Arterial Disease
PE	Preeclampsia
PH	Pulmonary Hypertension
PHC	Primary Health Care
PNS	National Health Survey (in Portuguese, <i>Pesquisa Nacional de Saúde</i>)
POS	Polycystic Ovary Syndrome
QoL	Quality of Life
REF	Risk-Enhancing Factor
RF	Risk Factor
RHD	Rheumatic Heart Disease
SAH	Systemic Arterial Hypertension
SBC	Brazilian Society of Cardiology (in Portuguese, <i>Sociedade Brasileira de Cardiologia</i>)
SCAD	Spontaneous Coronary Artery Dissection
SDH	Social Determinants of Health
SGLT2	Sodium-Glucose Cotransporter-2
STEMI	ST-Elevation Myocardial Infarction
UI	Uncertainty Interval
WHO	World Health Organization

Legends for the recommendation and level of evidence tables:

Recommendations:

	I – Conclusive evidence, or, failing that, general consensus that the procedure is safe and useful/effective.
	II – Conflicting evidence and/or divergence of opinion about the procedure's safety and usefulness/effectiveness. IIA – Evidence/opinion is in favor of the procedure. Most approve of it. IIB – The procedure's safety and utility/effectiveness is less well established, opinion is not predominantly in favor of it.
	III – Evidence and/or consensus that the procedure is not useful/effective and, in some cases, is harmful.

Evidence:

Level A	Data obtained from multiple large randomized studies, concordant and/or robust meta-analysis of randomized clinical studies.
Level B	Data obtained from less robust meta-analysis, from a single randomized study or from non-randomized (observational) studies.
Level C	Data obtained from expert consensus.

Statement

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Introduction

Of the noncommunicable chronic diseases, CVDs are the leading cause of death around the world and in Brazil, which has one of the highest mortality rates in South America.¹ The CVDs account for one third of the deaths from all causes, affect men and women at all ages, and represent more than twice the number of deaths from all neoplasms associated.¹ Among women, there is an increase in the prevalence of CVD and death from CVD after menopause, aggravating the perspectives in the near future due to aging and illness of the female population in Brazil.

Currently, IHD accounts for most deaths in all Brazilian Federative Units, followed by cerebrovascular diseases.¹ One aspect is the difference in the involvement of the regions and in the access to diagnosis and treatment, according to the peculiarities determined by the social and economic indicators in the macroregions, states, and cities of different sizes in Brazil. Half of the mortality from CVD before the age of 65 years can be attributed to poverty and social inequalities.² Inappropriate diets, low level of physical activity, and alcohol and tobacco consumption are important RFs for CVD in women, more prevalent among the less favored social classes of the population, including Brazilian children and adolescents.³ Thus, primary and secondary prevention programs, as well as easier access to diagnosis, for those populations might have an even greater impact on CVD morbidity and mortality.

Most of the times, CVD can be prevented with public health interventions that involve RF control and optimized clinical management of patients. Reducing women's CVDs in Brazil and worldwide is a complex task, which depends on several agents and continuous effort.

Most Brazilian cardiologists, one third of which are women, are members of the SBC, which has been developing continuous actions to reduce CVD morbidity and mortality through the Department of Women's Cardiology.

The *Arquivos Brasileiros de Cardiologia*, the official scientific publication of the SBC, has published the "Women's Letter",⁴ which represented an advance in establishing concrete actions to reduce CVD morbidity and mortality in women, such as: to work collectively towards the defense of the global goals to prevent and control noncommunicable chronic diseases, mainly Brazilian women's CVDs; to establish campaigns of cardiovascular prevention, promoting consistent efforts to reach the goal of 30% reduction in mortality rate by 2030; to elaborate and suggest governmental policies to promote favorable environments to reduce exposure to risk, facilitating the adoption of healthy habits at school, work and leisure environments to fight women's CVD; to work alongside governments in the development and application of a cardiovascular prevention program, in addition to the incorporation of cost-effective technologies for the reduction of CVD morbidity and mortality in women; engage with communication media to deliver continuous information on the importance of CVDs in women,

their major RFs and preventive measures, ensuring the importance of early diagnosis; to provide the highest level of continuous medical education; to promote technical-scientific, cultural, and social exchange among cardiologists in Brazil and around the world; and to foster scientific knowledge necessary to increase the participation of women in the sciences and scientific events in the areas of health and related sciences.

Even considering the huge scientific and technological advances already achieved in cardiology, we need to change the health and disease paradigm, aiming at a population approach that enables the extension of the benefit of those achievements to the entire population. Therefore, a large agreement is required involving the civil society, the societies of medical specialties, the government, and the community to refurbish the education of physicians and other health professionals in parallel with the promotion of a wide discussion in society, contributing to raise awareness and improve the prevention, diagnosis, and treatment of the diseases accounting for most deaths of men and women in Brazil.

Brazil, by establishing in the Federal Constitution the inalienable commitment to the preservation of human dignity, defined health as a social right, ensuring universal, total, and free access to health for all Brazilians.

Even with the constitutional guarantees, inequities regarding women persist in the Brazilian society. Thus, it is necessary, through affirmative actions, to emphasize the need to ensure the essential equality between men and women, particularly regarding the awareness of women's CVDs, which are neglected in Brazil.²

Thus, the "National Day of Awareness of Women's Cardiovascular Diseases" has been proposed by the authors of the "Women's Letter" and approved by the Law 14.320 of 2022, sanctioned by the President of Brazil and published in the *Diário Oficial da União* of April, the 1st, originated from the bill 1.136/2019, from the federal representative and cardiologist Mariana Carvalho. That day will be celebrated on May 14th, in honor of the birth of the physician Bettina Ferro de Souza, the first female president of the SBC.

It is fundamental to promote initiatives to enhance knowledge on the importance of cardiovascular health throughout women's lives. In addition, it is essential to better understand the local differences in women's cardiovascular health to define public policies and health care, reduce the gap, and promote sex equity regarding Brazilian health care.

Therefore, the SBC's Department of Women's Cardiology presents its **Position Statement on Women's Cardiovascular Health** focused on primary prevention. This document was aimed to help reach the objective stated in the "Women's Letter" of playing a leadership role in Brazilian health policies, providing managers with an overview of the relevance of women's CVDs. This view will enable them to elaborate strategies to reduce the prevalence of RFs and improve the diagnosis and therapeutic approach, thus reducing cardiovascular

outcomes, with impact on the Brazilian women's physical, mental, and spiritual health.

1. Highlights

In this chapter 1, the highlights of chapters 2 to 10 are presented.

Epidemiology of the cardiovascular diseases in women

- In the past 30 years, there was an increase in the CVD prevalence among individuals of both sexes aged 15-49 years. In addition, the CVD prevalence was higher in women until 2011; since then, the CVD prevalence in men has been higher.¹
- The CVDs, mainly IHD and cerebrovascular disease, are the major cause of death in adults of both sexes. The percent of deaths due to IHD was similar in women and men, while the percent of deaths due to stroke was higher in women than in men.⁵
- In the other age groups, from birth to the beginning of adulthood, cardiac malformations, cardiac complications from rheumatic fever, and cardiomyopathies play a key role in mortality of both sexes.⁶
- Of the traditional RFs, overweight, obesity and diabetes mellitus were the most frequent among women. It is worth emphasizing that the prevalence of self-reported SAH in Brazil was higher in the female than in the male sex.

Cardiovascular risk factors in women

- Recognizing women's RFs, either specific, most prevalent, or similar to those of men, as well as knowing the 10-year risk for atherosclerotic CVD, is of great importance for CVD risk stratification in the female sex.²
- In women, the most impacting traditional RFs for CVD include diabetes mellitus, SAH, dyslipidemia, tobacco use, obesity, and sedentary lifestyle.
- The prevalence of those traditional RFs has increased even among young women and, when associated with sex-specific RFs, contribute to increase morbidity and mortality; however, they are not usually considered in CVR stratification.^{7,8}
- Sex-specific RFs, such as polycystic ovary syndrome, use of hormonal contraception, gestational hypertension, adverse events of pregnancy, MHT, risks related to inflammatory and autoimmune diseases (rheumatoid arthritis, systemic lupus erythematosus), and depressive disorders are considered REFs.⁸
- The assessment of CVR in women should consider, in addition to risk stratifiers, the aggravating factors of the diabetes mellitus-associated risks, the REFs, and the sex-specific RFs to establish changes in lifestyle and recommend measures for primary prevention

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of CVD, aimed at identifying and treating earlier a larger number of women at risk.^{7,8}

Cardiovascular diseases in women

1 – Ischemic heart disease

- Currently, additional mechanisms of coronary ischemia are well defined, and it is more appropriate to refer to it as IHD because it comprises several coronary affections that cause ischemia, such as myocardial infarction with non-obstructive coronary arteries, ischemia with non-obstructive coronary arteries, spontaneous coronary artery dissection, microvascular disease, coronary vasospasm, and coronary embolism/thrombosis. In women, several pathophysiological mechanisms of IHD are related to one or more of those coronary affections, which can be present even in younger and pregnant women.

2 – Heart failure

- Considering HF pathophysiology, because of hormonal responses, women, as compared to men, differ regarding the HF epidemiology, clinical presentation, outcomes, and treatment.^{9,10} Regarding HF phenotypes, some are more prevalent in women, such as Takotsubo syndrome, and others are specific to women, such as peripartum cardiomyopathy. However, in both chronic and acute HF, clinical trials/registries targeting women are scarce and the evidence derives from subanalysis of large studies in which women are underrepresented. Multicenter prospective registries could provide more precise evidence about the female population, including a larger number of women in HF with both reduced and preserved ejection fraction.

3 – Arrhythmias

- Women more often have sinus tachycardia and nodal reentry tachycardia, and pregnancy increases the risk for supraventricular tachycardia.¹¹
- In long QT syndrome type 2 among women, there is a greater risk of sudden death and pro-arrhythmia. In the puerperium, long QT increases the risk for *torsades de pointes*.¹²
- In women, sudden death of cardiac etiology more often results from non-ischemic causes, and men are more often resuscitated and treated with a defibrillator. The use of an implantable cardioverter defibrillator for both primary and secondary prevention is more common in men; however, the risk of complications related to the procedure is higher in women.¹³
- Although the incidence of AF is higher among men, older women more often have AF, more symptoms, and worse quality of life. Strong risk predictors of AF in women are SAH and obesity. Women more often have paroxysmal AF, strokes

and thromboembolism, HF, higher CHA₂DS₂-VASC score, more hospitalizations, and a higher risk of cardiovascular and all-cause mortality.^{14,15}

4 – Cardiovascular disease and cancer

- Cardiotoxicity is a challenge in the treatment of female cancer, especially breast cancer, which is one of the most frequent neoplasms, and can lead to an increased incidence of cardiovascular events and of cardiovascular and all-cause mortality as compared to women without neoplasm. The risks vary according to the cancer treatment, which can harm the cardiovascular system leading to the following: ventricular dysfunction, from asymptomatic and reversible to symptomatic and irreversible HF; acute coronary syndrome; pericarditis; myocarditis; ventricular arrhythmias; SAH; peripheral vascular disease. Genetic variants are factors related to the risk of cardiomyopathy, explaining why some patients with the same profile develop cardiotoxicity and others do not.
- The prognosis of such patients is affected by some issues, such as the analysis of cardiovascular RFs before, during, and after the diagnosis and oncological treatment, the effective intervention on modifiable RFs, in addition to the early diagnosis and treatment of the chemotherapy-related cardiotoxicity.

5 – Stroke, peripheral artery disease, and dementia

- Future research on the recognition of female sex-specific RFs for stroke and a score to identify the group at higher risk are urgently needed to elaborate stroke prevention strategies for women.
- Peripheral artery disease correlates with IHD, and the treatment of traditional RFs is a preventive measure in both sexes. The recognition of women-specific RFs, such as pregnancy and its complications, or of predominantly female RFs may allow proper risk stratification and the adoption of early preventive measures.
- Women, as compared to men, seem to be at higher risk for developing dementia and memory disorders related to age. Although some studies have shown that estrogen plays a significant role in women's cognitive functioning, the MHT showed no beneficial effect on reducing those changes even in younger women.¹⁶
- In patients under the age of 55 years, regardless of sex, the major causes of cognitive changes and dementia are Alzheimer's disease, vascular dementia, frontoparietal dementia, and alcohol-related dementia.
- There are vascular RFs related to early dementia, such as stroke, transient ischemic attack, kidney disease, CVD, SAH, chronic alcoholism, and drug intoxication. The control of cardiovascular RFs plays

a key role in preventing dementia and cognitive diseases, mainly in younger women.

6 – Valvular heart diseases

- The follow-up of women with aortic valve stenosis or mitral valve disease requires careful and continuous reasoning about the best treatment model. The decisions regarding clinical or interventional management depend on the disease's anatomical and functional diagnosis and careful patient's assessment.
- When compared to men and considering the same degree of valve calcification, women have a tendency towards higher severity of aortic stenosis because of fibrosis of the valve apparatus, which is more pronounced than calcification. Men and women differ regarding clinical presentation, response to treatment, and results after valvular intervention.¹⁷
- In transcatheter aortic valve replacement, women are older and have better left ventricular function and lower prevalence of coronary artery disease; however, they have associated comorbidities, such as diabetes mellitus and AF. Anatomical characteristics of the female sex, such as shorter distance between the coronary artery ostia and the valvular ring, as well as the higher prevalence of valvular and aortic calcification, account for higher coronary artery obstruction during the procedure. In addition, the smaller diameter of the peripheral vessels causes greater vascular complications and bleeding.¹⁸
- Of the preventive measures in valvular heart diseases, the following stand out: primary and secondary prevention of rheumatic disease and antibiotic prophylaxis of infective endocarditis, mainly during childbirth. Valvular heart disease in women have peculiar characteristics with significant impact on treatment results and disease prognosis.
- The indications of infective endocarditis prophylaxis during pregnancy are women with rheumatic valvular heart disease, valvular prostheses, cyanogenic congenital heart disease, and history of infective endocarditis.

7 – Diabetes mellitus, preeclampsia, and pregnancy hypertensive disorders

- Gestational diabetes is associated with maternal and fetal complications, such as PE, premature birth, and perinatal death. Lifestyle changes, such as regular physical activity during pregnancy, in the absence of obstetric or cardiovascular contraindications, substantially reduce the risks of those complications.¹⁹
- There is a wealth of literature supporting gestational hypertension as a RF for future CVD; primigravida who develop GH are at higher risk for future

CVD, notably after menopause. Thus, the best recommendation is to initiate the prevention of PE and other forms of GH prior to pregnancy, which include proper body weight, healthy diet, and regular practice of physical exercises. In women at high risk, the use of acetylsalicylic acid in the first trimester and calcium replacement for pregnant women with low daily calcium intake should be indicated.²⁰

8 – Adolescent pregnancy

- Adolescent pregnancy increases maternal, fetal, and neonatal complications, worsens preexisting socioeconomic problems, and affects the future of generations. Thus, it should be managed efficiently and continuously in all socioeconomic levels.
- One of the most important preventive factors of adolescent pregnancy is education on sexuality and reproductive health, supported by scientific evidence and health promotion programs.²¹ It should include information on biological aspects, mutual respect, responsible sexual activities, and use of safe and effective contraceptive methods to prevent pregnancy and protect against sexually transmissible infections.²²
- Adolescents instructed by providers determined to face sensitive subjects, such as pregnancy prevention and contraception, are more engaged in their well-being. The qualified instruction about adolescent sexuality is an investment for a healthier and profitable future with high self-esteem.

Cardiac investigative methods: peculiarities in women

- Women's electrocardiographic findings differ from men's regarding the magnitude of the electric signals, with smaller amplitude of the QRS complex, of the J point, and of the T wave, and a longer corrected QT interval. Anterior T-wave inversion, that is, beyond V1, occurs in 2.3% of the population, being more common in women, regardless of their physical activity status. That is a benign pattern if it occurs in asymptomatic and low-risk women, because CMRI studies suggest it might reflect lateral displacement of the right ventricle.²³ Electrocardiographic changes that may lead to misinterpretations are observed in 45% of women with breast implants: T-wave inversion, inferolateral ST depression, poor R-wave progression from V1 to V4, prolonged QT interval, and left ventricular hypertrophy.²⁴
- On ET, women more often show false-positive depression of the ST segment and the test's accuracy varies with the pretest probability of IHD. In women, the association of stress/rest myocardial perfusion scintigraphy with ET has better diagnostic accuracy than ET alone. That association has excellent negative predictive value in women with pretest intermediate/high risk.²⁵

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- The measure of intimal-media thickness to reclassify risk can be used in women with at least two cardiovascular RFs.^{3,4} The presence of plaque as an aggravating factor for risk stratification can be used in women at intermediate risk.²⁶
- Women with coronary artery calcium score over zero and breast arterial calcification have higher risk of ischemic events as compared to men. Coronary computed tomography angiography evidences the non-obstructive coronary pattern, more prevalent in women.^{26,27}
- Normal coronary arteries on coronary angiography are more common in women. The risk of vascular complications from coronary angiography is higher among women, who have a higher tendency to develop acute kidney lesion due to contrast media.²⁸
- The CMRI is an excellent investigative option for women, especially those of childbearing age, pregnant women, and those undergoing treatment for breast cancer. In addition, the CMRI can evidence perfusion and/or myocardial changes, helping the differential diagnosis of chest pain and being particularly useful in the management of IHD in women.

Women's representation in clinical studies on cardiovascular disease and risk factors

- The major cause of death worldwide is CVD, which is more and more recognized as having sex-specific characteristics regarding the illness processes, clinical manifestations, and results of treatments. Therefore, the identification of sex differences in CVD expression determines that women should be equally represented in cardiovascular clinical trials.
- Although women's representation has increased in recent clinical studies, this has not occurred in all areas of CVD investigation. Women remain underrepresented in studies on arrhythmias, acute and chronic coronary artery disease, and HF, especially those involving interventions with implantable devices and highly complex procedures.
- The identification of barriers to equity in the representation of clinical trial subjects offers several opportunities to solve the problem, enabling equity in selection and maintenance of women as subjects of clinical studies on CVDs and their RFs.
- That equity is necessary for the accurate understanding of CVD expression and their RFs in women, as well as of the impact of treatment on women's cardiovascular prognosis.

Primary prevention measures for women

- Primary health care is usually the first contact of women with the health sector, occurring electively or through active search by community health agents. Primary health care should cover the needs of all women's life stages, with actions directed to

total health promotion, with emphasis on physical, mental, and spiritual well-being.

- Over time, there was a decentralization of public services initiated with the Women's Total Health Care Program and consolidated with the Women's Health Care Policy. The guarantee of women's access to all levels of health care and the integration of actions and services remain a challenge, as well as the local planning and monitoring of indicators to promote harm reduction and death prevention.
- A paradigm change is necessary in the public policies on women's total health, especially when considering that CVDs are the major cause of death among women in most phases of their life cycle.

Women's burnout, quality of life, and spirituality

- Burnout associates positively with alcohol consumption, sleep disorders, depression, sedentary lifestyle, obesity, and musculoskeletal pain, being a significant predictor of hypercholesterolemia and diabetes type 2, thus relating to a higher incidence of IHD and hospitalizations from CVD.²⁹
- Work conditions have a well-known impact on the health of workers. Women's labor force participation has been increasing, resulting in women's overload due to double journeys, with consequent high burnout rates among them.
- Women's life course is permeated by experiences of loss, stress, anxiety, and fear, which increase their psychological vulnerability, facilitating the appearance of symptoms of anxiety-depression. However, resilience, spirituality and personal beliefs seem to play a mediating role in some of those psychological variables, associating with better quality of life and lower frequency of CVD in women.

Cardiovascular implications of COVID-19 in pregnancy

- The severity of SARS-CoV-2 infection is higher in pregnant as compared to non-pregnant women, with more frequent intensive care unit admissions, mechanical ventilation use, and increased mortality and morbidity, including myocardial infarction, venous and other thromboembolic events, PE, and preterm labor and delivery.³⁰ In addition, COVID-19 has been associated with a higher rate (and combined proportions) of premature delivery, PE, cesarean delivery, and perinatal death.³¹
- The management of cardiac complications during pregnancy should comprise the multidisciplinary follow-up with a cardiologist, an obstetrician, and a neonatologist.
- SARS-CoV-2 infection during pregnancy should be included in the differential diagnosis with other complications, such as coronary artery dissection and peripartum cardiomyopathy.³²
- The beginning and duration of prophylactic anticoagulation in pregnancy associated with

SARS-CoV-2 infection should consider disease severity, need for hospitalization, temporal relation between disease occurrence and time of delivery, as well as the prothrombotic risk conferred by additional comorbidities.³¹

- In this population, vaccination should be emphasized, because it is the best way to prevent COVID-19-related complications. Preventive measures, such as face mask use, hand hygiene, and avoiding crowded areas, should be maintained.

Future perspectives on the improvement of women's cardiovascular care

- Women's mortality rates from CVD remain elevated and stagnant in most regions of the world, with little or no reduction in recent years. Women's CVR is still underestimated by the general population, and, especially, by women themselves and health care professionals. The non-implementation of the guidelines on women's CVD prevention delays the diagnosis of several CVDs, especially that of IHD, which is often neglected in women.³³
- Understanding the sex/gender-related differences in premature mortality from CVDs is essential for the development of preventive and control measures for those diseases. The scarcity of robust clinical studies and the female sex underrepresentation in clinical trials contribute to the scarce knowledge on women's CVD.³⁴ Further research on the role

played by sexual hormones in the female global CVR is mandatory.

- To reduce the CVD load in women by 2030 is an ambitious, but imperative, goal, especially because several cardiovascular RFs can be modified and mitigated.

2. Epidemiology of Women's Cardiovascular Diseases

According to data from the GBD 2019 Study, the prevalence of CVD was 6.1% of the population in 2019, 12 946 932 (95% UI, 11 899 752 – 13 617 524) individuals, 51% of the male sex. Men had a higher age-standardized prevalence rate as compared to women in 2019 (Figure 2.1). From 1990 to 2019, there was an 8.7% reduction in the CVD prevalence rate in men, smaller than that in women, 12.8%. There was an increase in the CVD prevalence in that period among individuals of both sexes aged 15-49 years. In addition, the CVD prevalence was higher in women until 2011; since then, the CVD prevalence in men has been higher (Table 2.1 and Figure 2.2).^{1,5}

In 2019, in Brazil, the age-standardized IHD incidence rates, mainly of myocardial infarction, were 78 and 148 per 100 000 inhabitants for women and men, respectively. Regarding chronic IHD (previous myocardial infarction, stable angina, or ischemic HF), the age-standardized prevalence rates were 1046 and 2534 per 100 000 inhabitants for women and men, respectively (Table 2.1).

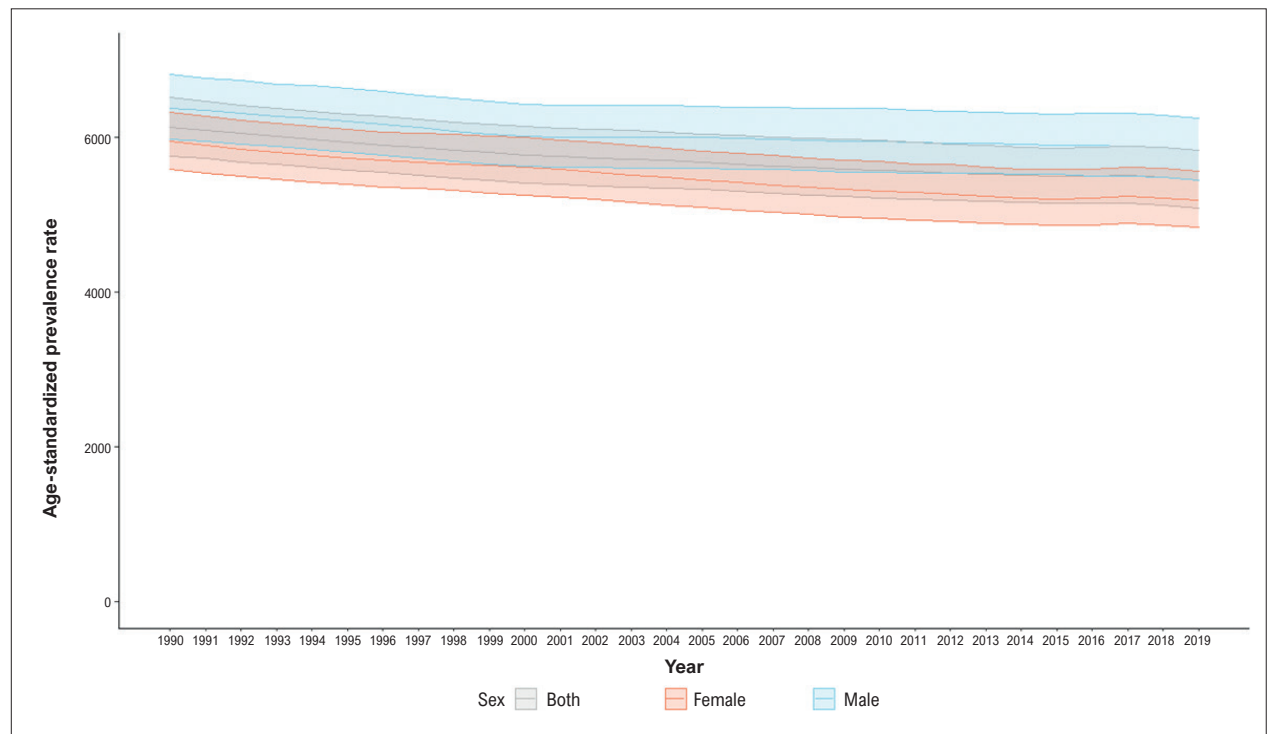


Figure 2.1 – Age-standardized prevalence rates of cardiovascular disease, per 100 000 inhabitants, according to sex, in Brazil, 1990-2019.
Source: Global Burden of Disease Study (GBD) 2019.¹

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Table 2.1 – Number of cases and age-standardized prevalence, incidence, death, and DALYs rates due to cardiovascular disease in women, per 100 000 inhabitants, and percent change of the rates, according to age group, in Brazil, in 1990 and 2019.

Age groups	1990		2019		Percent change (95% UI)
	Number (95% UI)	Rate (95% UI)	Number (95% UI)	Rate (95% UI)	
PREVALENCE					
15-49 years	81840.1 (71524.9;92783.6)	210.2 (183.7;238.3)	105700 (92430.3;120336.2)	180.7 (158.1;205.8)	-14 (-16.8;-10.9)
50-69 years	102496.1 (91526.7;114514.7)	1255.7 (1121.3;1402.9)	208399.3 (186607.1;232143.7)	973.2 (871.4;1084)	-22.5 (-25;-19.8)
5-14 years	26514.1 (17557.2;37666.8)	151.7 (100.4;215.5)	24476.1 (16014.6;34617.6)	154.6 (101.1;218.6)	1.9 (-1.4;5.7)
70+ years	77895.9 (69702.8;86822.5)	3321.7 (2972.3;3702.4)	200343.1 (180509.1;222408)	2653.3 (2390.6;2945.5)	-20.1 (-22.9;-17.2)
Age-standardized	294962.9 (275518.3;317426.8)	557.5 (523.8;597.3)	544515.2 (512491.4;581529.1)	437.4 (411;468.6)	-21.5 (-23.3;-20)
All ages	294962.9 (275518.3;317426.8)	391.9 (366;421.7)	544515.2 (512491.4;581529.1)	491.1 (462.3;524.5)	25.3 (21.7;29.1)
Under 5 years	6216.7 (4434;8521.4)	74.5 (53.1;102.1)	5596.8 (3974;7644)	73.8 (52.4;100.8)	-1 (-4;2.2)
INCIDENCE					
15-49 years	81840.1 (71524.9;92783.6)	210.2 (183.7;238.3)	105700 (92430.3;120336.2)	180.7 (158.1;205.8)	-14 (-16.8;-10.9)
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DEATHS					
15-49 years	769476.9 (739810.4;801490.1)	1976.3 (1900.1;2058.5)	679263.9 (631272.6;728617.3)	1161.5 (1079.5;1245.9)	-41.2 (-44.5;-37.8)
50-69 years	1154563.6 (1117881.8;1194713.4)	14144.8 (13695.4;14636.7)	1485239.2 (1407973.4;1568445)	6935.6 (6574.8;7324.2)	-51 (-53.4;-48.4)
5-14 years	38226.4 (34169.5;42955.7)	218.7 (195.5;245.7)	22398 (18744.9;26627.2)	141.4 (118.4;168.2)	-35.3 (-42.9;-28.7)
70+ years	976778.1 (898018.1;1019807.9)	41652.6 (38294.1;43487.5)	1661643.2 (1472104.5;1785160.2)	22006.3 (19496.1;23642.2)	-47.2 (-50.2;-44.7)
Age-standardized	3017512.3 (2897630.7;3117428)	6191.2 (5895.3;6408.3)	3875201.6 (3604407.9;4099252.4)	3019.5 (2810.8;3195.6)	-51.2 (-53.4;-49.1)
All ages	3017512.3 (2897630.7;3117428)	4008.9 (3849.7;4141.7)	3875201.6 (3604407.9;4099252.4)	3495.4 (3251.1;3697.5)	-12.8 (-17;-8.6)
Under 5 years	78467.3 (65203.6;97481.4)	940.3 (781.4;1168.2)	26657.3 (21657.1;32912.1)	351.4 (285.5;433.9)	-62.6 (-73.6;-49.5)
DALYs					
15-49 years	769476.9 (739810.4;801490.1)	1976.3 (1900.1;2058.5)	679263.9 (631272.6;728617.3)	1161.5 (1079.5;1245.9)	-41.2 (-44.5;-37.8)
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Source: Global Burden of Disease Study (GBD) 2019. Rate/100 000 inhabitants.¹ UI: uncertainty interval.

