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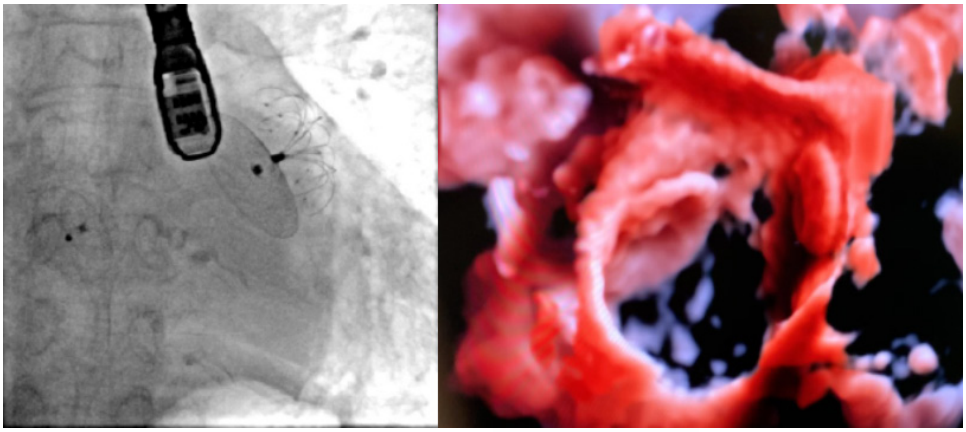

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Statins and Pregnancy – New FDA Recommendations

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The Food and Drug Administration (FDA), the agency responsible for controlling the safety and efficacy of drugs in the United States, has traditionally adopted a risk classification for the use of drugs during pregnancy. Statins were considered a Category X drug, which indicates that the demonstrated risk of these drugs to cause birth defects surpassed their benefits. However, in July 2021, the FDA withdrew this recommendation.[1]

Before this change, the FDA recommended the discontinuation of statins from conception attempts until the end of breastfeeding. In cases where dyslipidemia is not severe, statin discontinuation may confer no additional risk. However, based on this recommendation, the duration of discontinuation may be substantial. In a study with more than 100 women with familial hypercholesterolemia in Norway and Netherlands, the mean length of time without statins was longer than two years for each pregnancy.[2] Although two years is a long period, it still may be a conservative estimate. In this study, the mean interval between conception planning and pregnancy was two months. Data in the literature,[2] however, suggest that the median time to pregnancy is longer, probably around six months for nulliparous women.[3] Also, in this study,[2] mean breastfeeding duration was four months. Considering that the World Health Organization recommends exclusive breastfeeding for the first six months of life, and continued breastfeeding along with introducing complementary foods after this period, the real impact of statin discontinuation during the gestation period may be even greater than two years. Also, many women who use statins are older and may desire more than one child, which may prolong the period of time without statins for more than five years during their reproductive period.

In this context, the change of FDA's position may have a substantial impact on reproductive women willing to become pregnant. Also, the new recommendation is rather vague, as it states that statins should be discontinued by many pregnant women, albeit a shared decision-making, weighing risks and benefits, should be the routine strategy to be adopted. The FDA also advocates that the use of statins in the pre-conception period, during which women are trying to get pregnant, is safe. This change may have a particularly strong impact on 10-20% of couples that deal with infertility, and whose pre-conceptional period may be considerably long. Also, the new recommendation has an important impact on women with known cardiovascular disease who are trying to get pregnant, as data in the literature have shown that the benefit on cardiovascular events with the use of statins can be perceived even with the use of statins for periods shorter than four months in high-risk individuals.[1]

Despite limited data on statins in pregnancy, the new recommendation has an adequate scientific basis. The previous guidance based on the fetal risk related to statins has been constructed from data obtained from animal experimental studies with much higher doses than those usually used in humans.[4] Nevertheless, more recent studies, involving humans, have not demonstrated the same risks identified in experimental studies. A recent observational study has not shown an association of statins with a higher risk of fetal malformations but did show an association with a low birth weight and premature delivery. Similar data were found in a meta-analysis of five recently published cohort studies.[5] Since the use of statins has been associated with a higher number of comorbidities, it is possible that these complications are associated with comorbidities rather than with statins. Despite that, the potential residual risk of the use of statins makes the risk and benefit discussion the best strategy.

Even with a selective use of statins, considering risks and benefits, by patients with high cardiovascular risk and those with a previous history of cardiovascular disease, the FDA decision may have other ramifications. The main one consists of clinical trials with studies with women in the pre-conception, gestational and breastfeeding periods. These studies go beyond the known cardiovascular effects. One study published this year evaluated the impact of statins on results of *in vitro* fertilization in patients with dyslipidemia and infertility. Despite important limitations, the study suggests that pravastatin improved these results in the studied population. Further studies are needed before clinical implementation.[6]

Similarly, several studies have evaluated the use of statins in preeclampsia prevention. The rational of these studies is that statins could reverse the imbalance of pro- and anti-angiogenesis factors that precedes the clinical manifestations of preeclampsia. Despite numerous studies, the effect of statins, particularly pravastatin, on preeclampsia are still controversial. While small studies have suggested beneficial effects, recent randomized studies have suggested the contrary.[6] Apparently, additional studies are needed to best define those patients who would most benefit from statins, as well as the best moment to initiate the drug during pregnancy and the most

Keywords

Hydroxymethylglutaryl-CoA Reductase Inhibitors; Pregnancy; Dyslipidemias

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appropriate dose. Until then, the benefit of statins in these scenarios must be considered as uncertain.