Analysis of data from the GBD 2019 study showed a reduction in the age-standardized CVD mortality rate for women. In the beginning of the period, 1990, the mortality rates for women differed significantly between the Brazilian geographic regions, and that difference decreased by the end of the period. This can be explained by a more pronounced reduction in the Southeast and South, regions that concentrate the largest populations and incomes, and more modest in the North and Northeast (Figures 2.3 and 2.4).^{1,5}

In Brazil, CVDs are the major cause of death among women and men, despite their 50.6% decrease from 1990 to 2019 (Table 2.1). Although the age-standardized CVD mortality rates were higher in men during the entire period, the percent reduction was similar for both sexes, 48% for men and 52% for women. The proportional CVD mortality was higher in women during the entire period (1990 to 2019) (Figure 2.3).^{1,5}

According to GBD 2019 study estimates, of the CVDs, IHD was the first cause of death in Brazil, followed by stroke. The IHD accounted for 12.03% and 12.2% of the deaths of women and men, respectively, while the percent of deaths due to stroke was higher in women than in men, 10.39% and 8.41%, respectively. The estimated DALYs due to IHD were 1276.6 (1165.2;1359) and 2179.4 (2054.4;2296.3) and those due to stroke were 1235.6 (1133.8;1322.5) and 1410.1 (1323.5;1487.9) in women and men, respectively (Figures 2.5 and 2.6).^{1,5}

In 2019, the prevalence of AF and atrial flutter was higher in men than in women, although the age-standardized mortality and DALYs rates were higher in women. AF occurs in association with advanced RHD, especially mitral stenosis, more frequent in women, at the ratio of 3 to 2.

The age-standardized prevalence of RHD showed a slight 2.1% increase, being higher among women (3.5%). However, there was a reduction in the age-standardized mortality rates attributable to RHD, the percent reduction being similar in both sexes in the past 30 years (Figures 2.5 and 2.6). In addition, the proportional mortality from aortic stenosis was higher among women in Brazil in 2019, and the DALYs rates decreased from 1990 to 2019 similarly for men and women (Figures 2.5 and 2.6).^{1,5}

According to data from the Brazilian Ministry of Health Mortality Information System, from 1980 to 2018, HF was the underlying cause of death of 1 185 120 individuals (584.155 men [49.3%]).³⁵ The ratios between the crude mortality rates from HF in both sexes, according to age groups and geographic regions, are shown in Table 2.2. Ratios equal to or higher than 1 were observed in almost the entire period, all age groups, and geographic regions, with higher mortality in men, except for the North (1985-1989), Northeast (1980-1984) and South regions in the age group of 60 years and over, in which women's mortality was higher.^{35,36}

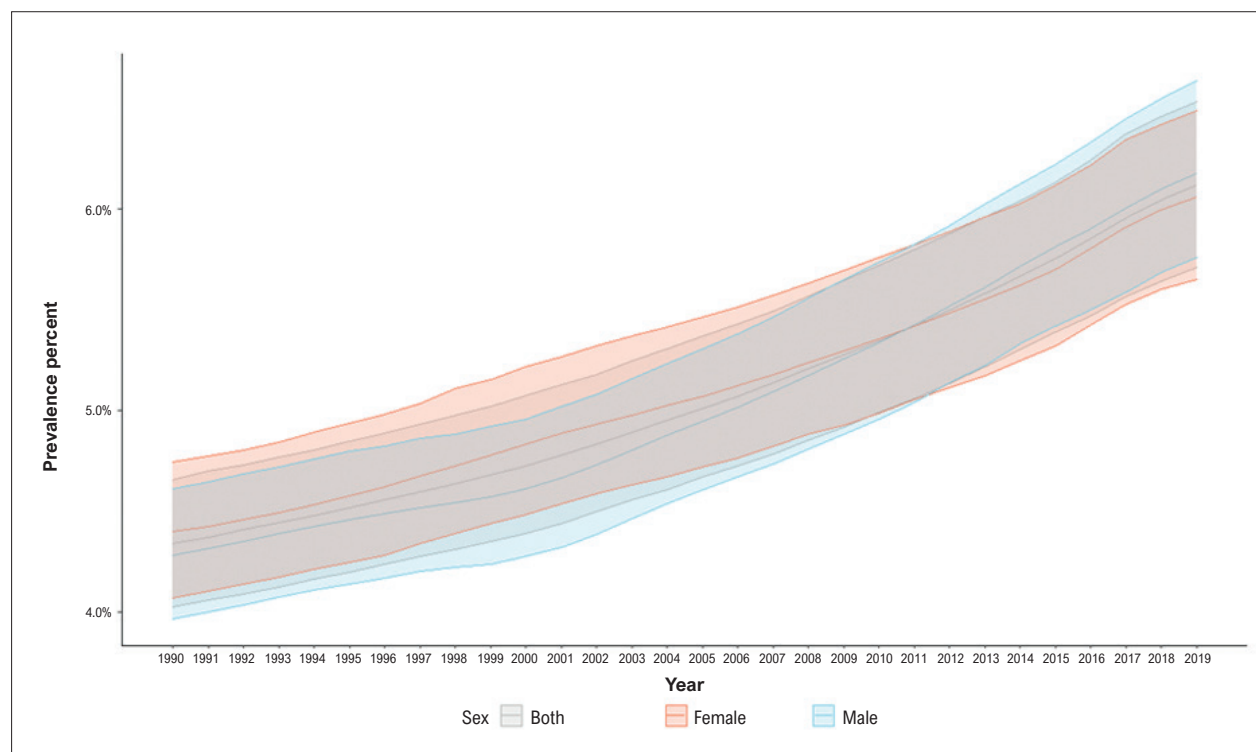


Figure 2.2 – Prevalence of cardiovascular disease, according to sex, in Brazil, 1990-2019. Source: Global Burden of Disease Study (GBD) 2019.¹

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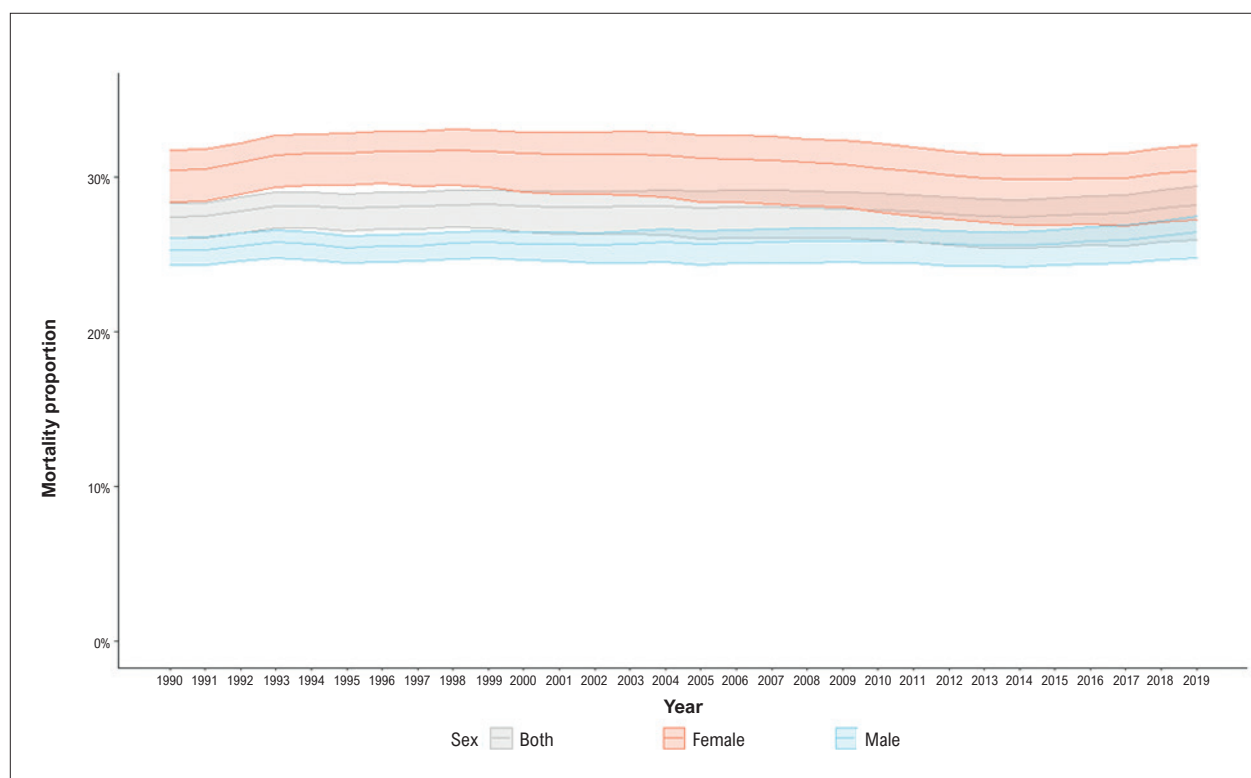


Figure 2.3 – Proportional mortality due to cardiovascular disease, according to sex, in Brazil, 1990-2019. Source: Global Burden of Disease Study (GBD) 2019.¹

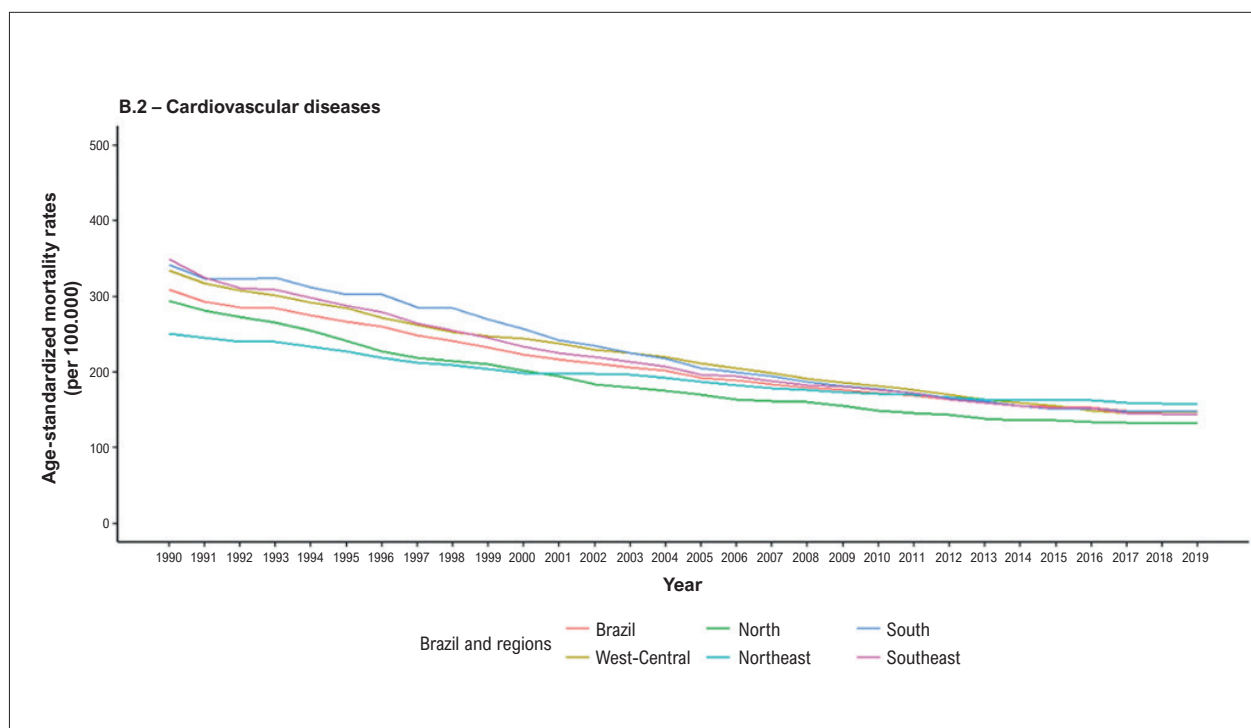


Figure 2.4 – Age-standardized mortality rates due to cardiovascular disease, per 100 000 inhabitants, in women, in Brazil and its regions, 1990-2019. Source: Global Burden of Disease Study (GBD) 2019.¹

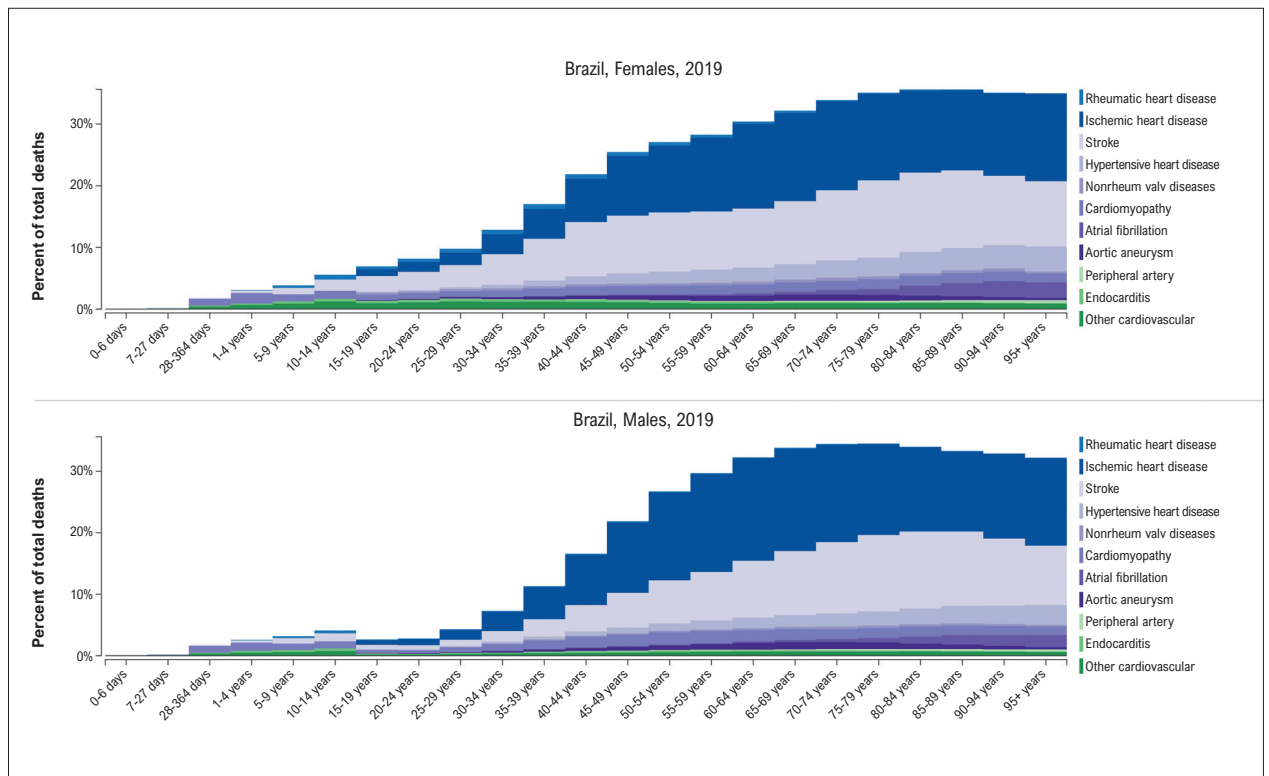


Figure 2.5 – Proportional mortality from cardiovascular disease in women (A) and men (B), according to age group, in Brazil, 2019. Source: Global Burden of Disease Study (GBD) 2019.¹

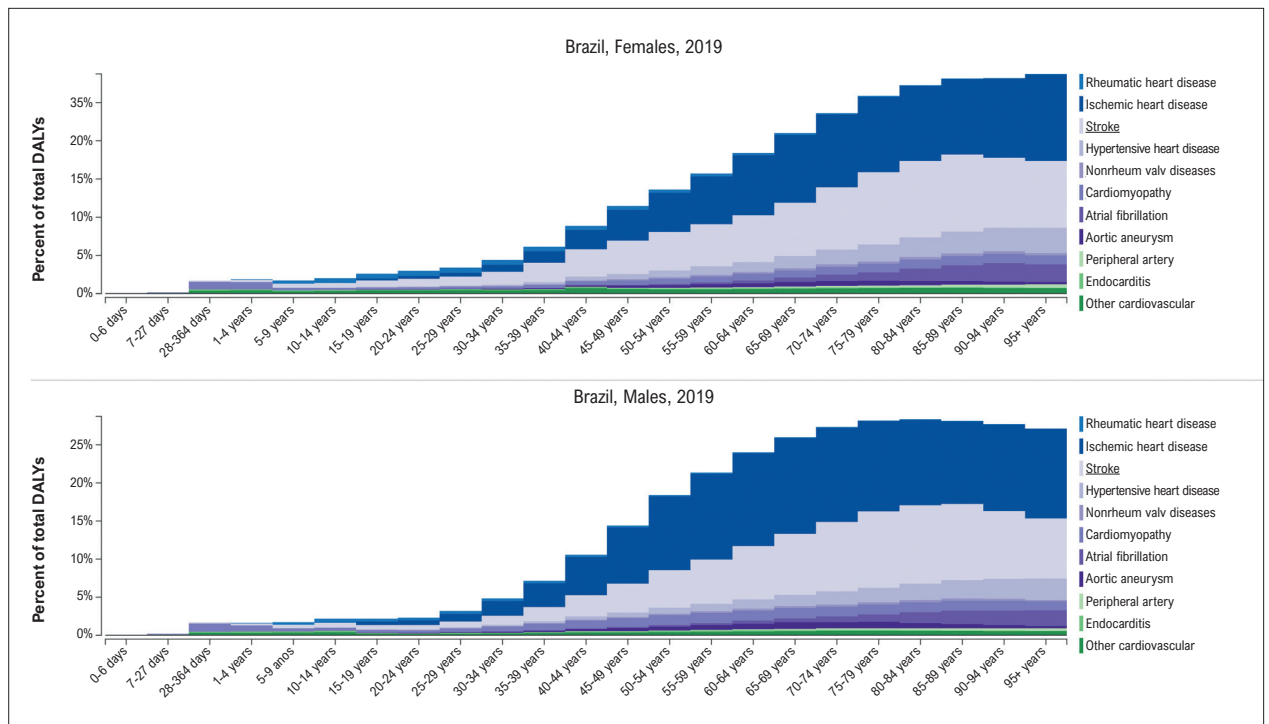


Figure 2.6 – DALYs (%) due to cardiovascular disease in women (A) and men (B), according to age group, in Brazil, 2019. Source: Global Burden of Disease Study (GBD) 2019.¹

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Table 2.2 – Ratio between the crude mortality rates in the male and female sexes, according to age groups and geographic regions, in 5-year periods.

Age group	Number Region / Period	1980-1984	1985-1989	1990-1994	1995-1999	2000-2004	2005-2009	2010-2014	2015-2018
0-29	North	1.0	0.9	1.2	1.0	1.2	1.3	1.3	1.8
	Northeast	0.9	1.0	1.0	1.1	1.1	1.4	1.4	1.5
	Southeast	1.1	1.2	1.3	1.3	1.2	1.6	1.5	1.8
	South	1.1	1.2	1.2	1.6	1.5	1.3	1.5	1.1
	West-Central	1.1	1.1	1.1	1.1	1.9	1.5	2.7	1.0
30-59	North	1.5	1.4	1.5	1.4	1.6	1.9	1.8	1.5
	Northeast	1.2	1.3	1.4	1.3	1.3	1.4	1.5	1.6
	Southeast	1.4	1.5	1.6	1.5	1.6	1.7	1.6	1.5
	South	1.4	1.5	1.5	1.4	1.4	1.5	1.4	1.2
	West-Central	1.2	1.5	1.6	1.6	1.8	1.9	1.7	1.7
60+	North	1.1	1.1	1.1	1.1	1.2	1.3	1.3	1.2
	Northeast	1.2	1.2	1.2	1.1	1.2	1.2	1.2	1.2
	Southeast	1.1	1.1	1.0	1.0	1.0	1.0	1.0	1.0
	South	1.1	1.0	1.0	0.9	0.9	0.9	0.9	0.9
	West-Central	1.1	1.1	1.0	1.0	1.1	1.1	1.1	1.2

Source: Brazilian Health Information System - Datasus.^{35,36}

Of the RFs for CVDs in Brazilian women, the following stand out: SAH, dietary risks, obesity, increased serum cholesterol levels, and elevated fasting glycemia (Figure 2.7).⁷ From 1990 to 2019, elevated BMI was the RF that increased most in Brazil.^{1,7} The specific RF in women with stroke include pregnancy, preeclampsia, gestational diabetes, oral contraception use, hormone use during menopause, and changes in the hormone status.⁷

The prevalence of self-reported SAH in Brazil in 2019 was 23.9%, higher in the female than in the male sex (26.4% versus 21.1%, respectively).³⁷ Cardiovascular mortality attributable to SAH was higher in women aged 65-79 years and in men aged 50-79 years.⁵ Dietary risks were the second most important RF for CVD in 2019, accounting for 5.0% and 5.7% of the deaths due to IHD and for 2.6% and 2.4% of the deaths due to stroke in women and men, respectively.² Physical inactivity, another behavioral RF, increased from 1990 to 2019 in Brazil, mainly among women, 4.7%, as compared to men, 3.1%.² According to data from the Brazilian Institute of Geography and Statistics (IBGE), in 2019, in Brazil, the percentages of overweight and obese adults

(age ≥ 18 years) were 62.6% and 29.5% for women, and 57.5% and 21.8% for men, respectively. There was a progressive increase of obesity with age increase, with a higher prevalence of overweight and obesity in women of all age groups.⁵ The prevalence of diabetes increases as the prevalence of obesity increases.⁵ Data from the 2014-2015 PNS in Brazil showed a higher prevalence of diabetes in women, individuals over the age of 30 years, and those with overweight or obesity.³⁷ Diabetes is a RF for CAD more important to women than to men, even to premenopausal women.^{7,37}

Anxiety, depression, and violence victimization were studied in 31 847 women from the 2013 PNS. The major depressive episodes and suicidal ideation were assessed with the *Patient Health Questionnaire*, while violence victimization was self-reported. Women had a higher prevalence of depressive episodes (OR = 2.36; 95% CI, 2.03-2.74), suicidal ideation (OR = 2.02; 95% CI, 1.73-2.36), and violence victimization (OR = 1.73; 95% CI, 1.45-2.06).³⁸

Sex-specific factors are of fundamental importance and affect the occurrence of CVD throughout a woman's life. A cross-sectional multicenter study with

A – Mortality rate - Women			A – DALYs rate - Women		
Position	Rate	Risk factor	Position	Rate	Risk factor
1 ^a	76.8	High systolic blood pressure	1 ^a	1552	High systolic blood pressure
2 ^a	38.4	Dietary risks	2 ^a	924	High body mass index
3 ^a	36.2	High body mass index	3 ^a	831	Dietary risks
4 ^a	33.8	High LDL-cholesterol	4 ^a	692	High LDL-cholesterol
5 ^a	27.2	High fasting glycemia	5 ^a	524	Tobacco use
6 ^a	20.0	Tobacco use	6 ^a	484	High fasting glycemia
7 ^a	12.3	Low physical activity level	7 ^a	262	Air pollution
8 ^a	11.0	Kidney dysfunction	8 ^a	204	Kidney dysfunction
9 ^a	10.8	Air pollution	9 ^a	197	Low physical activity level
10 ^a	3.9	Other environmental risks	10 ^a	69	Other environmental risks
11 ^a	3.1	Non-ideal temperature	11 ^a	55	Non-ideal temperature
12 ^a	0.2	Alcohol use	12 ^a	15	Alcohol use

B – Mortality rate - Men			B – DALYs rate - Men		
Position	Rate	Risk factor	Position	Rate	Risk factor
1 ^a	113.0	High systolic blood pressure	1 ^a	2561	High systolic blood pressure
2 ^a	65.7	Dietary risks	2 ^a	1546	Dietary risks
3 ^a	54.2	High body mass index	3 ^a	1315	High body mass index
4 ^a	47.9	High LDL-cholesterol	4 ^a	1311	High LDL-cholesterol
5 ^a	47.1	High fasting glycemia	5 ^a	972	Tobacco use
6 ^a	36.9	Tobacco use	6 ^a	906	High fasting glycemia
7 ^a	16.8	Kidney dysfunction	7 ^a	421	Air pollution
8 ^a	16.6	Air pollution	8 ^a	352	Kidney dysfunction
9 ^a	15.4	Low physical activity level	9 ^a	276	Low physical activity level
10 ^a	7.8	Other environmental risks	10 ^a	183	Alcohol use
11 ^a	6.5	Alcohol use	11 ^a	150	Other environmental risks
12 ^a	4.4	Non-ideal temperature	12 ^a	88	Non-ideal temperature

	Metabolic risks		Environmental/occupational risks		Behavioral risks
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Figure 2.7 – Ranking of the age-standardized mortality and DALYs rates due to cardiovascular diseases attributable to risk factors, in 2019, in Brazil, women (A) and men (B). DALY: disability-adjusted life years; CVD: cardiovascular disease; GBD: Global Burden of Disease; LDL: low-density lipoprotein. Source: Global Burden of Disease Study (GBD) 2019.^{1,5}

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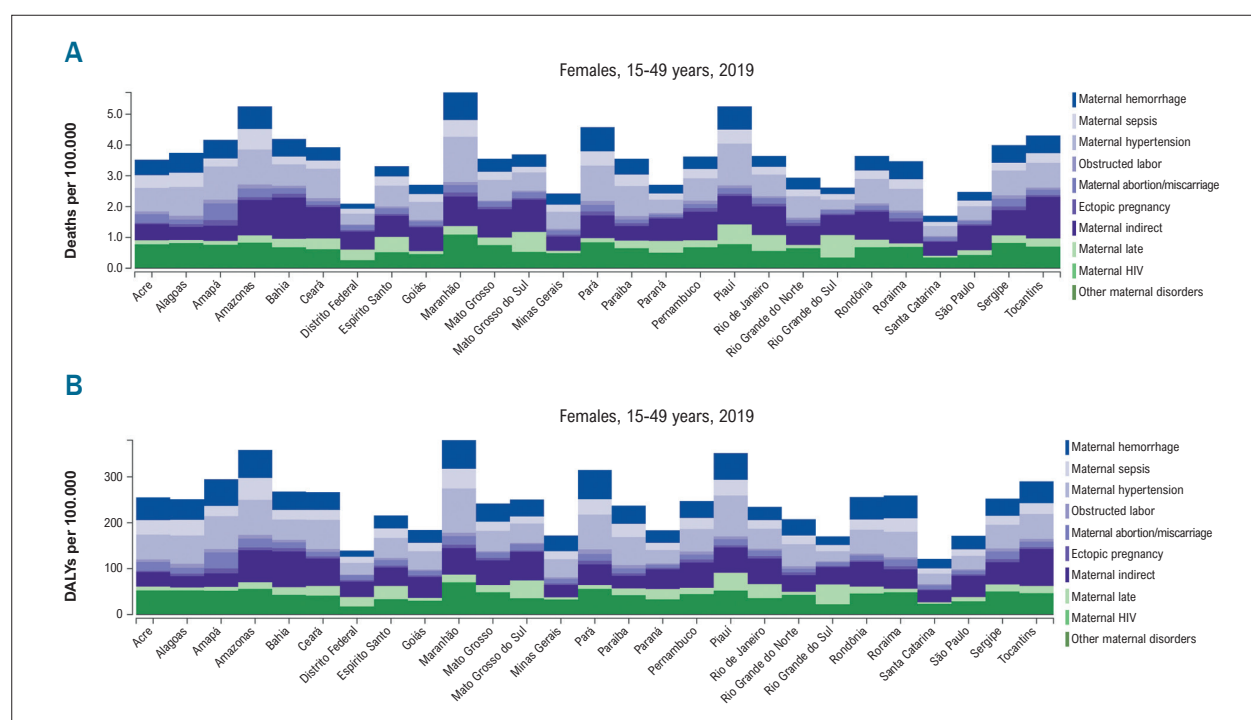


Figure 2.8 – Mortality and DALYs rates due to maternal causes in the federative units, per 100 000 inhabitants, in women, Brazil, 2019. Source: Global Burden of Disease Study (GBD) 2019.¹

Table 2.3 – Proportional mortality and mortality rate per group of causes of death in children, according to sex and age group, Brazil, 2000-2015.⁶

Causes of death		<20 years		Male						Female					
		Total	Total	<1year	1-4 years	5-9 years	10-14 years	15-19 years	Total	<1year	1-4 years	5-9 years	10-14 years	15-19 years	
MCS	Deaths	57.892	31.077	26.144	2.901	766	625	641	26.815	22.016	2.972	728	593	506	
	PM(%)	4.2	3.7	6.2	4.1	1.8	1.1	0.3	5.15	6.6	5.0	2.4	1.7	0.8	
	Mort	5.3	5.62	107.0 ₍₁₎	2.7 ₍₂₎	0.6	0.4	0.5	5.0	94.7 ₍₁₎	2.9 ₍₂₎	0.5	0.4	0.4	
Other CM	Deaths	86.165	45.237	39.715	3.133	956	725	708	40.928	35.729	3.009	870	720	600	
	PM(%)	6.3	5.4	9.3	4.4	2.3	1.3	0.3	7.78	10.8	5.1	2.9	2.0	0.9	
	Mort	7.9	8.2	162.6 ₍₁₎	2.9 ₍₂₎	0.7	0.5	0.5	7.7	153.7 ₍₁₎	2.9 ₍₂₎	0.7	0.5	0.4	
DCS	Deaths	29.904	16.706	3.735	2.084	1.493	2.749	6.645	13.198	3.280	2.045	1.376	2.197	4.300	
	PM(%)	2.2	2.0	0.9	2.9	3.6	4.8	2.6	2.54	1.0	3.4	4.5	6.2	6.6	
	Mort	2.8	3.0	15.3 ₍₁₎	1.9 ₍₂₎	1.1	2.0	4.7	2.5	14.1 ₍₁₎	2.0 ₍₂₎	1.0	1.6	3.1	
Ill defined	Deaths	85.458	49.940	25.907	7.692	3.019	3.679	9.643	35.518	19.414	6.431	2.408	2.700	4.565	
	PM(%)	6.2	5.9	6.1	10.9	7.2	6.5	3.8	6.82	5.9	10.8	7.9	7.7	7.0	
	Mort	7.9	9.0	106.0 ₍₁₎	7.0 ₍₂₎	2.2	2.6	6.8	6.7	83.5 ₍₁₎	6.2 ₍₂₎	1.8	2.0	3.3	
External	Deaths	340.974	274.627	10.816	16.304	16.384	29.287	201.836	66.347	7.431	10.328	8.801	11.992	27.795	
	PM(%)	24.9	32.5	2.5	23.0	39.1	51.6	80.4	12.75	2.2	17.4	28.8	34.0	42.5	
	Mort	31.4	49.7	44.3 ₍₁₎	15.0 ₍₂₎	11.9	20.9	142.5	12.5	32.0 ₍₁₎	9.9 ₍₂₎	6.6	8.9	20.2	
All causes	Deaths	1.367.355	845.481	424.932	70.854	41.904	56.775	251.016	521.874	331.269	59.430	30.518	35.293	65.364	
	PM(%)	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	
	Mort	126.0	153.0	1.739.3 ₍₁₎	65.2 ₍₂₎	30.4	40.5	177.3	98.0	1424.7 ₍₁₎	57.0 ₍₂₎	23.0	26.1	47.6	

MCS: malformations of the circulatory system; Other CM: other congenital malformations excluding MCS; DCS: diseases of the circulatory system; PM(%): proportional mortality in percentage; Mort: mortality rate per 100 000 (1) Mortality per 100 000 live births (2) Mortality per 100 000 in the population aged 0 – 4, live births excluded.

27 referral maternity hospitals from all Brazilian regions and 82 388 women giving birth, from July 2009 to June 2010, identified 9555 cases of severe maternal morbidity, 140 deaths, and 770 maternal near misses. The major determinant cause of maternal complications was hypertensive disease.³⁹ Preeclampsia, gestational diabetes, pregnancy-induced hypertension, preterm delivery, and small for gestational age newborn are early indicators of maternal cardiovascular risk. According to data from the GBD 2019 study, hypertensive diseases of pregnancy were the second cause of mortality and DALYs in women of childbearing age (Figure 2.8).¹

2.1. Diseases of the Circulatory System in Children and Adolescents of the Female Sex in Brazil

The etiologies of the DCS in individuals under the age of 20 years in Brazil vary according to age group, sex, and place of residence. The MCS are the major cause of death up to the age of 4 years, and cardiomyopathies are the major cause for ages 5 to 19 years.⁴⁰

In Brazil, the deaths due to MCS from 2000 to 2015 were more frequent under the age of 4 years, mainly in the first year of life and in the male sex (Table 2.3).⁶ In the female sex, the following MCS had the highest incidence: persistent truncus arteriosus, Ebstein's anomaly (tricuspid valve), and ostium secundum atrial septal defect. The DCS more often occurred at the age of 5-19 years, predominantly in the female sex, probably because of competition of external causes of death, more prevalent in the male sex.⁶

The importance of deaths from DCS increases with age progression (Figure 2.9).^{6,40} One should consider that children with MCS, even repaired ones, and

who did not die in their first year of life can have complications and sequelae, such as HF, arrhythmias, and endocarditis, with death in adolescence. Another possible explanation is the higher diagnostic negligence of MCS and DCS in the female sex at all age groups in Brazil, resulting from the poorer access to the health system and diagnostic resources in the female sex as compared to that in the male sex.^{3,6,40}

Table 2.4 shows the proportional mortality attributed to DCS and MCS in the first year of life due to specific causes and according to Brazilian regions.¹³ More than 83% of the deaths due to DCS resulted from MCS in all regions, with emphasis to the South region, where that percentage was 93%. The non-specified MCS corresponded to half of the deaths under the age of 1 year in Brazil, with no difference between the sexes and predominance in the Southeast region (44%). The proportional mortality from DCS was 2.5 times higher in the North region than in the South region, predominating in the female sex. Cardiomyopathy accounted for 32% of the deaths from DCS, being the leading cause of death in all regions and both sexes.⁴¹

In the past decade, the increase in obesity, insulin resistance, and SAH in children and adolescents contributed to increase the cardiovascular risk in young individuals. An increase in the prevalence of DCS in that population is estimated to occur in coming years.^{26,42}

More girls and female adolescents died from DCS than their male counterparts, indicating the need for public health strategies directed to the female sex, such as equity of access to health resources, early diagnosis, and institution of female sex-specific therapeutic measures.

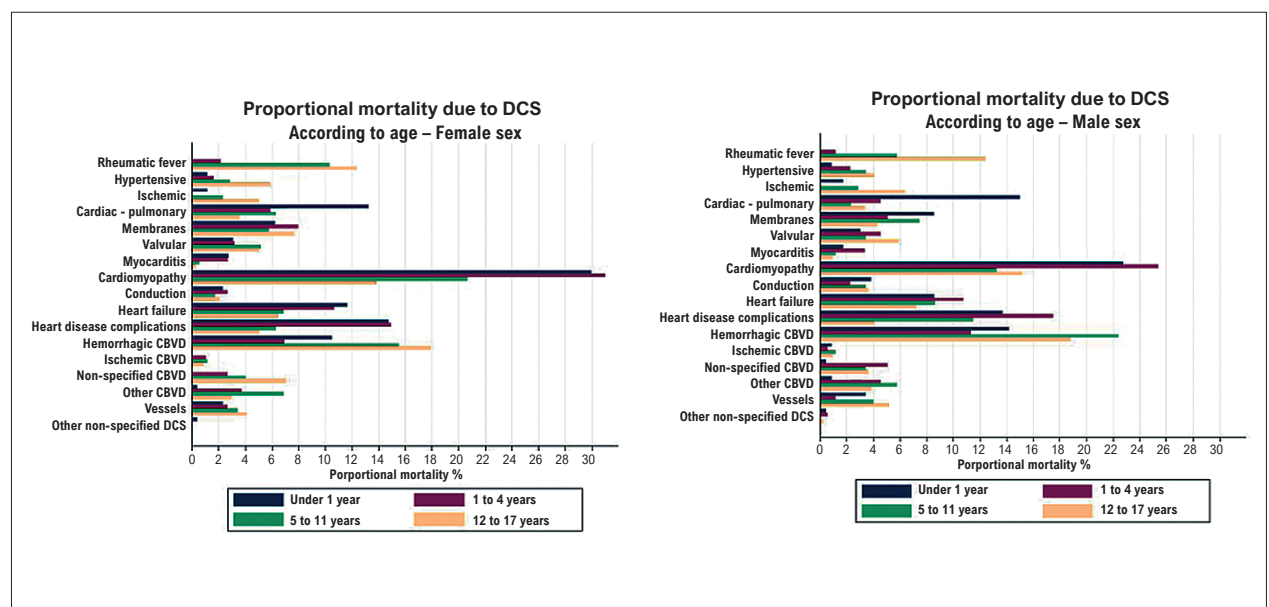


Figure 2.9 – Annual proportional mortality due to specific causes of the circulatory system in children and adolescents, per sex and age group, in the state of Rio de Janeiro, 1995 to 2012.⁴⁰ DCS: Diseases of the Circulatory System; CBVD - Cerebrovascular Diseases.

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Table 2.4 – Proportional mortality due to diseases of the circulatory system and malformations of the circulatory system, subdivided into specific causes, in the first year of life, female sex, according to Brazilian regions, 2000 to 2015.⁴¹

CAUSES OF DEATH		NORTH	NORTHEAST	SOUTHEAST	SOUTH	WEST-CENTRAL	TOTAL
CARDIAC-PULMONARY AND PULMONARY CIRCULATION DISEASES	Deaths	77	131	244	39	41	532
	PM(%)	3.09	1.99	2.33	1.15	1.75	2.10
PERICARDITIS AND ENDOCARDITIS	Deaths	13	32	69	9	14	137
	PM(%)	0.52	0.48	0.66	0.27	0.60	0.54
MYOCARDITIS	Deaths	3	14	49	23	4	93
	PM(%)	0.12	0.21	0.47	0.68	0.17	0.37
CARDIOMYOPATHIES	Deaths	130	360	469	61	71	1091
	PM(%)	5.22	5.46	4.47	1.80	3.02	4.31
HEART FAILURE	Deaths	74	170	140	33	25	442
	PM(%)	2.97	2.58	1.33	0.98	1.06	1.75
CEREBROVASCULAR DISEASES AND OF OTHER VASSELS	Deaths	46	91	187	31	34	389
	PM(%)	1.84	1.38	1.78	0.92	1.45	1.64
OTHER DISEASES OF THE CIRCULATORY SYSTEM	Deaths	83	188	243	37	45	596
	PM(%)	3.33	2.85	2.32	1.09	1.92	2.36
SUBTOTAL DCS	Deaths	426	986	1401	233	234	3280
	PM(%)	17.11	14.97	13.36	6.89	9.96	12.97
CHAMBERS AND SEPTA	Deaths	300	715	1943	630	370	3985
	PM(%)	12.05	10.75	18.52	18.64	15.75	15.75
VALVES	Deaths	87	196	691	293	138	1405
	PM(%)	3.49	2.97	6.59	8.67	5.87	5.55
NON-SPECIFIED	Deaths	1284	3749	4666	1733	1324	12756
	PM(%)	51.57	56.90	44.48	51.27	56.36	50.43
OTHERS	Deaths	235	547	712	166	126	1786
	PM(%)	9.57	8.30	6.79	4.91	5.36	7.06
VESSELS	Deaths	158	395	1049	325	157	1727
	PM(%)	6.34	5.99	10.00	9.62	6.68	8.24
SUBTOTAL MCS	Deaths	2064	5602	7859	3147	2115	22016
	PM(%)	82.89	85.04	74.93	93.11	90.04	87.03
TOTAL DCS+MCS	Deaths	2490	6588	10489	3380	2349	25296
	PM(%)	100.00	100.00	100.00	100.00	100.00	100.00

DCS: Diseases of the Circulatory System; MCS: Malformations of the Circulatory System; PM(%): Proportional Mortality in percentage.

3. Cardiovascular Risk Factors

3.1. Introduction

According to data from the GBD Study 2019, there was a global reduction in the CVD mortality rate in past decades, tending to stagnation in recent years.¹ In women aged 35-54 years, there was a growing increase in the IHD mortality rate in the United States of America,^{8,43} attributed to the higher prevalence of traditional CVRFs.

According to data from the GBD Study 2019 and regarding Brazilian women (Figure 2.7), in the ranking of age-standardized mortality and DALYs rates attributable to risk factors, the following risk factors stood out in decreasing order: elevated systolic blood pressure, elevated BMI, dietary risks, high LDL-cholesterol, tobacco use, and high fasting glycemia. It is worth emphasizing the increased CVD prevalence in young women aged 15-49 years, from 1990 to 2019.^{7,44}

Regarding the risk of atherosclerotic CVD, women share some traditional CVRFs with men, while some other CVRFs are underrecognized in women (Chart 3.1 and Figure 3.1)² and others are female-sex/gender specific (Figure 3.2).

In clinical trials, despite the important relationship between CVRFs and CVD, women are underrepresented,

Chart 3.1 – Aggravating factors of the cardiovascular risk from diabetes mellitus in women.⁵⁰

- Women's age > 56 years and diabetes diagnosis >10 years
- Family history: first-degree relative with premature CVD (men <55 years and women <65 years)
- Tobacco use
- Systemic arterial hypertension
- Metabolic syndrome
- Albuminuria: creatinine >30 mg/g
- Glomerular filtration rate <60 ml/min
- Non-proliferative retinopathy
- Incipient cardiovascular autonomic neuropathy

and the scores used for cardiovascular risk stratification, such as Framingham, SCORE (*Systematic COronary Risk Evaluation*), SBC/SBD/SBEM, do not contemplate female sex-specific CVRFs, such as (Figure 3.2): POS, hormonal contraception use, GH, adverse events of pregnancy,

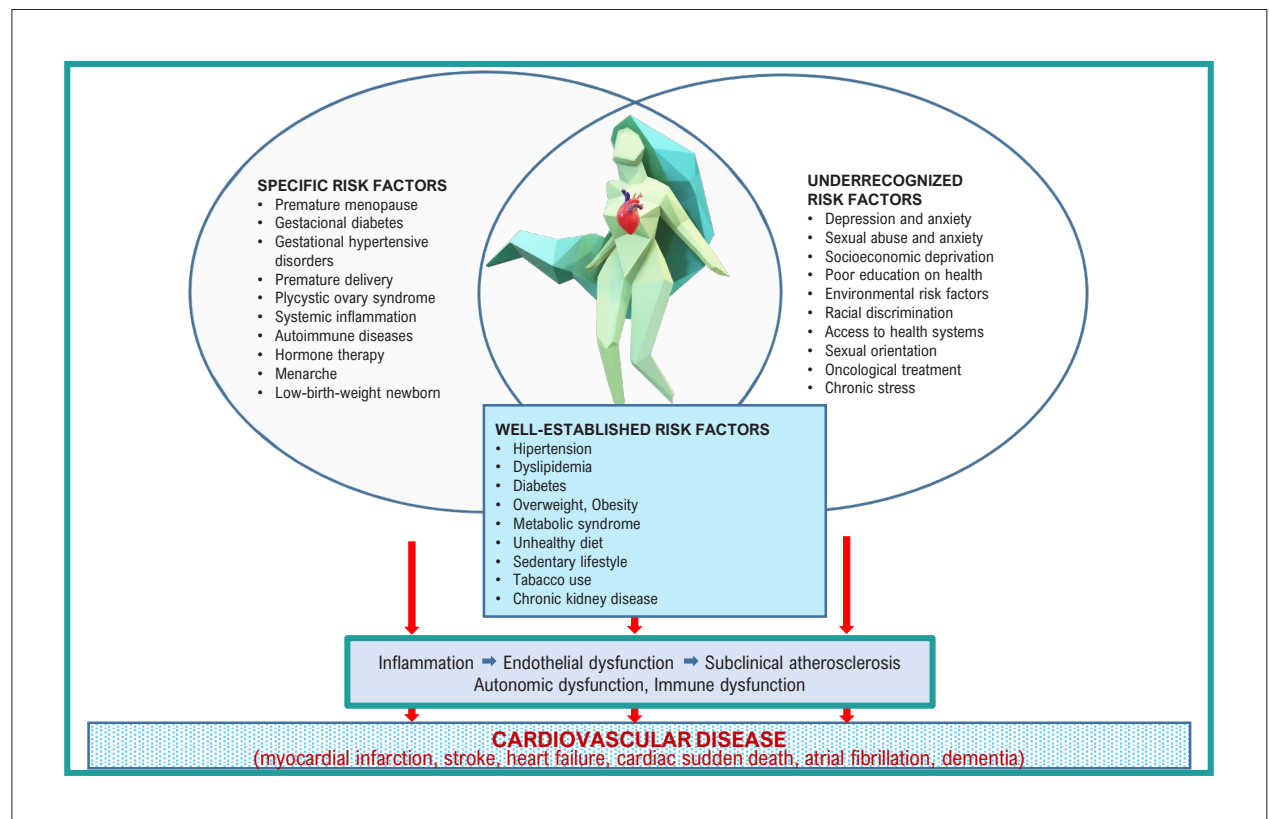


Figure 3.1 – Risk factors for cardiovascular disease in women. The well-established risk factors common to both sexes are incorporated into the risk scores of atherosclerotic cardiovascular disease. However, the sex-specific and the underrecognized risk factors interact with the traditional ones, aggregating risk, especially in women.

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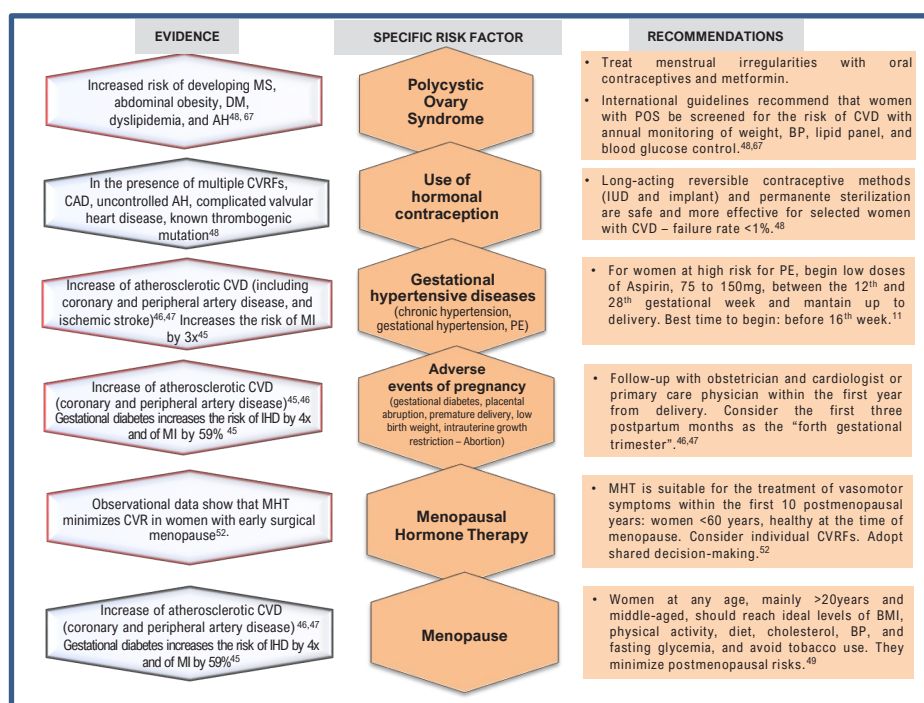


Figure 3.2 – Female sex-specific risk factors for cardiovascular diseases, with evidence and recommendations.^{11, 45–49} AH: arterial hypertension; BMI: body mass index; BP: blood pressure; CAD: coronary artery disease; CVD: cardiovascular disease; CVR: cardiovascular risk; CVRF: cardiovascular risk factor; DM: diabetes mellitus; IHD: ischemic heart disease; IUD: intrauterine device; MHT: menopausal hormone therapy; MI: myocardial infarction; MS: metabolic syndrome; PE: preeclampsia; POS: polycystic ovary syndrome.

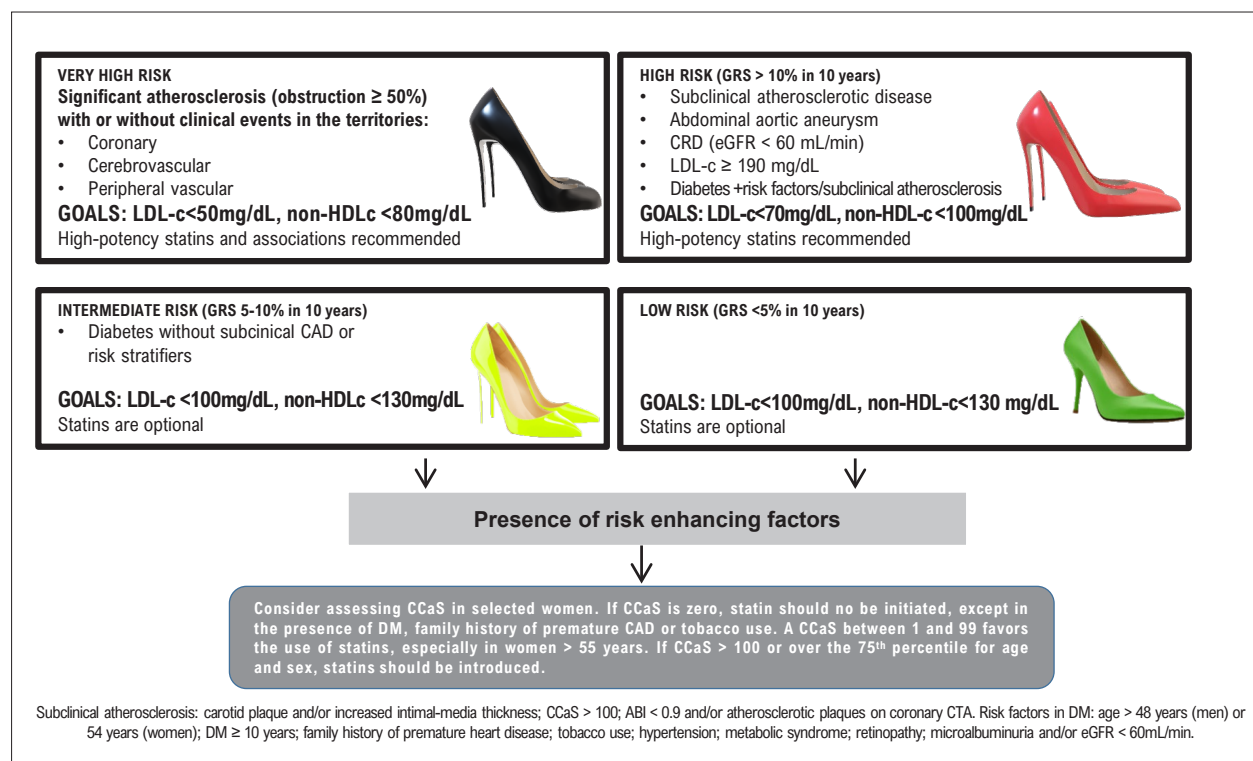


Figure 3.3 – Algorithm for the assessment of women's cardiovascular risk and the recommendation of statin use.⁵³ ABI: ankle-brachial index; CAD: coronary artery disease; CCaS: coronary calcium score; CRD: chronic renal disease; CTA: computed tomography angiography; DM: diabetes mellitus; eGFR: estimated glomerular filtration rate; GRS: Global Risk Score.

Chart 3.2 – Most prevalent risk factors for CVD in women, as well as the cardiovascular risk factors shared by men and women, with evidence. ^{11,43,45,53,55–58,65–67}

Risk factor	> risk for CVD in women	Evidence
Diabetes mellitus	X	SAH and inadequate diet are associated with high risk of pre-diabetes. Women with DM have a 45% higher risk of IHD. ^{45,67} DM2 is more common in women < 40 years and results in higher mortality. Relative risk of CVD mortality is higher in women than in men; the excessive risk of CVD mortality is higher in women. ^{45,67} Atherosclerotic events cause more congestive HF in women. ⁶⁷
Systemic arterial hypertension	X	Higher risk of myocardial infarction (INTERHEART). ⁶⁷ Higher prevalence of pre-menopausal secondary hypertension. Post-menopausal women less often have nocturnal blood pressure decrease, but more events. Women more often develop ventricular hypertrophy, HFpEF, arterial stiffness, CRD, and DM. Women more often have adverse effects with anti-hypertensive drugs. SAH affects 80% of women > 75 years. Only 29% have proper control of SAH. ⁴⁵
Dyslipidemia (*)		In the SWAN study, the levels of TC, LDL-c, and triglycerides showed a peak in the transition from menopause to the early post-menopausal phase. ⁶⁵ Recent meta-analysis showed no significant difference in HDL-c levels between pre- and post-menopause. ⁶¹
Obesity (*)		The Framingham Heart Study showed an increase in the risk of CAD: 64% in women versus 46% in men. ⁴⁵ More prevalent in Brazilian women than men. The most important RF for SAH in women. Associated with adverse outcomes in pregnancy.
Sedentary lifestyle (*)		Higher prevalence of inactivity among women. 25% of women do not practice physical activity regularly. ^{43,45}
Tobacco use (*)		Women have a 25% higher risk of CAD as compared to men, except in the younger age group (30–44 years). ^{43,67}
Atrial fibrillation	X	As compared to men with AF, women have a 20–30% higher risk of stroke, higher severity, and worse long-term result regarding permanent disability. The female sex was associated with age >65 years or >2 risk factors in the CHA2DS2-VASc regarding nonvalvular AF. ⁶⁷
Metabolic syndrome (*)		In the SWAN study, the risks of MS in pre-menopausal and menopausal women are 1.45x and 1.25x higher, respectively. ⁶⁵
Rheumatoid arthritis		50% increase in the risk of CVD mortality as compared to that of the general population. ⁶⁷
Systemic lupus erythematosus		The risk of IHD is three times higher. ⁴⁵ More prevalent in Asian, Afro-American, Afro-Caribbean, and Hispanic women as compared to Caucasian women. Black women are 2–4 times more likely to have SLE than white women. IHD is the major cause of mortality in SLE. ⁶⁷
Depression (**)	X	Common in women with IHD. Independent risk factor for worse outcomes. ⁵⁶ Women are more susceptible, with a 2-time increase in the risk of IHD. ⁴⁵
Mental stress (anxiety, psychosocial stress) Vital exhaustion	X	Studies have shown the association of mental stress, microvascular dysfunction, and coronary vasospasm in patients with INOCA, ⁵⁸ mainly women.
Social Determinants of Health		SDH have negative outcomes that, added to the classical and sex/gender-specific CVRFs, cause vascular inflammation and endothelial dysfunction, culminating in CVD. ⁵⁹

(*) risk factors with attributed risk similar in both sexes. (**) Basic questions: How do you think your health will be in the future? How often do you feel pleasure or happiness? Have you ever been grateful for your health or any other thing in your life? - Analyzes optimism, positive affection, and gratitude, respectively,⁵⁶ and might help recognition and specific approach. ACEI: angiotensin-converting-enzyme inhibitor; AF: atrial fibrillation; BMI: body mass index; BRA: angiotensin-receptor blocker; CAD: coronary artery disease; CVD: cardiovascular disease; CRD: chronic renal disease; SDH: social determinants of health; RF: risk factor; CVRF: cardiovascular risk factor; DM: diabetes mellitus; DM2: diabetes mellitus type 2; DOAC: direct oral anticoagulants; HDL-c: high-density lipoprotein cholesterol; HF: heart failure; HFpEF: heart failure with preserved ejection fraction; IHD: ischemic heart disease; INOCA: ischemia with non-obstructive coronary arteries; LDL-c: low-density lipoprotein cholesterol; MS: metabolic syndrome; SAH: systemic arterial hypertension; SLE: systemic lupus erythematosus; TC: total cholesterol.

Statement

Chart 3.3 – Recommendations for the management of dyslipidemia in women.

Recommendations for the management of dyslipidemia in women			
Recommendation	CR	LE	References
Nutritional therapy, body weight loss, and physical activity should be recommended for all patients.		A	26,43,51,67
Reduce sodium intake and maintain adequate consumption of fresh fruits, vegetables, and low-fat dairy products. Maintain body weight and waist circumference within normal range.		A	26,51,53,67
At least 30 minutes of moderate dynamic aerobic exercise (walking, running, biking, or swimming) 5 to 7 days per week. Gradually increase aerobic physical activity to 300 minutes per week of moderate intensity or 150 minutes per week of vigorous aerobic physical activity, or an equivalent combination of both, ideally with daily supervised exercise.		A	26,43,51,67
Women at very high and high cardiovascular risk: LDL-c should be reduced to < 50 mg/dL and < 70 mg/dL, and non-HDL-c to < 80 mg/dL and < 100 mg/dL, respectively.		B	51,52,53,
Women at intermediate cardiovascular risk: LDL-c should be reduced to < 100 mg/dL, and non-HDL-c to < 130 mg/dL.		A	51,52,53
Women at low cardiovascular risk: the goal is LDL-c < 130 mg/dL and non-HDL-c < 160 mg/dL.		A	51,52,53
Medicamentous treatment is not recommended for pregnant women.		A	11,43,47,67
Bile acid sequestrants are considered safe for use while breastfeeding.		B	11,43,47,67
Rosuvastatin and pravastatin at low doses have been studied and their use can be considered while breastfeeding if the benefits exceed the potential risks.		B	11,43,47,67

CR: class of recommendation; LE: level of evidence; HDL-c: high-density lipoprotein cholesterol; LDL-c: low-density lipoprotein cholesterol. The minimum reassessment time after medicamentous treatment should be of one month. Adapted from Update of the Guideline on Dyslipidemias and Atherosclerosis Prevention.⁶³ Similarly to the recommendation on the use of medicines during pregnancy, the authors of this article recommend a shared decision-making between patient and clinician to determine the ideal clinical management for individual patients.

menopausal hormone therapy, and risks associated with the socioeconomic, psychosocial and environmental status. In addition, the scores do not contemplate the association with inflammatory (HIV) and autoimmune (rheumatoid arthritis, systemic lupus erythematosus, psoriasis) diseases,⁸ anxious-depressive disorders, and SDH, considered REFs in women.

When assessing cardiovascular risk, it is essential to consider, in addition to risk stratifiers (Figure 3.3), the aggravating risk factors associated with diabetes mellitus (Chart 3.2), the REFs, and the sex-specific RFs to establish changes in lifestyle and recommend measures for primary prevention of CVD, aimed at identifying and treating earlier a larger number of women at risk.^{7,8,44}

Chart 3.4 – Recommendations for the management of diabetes and metabolic syndrome in women.

Recommendations for the management of diabetes and metabolic syndrome in women			
Recommendation	CR	LE	References
The strategies of body weight control, physical activity, dietary guidance, and smoking cessation should be provided to all women with glucose intolerance, MS, or DM to reduce CV risk.		A	26,43,50,51,52,67
The risk of coronary events should not be stratified by use of anatomic or functional methods in asymptomatic women with MS or DM.		A	26,43,50,51,52,67
The CCaS should be used in women with DM or MS and intermediate CV risk (GRS 5-10% in 10 years). If CCaS = 0, statins should not be initiated.		B	26,43,50,51,52,53,67
In primary prevention, women with DM or MS for whom statin therapy is indicated should receive high-potency doses and/or ezetimibe, and the goal should be LDL-c < 70 mg/dL.		A	26,43,50, 51,52,67
Alternatively, in women with DM or MS at high or very high risk, the goal should be LDL-c < 50 mg/dL.		B	
The use of ASA is not recommended for primary prevention in women with MS or DM, regardless of their CV risk.		A	26,43,50,51,53,67
The use of ASA is recommended for prevention in women with MS or DM, at high or very high risk, in the absence of contraindication or risk of bleeding.	 a	B	26,43,50,51,52,67
Regarding pharmacological treatment, there is no gender difference in the recommendations, except for those related to pregnancy.		A	11,26,43,50,51,52,67

CR: class of recommendation; LE: level of evidence; ASA: acetylsalicylic acid; CCaS: coronary calcium score; CV: cardiovascular; DM: diabetes mellitus; GRS: global risk score; LDL-c: low-density-lipoprotein cholesterol; MS: metabolic syndrome.

The risk estimation of cardiovascular events in women aimed at primary prevention is limited. The ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease identifies situations involving apparently healthy women with REFs, which require a shared decision-making with a cardiologist, an obstetrician gynecologist, and the patient about the use of mid-potency statin for low or intermediate risk. There is no evidence about the use of statins, and the assessment of the CCaS is necessary in selected women. If the CCaS is zero, statin should not be initiated, except in the presence of: DM, family history of premature CAD, or tobacco use. A CCaS between 1 and 99 favors the use of statins, mainly in women > 55 years. If CCaS > 100 or above the 75th percentile for age and sex, statins should be introduced (Figure 3.3).^{51,52}

The 2017 Brazilian Guideline on Dyslipidemias and Atherosclerosis Prevention⁵³ and the 2019 SBC Update of the Guideline on Cardiovascular Prevention²⁶ recommend the use of the Global Risk Score,⁵⁴ which estimates the 10-year risk of fatal or nonfatal myocardial infarction and stroke, heart failure, and peripheral vascular failure. Figure 3.3 suggests an algorithm for the assessment of women's cardiovascular risk and the recommendation of statin use.

The anxiety-depression disorders, such as mood, behavior, and affection changes, accompanied or not by somatic changes or cognitive deficit, are common causes of disability in developed countries and considered REFs by the AHA/ACC and the European Society of Cardiology. Women are more susceptible to anxiety-depression

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Chart 3.5 – Recommendations for the management of tobacco use in women.

Recommendations for the management of tobacco use in women			
Recommendation	CR	LE	References
Women's tobacco use and exposure should be routinely assessed at all consultations with healthcare professionals and written down in the medical chart.		A	26,43,51,52,67
Systematic counseling of all women for tobacco use cessation.		A	26,43,51,52,67
A combination of cognitive-behavioral and pharmacological interventions is recommended to all women to maximize the cessation rates.		A	26,43,51,52,67
Smoking abstinence is recommended for all women to reduce the cardiovascular risks.		A	26,43,51,52,67
Multidisciplinary teams should be assigned to facilitate smoking cessation in all healthcare systems.	 a	B	26,43,51,52,67

CR: class of recommendation; LE: level of evidence.

Chart 3.6 – Recommendations for the management of overweight and obesity in women.

Recommendations for the management of overweight and obesity in women			
Recommendation	CR	LE	References
For overweight and obese women, body weight loss is recommended to improve the cardiovascular risk profile.		B	26,43,51,52,67
Counseling and comprehensive interventions in lifestyle, including caloric restriction, are recommended to achieve and maintain weight loss in overweight and obese women. Emphasize the relationship between overweight and obesity with increased cardiovascular risk.		B	26,43,51,52,67
Calculate the body mass index and take anthropometric measures in medical visits to identify overweight and obese women aiming at intervening.		C	26,43,51,52,67
The treatment should involve a multidisciplinary team, and, when proper weight reduction is not achieved, pharmacological treatment and bariatric surgery should be considered. Medication should be used if BMI > 30 or >27 in the presence of comorbidities.		B	26,43,51,52,67
Assess waist circumference to identify women at higher cardiometabolic risk.	 a	B	26,43,51,52,67
The use of pharmacological drugs to reduce body weight during pregnancy and while breastfeeding is not recommended. Special attention should be paid to women at childbearing age.		B	26,43,51,52,67

CR: class of recommendation; LE: level of evidence; BMI: body mass index.

disorders, which double the risk of IHD. Behavioral, hormonal, genetic, and psychosocial changes overlap and, from the pathophysiological viewpoint, promote endothelial dysfunction, atherothrombosis, and immune and hemostasis

dysfunctions from changes in the hypothalamus-hypophysis-adrenal axis and autonomous nervous system (Figure 3.1). In addition, the estrogens stimulate T and B lymphocytes, propitiating a higher immune and inflammatory response.

Chart 3.7 – Recommendations for the management of arterial hypertension in women.

Recommendations for the management of arterial hypertension in women			
Recommendation	CR	LE	References
For all women with high BP or hypertension, nonpharmacological measures are indicated to reduce BP: body weight loss, healthy dietary pattern, sodium reduction, dietary potassium supplementation, increase in physical activity with a structured exercise program, and limited alcohol intake.		A	26,43,51,52,67
Anti-hypertensive medication is recommended for women with an estimated risk $\geq 5\%$ in 10 years and mean systolic BP ≥ 130 mm Hg or mean diastolic BP ≥ 80 mm Hg, for primary prevention of CVD.		A	26,43,51,52,67
For women with confirmed hypertension and CV risk $\geq 10\%$, target BP $< 130/80$ mm Hg is recommended.		B	26,43,51,52,67
For women with arterial hypertension and chronic renal disease, target BP $< 130/80$ mm Hg is recommended.		B	26,43,51,52,67
For women with arterial hypertension and type 2 diabetes, target BP $< 130/80$ mm Hg is recommended, and anti-hypertensive medication should be initiated if BP $\geq 130/80$ mm Hg.		B	26,43,51,52,67
For women with estimated risk $< 10\%$ in 10 years and BP $\geq 140/90$ mm Hg, anti-hypertensive medication is recommended for primary prevention of CVD.		C	26,43,51,52,67
For women with confirmed hypertension and no additional markers of increased CV risk, target BP $< 130/80$ mm Hg is recommended.	 b	B	26,43,51,52,67
Use neither ACEI nor ARB for women at childbearing age and with perspective of pregnancy because of their possible teratogenic effects.		A	26,43,51,52,67
Secondary hypertension is common in young and older women, and hypertensive adolescents and young adults should be screened to prevent long-term CV complications and specific treatment should be initiated		A	26,43,51,52,67

CR: class of recommendation; LE: level of evidence; ARB: angiotensin-receptor blocker; CV: cardiovascular; CVD: cardiovascular disease; ACEI: angiotensin-converting-enzyme inhibitor; BP: blood pressure.

Statement

Chart 3.8 – Recommendations for the management of physical activity in women.

Recommendations for the management of physical activity in women			
Recommendation	CR	LE	References
During medical visits, physicians should advise their patients to practice physical activity.		B	26,43,51,52,67
Physical activity: ≥ 150 minutes/week of moderate intensity exercise or 75 minutes/week of vigorous exercise reduce cardiovascular risk.		A	26,43,51,52,67
Physical activity: < 150 minutes/week of moderate intensity exercise or < 75 minutes/week of vigorous exercise reduce cardiovascular risk.	 a	B	26,43,51,52,67
Physical activity: > 150 minutes/week of moderate intensity exercise throughout pregnancy without complications.		A	26,43,51,52,67

CR: class of recommendation; LE: level of evidence.

Such overlaps justify the relationship between depression and CVD, mainly IHD. In this context, physical exercise has been recognized as effective for the treatment of depression, similarly to psychotherapy and the use of serotonin inhibitors. Aerobic exercises seem to promote better benefit.⁵⁵⁻⁵⁹

Regarding the SDH, the diversity of race and ethnicity, educational level, racism, and discrimination, inaccessibility to health care systems, absence of social support, economic instability, sexual orientation, and violence are factors that lead to disparities, affect women, and generate negative outcomes, which, added to the classic CVRFs and sex/gender-specific risk factors, promote vascular inflammation and endothelial dysfunction, culminating in CVD (Figure 3.1).^{26,59-63}

A cross-sectional study to calculate the cardiovascular risk, using laboratory data from a subsample of the PNS with 3584 women, has found 58.4% at low cardiovascular risk, 32.9% at intermediate risk, and 8.7% at elevated risk. The risk increased with age, being high in the population with low educational level. The proportion of the components of the Framingham model, according to risk groups and sex, shows that, for women at high risk, the major contributors to cardiovascular risk were: systolic blood pressure, total cholesterol, HDL, DM, and tobacco use.⁶⁴

Charts 3.3, 3.4, 3.5, 3.6, 3.7 and 3.8 show recommendations for the management of dyslipidemia, diabetes, metabolic syndrome, tobacco use, overweight and obesity, arterial hypertension, and physical activity in women.

4. Cardiovascular Diseases in Women

4.1. Ischemic Heart Disease

In women, IHD accounts for 47% of the deaths from CVD, while stroke, to 36%.¹ The IHD pathophysiology,

clinical presentation, diagnosis, treatment, and prevention are shown in Table 4.1.

Currently, the term 'IHD' is more suitable to refer to the coronary disorders causing ischemia, previously referred to as CAD. Ischemic heart disease includes CAD, INOCA, MINOCA, SCAD, MVD, CVP, and coronary embolism/thrombosis.

4.1.1. Coronary Artery Disease

CAD is the major cause of myocardial infarction in women. Sex/gender-related differences are especially pronounced in CAD and its peculiarities are shown in Table 4.1.

4.1.2. Ischemia with Non-obstructive Coronary Arteries

INOCA is more common in women than in men, with especially high prevalence among women aged 45-65 years. It is not a benign condition, being associated with an increased risk of adverse cardiovascular events.⁶⁹ The strategies for the management of INOCA have not been well defined, mainly because there is not enough evidence on the treatment of the microvascular dysfunction associated with INOCA.⁷⁰

4.1.3. Myocardial Infarction with Non-obstructive Coronary Arteries

MINOCA is related to several pathophysiological mechanisms of coronary disorders (Table 4.1). Its prevalence is 5-10%, considering all AMI, and two-thirds of the patients have NSTEMI.⁶⁹

It is more common in younger women than men (10.5% vs 3.4%; $p < 0.0001$). Cardiovascular RFs can be present, although less prevalent than in patients with CAD.⁶⁹

Table 4.1 – General characteristics of ischemic heart disease.

	CAD ⁷⁰	INOCA ⁶⁹	MINOCA ⁷¹	SCAD	Vasospasm ⁷²	Microvascular disease ⁷⁰	Coronary thrombosis/embolism ⁷³
Pathophysiology	- Smaller atherosclerotic plaque - Plaque erosion with distal embolization - Diffuse atherosclerosis associated with microvascular and endothelial dysfunction	- Microvascular dysfunction and/or epicardial and microvascular vasospasm	- Coronary vasospasm, microvascular dysfunction, spontaneous coronary thrombosis and rechanneled emboli, plaque rupture, and spontaneous coronary artery dissection	- Nontraumatic, non-iatrogenic, and non-atherosclerotic separation of the coronary artery wall, due to spontaneous rupture of the intima or vasa vasorum within the arterial wall - Intramural hematoma within the false lumen, compressing the true lumen, causing ischemia or myocardial infarction - Increased shear stress - Emotional/physical triggers	- Epicardial or microvascular vasoconstriction related to endothelial dysfunction - Multiple mechanisms: autonomous nervous system (circadian variation with morning predominance), endothelial dysfunction, chronic inflammation, oxidative stress, and smooth muscle hypercontractility	- Structural remodeling - Microvascular spasm - External compression (myocardial hypertrophy) - Reduced microcirculatory conductance and/or dynamic arteriolar obstruction	- Thrombophilia, atrial fibrillation, valvular disease, patent <i>foramen ovale</i>, infective endocarditis, and non-bacterial thrombotic endocarditis
Clinical presentation	- Older women - Chest pain (precordial/retrosternal); jaw/neck pain - Fatigue, nausea - Stable/unstable angina - AMI	- Wide spectrum: from clinical manifestations, such as chest discomfort, to angina and anginal equivalents	- AMI - 2/3 of the cases are NSTEMI (exclude myocarditis, Takotsubo, PPCM and PE) - Rule out: sepsis, PE, non-cardiac causes of troponin elevation	- Wide spectrum: from mild chest pain, ACS, AMI to sudden cardiac death - Most common cause of AMI in pregnancy and puerperium	- Wide spectrum: from silent disease to sudden cardiac death Angina/AMI	- Angina - Dyspnea on exertion	- AMI
Clinical diagnosis / complementary tests	- Similar in women and men	- Non-invasive tests: CMRI associated with adenosine; PET - Invasive tests: intracoronary acetylcholine and hyperemia with intracoronary adenosine (CFR and IMR)	- Transient until the cause is established - Clinical findings of AMI - Troponin - Coronary angiography without obstructive CAD, CCT, ICUS - CMRI	- No traditional CVRF - Knowledge about the predisposing RF: fibromuscular dysplasia (50-86%), connective tissue disorders (5%), systemic inflammatory diseases (5-12%), hormone therapy (estrogen, progesterone, gonadotropin, clomiphene, or infertility treatment) - Previous multiple pregnancies - Coronary CTA - Coronary angiography	- Coronary angiography associated with intracoronary acetylcholine provocation test	- Association with inflammatory markers (systemic lupus erythematosus and rheumatoid arthritis) - Non-invasive tests: reversible defects - Invasive tests: FFR > 0.8; CFR < 2.0; IMR ≥ 25	- Coronary angiography / aspiration thrombectomy
Prevention	- Knowledge about the differences in ACS/CCS clinical findings - Improve diagnosis and treatment - Identify and treat classical CVRFs and women-specific RFs	- Identify and aggressively treat classical CVRFs and women-specific RFs - Identify risk enhancing factors (psychosocial factors and social determinants of health)	- Identify and treat classical CVRFs and women-specific RFs - Identify risk enhancing factors (psychosocial factors and social determinants of health)	- Reduce emotional triggers, avoid hormone therapy (estrogen, progesterone, chorionic gonadotropin) - Prevent pregnancy - Cardiac rehabilitation, preferably with modified protocol, avoiding heavy isometric exercises and intense aerobic activities	- Avoid aggravating factors: use of illegal drugs, amphetamines, butane gas, alcohol, and medications for migraines	- Modification of CVRFs (weight loss and stress control)	- Early diagnosis of the underlying causes and thrombosis/infection prophylaxis
Outcomes	- Woman: higher in-hospital and 30-day mortality - Higher mortality in women under 50 years of age	- Recurring angina - Frequent hospitalizations - Repeated coronary angiographies - High rates of major CV events	- Prognosis depends on the underlying cause - Mortality: similar to that of CAD - Disability: similar to that from CAD	- Frequent recurrence, mainly in the postpartum period and in women with connective tissue diseases	- Recurrence rate from 3.9% to 18.6% - Arrhythmia and sudden death	- Recurring angina - Frequent hospitalizations - Repeated coronary angiographies - High rates of major CV events	- Good prognosis in most cases undergoing early thrombectomy

ACS: acute coronary syndrome; AMI: acute myocardial infarction; CAD: coronary artery disease; CTA: computed tomography angiography; CCS: chronic coronary syndrome; CFR: coronary flow reserve; CMRI: cardiac magnetic resonance imaging; CV: cardiovascular; CVRF: cardiovascular risk factor; FFR: fractional flow reserve; IMR: index of microcirculatory resistance; NSTEMI: non-ST elevation myocardial infarction; PE: pulmonary embolism; PET: PET scan; PPCM: peripartum cardiomyopathy; RF: risk factor; CCT: coronary computed tomography; ICUS: intracoronary ultrasound.

Statement

MINOCA is a transient diagnosis that requires confirmation of its causes. First, AMI due to epicardial coronary obstruction should be excluded. Then, it is paramount to search for the underlying cause; failure in identifying that cause can result in inadequate treatment and information.⁷⁰

4.1.4. Spontaneous Coronary Artery Dissection

SCAD is a rare cause of myocardial infarction, representing 1-4% of all ACS. Corresponds to the spontaneous rupture of the intima or of the *vasa vasorum* within the arterial wall, resulting in accumulation of intramural hematoma in the false lumen, which can compress the true lumen, causing ischemia or myocardial infarction.

SCAD is increasingly recognized as an important cause of myocardial infarction in women under the age of 50 years. According to some studies, 25-35% of the cases of SCAD occur in women under the age of 50 years and 25% in women over the age of 60 years. In addition, it is the most common cause of myocardial infarction associated with pregnancy (up to 43% of the cases), occurring mainly in the third trimester or postpartum period. The risk of recurring events is substantial.⁷⁰

4.1.5. Microvascular Disease

Its pathophysiology results from structural remodeling with consequent conductance reduction or arteriolar vasomotor disorders, or both. The diagnostic confirmation of MVD should meet the following criteria: presence of symptoms (angina and/or dyspnea on exertion); absence of obstructive disease; objective evidence of ischemia; and changes in the microvascular function (reversible defects, abnormalities on the invasive functional tests – IMR > 25).⁶⁹

MVD associates with pro-inflammatory markers in women with INOCA; thus, there is increased risk in diseases such as systemic lupus erythematosus and rheumatoid arthritis. After menopause, these diseases are more frequent in women, which can contribute to the sexual differences of MVD.⁶⁹

4.1.6. Coronary Vasospasm

CVP is defined by reversible diffuse or focal vasoconstriction, common in patients with IHD and present in the mechanisms of INOCA, MINOCA and MVD, regardless of racial, genetic, and geographic variations. It is more prevalent in women aged 40-70 years.⁶⁹

The intracoronary acetylcholine provocation test remains the fundamental tool for the diagnosis of CVP, and women have a higher response to smaller doses. This test allows the reproduction of CVP and the assessment of reactivity to nitrates.

4.1.7. Coronary Thrombosis/Embolism

Coronary artery embolism is an underdiagnosed cause of ACS, and can be classified into three types:

direct, paradoxical (thrombus originated from deep venous thrombosis that transposes the *foramen ovale*), and iatrogenic. In the third type, percutaneous coronary intervention is the most common cause of the embolism, and the risk is increased with rotation techniques, valvuloplasty, and inadequate anticoagulation of the procedure.

4.2. Heart Failure

Epidemiological studies have shown similar incidence of HF in men and women. However, hormonal changes, mainly postmenopausal, are responsible for peculiar characteristics of HF in women, which contribute to the higher prevalence of HFpEF (EF ≥ 50%) as compared to HFrEF (EF ≤ 40%).^{9,74,75} Figure 4.1 shows the pathophysiological mechanisms related to HF in women due to the hormone cycle.¹⁰

There are sex/gender-related differences not only regarding HF epidemiology, but also regarding HF clinical presentation, outcomes, and treatment (Figure 4.2).^{74,75} Those differences are even more evident when the different phenotypes of HF are analyzed in isolation: HFrEF (EF ≤ 40%) and HFpEF (EF ≥ 50%).⁹

Two clinical conditions that can evolve to HF in women are worth noting: Takotsubo syndrome, a reversible acute left ventricular dysfunction, in which 90% of the patients are women, especially after menopause;¹⁰ and peripartum cardiomyopathy, defined as left ventricular dysfunction at the end of pregnancy or in the first months after delivery, without any other evident cause.⁷⁶ Table 4.2 shows the major characteristics of those pathologies.

Data from acute HF registries have shown that women and men are equally affected (50%), with no evidence of differences in mortality between men and women (Table 4.3),⁷⁷ although women have a higher risk profile (older age and higher number of comorbidities). However, in clinical studies/registries of cardiogenic shock/ mechanical circulatory support, women are underrepresented.

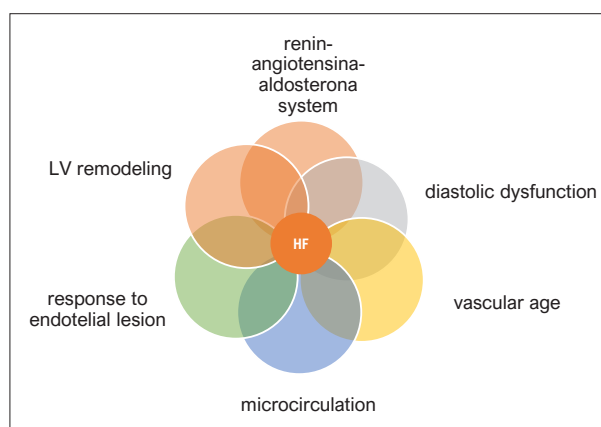


Figure 4.1 – Pathophysiological mechanisms related to heart failure in women. LV: left ventricular; HF: heart failure

The best way to prevent progression to advanced HF is the institution of adequate treatment for HF. However, when not sufficient, the gold-standard treatment is CT for both sexes. The mean long-term survival is significantly higher in the female sex, and sex-mismatch transplant (female donor/male receptor) has worse prognosis.⁷⁰ Regarding the use of long-term ventricular assistance devices, the results have improved. One indication for ventricular assistance device use is contraindication to CT, such as hypersensitization, which is frequent in multiparous women. Women tend to have a higher risk for stroke and right ventricular dysfunction, in addition to be underrepresented in most registries.⁷⁷

4.2.1. Pharmacological and Nonpharmacological Treatment of HFrEF and HFpEF

Considering that ischemic cardiomyopathy is the most frequent etiology of HFrEF in women, establishing measures to prevent CAD, such as dyslipidemia and hypertension control, tobacco use cessation, and physical activity encouragement, is essential (Figure 4.2). The pharmacological treatment of HFrEF with angiotensin-converting-enzyme inhibitors, beta-blockers, mineralocorticoid antagonists, ARNI, and SGLT2 inhibitors has shown to unequivocally reduce general death or cardiovascular mortality and hospitalization due to HF.⁹ Those benefits are similarly for men and women, and, thus, the pharmacological treatment prevents sudden death and disease progression

to advanced HF that requires specific therapies. However, women are underrepresented in most studies on HFrEF (20-30%); therefore, studies involving a higher number of women with HFrEF are required (Table 4.4).¹⁰

The pathophysiology of HFpEF is directly related to obesity, increased insulin resistance and metabolic syndrome. Thus, weight reduction and physical activity encouragement are essential to prevent HFpEF, especially in women (Figure 4.2). Regarding pharmacological treatment, the evidence is not so robust, and, even until recently, there was no medicamentous therapy recommended.⁹ Randomized studies have shown a neutral effect of the major drugs used for HF.⁷⁷ Subanalyses of two of those studies, one involving spironolactone (TOPCAT) and another involving ARNI (PARAGON-HF), have suggested different responses to therapy according to sex. In addition, SGLT2 inhibitors have shown benefits in HFpEF with similar results in men and women (Table 4.5).¹⁰ Thus, current evidence points to benefit from iSGLT2 in both sexes and potential benefit from spironolactone and sacubitril-valsartan in women.⁷⁶ Prospective studies to assess differences between sexes are necessary.

Usually, in both chronic and acute HF, clinical trials especially directed to women are scarce and the evidence derive from subanalysis of large studies in which women are underrepresented. However, the identification of potential RFs for the development of HF in women and

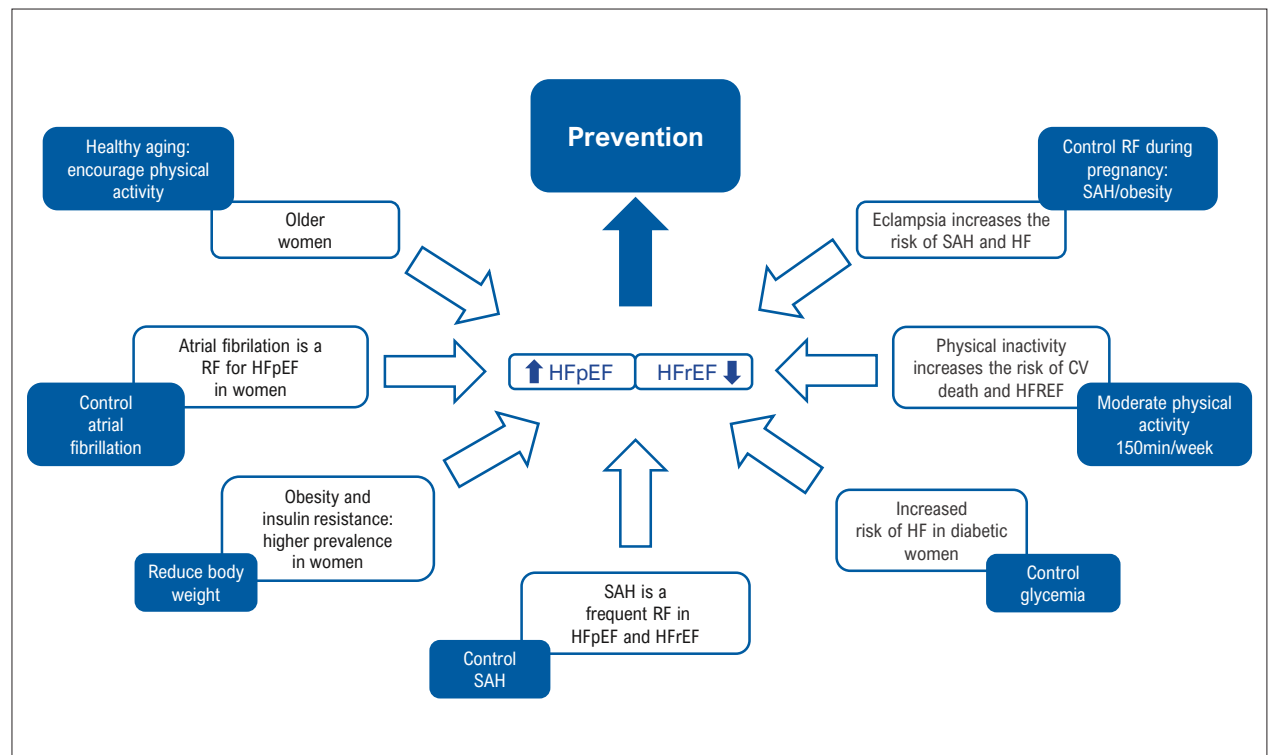


Figure 4.2 – Risk factors, characteristics, prognosis, and measures to prevent HFrEF and HFpEF in women. HF: heart failure; HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction; SAH: systemic arterial hypertension; RF: risk factor; CV: cardiovascular.

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Table 4.2 – Characteristics of the Takotsubo syndrome and peripartum cardiomyopathy.

Clinical condition	Takotsubo Syndrome	Peripartum Cardiomyopathy
Women (%)	90%	100%
Mean age	Elderly – frequently postmenopausal (90% aged 58-75 years)	Childbearing age
Definition	Reversible acute left ventricular dysfunction	Left ventricular dysfunction at the end of pregnancy or first postpartum months
Risk factors	Typical emotional or physical trigger, but not always present More common in postmenopausal women	✓ Afro-American ethnicity ✓ Advanced maternal age ✓ SAH or preeclampsia ✓ Multiple pregnancies
Characteristics	✓ Acute chest pain suggestive of ACS ✓ Electrocardiographic changes suggestive of ACS ✓ Dyspnea ✓ Palpitation ✓ Pre-syncope / syncope due to ventricular arrhythmia or ✓ Cardiogenic shock	✓ Dyspnea, orthopnea, lower limb edema, palpitation ✓ Signs of congestion at the end of pregnancy ✓ Thromboembolic events ✓ Ventricular arrhythmias ✓ Cardiogenic shock
Diagnosis	✓ ECG: ST elevation or T inversion + prolonged QTc ✓ ECHO: segmental alteration that extends beyond a single artery territory ✓ High natriuretic peptides ✓ Mild troponin elevation (occurs in more than 90%) ✓ Disparity between the degree of troponin elevation and the severity of LV dysfunction ✓ MRI: LV dysfunction; RV assessment; thrombus; no late enhancement (different from myocarditis) ✓ Coronary angiography: absence of coronary lesions with apical and middle-apical hypokinesia on ventriculography	✓ Diagnosis can be delayed due to confusion with usual symptoms of pregnancy ✓ Differential diagnosis with myocarditis, Takotsubo, hypertrophic cardiomyopathy, etc ✓ ECHO: left ventricular dysfunction; presence of thrombus ✓ High natriuretic peptide levels ✓ Holter: might reveal ventricular arrhythmias
Prevention	✓ Related to menopause (estrogen deficiency, but hormone replacement does not reduce the risk for HF)	✓ Control risk factors that predispose to PPCM: hypertension, diabetes, obesity, eclampsia
Treatment	✓ Beta-blocker if LVEF < 45%, AF, ventricular arrhythmia ✓ ACEI if LVEF < 45% ✓ Anticoagulation if apical thrombus ✓ MCS if cardiogenic shock	BOARD ✓ B: Bromocriptine is indicated (increasing doses according to PPCM severity) ✓ O: Oral treatment for HF according to guidelines ✓ A: Anticoagulation (at least prophylactic) ✓ R: Relaxant (vasodilators) IV and inotropic drugs for severe PPCM ✓ D: Diuretics if congestion For the most severe cases: ✓ IAB, ECMO for cases of rapid deterioration despite inotropic drugs ✓ Transplant or VAD if symptoms persist despite optimal therapy
Prognosis	Usually good prognosis with early recovery of LV function, but severe complications can occur before recovery Cardiogenic shock (6-20%) In-hospital mortality (<5%)	Usually good prognosis (40% increase LVEF to > 50%) Persistent dysfunction or rapid deterioration can occur LVEF < 35% at presentation confers worse prognosis
Follow-up	Imaging test to confirm LV function recovery: ECHO or MRI Recurrence in up to 22%	Improvement from 6 months to 5 years in general New pregnancy is not advised because of the risk of recurrence

ACS: acute coronary syndrome; AF: atrial fibrillation; ACEI: angiotensin-converting-enzyme inhibitor; CATH: cardiac catheterization; ECG: electrocardiogram; ECHO: echocardiogram; ECMO: extracorporeal membrane oxygenation; HF: heart failure; IAB: intra-aortic balloon; IV: intravenous; LV: left ventricular; LVEF: left ventricular ejection fraction; MCS: mechanical circulatory support; MRI: magnetic resonance imaging; PPCM: peripartum cardiomyopathy; RV: right ventricular; SAH: systemic arterial hypertension; VAD: ventricular assistance device.

Table 4.3 – Differences in characteristics and outcomes between men and women with decompensated heart failure and/or cardiogenic shock.

CLINICAL STUDY	ADHERE Decompensated HF	IABP-SHOCK II Cardiogenic shock – IAB	cVAD Registry Cardiogenic shock – IMPELLA
Women (%)	52%	31%	27%
Year	2001-2004	2009-2012	2007-2013
	Older women (75 vs 70 years)	Older women (74 x 68 years)	Older women (71 x 64 years)
Characteristics	Higher % of comorbidities: ✓ SAH ✓ Thyroid disease Smaller % of ischemic etiology (19% vs 32%) Higher LVEF(42% vs 33%)	Higher % of comorbidities: ✓ SAH (76% vs 66%) ✓ DM (40% vs 29%) Smaller % of ischemic etiology (16% vs 25%) Higher LVEF (40% vs 35%)	Higher % of comorbidities: ✓ SAH (80% vs 70%) ✓ DM (54% vs 41%) Smaller % of ischemic etiology (33% vs 35%) Higher LVEF (30% vs 24%)
Mortality	No difference in adjusted in-hospital mortality	No difference in adjusted 30-day, 6-month, and 1-year mortality	No difference in mortality on hospital discharge

DM: diabetes mellitus; HF: heart failure; IAB: intra-aortic balloon; LVEF: left ventricular ejection fraction; SAH: systemic arterial hypertension.

Table 4.4 – Differences in outcomes between men and women in studies on HFrEF.

CLINICAL STUDY	% Women	OUTCOME	GENERAL RESULT	MEN / WOMEN	P interaction
SOLVD (Enalapril)	20%	General death	HR 0.84 (0.74 – 0.95)	-----	-----
CIBIS II (Bisoprolol)	20%	General death	HR 0.66 (0.54 – 0.81)	H: HR 0.53 (0.42 – 0.67) M: HR 0.37 (0.19 – 0.89)	NS
RALES (Spironolactone)	27%	General death	HR 0.69 (0.58 – 0.82)	H: HR 0.71 (0.60 – 0.82) M: HR 0.72 (0.57 – 0.97)	NS
PARADIGM-HF (Sacubitril-Valsartan)	21%	CV death or hospitalization due to HF	HR 0.80 (0.73 – 0.87)	H: HR 0.80 (0.73 – 0.87) M: HR 0.79 (0.66 – 0.94)	NS
DAPA-HF (Dapagliflozin)	23%	CV death or hospitalization due to HF	HR 0.75 (0.65-0.85)	H: HR 0.73 (0.63 – 0.85) M: HR 0.79 (0.59 – 1.06)	NS
EMPEROR-Reduced (Empagliflozin)	24%	CV death or hospitalization due to HF	HR 0.75 (0.65– 0.86)	H: HR 0.80 (0.68 – 0.93) M: HR 0.59 (0.44 – 0.80)	NS

CV: cardiovascular; M: men; HR: hazard ratio; HF: heart failure; W: women; NS: nonsignificant.

the institution of measures for their control, or even their reversion, can impact prognosis. Prospective multicenter registries could provide more accurate evidence in the female population.

4.3. Arrhythmias

There are some electrophysiological differences between sexes regarding the occurrence, clinical symptoms, and prognosis of arrhythmias, and they can affect both

depolarization and repolarization. Women more often have sinus tachycardia and nodal reentry tachycardia, while ventricular arrhythmias are less common. In the long QT syndrome type 2, women are known to have a higher risk of sudden death and of pro-arrhythmia from cardiovascular or non-cardiovascular drugs. Pregnancy increases the risk of supraventricular tachycardia and reduces the occurrence of *torsades de pointes*, whose risk is increased in the long QT syndrome during the puerperium.⁷⁰

Statement

4.3.1. Ventricular Tachycardia and Cardiac Sudden Death

The CSD is an important public health problem of high global incidence. In the United States of America, in 2016, there were 366 494 CSD, and 178 823 (48.8%) in women. The most common cause of CSD is IHD; in women, however, CSD more often is due to non-ischemic

causes. In women, ventricular tachycardia/fibrillation is less documented (19.4% women vs 26.7% men, $p < 0.001$), which reduces the probability of survival as compared to men, who are resuscitated and treated with defibrillator.⁷⁰

The ICD is the therapy of choice for the primary or secondary prophylaxis of CSD. However, women are underrepresented in clinical trials (inclusion of women

Table 4.5 – Differences in outcomes between men and women in studies on HFpEF.

CLINICAL STUDY	% Women	OUTCOME	GENERAL RESULT	MEN / WOMEN	DIFFERENCES between sexes	P interaction
TOPCAT (Spironolactone)	52%	CV death or hospitalization due to HF or CPA	HR 0.89 (0.77 – 1.04)	General death H: $p=0.68$ M: HR 0.66 (0.48 – 0.90)	Significant reduction of general death only in women	0.02
PARAGON-HF (Sacubitril-Valsartan)	52%	CV death or hospitalization due to HF	HR 0.87 (0.75 – 1.01)	H: HR 1.03 (0.85 – 1.25) M: HR 0.73 (0.59 – 0.90)	Significant reduction of CV death or hospitalization due to HF and total hospitalizations only in women	0.017
EMPEROR-Preserved (Empagliflozin)	45%	CV death or hospitalization due to HF	HR 0.79 (0.69 – 0.90)	H: HR 0.81 (0.69 – 0.96) M: HR 0.75 (0.61 – 0.92)	Significant reduction of CV death or hospitalization due to HF in men and women	NS
DELIVER (Dapagliflozin)	44%	CV death or hospitalization due to HF or visit to the emergency room	On going			

CV: cardiovascular; M: men; HR: hazard ratio; HF: heart failure; W: women; NS: nonsignificant; CPA: cardiopulmonary arrest.

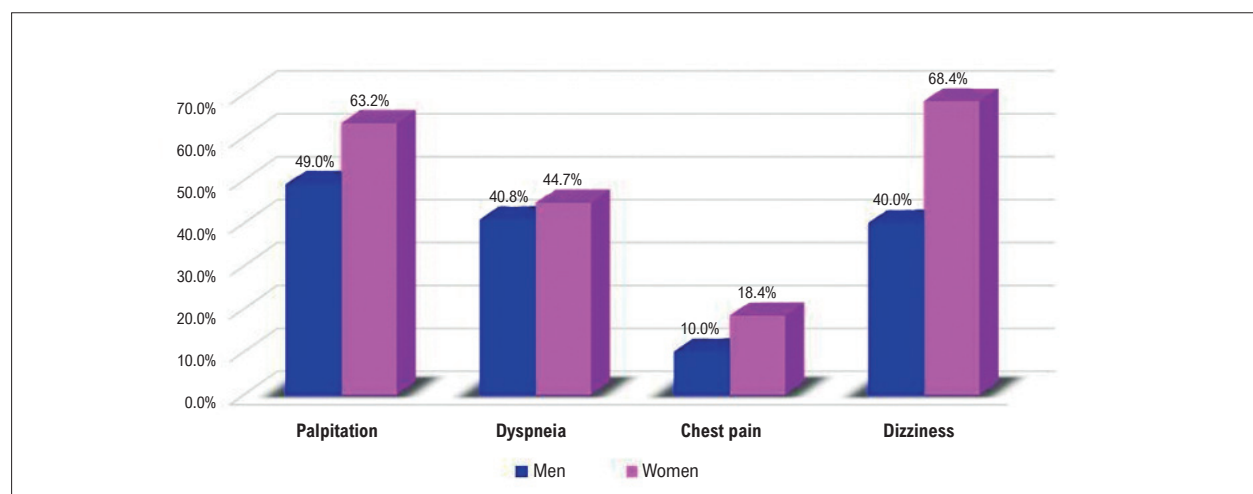


Figure 4.3 – Differences of symptoms between women and men with atrial fibrillation.⁷²

varies from 16% to 29%) and the sex-based analyses of subgroups are limited.⁷⁸ One registry of 236 084 Medicare beneficiaries from 1991 to 2015 evidenced that men received more ICD than women in both primary (3.2 times more) and secondary (2.4 times more) prevention. In addition, women are at a higher risk for complications related to the ICD procedure (7.2% vs 4.8%, $p < 0.001$), particularly pneumothorax requiring intervention, cardiac tamponade, and ICD mechanical complications that need revision.¹³

4.3.2. Atrial Fibrillation

Around the world, 29.4 million women are estimated to have AF. Although the AF incidence is higher among men, older women more often have AF, considering their life expectancy is longer.¹ Women with arrhythmia have more symptoms and report poorer quality of life as compared to men (Figure 4.3),⁷⁹ in addition to having peculiar predictors of AF. A study with 34 221 women has reported that SAH was a risk predictor, obesity was another important risk marker, and the dynamic weight changes were deleterious. Women who practice vigorous physical activity have a 28% reduction in the incidence of AF. Regarding middle-aged healthy women, an increased incidence of AF was observed in those who had two or more drinks per day, the excessive consumption of alcohol being a predictor of AF among them. A large prospective study has shown the association of multiparity and higher risk. Another prospective study, assessing 30 034 menopausal women, has shown no increase in the risk in addition to that related to age, while monotherapy with estrogen associated with an increased risk of arrhythmia.⁸⁰

Women more often have paroxysmal AF and higher CHA₂DS₂-VASc score, but are less often submitted to both cardioversion and AF and flutter ablation. In addition, they more often undergo ablation of the atrioventricular node and pacemaker implantation, more often have strokes and

thromboembolism, and are more often hospitalized due to all causes.¹⁴

Few studies on heart rate and rhythm control have assessed the differences between sexes. Women less often undergo catheter ablation with isolation of the pulmonary veins and usually have worse results, because of later indication, more comorbidities, or higher presence of atrial fibrosis and foci outside the pulmonary veins.¹⁵ A study with 2789 patients with recent-onset AF and large women's representativity (46%) has shown that early rhythm control associated with a smaller risk of adverse cardiovascular events, without affecting the length of hospital stay.⁸¹

Women with AF are at higher risk for stroke, which is even more severe and extensive at ages over 65 years.^{15,70} Studies with DOACs (dabigatran, apixaban, rivaroxaban, and edoxaban) have shown a smaller risk of major bleeding in women, but a higher risk of stroke/systemic embolism with the use of warfarin, although women represented only 35% to 40% of those studies' samples.¹⁵ There was a reduction in all-cause mortality and a significant reduction in the risk of intracranial hemorrhage with the use of DOACs as compared to warfarin in women. In studies assessing the left atrial appendage occlusion as an alternative to anticoagulation for stroke prevention in AF, women were underrepresented and the primary outcome of efficacy composed by stroke, systemic embolism, and cardiovascular death did not vary between sexes.^{15,70} Women with AF have a higher risk of cardiovascular and all-cause mortality, in addition to more cardiac events, and a higher risk of stroke and HF.¹⁵ The major differences of symptoms between sexes in AF are shown in Chart 4.1.

4.4. Cardiovascular Disease and Cancer

Cardiovascular diseases and cancer are the major causes of death worldwide, and they share RFs, such as age, obesity, tobacco use, family history, and diet.

WOMEN		MEN	
EPIDEMIOLOGY AND RISK			
- Higher than in the total population - Higher risk of death and stroke due to AF	Increase of incidence and prevalence with time	Age-adjusted prevalence	
SYMPTOMS AND QUALITY OF LIFE			
- Longer symptom duration - Worse quality of life in the scores			
PREVENTION AND RISK OF STROKE			
Stroke due to AF is more severe and disabling		- Receive more anticoagulation for prevention - Longer time in the therapeutic range with warfarin	
HEART RATE AND RHYTHM CONTROL			
- Higher risk of CV events and pro-arrhythmia with AAD - Higher risk of adverse events with catheter ablation		Higher indication for cardioversion and AF ablation	

AAD: antiarrhythmic drugs; AF: atrial fibrillation; CV: cardiovascular.

Chart 4.1 – Summary of the differences of symptoms between sexes in individuals with atrial fibrillation.¹⁵

Statement

Women's most common malignant neoplasms are breast, lung, and colorectal cancers, responsible for 50% of the new diagnoses, of which breast cancer represents 30%.⁸²

Advances in the early diagnosis and treatment of cancer caused an important reduction in mortality, mainly due to the perception of acute and chronic adverse cardiovascular effects resulting from the oncological treatment, which affect the quality and expectancy of life of the survivors, who require lifelong follow-up.

The different forms of treatment, such as chemotherapy and radiotherapy, can lead to cardiotoxicity through different mechanisms, the risk being directly related to detection of the underlying cardiac disease, cardiovascular RFs, and previous cardiotoxic oncological treatment.

Although there is no risk score validated, age and LVEF previous to treatment are two strong risk predictors suggested.⁸³

The diagnosis of cardiotoxicity can be done through the confirmation of new cardiovascular change during or even years after treatment, such as a clinical change and/or alteration in cardiovascular biomarkers and/or imaging, and it is an exclusion diagnosis done after investigating other etiologies.

According to the Brazilian Guidelines on Cardio-Oncology, ventricular dysfunction related to cancer therapy is defined as a reduction $\geq 10\%$ in LVEF to a value below the lower limit of normality (LVEF $< 50\%$), and cardiovascular imaging should be repeated in 2 to 3 weeks.⁸⁴

Ventricular dysfunction can occur during treatment or even years after its end, and that is the reason long-term surveillance is important, mainly in those who develop cardiotoxicity during treatment or are at high risk for that.

Echocardiography is the method of choice to detect myocardial dysfunction before, during, and after cancer treatment. Three-dimensional echocardiogram has better accuracy to assess ventricular function. In its absence, two-dimensional Simpson is recommended to assess volumes and LVEF. The SLG is a tool to predict with high sensitivity the later reduction in LVEF. A reduction $\geq 15\%$ in SLG as compared to baseline is considered abnormal and an early ventricular dysfunction marker. Magnetic resonance imaging is gold-standard for the assessment of cardiac function, indicated in cases with limitation of echocardiography.⁸⁴

It is fundamental to detect subclinical cardiac abnormalities that can influence the clinical decisions regarding the choice of treatment, indication for cardioprotection, or increase of surveillance, such as asymptomatic ventricular dysfunction.

Anthracycline is the most used CTX drug for breast cancer treatment and has a histologically proven cardiotoxic effect via necrosis of cardiomyocytes, which leads to irreversible lesions. The association of cumulative anthracycline doses and the risk of HF is exponential: 5% incidence of HF with a cumulative dose of 400 mg/m², and 48% incidence of HF with a cumulative dose of 700 mg/m².⁸⁵

Another CTX drug used for breast cancer treatment, trastuzumab, can cause cardiotoxicity, and, because it is not associated with necrosis of cardiomyocytes, the lesions caused are partially or totally reversible after treatment interruption.

Fluoropyrimidine, used to treat colorectal cancer, can cause vasospasm and consequent myocardial ischemia, with or without electrocardiographic changes. The symptoms can appear at any time during treatment, but bolus injection can be less cardiotoxic, because the vasospasm can be related to accumulation of metabolites rather than to the peak effect of the drugs.⁸⁶

If the patient develops HF and LVEF $< 40\%$ during treatment, the CTX drug should be temporarily suspended according to a decision shared by the cardiologist and the oncologist, and the HF therapy should be initiated based on guidelines and consensus.

Cardiotoxicity prevention should be performed in all patients undergoing cancer treatment. General measures, such as proper control of RFs, specific cardioprotective pharmacological interventions, and imaging- and biomarker-based surveillance strategies have an overall beneficial effect, but there is heterogeneity in results and no consensus on the recommendations for cardioprotective pharmacotherapy (Figure 4.4).⁸⁵

Although the recommendations are controversial, cardioprotective drugs have been tested, such as dexrazoxane, an iron chelator with proven cardioprotective action, and neurohormonal inhibitors that have a cardiac anti-remodeling action, such as renin-angiotensin-aldosterone system inhibitors, beta-blockers, and statins.⁸⁶ The use of dexrazoxane in patients with metastatic breast cancer with high cumulative dose of anthracycline (doxorubicin dose > 250 mg/m²) should be considered.⁸⁶

Aerobic exercise is considered a promising nonpharmacological strategy to prevent and/or treat CTX-induced cardiotoxicity. If there is a reduction in LVEF that meets the definition of cardiotoxicity, the guideline-based treatment of HF should be considered.

Figure 4.5 summarizes the major aspects related to cardiotoxicity.

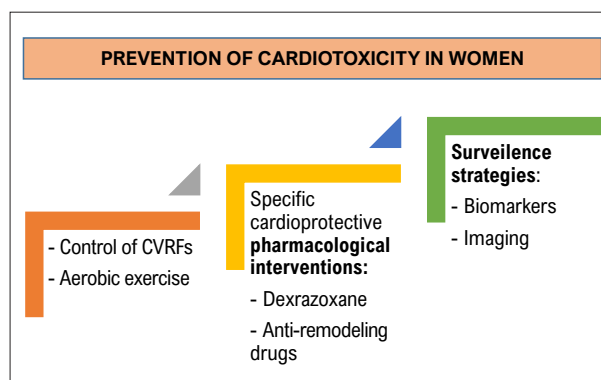


Figure 4.4 – Measures for the prevention of cardiotoxicity in women.
CVRF: cardiovascular risk factor

PATIENTS AT HIGH RISK FOR CARDIOTOXICITY	DIAGNOSIS OF CARDIOTOXICITY
• Previous treatment with anthracyclines or trastuzumab associated • Baseline EF < 50% • Elderly (>75years) or young (< 10years) women • Previous chest or mediastinal radiotherapy • Previous risk factors: SAH, tobacco uso, DM • High cardiac biomarkers before treatment	• Biomarkers: troponin; BNP, pro-BNP • Eletrocardiogram • 2D and 3D echocardiogram: tissue doppler, strain, diastolic function • Cardiac MRI • Holter • Nuclear medicine
TYPES OF CARDIOTOXICITY	CARDIOTOXICITY MANAGEMENT
• Heart failure • Arterial hypertension • Thromboembolism • Cardiac arrhythmia • Myocarditis, pericarditis, valvular heart disease • Coronary artery disease	• Treat CVRFs and heart disease • Limit cumulative CTX dose • Minimize radiation • Temporary suspension of treatment • Cardioprotective drugs

Figure 4.5 – Summary of the major aspects related to cardiotoxicity. 2D: two-dimensional; 3D: three-dimensional; CVRF: cardiovascular risk factor; CTX: chemotherapy; DM: diabetes mellitus; EF: ejection fraction; MRI: magnetic resonance imaging; SAH: systemic arterial hypertension.

Chart 4.2 – Recommendations for the management of ischemic heart disease in women.

Recommendations for the management of ischemic heart disease in women			
Recommendation	CR	LE	References
In obstructive and non-obstructive coronary disease, the differences in clinical findings of ACS/CCS should be known, diagnosis and treatment should be improved, and the classical CVRFs and female-sex-specific RFs should be identified and treated.		B	69-73
In obstructive and non-obstructive coronary disease, the risk enhancing factors should be identified (psychosocial factors and social determinants of health).		B	69-73
In spontaneous dissection, minimize the emotional triggers, avoid hormone therapy (estrogen, progesterone, β -human chorionic gonadotropin), avoid future pregnancies, cardiac rehabilitation, preferably with modified protocol, avoiding heavy isometric exercises and intense aerobic activities.		B	69-71,73
In vasospasm, avoid aggravating factors: use of illegal drugs, amphetamines, butane gas, alcohol, and medications for migraine.		B	69,71-73
In microvascular disease, it is important to modify CVRFs (body weight loss and stress control).		B	69,72
In coronary thrombosis and embolism, early diagnosis of the underlying causes and thrombosis/infection prophylaxis are important.		B	69,73

CR: class of recommendation; LE: level of evidence; ACS/CCS: acute coronary syndrome/chronic coronary syndrome; CVRF: cardiovascular risk factor; RF: risk factor.

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Charts 4.2, 4.3, 4.4 show the recommendations for the management of ischemic heart disease, heart failure, and arrhythmia in women.

4.5. Stroke

Women face a disproportionately high burden of mortality and disability from stroke.⁸⁷ Multiple specific

Chart 4.3 – Recommendations for the management of heart failure in women.

Recommendations for the management of ischemic heart failure in women			
Recommendation	CR	LE	References
Takotsubo syndrome is related to menopause (estrogen deficiency), but hormone replacement has no impact on reducing the risk of HF.		C	10,76
Control risk factors that predispose to PPCM: hypertension, diabetes, obesity, eclampsia.		B	10,76
In HFpEF and HFrEF, control risk factors, such as body weight and glucose, lipid and blood pressure levels, practice regular physical activity, and cease tobacco use.		B	10,74–76
Use of statin would have a potential benefit, but there is scarce specific sex-related evidence, thus, it should not be recommended.		C	10
The identification of potential risk factors for the development of HF in women and the institution of measures to control them or even reverse them could impact prevention.		B	10,70,76

CCR: class of recommendation; LE: level of evidence; HF: heart failure; HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction; PPCM: peripartum cardiomyopathy.

Chart 4.4 – Recommendations for the management of arrhythmias in women.

Recommendations for the management of arrhythmias in women			
Recommendation	CR	LE	References
Obesity and SAH are predictors of risk for AF in women; the control of body weight and blood pressure levels is an important preventive measure.		B	14,15,81
The prevalence of AF increases with age and in women after menopause; menopausal hormone therapy has no beneficial effect.		C	80
Vigorous physical activity seems to reduce the incidence of AF in women.		B	80
Excessive alcohol consumption is a predictor of AF in women; alcohol consumption control to less than 2 drinks/day can reduce the risk.		B	80

CR: class of recommendation; LE: level of evidence; AF: atrial fibrillation; SAH: systemic arterial hypertension.

RF have been observed, such as pregnancy, PE, GD, use of oral contraceptives, postmenopausal use of hormones, and women's hormonal variations.⁸⁸ The strongest or most prevalent RF for stroke in women are: AF, migraine with aura, DM, SAH, depression, and psychosocial stress. Despite the higher proportion of stroke throughout life, there are no specific guidelines on screening and treatment to reduce the risk of stroke in women.⁶⁸

It is worth emphasizing the need for awareness and systematic education of the youngest age groups, including women at childbearing age, alerting to the increasing incidence of stroke with age and its association with obstetric complications, such as GH, premature births, and GD, in addition to hormonal contraception. The risk is progressively higher in the presence of classical RF, such as obesity, dyslipidemias, SAH, and DM, which can appear throughout life, including at younger ages.⁸⁷

Although more than half of the cases of stroke occur in women, the inclusion of women in clinical trials on stroke treatment has been smaller than that of men. A better representation of the female sex in those studies is necessary.^{89,90}

4.6. Peripheral Artery Disease

Peripheral artery disease is a prevalent condition with substantial morbidity and mortality, rarely diagnosed and treated in the general population.⁹¹ Its frequency in women is equal to that in men.⁹² Differences in pathophysiology and RFs can contribute to the late and often atypical presentation of PAD in women (Figure 4.6).

Unawareness about PAD hinders the outcomes of all patients, but the challenges are even bigger for women, who, as compared to men, suffer from more severe pain, have poorer quality of life, and are at higher risk for CVD and their concomitant events.^{93–97} In addition, the use of evidence-based therapy is less frequent in women as compared to men.⁹⁷

Although the recognition and control of traditional RFs are important in both sexes, they seem to have a different effect and smaller general significance for women with PAD than for men.^{98,99} Because the treatment of traditional RFs offers protection for both sexes, ideal care should be ensured to everybody.¹⁰⁰ Recognizing sex-specific RFs (ex. pregnancy) or predominantly female factors (ex. depression) can allow adequate risk stratification and adoption of early preventive measures.^{101,102}

4.7. Dementia

Although the impacts of menopausal estrogen deprivation on women's cognitive function are not clearly known, literature data have shown that women seem to be at higher risk of developing dementia and age-related memory changes than men, and little is known about such differences at younger ages.¹⁶ Studies have shown that perimenopausal women respond better to memory-related tasks, which attenuates years after menopause.^{16,103}

There is epidemiological and biological evidence that serum estrogen concentration and, thus, ovarian activity relate to better memory and cognition performance.^{16,103} Symptoms, such as dullness of mind, forgetfulness, and

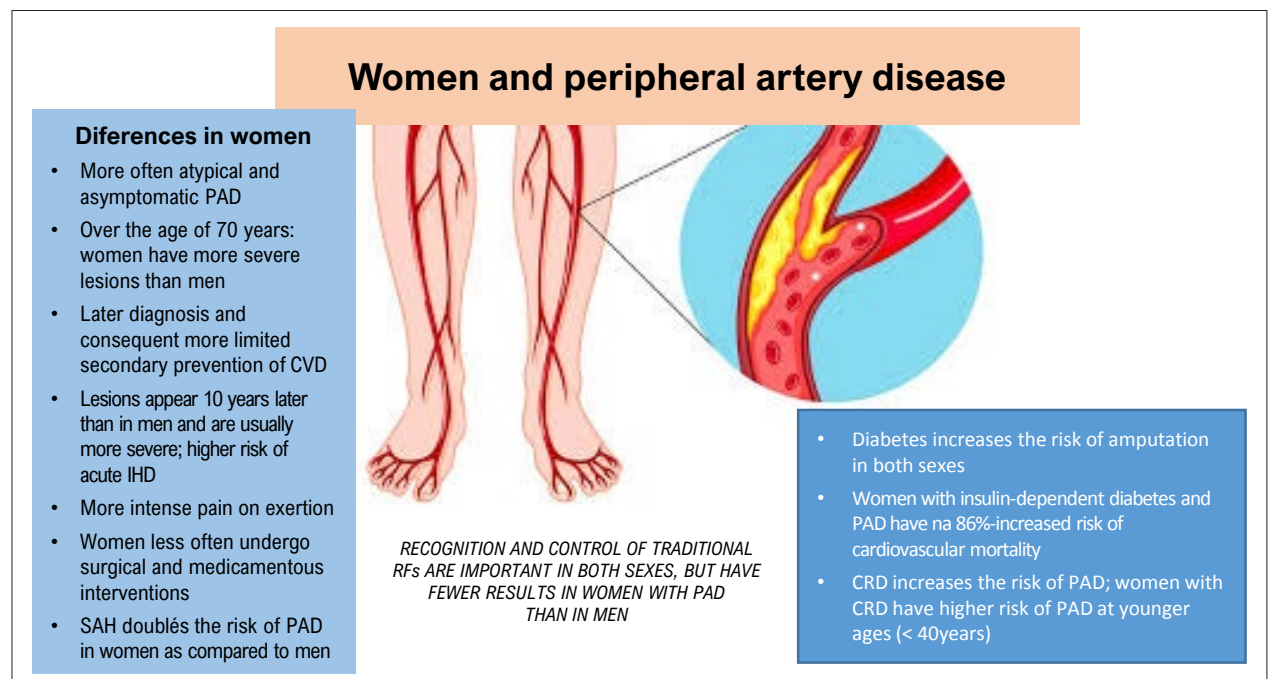


Figure 4.6 – Differences in peripheral artery disease presentation in women. CVD: cardiovascular disease; CRD: chronic renal disease; IHD: ischemic heart disease; PAD: peripheral artery disease; RF: risk factor; SAH: systemic arterial hypertension.

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difficulty to find the words are common in perimenopausal women.¹⁶ In addition, as shown in the SWAN study, the reduced cognitive function in women seems to be related to neither anxiety nor depression, factors known to be increased in that phase of women's life.⁶⁵

One of the major pathologic characteristics of AD, a cause of dementia in the general population, is the accumulation of amyloid plaques in the central nervous system. Data from the literature have suggested that estrogen can have an important role in preventing amyloid buildup, in addition to acting on the cognitive function.¹⁰⁴ Researchers have suggested that the reduced concentration of sexual steroid hormones after menopause can account for the higher prevalence and severity of AD in women.¹⁰⁵ Several studies have been performed to define whether MHT would be effective to prevent those neurological disorders.^{105,106}

Despite the conflicting epidemiological evidence regarding the use of MHT as a preventive measure against cognitive dysfunction and AD reduction in menopause, a meta-analysis of clinical trials has shown the absence of those benefits. Women over the age of 65 years without dementia who used estrogen isolated or associated with progesterone showed no consistent evidence regarding those benefits, not even the younger ones (early menopause and perimenopause).¹⁰⁶

Thus, we suggest that MHT should not be prescribed to preserve cognitive function in postmenopausal women. In addition, there is lack of robust evidence of cognitive benefits for women using MHT at younger ages (for example, perimenopausal). Thus, MHT should not be prescribed to preserve cognitive function in younger women. Even results of the WHI study have not shown that the early initiation of MHT would be necessary to provide later cognitive benefits in women, not even prevent IHD ("the critical window hypothesis").¹⁰⁷

A cohort study has shown the major causes of cognitive changes and dementia in younger men and women (under the age of 55 years): AD (34%), vascular dementia (18%), frontoparietal dementia (12%), alcoholism-related dementia (10%), and others, such as Parkinson's disease and multiple sclerosis.¹⁰⁸ In AD, 10% of the cases related to a genetic mutation and the prevalence of dementia doubled every 5 years after the age of 35 years.

There are vascular RFs related to early dementia, such as stroke, transient ischemic attack, renal disease, CVD, SAH, chronic alcoholism, and drug intoxication.¹⁰⁹

4.8. Valvular Heart Disease

Rheumatic disease is the major cause of acquired valvular heart disease in children and young adults aged less than 40 years in emerging countries.¹¹⁰

4.8.1. Aortic Stenosis

In young women, the etiology of aortic stenosis isolated is congenital and often the structural lesion is bicuspid valve.¹⁷ Aortic stenosis isolated of rheumatic etiology is

rare, usually concomitant with other valvular lesions, such as aortic insufficiency or mitral lesions. With aging, degenerative valvular calcification is the major mechanism of disease. When compared to men, considering the same degree of valvular calcification, women tend to higher severity of aortic stenosis due to the valvular apparatus fibrosis, which is more pronounced than calcification.

Women with low-gradient aortic stenosis and low ejection fraction do not value their symptoms and present at more advanced disease stages, with worse functional capacity, more frequent syncope, and more eccentric left ventricular remodeling. Such manifestations can justify their higher mortality as compared to men (Figure 4.7).¹⁷

Women referred for aortic valve surgical replacement have more severe dyspnea on exertion, higher frailty scores, and more severe valvular obstruction degree for the same anatomic pattern of valvular area and mean transvalvular aortic pressure gradient.¹⁸ Women's smaller body surface implicates in technically more delicate surgical interventions, explaining the worse postoperative survival.

Of the patients submitted to transcatheter aortic valve implantation, women are older, have better left ventricular function, lower prevalence of CAD, but have comorbidities associated with DM and AF. Anatomical characteristics of the female sex, such as the shorter distance between coronary ostia and valvular ring and

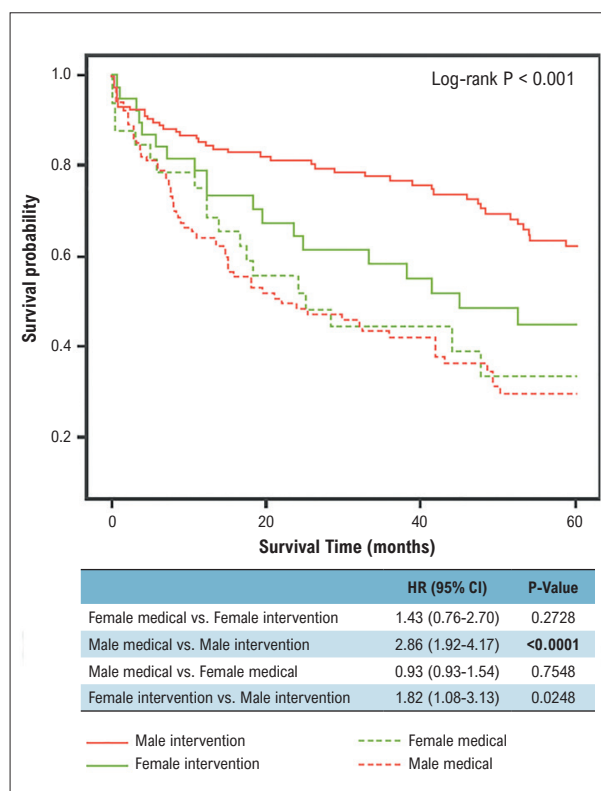


Figure 4.7 – Sex-related differences in clinical course of low-gradient aortic stenosis with low ejection fraction. Adapted from Bartko et al.¹¹⁰

higher prevalence of valvular and aortic calcification, account for the higher incidence of coronary obstruction during the procedure. The smaller diameter of peripheral vessels causes more vascular complications and bleeding.¹¹¹

Currently, there is no therapy to prevent the progression of aortic stenosis.¹⁸ However, clinical trials have formulated strategies to delay disease progression with DPP-4 inhibitors,¹⁸ tested in elderly and individuals with DM, but with no specific reference to women. The lack of control of tobacco use, dyslipidemia, creatinine serum levels and plasma calcium levels seems to cause an annual absolute and percent reduction in the aortic valve area.^{111,112}

4.8.2. Mitral Valve Disease

Mitral insufficiency has an etiology-dependent natural history, and its clinical follow-up requires preventive measures based on the stratification of the disease's anatomical degree. Mitral insufficiency can have an insidious course, thus it requires the periodic assessment of the development of anatomical and/or functional changes secondary to valvular disease and the appearance of complicating factors. Mitral insufficiency resulting from valvular prolapse is prevalent among women and its peculiar anatomic characteristics show predominance of myxomatous valves with anterior and bilateral leaflet prolapse, and extensive thickening of leaflets, which are less flaccid than in men.¹¹³

Women have smaller regurgitation volumes and atrial dimensions when indexed to body surface; therefore, many do not meet surgical criteria based on the increase of ventricular cavities in mitral insufficiency,¹¹³ which can result in worse results after surgery.¹¹⁴ However, those data are controversial because they are based on retrospective studies with a very limited cohort (Figure 4.8).

In Brazil, rheumatic mitral stenosis is the major cause of acquired valvular disease in young women; however, calcification of the mitral valve apparatus can occur as age advances. In industrialized countries, with the eradication of

rheumatic disease, the degenerative causes predominate,¹¹⁵ with calcification and involvement of the base of leaflets and absence of commissural fusion, structural characteristics that limit percutaneous intervention. Therefore, surgical replacement of the mitral valve has been preferred to percutaneous/surgical commissurotomy, except in the presence of comorbidities that increase the surgical risk.

4.8.3. Rheumatic Disease

Primary prevention of acute rheumatic fever involves the prompt diagnosis and antibiotic treatment of the group A streptococcal infection with benzathine penicillin or other alternatives.¹¹⁶ For both sexes, hygiene measures are essential to prevent disease spread and should be reinforced. Patients with history of acute rheumatic fever are at a high risk of recurrence and cardiac involvement in the case of subsequent group A streptococcal infection. For patients at risk of recurrence, long-lasting secondary antibiotic prophylaxis should be done, as recommended by the current guidelines in both sexes.

Of the preventive measures against valvular heart disease in women, prophylaxis of infective endocarditis during delivery should be emphasized. Although controversial, the Brazilian Society of Cardiology Statement for Management of Pregnancy and Family Planning in Women with Heart Disease recommends prophylaxis in high-risk situations, indicating specific antibiotics for the genitourinary tract, such as ampicillin and gentamicin or vancomycin, in case of allergy to penicillin (Figure 4.9).¹¹

4.9. Diabetes Mellitus, Preeclampsia, and Pregnancy Hypertensive Disorders

4.9.1. Diabetes Mellitus

Diabetes mellitus manifests during pregnancy as type 1 DM, type 2 DM, or GD, and associates with maternal and

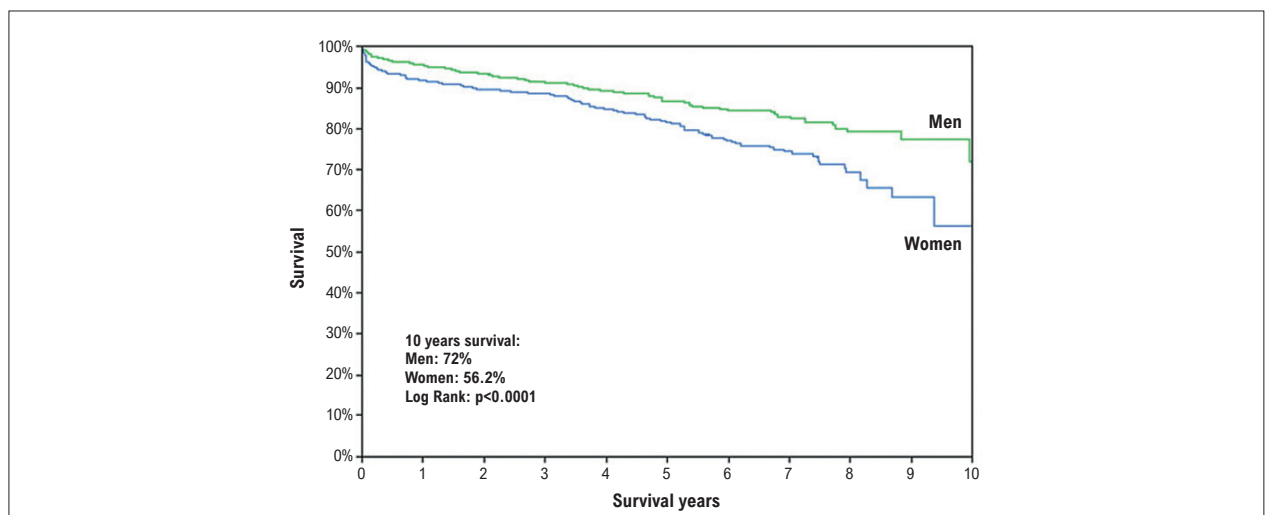


Figure 4.8 – Comparative evolution after minimally invasive surgery of the mitral valve between women and men. Adapted from Seeburger et al.¹¹³

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fetal complications, such as PE, prematurity, and perinatal death. Management of DM during pregnancy should be individualized according to the presence of prognostic determinants of pregnancy, such as blood glucose level, disease duration, presence of comorbidities, target-organ lesions, polyhydramnios, fetal macrosomia, and other fetal malformations.¹⁹

The prevention of those complications involves lifestyle changes, mainly body weight control and healthy diet before and during pregnancy. A meta-analysis with 44 studies, assessing the influence of physical activity and nutrition on body weight control in 7278 pregnant women, has shown a mean reduction of 1.42 kg in weight gain and a reduction in the risk of PE (RR 0.74; CI 0.60 – 0.92), with no fetal impairment.¹¹⁷

Regular physical exercise practice improves functional capacity, reduces the risk of depression, prevents excessive weight gain, helps control metabolic and cardiovascular disorders, mainly PE, other forms of SAH, and DM developed during pregnancy. When physical activity is moderate or vigorous, there is a reduction in the GD risk by 50% and in the PE occurrence by 22% and 35%, respectively. The risk is even lower if the physical activity is initiated before and maintained since the beginning of pregnancy. Studies have shown that 5 to 6 hours/week of physical exercise reduce the risk of PE by 40%. Thus, women without obstetric or cardiovascular contraindications should be physically active throughout the entire pregnancy. The recommendation is 150 minutes of moderate exercise, comprising aerobic and resistance training, stretching, and yoga, distributed in at least three days per week.¹¹⁸

4.9.2. Pregnancy Hypertensive Disorders

Pregnancy hypertensive disorders, comprising different forms of SAH, are among the major causes of maternal and perinatal complications and mortality around the world, being considered indisputable markers of future CVD.¹¹⁹

Several strategies have been proposed to prevent PE; however, none is unequivocally effective. Nutritional interventions, such as vitamins C and E, fish oil, garlic supplementation, vitamin D, folic acid, or sodium restriction,¹²⁰ have no proven efficacy. Calcium replacement is one of the few strategies that showed benefit for patients at high risk for SAH or PE, mainly those whose daily dietary calcium intake is insufficient. A systematic review of 13 studies including 15 730 patients with low daily dietary calcium intake (< 600 mg/day) has shown that a supplementation equal to or higher than 1.0 g/day reduced the relative risk of SAH by 35% and that of PE by 55%, and higher doses (≥ 1 g) were more beneficial regarding those outcomes.¹²¹

The use of ASA between the 12th and 16th weeks of pregnancy at daily doses between 75 mg and 150 mg is considered moderately effective to reduce the risk of PE in high-risk patients (Figure 4.10).¹¹

The ASPRE trial (*Performance of Screening for Preterm Preeclampsia*), using a PE prediction model (Doppler ultrasound in the first trimester, mean blood pressure measurement, and inflammatory markers), has shown a 62% reduction in the relative risk of PE with 150 mg of ASA at night, initiating between the 11th and 13th gestational week and ending at the 36th gestational week.¹²² A recent review corroborated the 18% reduction in the relative risk of proteinuria in PE, as well as a reduction in the number needed to treat to 61, with low fetal, neonatal, and postpartum bleeding risk.¹²³

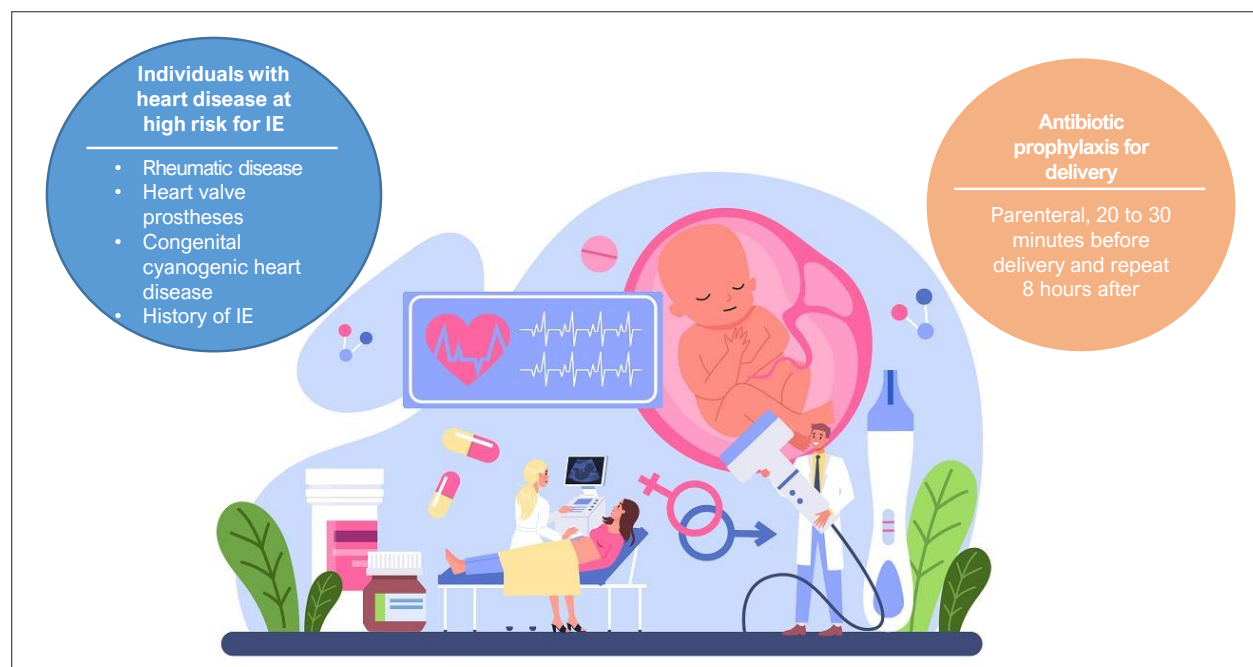


Figure 4.9 – Guidance for prophylaxis against infective endocarditis in pregnancy. IE: infective endocarditis.

Regarding GH as a RF for future CVD, a systematic analysis²⁰ has shown that GH in primigravida was associated with a higher risk of CVD (RR, 1.45; 95% CI, 1.17-1.80) and IHD (RR, 1.46; 95% CI, 1.23-1.73), but of neither stroke (RR, 1.26; 95% CI, 0.96-1.65) nor thromboembolic events (RR, 0.88; 95% CI, 0.73-1.07). Women with one or more pregnancies with GH had a higher risk of CVD (RR, 1.81; 95% CI, 1.42-2.31), IHD (RR, 1.83; 95% CI, 1.33-2.51) and HF (RR, 1.77; 95% CI, 1.47-2.13), but not of stroke (RR, 1.50; 95% CI, 0.75-2.99). Additional studies are necessary to assess the correlation between GH and subsequent CVD.

4.10. Adolescent Pregnancy

Of the health problems in adolescence (individuals between 10 years and 20 years incomplete), pregnancy represents 400 000 cases per year, and children from adolescent mothers represented 18% of the live births in Brazil in 2015, with demographic predominance in the Northeastern region.⁴⁶ Of the factors contributing to increase the occurrence of adolescent pregnancy, the following stand out: early sexual activity start, inadequate use of contraceptives, difficulty in accessing family planning programs, and mainly misinformation on sexual and reproductive rights (Figure 4.11).¹²⁵

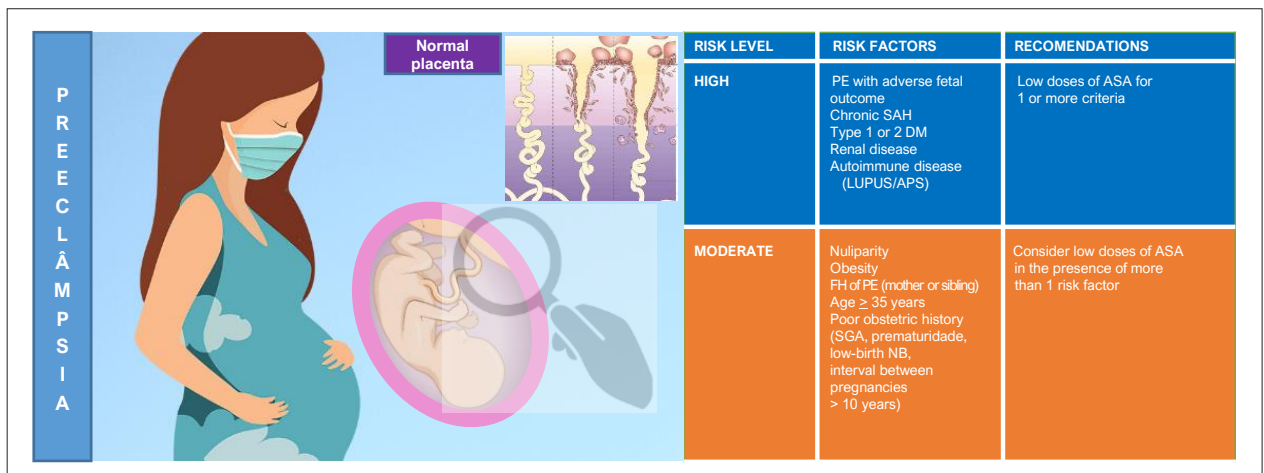


Figure 4.10 – Recommendations for the use of acetylsalicylic acid in preeclampsia prophylaxis. Adapted from the Brazilian Society of Cardiology Statement for Management of Pregnancy and Family Planning in Women with Heart Disease – 2020.¹¹ APS: antiphospholipid antibody syndrome; ASA: acetylsalicylic acid; BMI: body mass index; DM: diabetes mellitus; FH: family history; NB: newborn; PE: preeclampsia; SAH: systemic arterial hypertension; SGA: small for gestational age.

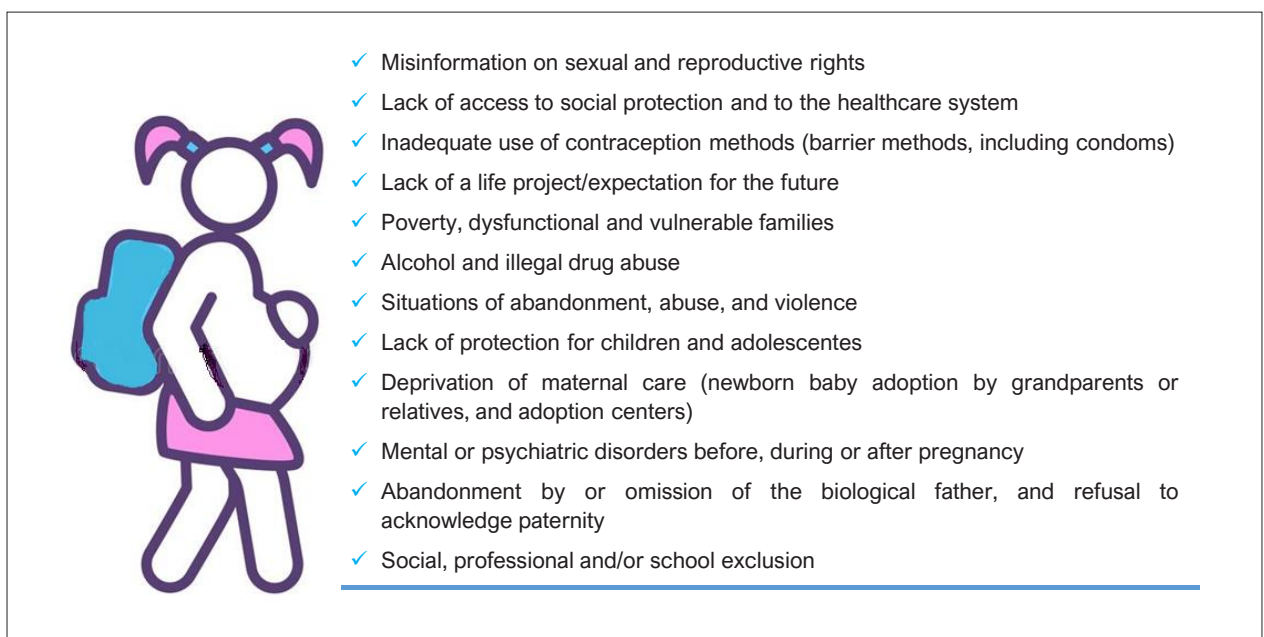


Figure 4.11 – Significant factors of teenage pregnancy.¹²⁵

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Figure 4.12 – Factors contributing to maternal complications of adolescent pregnancy.¹²⁵

According to the WHO, adolescent pregnancy increases the likelihood of maternal, fetal, and neonatal complications, in addition to worsening previous socioeconomic problems and influencing the future of generations.¹²⁶ The factors contributing to maternal complications in adolescent pregnancy are shown in Figure 4.12.¹²⁵

According to the Brazilian Society of Pediatrics, sexual abstinence isolated is not a strategy to reduce the adolescent pregnancy rates. In addition, studies have shown that abstinence neither contributes to delay the start of sexual life nor reduces the number of partners among adolescents. According to those studies, sexual education alone for abstinence has no significant effect on reducing adolescent pregnancy (OR 0.7; 95% CI, 0.38-1.45; $p = 0.38$) as compared to broader sexual education, which proved more effective (OR 0.4; 95% CI, 0.22-0.69; $p = 0.001$).²¹

The Brazilian Society of Pediatrics' Practical Guide to Prevent Adolescent Pregnancy considers that one of the most important prevention factors is education on sexuality and reproductive health supported by scientific evidence and health promotion programs.¹²⁵ The guidance should focus on biological aspects, mutual respect, responsible sexual activities, and use of safe and effective contraceptive methods to prevent pregnancy and protect against sexually transmitted infections.¹²⁷

Prescribing contraception to adolescents is a hard task, because building a trustful relationship requires time. However, pediatric healthcare providers are considered the most reliable professionals by adolescents and their families, and usually the only source of reproductive counselling.¹²⁸ Strategies for successful reproductive counselling are shown in Chart 4.5.

In the clinic for adolescents, have an exclusive space to provide information on sexual health and contraceptive methods
Ensure confidentiality about the discussions on one's sexuality
Present contraceptives emphasizing efficacy, tolerance, side effects, contraception advantages, and clinical benefits of the methods
After prescription, follow up to identify side effects, adhesion, and satisfaction
Regulate long-acting reversible contraceptive methods and hormonal contraceptives in the pediatric practice

Chart 4.5 – Strategies for pregnancy prevention.¹²⁵

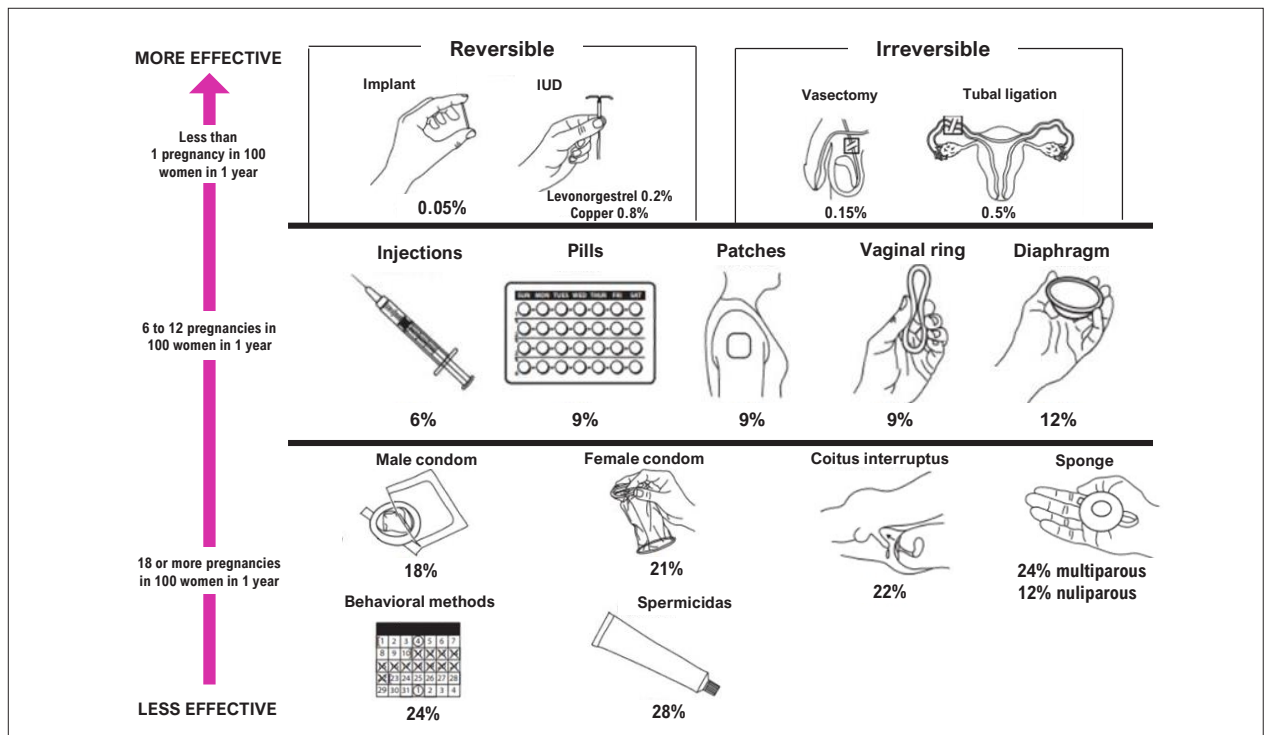


Figure 4.13 – Methods of contraception and Pearl index (pregnancies/100 women/year). Source: Adapted from U.S. Medical Eligibility Criteria for Contraceptive Use, 2016.¹³² IUD: intrauterine device.

Chart 4.6 – Recommendations for the management of cardiotoxicity in women.

Recommendations for the management of cardiotoxicity in women			
Recommendation	CR	LE	References
Identification and control of risk factors for cardiovascular diseases, such as hypertension, diabetes, obesity, tobacco use, and dyslipidemia.		B	85,86
Use of cardioprotective drugs: anti-remodeling drugs can be considered for patients with signs of subclinical cardiotoxicity or patients at high cardiovascular risk.		B	85,86
For patients with EF of 40-50%, ACEI/AT1 and beta-blocker should be initiated before treatment.		A	85,86
Consider the use of dexrazoxane for patients with metastatic breast cancer with elevated cumulative dose of anthracycline (doxorubicin > 250 mg/m ²).		A	85,86
Surveillance strategies with biomarkers and imaging.		C	85
Aerobic exercise is considered a promising nonpharmacological strategy to prevent chemotherapy-induced cardiotoxicity.		B	85,86

CR: class of recommendation; LE: level of evidence; ACEI: angiotensin-converting-enzyme inhibitor; AT1: angiotensin receptor type 1; EF: ejection fraction.

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Chart 4.7 – Recommendations for the management of stroke, PAD, and dementia in women.

Recommendations for the management of stroke, PAD, and dementia in women			
Recommendation	CR	LE	References
Strengthen women's awareness of the progressive incidence of stroke and its association with obstetric complications (GH, premature birth, GD) and hormonal contraception.		A	87
Alert women about the progressively higher risk of stroke in the presence of classical risk factors, such as obesity, dyslipidemias, SAH, and DM.		B	87
Treatment of traditional risk factors protects against PAD in both sexes.		B	100
In PAD, the recognition of sex-specific risk factors, such as pregnancy complications, or predominantly female factors, such as depression, allows proper risk stratification and adoption of early preventive measures.		B	101,102
Estrogen is suggested to have an important role in preventing amyloid buildup in Alzheimer's disease, in addition to acting in the cognitive function.		A	107

CR: class of recommendation; LE: level of evidence; DM: diabetes mellitus; GD: gestational diabetes; GH: gestational hypertension; PAD: peripheral artery disease; SAH: systemic arterial hypertension.

Current guidelines and best practices for contraception include the U.S. Medical Eligibility Criteria for Contraceptive Use (MEC),¹³² the WHO Selected Practice Recommendations for Contraceptive Use, and the Recommendations and Reports of the U.S. Center for Disease Control.¹²⁹ The Brazilian Federation of Gynecology and Obstetrics reinforces the last version of the MEC-WHO document, which indicates that age alone is not the reason to delay the use of any reversible method, and that social and behavioral issues should be considered individually.¹³¹

Contraceptives can be divided into hormonal and non-hormonal (behavioral, mechanical and barrier methods) and have variable contraceptive failure. Their efficacy can be calculated by use of the Pearl index, which considers the number of pregnancies/100 women/year (Figure 4.13).^{128,132}

Charts 4.6, 4.7, and 4.8 show the recommendations for the management of cardiotoxicity, stroke, PAD, dementia and other female-sex-specific diseases and situations.

5. Cardiac Investigative Methods: Peculiarities in Women

In clinical practice, risk scores and symptoms are used to estimate the probability of CVR and identify individuals who would benefit from tests. Most prediction models overestimate risk, and imaging tests are usually used when

the pretest probability is intermediate. Based on Bayes theorem, the proportion of false-positive tests reduces as the disease prevalence in a population increases, while the proportion of false-negative decreases as the disease prevalence in a population decreases. In women, coronary obstructive lesions are less common and the pathophysiology of IHD have peculiarities, such as involvement of the microcirculation, thinner vessels, and higher vascular reactivity with consequent vasospasm. Thus, sensitivity and specificity of the tests in women can be different from those in men. This chapter aimed to report the differences in interpretation, accuracy, and indication of the tests that help diagnose IHD in women.

5.1. Electrocardiogram

The ECG is influenced by sex, mainly regarding the magnitude of the electrical signals. The QRS amplitude is smaller in women, mainly in the precordial leads, such as S wave in V2 and R wave in V5, interfering with the accuracy of the LVH diagnosis. Smaller left ventricular mass and presence of large breasts are the reasons for that. The Cornell criteria to assess LVH (addition of the R wave amplitude in aVL and the S wave in V3) improve precision by considering sex, being abnormal when > 28 mm in men and > 20 mm in women.

The J point and T wave amplitude is smaller in women. However, the corrected QT interval is longer in women,

Chart 4.8 – Recommendations for the management of pregnancy-specific situations.

Recommendations for the management of pregnancy-specific in women			
Recommendation	CR	LE	References
For infective endocarditis prophylaxis during delivery, the association of ampicillin (2.0g) and gentamicin (1.5mg/kg) should be administered one hour before delivery in patients at high risk for infective endocarditis.		C	11
Changes in lifestyle, mainly body weight control and healthy diet, before and throughout pregnancy are important to prevent gestational diabetes.		B	117
Regular physical exercise practice during pregnancy for women without obstetrical contraindication reduces the risk of depression, prevents excessive weight gain, helps control metabolic and cardiovascular disorders, mainly PE, other forms of SAH, and DM.		A	118
Nutritional interventions, such as vitamins C and E, fish oil, vitamin D, folic acid, and sodium restriction are measures to prevent PE.		C	119
The use of ASA before the 16th gestational week reduces the risk of early PE (before the 34th week) in high-risk patients.		A	122
Calcium replacement can be beneficial to prevent PE in patients considered to be at high risk and whose daily dietary calcium intake is insufficient (< 600 mg/day).		B	121
Sexual abstinence as a measure to prevent adolescent pregnancy contributes neither to delay the beginning of sexual life nor to reduce the occurrence of pregnancy.		B	126
The prevention of adolescent pregnancy requires education on the efficacy, safety, and tolerance of the contraceptive measures available, as well as supervision until adulthood.		B	129
The prescription of contraceptives should be based on the WHO eligibility criteria.		B	132

CR: class of recommendation; LE: level of evidence; ASA: acetylsalicylic acid; DM: diabetes mellitus; PE: preeclampsia; SAH: systemic arterial hypertension; WHO: World Health Organization.

being abnormal when > 470 ms in women and > 450 ms in men.¹³³

5.2. Exercise Test

The ET is safe and physiological, indicated to investigate myocardial ischemia, exertion-induced arrhythmias, and prognosis predictors in IHD. In women, the lower levels of hemoglobin, the smaller size of the coronary arteries, the inappropriate increase in catecholamines on exertion, and estrogen, because of its similarities with the digitalis molecule, can cause a false-positive depression of the ST segment.

Because of the high prevalence in women of non-obstructive CAD, single-vessel lesions, and microvascular disease, the accuracy of ET varies with the pretest

probability of IHD. According to the ACC/AHA guidelines, ET should be chosen to assess IHD in women with intermediate pretest probability, normal ECG, and who can reach maximum exercise. The ET has similar negative predictive value in women and men (78% and 81%, respectively), its positive predictive value being around 47%. Small electrocardiographic amplitude and poorer exercise performance hinder IHD assessment in women.^{25,134}

5.3. Carotid Ultrasound

Measurement of IMT and atherosclerotic plaque detection are auxiliary tools to assess CVR. The IMT seems to reflect the presence of CVRFs and differs between sexes. Carotid

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atheromatous plaque reflects atherosclerotic burden, seems to be a stronger predictor of CVR than IMT, and does not differ between sexes. The IMT measure for risk reclassification can be used in some specific groups, in which classification by usual criteria is difficult or incomplete (family hypercholesterolemia, autoimmune disease, use of medications that induce increase in cholesterol levels) or women with at least two CVRFs. The IMT measure was studied and published in the ELSA project (Brazilian Longitudinal Study of Adult Health), which showed differences not only between sexes, but between ethnicities, and, as well known, between age ranges of a Brazilian population. Thus, the risk can be stratified in specific situations using data from the Brazilian population.¹³⁵

The Brazilian and international guidelines recommend that the presence of atheromatous plaque be considered an aggravating factor in patients at intermediate risk, a situation in which several women can be.¹³⁶

5.4. Echocardiography

Echocardiography is the most used tool in the CV diagnostic and prognostic investigation in men and women, without specific differences between the sexes. In addition to the diagnosis of regional contractility changes, it identifies other causes of chest pain, such as valvular heart diseases, cardiomyopathies, aortopathies, and pericardial diseases.¹³⁷

Stress echocardiography is an appealing technique, mainly for young women or those at risk for breast cancer, because it does not rely on radiation. There are few studies assessing differences in stress echocardiography performance between the sexes. However, its specificity and precision are significantly higher than those of ET isolated, without significant differences between men and women. Stress echocardiography with dobutamine *versus* ET for the detection of IHD was more accurate in coronary stenosis > 50% in women with chest pain, with sensitivity of 70.4% vs 53.7% and specificity of 94.6% vs 73.6%. Higher accuracy was maintained after the exclusion of patients who did not achieve more than 85% of the heart rate predicted for age before ischemia induction. The AHA recommends adding images to exercise when assessing women at intermediate risk with an abnormal baseline ECG.^{25,138}

5.5. Myocardial Perfusion Scintigraphy

The accuracy of stress myocardial perfusion scintigraphy in women is similar to that of stress echocardiography, but lower as compared to that in men, possibly because of the smaller diameter of the cardiac chambers, which leads to lower image resolution in conventional gamma cameras. Another challenge is the attenuation caused by the breasts, which can lead to false-positive results.²⁵ In a meta-analysis comparing ET, stress myocardial perfusion scintigraphy, and stress echocardiography, the sensitivity and specificity of each method were 61% and 70%, 78% and 64%, and 86% and 79%, respectively, and were similar to those in men, except for ET, whose values were lower in women.¹³⁹

The WOMEN Trial has compared the effectiveness of ET with or without myocardial scintigraphy in symptomatic women at low/intermediate risk for CAD with ability to exercise. The authors showed that, only in women

with intermediate/high pre-test risk, diagnostic accuracy improved when ET was combined with myocardial scintigraphy, and accuracy was higher for obstructive CAD: stress myocardial perfusion scintigraphy had sensitivity of 78% (95% CI, 72%-83%) and ET had sensitivity of 61% (95% CI, 54%-68%). A negative stress myocardial perfusion scintigraphy showed an excellent prognostic value in women, with 99% survival without events, including older women and different ethnicities, and similar to that in men. Thus, the pretest probability assessment for CAD is important in deciding which method use.^{140,141}

Exposure to radiation on scintigraphy in women seems little harmful; however, although controversial, it should be avoided in young women, for whom stress echocardiography should be preferred.

5.6. Coronary Calcium Score and Coronary Computed Tomography Angiography

Population scores to predict CVR have lower accuracy in women, especially in the younger ones. Currently, the radiation dose of CCaS is similar to that of mammography (< 1 mSv), and the CCaS has equal accuracy in men and women for risk stratification and prediction of events. For women with a CCaS greater than zero, the risk of events is higher than for men. Similarly, breast arterial calcification visualized on mammography correlates with the presence of coronary atherosclerosis and indicates the need for cardiological assessment.

The CCaS has prognostic value in asymptomatic women at intermediate risk. A positive CCaS in asymptomatic women at intermediate risk is associated with a significantly higher rate of events, including death, acute myocardial infarction, CABG, and percutaneous coronary intervention (3.3% in those with CCaS > 0 *versus* 1.0% in those with CCaS = 0, after a 37-month follow-up).²⁷

Coronary CTA is a non-invasive anatomical test for IHD that provides information on the occlusion severity, plaque burden, and plaque instability risk. Considering the characteristics of IHD in women, coronary CTA can evidence the most prevalent non-obstructive pattern, which cannot be assessed on functional modalities. When compared to the latter, coronary CTA resulted in higher probability of coronary angiography in a obstructive IHD, in addition to a better correlation with future events. In the context of acute chest pain, because of the atypical characteristics of that complaint in women at the emergency unit, coronary CTA had a higher impact in the reducing the length of hospital stay in women than in men.^{142,143}

5.7. Cardiac Magnetic Resonance Imaging

Cardiac magnetic resonance imaging is a highly accurate method to investigate CV diseases without using radiation. This makes it an excellent option for women, especially those at childbearing age, pregnant, and undergoing breast cancer treatment. It is well known that a considerable part of female patients (25%) with ventricular ejection fraction < 50% na CMRI do not have echocardiographic changes when investigating cardiotoxicity.¹⁴⁴

Chart 5.1 – Diagnostic complementary tests for ischemic heart disease: differences between sexes in the interpretation of the tests, accuracy, advantages, and disadvantages when used in women.

COMPLEMENTARY TEST	Test interpretation differences between sexes	Accuracy in women	ADVANTAGES	DISADVANTAGES
ELECTROCARDIOGRAM	Smaller QRS amplitude: S wave in V2 and R wave in V5 QT interval is longer in women (RV >470ms) J point and ST amplitude smaller in women	No difference between sexes	Uses Cornell criteria to diagnose LVH in women (RV > 20mm)	Interferes with the accuracy of LVH diagnosis by use of the Sokolow criteria
EXERCISE TEST	ST-segment depression as false-positive	Accuracy: 47% Negative predictive value similar to that in men: 78%	Low cost Good negative predictive value when performed in patients who reach maximum exertion	Low accuracy
CAROTID ULTRASOUND	IMT is smaller in women	Similar	No radiation, good availability, and relatively low cost Atherosclerotic plaque is better risk predictor than IMT May be useful in special subgroups in which the applicability of risk scores is worse	Less accurate than CCaS
ECHOCARDIOGRAPHY	No difference between sexes	Rest echo: No difference between sexes Stress echo: similar accuracy in both sexes	Stress echo is more accurate than ET, especially when baseline ECG is abnormal Identifies other diseases that can cause precordial pain No radiation exposure	Echo is examiner-dependent
SCINTIGRAPHY	Image attenuation due to the breasts Worse image resolution in conventional gamma cameras	Sensitivity 78% Specificity 64%	More accurate than ET in women with intermediate/high PTP Excellent prognostic value when normal	Breast exposure to radiation
CORONARY CALCIUM SCORE	CCaS > 0 in women indicates higher risk than in men	Similar accuracy for risk stratification and event prediction	Radiation similar to that of mammography (<1mSv)	Limited availability of the test
COMPUTED TOMOGRAPHY ANGIOGRAPHY	No difference between sexes	Similar accuracy	Identifies non-obstructive CAD, which is more prevalent in women, and better correlation with future events Reduction in the emergency department length of stay	Limited availability of the test Radiation exposure
CARDIAC MAGNETIC RESONANCE IMAGING	No difference between sexes	Similar accuracy	No radiation exposure Evidences perfusion and/or myocardial changes, improving the differential diagnosis scope of chest pain	Limited availability of the test
CORONARY ANGIOGRAPHY	No difference between sexes Women have a higher frequency of normal coronary arteries on coronary angiography when that is requested	No difference between sexes	Can diagnose vasospastic angina, when performed for that purpose	Higher risk of procedural complications: bleeding and acute renal lesion Does not assess ischemia due to microvascular disease

CCaS: coronary calcium score; CAD: coronary artery disease; Echo: echocardiography; ET: exercise test; IMT: intimal-media thickness; LVH: left ventricular hypertrophy; PTP: pretest probability; RV: reference value.

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In the functional assessment of women's IHD, the impact of the breasts and of the smaller myocardial mass in imaging tests is well known. This limitation does not apply to CMRI, which has similar accuracy in men and women. Considering the characteristics of the IHD pattern in the female population, that is the disparity between symptoms and anatomical findings, the CMRI became an excellent option for myocardial perfusion assessment because of its high spatial resolution and identical performance, regardless of sex. In addition, CMRI can evidence perfusion and/or myocardial changes, widening the differential diagnosis scope of chest pain (ex: infarctions due to thromboembolism or coronary dissection), and be particularly useful in approaching that symptom in women.^{142,144}

5.8. Coronary Angiography

There is evidence that the number of coronary angiographies performed in women is smaller than in men.

However, when stratifying risk for women, the indication of coronary angiography is similar to that for men.¹⁴⁴ The CURE study shows that the indication of coronary angiography, angioplasty, and CABG was lower for women (48% x 61%).¹⁴⁵ The socioeconomic level results in higher vulnerability of access for low-income women, which could cause higher short-term mortality in ACS.¹⁴⁶

A cross-sectional study with data from the VICTIM Registry has assessed patients diagnosed with STEMI from four hospitals (one public and three private hospitals) that offered primary angioplasty. The study included 878 patients with STEMI, 33.4% of whom were women. Women had smaller rates of fibrinolysis (total: 2.3%; women: 1.7%; and men: 2.6%) and of primary angioplasty (44% in women; 54.5% in men), resulting in higher in-hospital mortality (16.1% versus 6.7%).¹⁴⁶

Normal coronary arteries on coronary angiography are more common in women, including in ACS, and

Chart 5.2 – Recommendations of diagnostic tests for ischemic heart disease in women.

Recommendations for the management of ischemic heart disease in women			
Recommendation	CR	LE	References
In chest pain, ECG maintains the usual classes of recommendation, especially in low/intermediate-risk women, considering the sex-related changes.		A	25,133
Exercise test is recommended in symptomatic women at intermediate risk for IHD, with normal baseline ECG and who can achieve maximum exercise.		B	25
Exercise test with imaging is recommended in women with ST segment-T changes at rest and who cannot exercise properly.		B	25,140
CCaS: women at low/intermediate or inconsistent risk: improves risk assessment. High negative predictive value. It is a "bridge" test for coronary CTA when CCaS is positive in low-risk patients.	 a	A	143
Coronary CTA: risk stratifier in women; as effective as exercise test.	 a	A	143
Coronary CTA: high predictive accuracy to identify obstructive CAD and when present in low-risk women.	 a	A	143
MRI indicated in women with suspected non-obstructive IHD (microvascular disease); advantage: it involves no ionizing radiation.	 b	B	144
MRI in women with intermediate pretest probability, ST segment-T changes at rest on ECG and who cannot exercise properly.	 a	B	144

CR: class of recommendation; LE: level of evidence; CCaS: coronary calcium score; CTA: computed tomography angiography; ECG: electrocardiogram; IHD: ischemic heart disease; MRI: magnetic resonance imaging.

can represent microvascular disease, vasospasm, or spontaneous thrombolysis.²⁸

The risk of vascular complications from coronary angiography can be higher in women with thinner femoral arteries, even with manual compression or use of collagen plug. In addition, women have a higher tendency to develop contrast-induced acute kidney injury, because they have more glomeruli, and to develop anemia.²⁸

Chart 5.1 shows the differences in the interpretation of the complementary tests for IHD between sexes, and their accuracy, advantages, and disadvantages in women.

Chart 5.2 shows the recommendations and levels of evidence of the diagnostic tests for IHD in women.

6. Women's Representation in Clinical Studies on Cardiovascular Disease and Risk Factors

Sex and gender associate with environmental and occupational risks, risky behaviors, health care, and its perception by human beings, influencing the prevalence of diseases and the results of their treatments differently in men and women.^{147,148} Considering that the pharmacokinetics and pharmacodynamics of medications differ between sexes, men and women differ in the profile of adverse events and the results of treatments.¹⁴⁸ Knowing this, clinical trials on diagnosis and treatment need to maintain in their samples the representativeness of men and women

observed in the human population and proportional to the prevalence of the disease studied.

However, the analysis of clinical studies performed in recent decades about CVDs and their risk factors has shown that, despite some advances, women are still underrepresented in those studies.^{34,67,149–153}

In 121 clinical trials funded by the National Heart, Lung, and Blood Institute (NHLBI) between 1965 and 1998, excluding the studies performed with only one sex, women represented on average 38% of the samples, without significant profile changes over time.⁶⁷ The analysis showed that the women's representation in studies on CAD and SAH was proportional to the prevalence of those diseases in the female sex; however, in studies on HF and arrhythmias, the women's representation was lower than the prevalence of those diseases in the female sex.⁸⁷

The systematic review of 135 clinical trials used to support the recommendations of the American Heart Association's Evidence-based guidelines for cardiovascular disease prevention in women: 2007 update has shown that the women's representation in studies published between 1970 and 2006 increased over time (from 18% in 1970 to 34% in 2006), being higher in primary than in secondary prevention (43% versus 27%) and in studies on SAH, DM, and stroke, but lower in studies on HF, CAD, and dyslipidemia.¹⁵⁰ Despite that increase, the authors concluded that women were still underrepresented in clinical studies on CVDs and their risk factors, emphasizing that in only 31% of those studies the results were discussed based on differences between sexes.¹⁵⁰

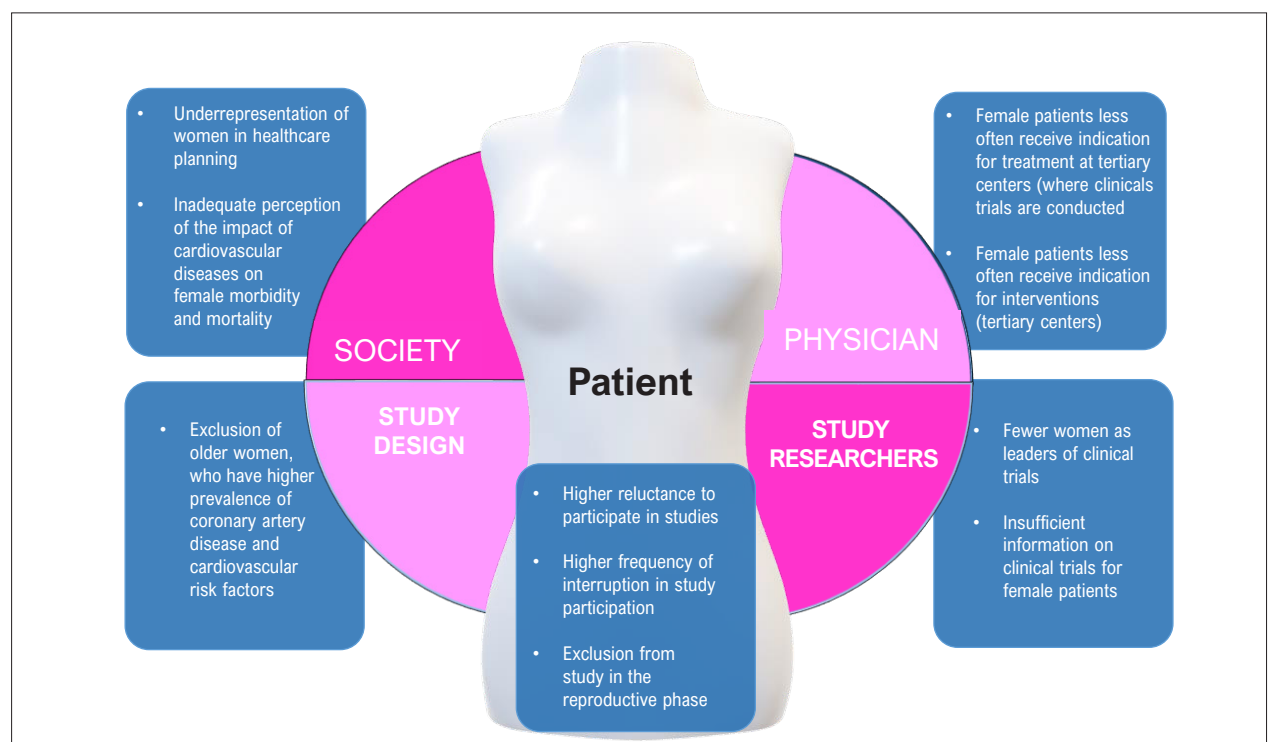


Figure 6.1 – Barriers that contribute to the low representation of women in clinical studies on cardiovascular diseases and their risk factors.^{152,153}

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The analysis of women's participation and of the safety and efficacy reported according to sex in clinical studies on CVD that supported 36 approvals of medications from 2005 to 2015 by the USA Food and Drug Administration has shown that women represented, on average, 46% of those studies' samples.³⁴ The authors concluded that there was proper representation of women in clinical studies on SAH, AF, and PH, but underrepresentation in studies on HF, CAD, and ACS. Minimal differences between sexes were reported in the efficacy and safety profiles of the medications assessed and approved.³⁴

The participation of women in 740 clinical studies on CVD registered in ClinicalTrials.gov (<https://clinicaltrials.gov>) between 2010 and 2017 was, on average, 38.2% of the total of 862 652 adults. Women were younger (≤ 55 years) and participated in studies of lifestyle intervention and on SAH, AF, and PH, although those studies were of shorter duration. However, in studies on high-complexity procedures, CAD, ACS, and HF, women were underrepresented.¹⁵¹

The analysis of this scenario evidences several barriers to be overcome to reach equity in representation of the subjects in clinical studies, to properly contemplate women in general as well as women from minority populations (ethnic and racial).^{152,153} Those barriers seem to relate to patients, assistant physicians, research team, study's design, and society,¹⁵² and are shown in Figure 6.1.

Recommendations: A) scientific journals should ask authors of cardiovascular clinical studies to analyze sex/gender-specific differences; B) health equity should be integrated in the design of clinical studies, using a structure such as *PROGRESS Plus* (**P**lace of residence; **R**ace; **O**ccupation; **G**ender; **R**eligion; **E**ducation; **S**ocioeconomic status; **S**ocial capital; **P**lus=others); C) more women should integrate the research teams of clinical studies; D) medical education should comprise sex and gender particularities; E) population access to clinical trial sites should be facilitated.^{152,153}

7. Primary Prevention Measures in Women

Women's PHC occurs via the Health Care Network, according to the guidelines of the National Policy of Women's Total Health Care from the Brazilian Ministry of Health.^{154,155} Through the Basic Health Units, public health actions are implemented to reduce women's morbidity and mortality throughout their life cycle, extending to their family and community.^{154,155}

Reproductive life planning, the set of actions to regulate fertility, and the contraceptive practices that are mainly adopted by women, including lesbians and bisexuals, whose desire or right to maternity need to be ensured, should be contemplated by the PHC teams, which need to initiate the necessary measures for their implementation.^{154,155}

In prenatal care, the Family Health Teams should stratify maternal and fetal risks, considering reproductive history, individual characteristics, and unfavorable

sociodemographic conditions. The recruitment of women of reproductive age (10-49 years) is essential to stratify pregnancies at risk for complications, such as: extremes of age (under 15 years and over 35 years), low body weight and overweight or obesity, unsafe family situation, non-acceptance of pregnancy (mainly in adolescents), low schooling, women with heart disease, chronic hypertension and/or history of gestational hypertensive disorder, and gestational diabetes mellitus. In puerperium, special attention should be given to women's psychic and social conditions, as well as protection and support to breastfeeding, which should be exclusive in the first six months of life.^{154,155}

Menopausal transition is associated with an increased risk for CVD, mainly attributed to atherogenic dyslipidemia, central obesity, and insulin resistance, and with an increased risk for arterial hypertension.¹⁵⁶ The MHT should be individualized, considering personal and family risks for gynecological neoplasia, in addition to cardiovascular risk stratification. The MHT should be systematically accompanied in PHC. Estrogen replacement can reduce the serum levels of total cholesterol and LDL-c because of the increased synthesis of LDL-c receptors. Benefits from MHT were observed when introduced before the age of 60 years and in women whose menstrual cycles ceased less than 10 years before (preferably in the first 5 years); however, it can be harmful if outside the window of opportunity, increasing cardiovascular risk.⁴⁹

In 2019, some of the indicators of woman's health agreed upon in the Brazilian prevention program, *Programa Previne Brasil*, were as follows: pregnant women registered in the PHC, mean number of prenatal visits, prenatal follow-up initiated in the first trimester, pregnant women with up-to-date vaccines, home visits for pregnant women, adolescent pregnancy, proportion of normal deliveries, maternal deaths, cytopathology of the uterine cervix, screening with mammography in women from 50 to 69 years. It is worth noting the lack of any cardiovascular health indicator agreed upon in that prevention program.¹⁵⁷ In addition, the OECD has recently released a report on the PHC in Brazil, in which women's CVDs have not been mentioned. Regarding women, that report only made suggestions for the management of breast and ovary neoplasms; however, in percentage terms, CVDs cause twice more deaths than all other neoplasms in Brazil.¹⁵⁸

A paradigm change in the basic assumptions of the public policies on women's total health is necessary, especially considering that CVDs are the major cause of death of women in most of their life cycle (Figure 7.1).

Nonpharmacological therapies incorporating lifestyle changes (exercises, body weight loss, smoking cessation, and healthy diet) should be recommended as first-line strategy in PHC. The efficacy of such measures is directly associated with better understanding, sensitization, and motivation built during the Family Health Team follow-up. The management of healthy dietary habits, regular physical activity practice, and mental health should be individualized.²⁶ Examples of validated tools for patients' assessment, in addition to clinical history and physical

exam, are the food guide for the Brazilian population (*Guia Alimentar para a População Brasileira*), the World Health Organization guidelines on physical activity and sedentary behavior, the stress and depression scales, and the questionnaires of spirituality.²⁶

Of all possible interventions in PHC, the most cost-effective is smoking cessation. The harmful effects of regular and electronic cigarette smoking are greater in women, specifically because of the loss of estrogen protection on the vascular endothelium.¹⁵⁹

In Brazil and around the world, violence against women is a serious public health problem, because it is one of the major causes of female morbidity and mortality. In PHC, actions that can ensure sexual rights in the perspective of women's autonomy regarding their bodies should be developed.¹⁶⁰

Considering the challenges to control CVD in Brazil and recognizing PHC as an important strategy for health promotion, risk factor prevention, early diagnosis, and care to individuals with CVD, a critical review to improve health actions for women in the Family Health Teams and PHC is suggested (Figure 7.1).¹⁶⁰

8. Women's Burnout, Quality of Life and Spirituality

8.1. Burnout

Burnout is a psychological syndrome resulting from chronic stress at work, characterized by emotional

exhaustion, cynicism/disengagement, and reduced professional efficacy.¹⁶¹ The dimensions of burnout were significantly associated with an increased risk for diseases, regardless of sociodemographic factors and depressive symptoms. In a study with 5671 participants [predominantly physicians, mean age of 44.1 years (range, 18 to 70 years), 62.4% women], a digital health app was used for online research about professional burnout measured with the Maslach Burnout Inventory General Survey. By use of network analysis and logistic regression, the study has shown the association of high emotional exhaustion with arterial hypertension and other chronic diseases after adjusting for age, sex, educational level, and depressive symptoms.¹⁶²

Work conditions have a well-known impact on the health of workers, and women, because they make up a great proportion of the global workforce and are overloaded with double journey, show high rates of burnout. A study conducted with Brazilian female physicians during the COVID-19 pandemic has reported that 61.6% of the participants had signs of burnout, such as emotional exhaustion, frequent negative feelings, and dissatisfaction with their capability for work (Figure 8.1).¹⁶²

It is worth noting that women are more exposed to stress and psychosocial adversities than men are, in addition to being more vulnerable to the effects of such exposures. Depression, unfavorable socioeconomic factors, and post-traumatic stress disorder are more prevalent in women than in men and tend to show more robust associations with cardiometabolic risk in women.⁶⁷

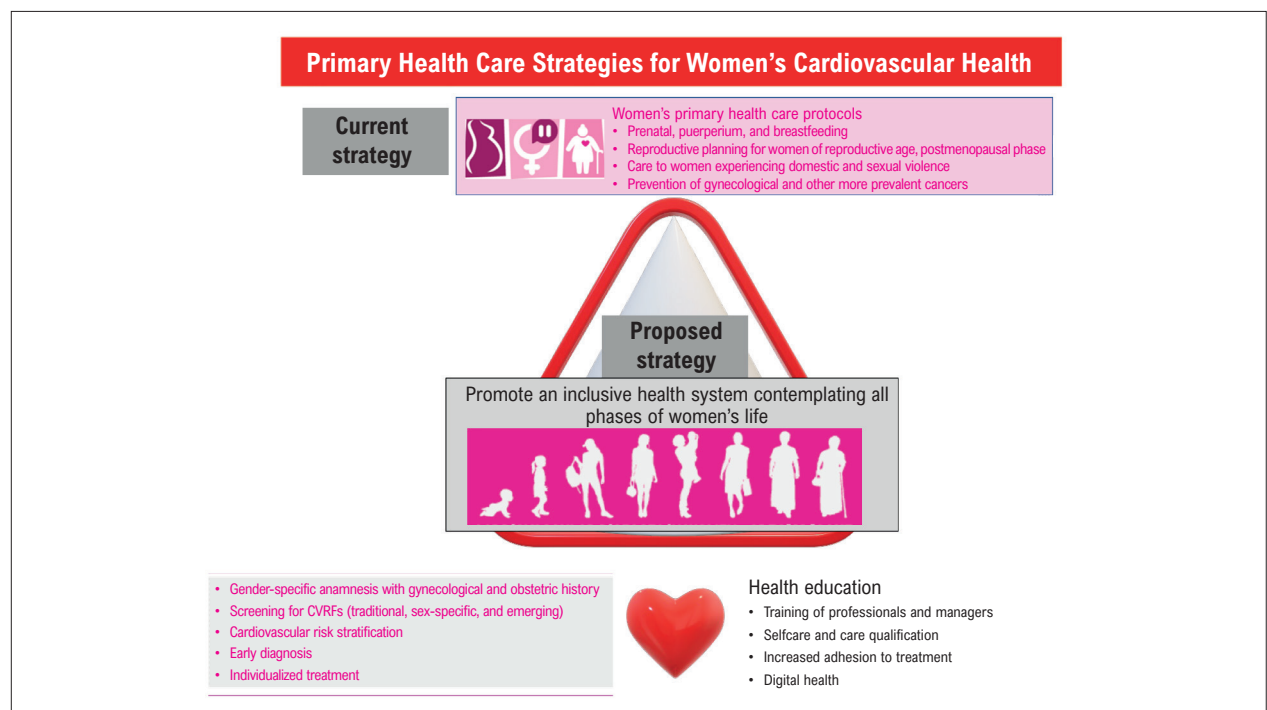


Figure 7.1 – Primary Health Care strategies for women's cardiovascular health. CVRF: cardiovascular risk factor

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8.2. Quality of Life

According to the World Health Organization, QoL is “an individual’s perception of their position in life in the context of the culture and value systems in which they live and in regard to their goals, expectations, standards and concerns”. The QoL is directly related to the higher incidence of chronic diseases, mainly CVD. The standard indicators of QoL include job, wealth, environment, physical and mental health, education, recreation and leisure, socialization, religious beliefs, safety, protection, and liberty.¹⁶³

In a study assessing the QoL of Brazilian female physicians, most participants reported having good QoL (71.7%) and being satisfied with their health (55%), but 64.8% reported not really enjoying their lives. In addition, they considered the following aspects of their lives satisfactory: sleep, 62.9%; ability to perform daily chores, 54.7%; capability for work, 64.4%; personal relationships, 57.7%; support from friends, 61%; conditions of the household, 84%; and access to healthcare, 81.4%. Only 36.6% considered their sexual life satisfactory, and around 94% had, at least occasionally, negative feelings (Figure 8.1).¹⁶²

A study conducted with 1387 women in the city of Uberaba, Minas Gerais state, has assessed the QoL by using the WHOQOL-Brief and according to four domains. The authors reported that women with CVD were older than 50 years and had low educational level and statistically significant lower values for all four domains

as compared to women without disease or those with chronic respiratory disease. The domain with the lowest score was environment, which relates to socioeconomic condition because it contains questions related to financial resources, leisure opportunities, safety, etc. These findings emphasize the higher susceptibility of women with CVD to psychosocial factors, with significant impact on QoL.¹⁶⁴

8.3. Spirituality

“Spirituality is a set of moral, mental, and emotional values that guide thoughts, behaviors, and attitudes in the circumstances of intra- and interpersonal relationships, motivated by the will, and capable of being observed and measured”. Spirituality must be differentiated from religiousness. “Religion is an organized system of beliefs, practices, and symbols destined to facilitate the proximity with the Divine and promote the understanding of one’s relationships and responsibilities with the others in the community”.²⁶

In addition to the behavioral aspects, the beneficial relationship of spirituality, religiousness, and the physiological and pathophysiological variables of several clinical entities, including women’s CVDs, has been shown.¹⁶⁵ Spiritual anamnesis has been more and more introduced in medical offices and hospitals, being part of the clinical history, especially in severe, chronic, progressive, debilitating, and terminal diseases. There

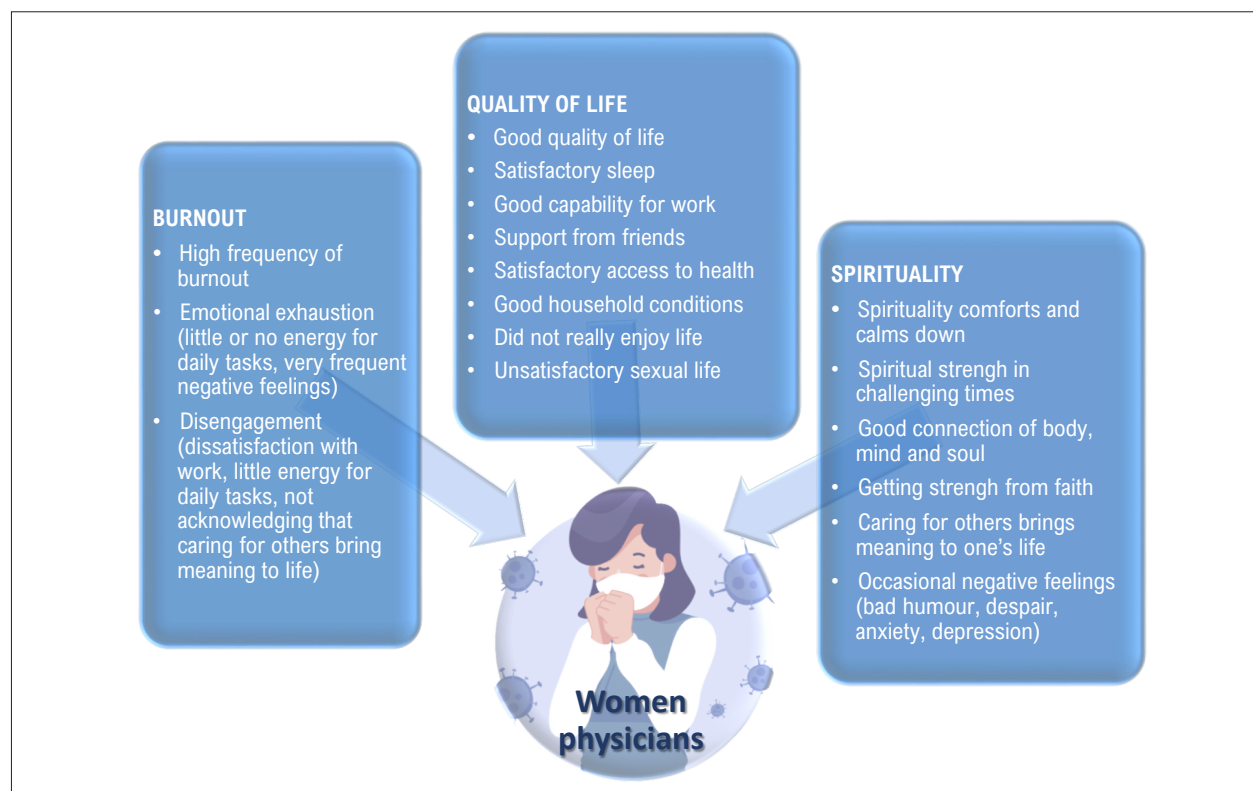


Figure 8.1 – Study performed with Brazilian female physicians during the COVID-19 pandemic. The findings emphasized the higher susceptibility of women to psychosocial factors, with a significant impact on quality of life, which can cause burnout, minimized by spirituality, especially in the COVID-19 pandemic.¹⁶²

are validated tools for assessment, based on health scales (FICA, FAITH, SPIRIT e HOPE).^{26,163-173}

A study with Brazilian female physicians, using a survey with questions based on the World Health Organization Quality of Life Spirituality, Religiousness and Personal Beliefs field-test instrument (WHOQOL-SRPB), has reported that the respondents believed that spirituality comforted and reassured them (73.2%) and that they found spiritual force in hard times (70.6%), with good connection of body, mind, and spirit (67.8%), even though only 53.4% reported inner peace and 50.7% reported being optimistic. In addition, 72.7% of the respondents reported finding strength in faith, and 44.3% found support in religious or spiritual communities (Figure 8.1).¹⁶²

In conclusion, health needs to be understood in the physical, social, psychoemotional, and spiritual context, respecting the individuality and singularity of the female sex.⁴⁴

Chart 8.1 shows the recommendations for the management of women's spirituality and health.

9. Cardiovascular Implications of COVID-19 in Pregnancy

The major complications reported in patients with COVID-19 are: myocardial injury, heart failure, arterial and venous thromboembolism, acute coronary syndrome, myocarditis, Takotsubo syndrome, and cardiac arrhythmias.¹⁹¹ Those complications are more frequent in

Chart 8.1 – Recommendations for the management of women's spirituality and health.

Recommendations for the management of women's spirituality and health			
Recommendation	CR	LE	References
Brief screening on spirituality and religiousness.		B	26,163-173
Spiritual anamnesis of patients with chronic diseases or of poor prognosis.		B	26,163-173
Respect and support patient's religion, beliefs, and personal rituals that do not jeopardize treatment.		C	26,163-173
Offer professional support to patients in pain or with spiritual demands.		C	26,163-173
Organizational religiousness associates with mortality reduction.		B	26,163-173
Spiritual anamnesis of stable or ambulatory patients.	 la	B	26,163-173
Questionnaires (DUREL, FICA, HOPE, or FAITH) to assess spirituality.	 a	B	26,163-173
Meditation, techniques for relaxation and fighting stress.	 a	B	26,163-173
Techniques for spiritual strengthening, such as forgiveness, gratitude, and resilience.	 b	C	26,163-173

CR: class of recommendation; LE: level of evidence.

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older women, with risk factors for cardiovascular diseases and with comorbidities.¹⁹¹ There is great concern about women during pregnancy and puerperium, who are more susceptible to severe forms of COVID-19, which can result in premature or emergency cesarean delivery, elevating the risk of neonatal and maternal death (Figure 9.1).¹⁹²

During pregnancy, the predominant immune response is via T-helper 2 (Th2) cells, which protects the fetus, but increases mother's vulnerability to viral infections, which are more effectively fought by Th1 cells.¹⁹³ The vertical transmission of SARS-CoV-2 can occur through the transplacental route, during delivery and while breastfeeding. The SARS-CoV-2 transmission via blood is still uncertain.¹⁶² The physiological changes of pregnancy comprise the increase in plasma and systolic volume, and in cardiac output in the first half of pregnancy, with a gradual increase in heart rate, in addition to a decrease in systemic and pulmonary vascular resistance. Furthermore, pregnancy is a hypercoagulable state associated with increased risk of venous and pulmonary thromboembolism.¹⁹⁴

The COVID-19 clinical findings have some particularities in pregnancy, such as longer persistence of symptoms and lower frequency of fever and myalgia, as compared to non-pregnancy. The major risk factors for severe infection are older maternal age, high body mass index, and preexisting comorbidities, such as hypertension, preeclampsia, and

diabetes.¹⁹⁴ Pregnancy was associated with severe infection in 10%, admission to the intensive care unit in 4%, mechanical ventilation in 3%, and use of extracorporeal membrane oxygenation in 0.2%.^{194,195}

In addition, perinatal complications were also more prevalent. When compared to pregnant women without infection, those with COVID-19 had a higher risk of premature delivery and stillbirth. Overall, 33% of the newborns from women with COVID-19 were admitted to the neonatal intensive care unit.^{192,194} Even after adjusting to race, comorbidities, and age, pregnant women had a high likelihood to die as compared to their non-pregnant counterparts.¹⁹⁶

The severe cardiovascular complications in COVID-19 are acute myocardial injury, myocarditis, arrhythmia, fulminant heart failure, cardiogenic shock, and spontaneous dissections of the coronary and vertebral arteries, which have higher mortality.¹⁹²

The potential contributors to acute cardiac injury in COVID-19 are:¹⁹¹ acute changes in myocardial supply and demand due to tachycardia, hypotension, and hypoxemia, resulting in type 2 myocardial infarction;¹⁹² acute coronary syndrome due to acute atherothrombosis in a virus-induced thrombotic and inflammatory condition;¹⁹³ microvascular dysfunction due to diffuse microthrombi or vascular lesion;¹⁹⁴ stress-related cardiomyopathy (Takotsubo syndrome);¹⁹⁵ non-ischemic myocardial injury due to

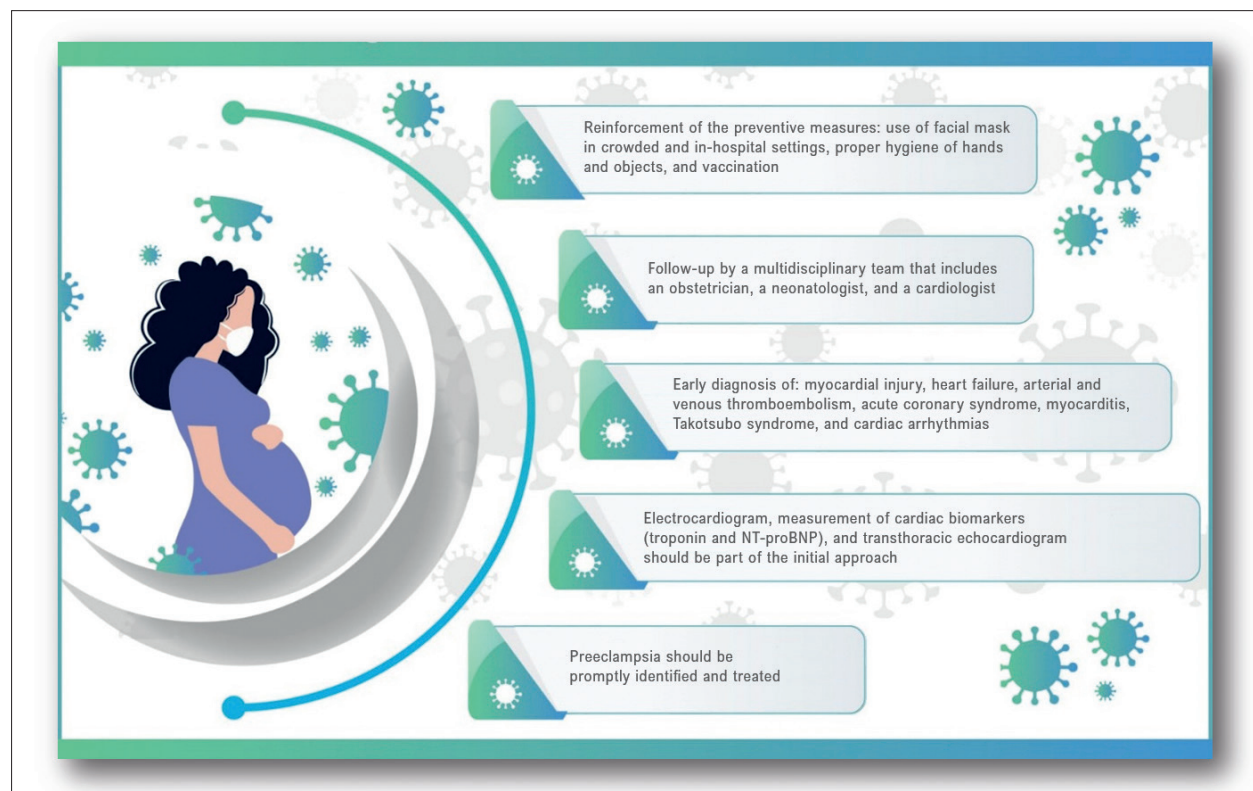


Figure 9.1 – Preventive measures for pregnant women with COVID-19. NT-proBNP: N-terminal fragment of pro-B-type natriuretic peptide.

hyperinflammatory cytokine storm;¹⁹⁶ or direct viral toxicity to cardiomyocytes and myocarditis. The medicamentous treatment of heart failure in pregnancy has particularities that should be considered to avoid teratogenicity.¹⁹³

In cases of ST-elevation acute coronary syndrome, coronary angiography should be preferentially performed and followed by percutaneous treatment. In 15 pregnant patients with COVID-19 and myocardial injury, 13.3% had atrial fibrillation, 2 had supraventricular tachycardia, and 2 patients developed *torsades de pointes*.¹⁹⁷ The use of medications that can prolong the QT interval should be carefully considered.

COVID-19 can both predispose to preeclampsia and worsen its course. The virus generates a pathophysiological state similar to that of preeclampsia, characterized by systemic hyperinflammation, direct endothelial injury, thrombogenesis, and immune dysregulation; in addition, the virus affects the renin-angiotensin-aldosterone system, increasing the incidence of preeclampsia in infected patients.¹⁹⁸

The decision about interrupting pregnancy should be based on the usual guidelines, which consider gestational age, hemodynamic conditions, fetal suffering, and maternal risk. Non-complicated COVID-19 should not be an indication for pregnancy interruption. The type of delivery should follow the obstetrical recommendations.¹⁹⁹

10. Future Perspectives on Women's Cardiovascular Healthcare

A multidisciplinary team is always recommended for preventive care and treatment in the follow-up of women with CVD. To raise awareness includes the creation of integrative health programs, involving communitarian leaders and agents, with new centers specializing in women's cardiovascular health. It is important to specifically educate on self-care to prevent CVD, proper use of oral contraception, prenatal follow-up, long-term follow-up of CVRFs, as well as the psychosocial and socioeconomic aspects involving CVDs in the female sex.²⁰⁰

Primary prevention in women should focus on the effective treatment of traditional risk factors, such as SAH, dietary risks, dyslipidemia, diabetes, obesity, and physical inactivity. The lack of specific risk scores for women indicates long-term risk stratification, considering life course and the female-sex-specific factors, such as the presence of depression, as well as the psychosocial factors.²⁰⁰ It is worth emphasizing that the frequency of HFpEF in women is higher than in men; in addition, women more often have HFpEF than HFrEF, and treatment should

be initiated with the clinical diagnosis of HF, regardless of the ejection fraction, because of the greater relevance of the cognitive deficit associated with HF in the female sex.²⁰¹

The major attributable risk factor for the development of cardiovascular outcomes in both sexes is SAH. The BP control is essential to reduce the incidence of HFpEF and HFrEF.^{202,203} However, women have lower rates of BP control as compared to men, mainly at more advanced age groups.²⁰⁴ Strategies that include BP measurement outside the medical office, such as BP self-measurement, home and ambulatory BP monitoring, using semi-automated equipment are desirable. In addition, remote monitoring using digital platforms and apps, with continuous BP monitoring without cuffs and synchronized with smartphones, represents the use of technology and wearables of easy access, favoring the clinical results, and might help better BP control.^{205,206}

Because of the medical, surgical, and technological evolution in recent decades, more than 90% of individuals with CC born nowadays survive until adulthood. The especial attention to women with CC requires planning strategies to address their needs.¹¹ Thus, centers specialized in CC should be created with multidisciplinary teams that include physicians, nurses, psychologists, and social workers for contraception counselling or pregnancy planning. The risks of an adult patient with CC, treated or not during childhood, especially regarding contraception and pregnancy, should always be considered, because 3% to 10% of the babies from those mothers can have congenital cardiac lesions.²⁰⁷ Women of reproductive age with cardiopathy should be approached by a multidisciplinary team, a "cardio-obstetrical team", for pre-conceptional counselling to define pregnancy, delivery and puerperium planning, including specialized cardiological care and family planning after delivery.²⁰⁸

The prevention and treatment of CVDs in women require solid health systems supported by professionals knowing the specificities of CVDs in women, in addition to coordinated efforts with productive partnerships between society, physicians, researchers, and the community.⁷⁰

The "Women's Letter", published in 2019, suggests the creation of a permanent group to promote and implement policies directed to women's cardiovascular health. That group should play a leadership role in Brazilian health policies, providing managers with an overview of the relevance of CVD in the female sex, so that strategies can be developed to reduce the prevalence of risk factors and improve diagnosis and treatment, therefore reducing CVD mortality and morbidity (Figure 10.1).⁴

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Figure 10.1 – Perspectives for management of cardiovascular diseases in women according to the 'Women's Letter'.⁴ CV: cardiovascular; NCD: noncommunicable disease; CVD: cardiovascular disease.

Erratum

November 2022 issue, vol. 119(5), pages 815-882

In the "Position Statement on Women's Cardiovascular Health – 2022", with DOI: <https://doi.org/10.36660/abc.20220734>, published in the journal *Arquivos Brasileiros de Cardiologia*, Arq Bras Cardiol. 2022; 119(5):815-882, on page 818, make the following correction:

Correct the conflict of interest statement of the author Maria Cristina de Oliveira Izar:

"Financial declaration

A - Economically relevant payments of any kind made to (i) you, (ii) your spouse/partner or any other person living with you, (iii) any legal person in which any of these is either a direct or indirect controlling owner, business partner, shareholder or participant; any payments received for lectures, lessons, training instruction, compensation, fees paid for participation in advisory boards, investigative boards or other committees, etc. From the Brazilian or international pharmaceutical, orthosis, prosthesis, equipment and implants industry:

- Bayer/Xarelto; Daiichi Sankyo/Lixiana; Libbs/Propafenona e Amiodarona; Pfizer/Eliquis."

Continues on next page

To:

“Financial declaration

A - Economically relevant payments of any kind made to (i) you, (ii) your spouse/partner or any other person living with you, (iii) any legal person in which any of these is either a direct or indirect controlling owner, business partner, shareholder or participant; any payments received for lectures, lessons, training instruction, compensation, fees paid for participation in advisory boards, investigative boards or other committees, etc. From the Brazilian or international pharmaceutical, orthosis, prosthesis, equipment and implants industry:

- Amgen: Repatha; Amryt Pharma: Lojuxta; AstraZeneca: Dapagliflozina; Aché: Trezor, Trezete; Biolab: Livalo; Abbott: Lipidil; EMS: Rosuvastatina; Eurofarma: Rosuvastatina; Sanofi: Praluent, Zympass, Zympass Eze, Efluelda; Libbs: Plenance, Plenance Eze; Novo Nordisk: Ozempic, Victoza; Servier: Acertamlo, Alertalix; PTCBio: Waylivra.

B - Research funding under your direct/personal responsibility (directed to the department or institution) from the Brazilian or international pharmaceutical, orthosis, prosthesis, equipment and implants industry:

- PTCBio: Waylivra; Amgen: Repatha; Novartis: Inclisiran, Pelacarsen; NovoNordisk: Ziltivekimab.

Other relationships

Funding of continuing medical education activities, including travel, accommodation and registration in conferences and courses, from the Brazilian or international pharmaceutical, orthosis, prosthesis, equipment and implants industry:

- Novo Nordisk: Diabetes.”

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