It was a small step, but the change in the language and recommendation proposed by the FDA has had important clinical repercussions and future scientific implications. So far, the flexibility in the use of statins in the pre-conception period and during pregnancy will already have a strong effect on routine clinical practice with women of fertile age, at high cardiovascular risk and established atherosclerosis, trying to become pregnant.

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Relationship between Urinary Norepinephrine, Fibrosis, and Arrhythmias in Chronic Chagas Heart Disease with Preserved or Mildly Reduced Ejection Fraction

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Abstract

Background: In Chronic Chagas Cardiomyopathy (CCC), studies are needed to identify arrhythmogenic risk factors in patients in which moderate to severe ventricular dysfunction is not present.

Objective: To verify the correlation between frequent ventricular arrhythmias (PVC), left ventricular ejection fraction (LVEF), extension of fibrosis by cardiac magnetic resonance (CMR), and urinary norepinephrine measurement (NOREPI) in CCC with preserved or mildly compromised LVEF.

Methods: The presence of ventricular extrasystoles > 30/h was analyzed on Holter. At CMR, LVEF and quantification of fibrosis mass were evaluated. The dosage of NOREPI was performed using the Muskiet method. The correlation coefficient matrix was calculated to measure the predictive ability of the variables to predict another variable, with $p < 0.05$ being considered significant.

Results: A total of 59 patients were included. The mean age was 57.9 + 10.94 years. PVC was detected in 28 patients. The fibrosis variable was inversely proportional to LVEF (R of -0.61) and NOREPI (R of -0.68). Also, the variable PVC was inversely proportional to LVEF (R of -0.33) and NOREPI (R of -0.27). On the other hand, LVEF was directly proportional to NOREPI (R of 0.83).

Conclusion: In this sample, in patients with CCC with preserved or slightly reduced LVEF, integrity of the autonomic nervous system is observed in hearts with little fibrosis and higher LVEF despite the presence of traditional risk factors for sudden cardiac death. There is correlation between the levels of NOREPI, LVEF, and myocardial fibrosis, but not with PVC.

Keywords: Cardiac Arrythmias; Myocardial Fibrosis; Chagasic Cardiomyopathy; Autonomic Denervation; Norepinephrine.

Introduction

Chagas disease (Cd) remains of marked epidemiological importance due to the contingent of infected individuals who are at risk of progression to more severe forms. In Brazil, 1.2 million people are estimated to be infected.[1] One-third of them have heart disease, two-thirds of these being mild.[2]

Chronic Chagas Cardiomyopathy (CCC) is considered arrhythmogenic due to its potential to cause several fatal types of arrhythmias,[3,4] especially in more advanced stages of disease (group with increased risk of sudden cardiac death). Although patients at high risk for sudden death can be identified by their risk factors, most sudden deaths occur in patients who were not categorized as high risk.[3] This apparent paradox hampers the implementation of large-scale preventive measures and justifies research on this group of patients with preserved or mildly reduced ejection fraction.[3,4]

The mechanism behind ventricular arrhythmias in the early stages of CCC may be associated with autonomic denervation, a hallmark of Cd.[4-6] Studies in the last decade[7-9] have shown that cardiac autonomic denervation is a common finding in patients with Cd and is caused by neuronal and ganglion inflammation. The destruction and loss of neural cells begin in the acute stage of the disease and continue through the chronic phase, caused by immune or parasitary mechanisms, both acting exclusively or in combination.[10,11] Autonomic denervation is important in understanding the pathogenesis, as well as the natural history of CCC.

Several authors demonstrated the direct association between sympathetic neural stimulation and the levels of norepinephrine, justifying the use of norepinephrine as a marker of sympathetic activity.[12-14]

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In patients with heart failure, sympathetic hyperactivity is persistent and associated with classic adrenergic symptoms, such as tachycardia, sudoresis, diarrhea, and anxiety. However, in Chagas heart disease, these aspects remain controversial, and it has been indicated that the sympathetic system heads towards exhaustion as the cardiac dysfunction progresses.

The common involvement of distal areas of the left ventricle (LV) myocardium, such as the apex and basal inferolateral segments, suggests an acute inflammation leading to myocardial ischemia due to microvascular dysregulation as the pathogenesis of myocardial fibrosis in these patients. Corroborating this, the regulation of abnormal microvascular flow in the presence of chronic myocardial inflammation in CCC was demonstrated by scintigraphy[15-17] and also magnetic resonance imaging.[18] These perfusion defects usually precede the appearance of wall motion abnormalities, suggesting that microvascular disorders may develop before the onset of myocardial damage and may be a causative agent of myocardial fibrosis.

The association between CMR findings and arrhythmias in CCC has been studied previously. CMR is currently recommended for patients with severe ventricular arrhythmias in order to quantify myocardial fibrosis and for risk stratification of sudden cardiac death.[19]

Thus, the population with Cd and the potential to develop a cardiac complication is large enough to justify diagnostic strategies that identify patients at increased risk.[20] Therefore, this study aims to verify the relationship between frequent ventricular arrhythmias, fibrosis extension, ventricular function, regional wall motion abnormalities (RWMA), and urinary norepinephrine dosage in patients with CCC.

Methods

Patients with CCC aged over 21, with preserved or mildly reduced left ventricular function (EF > 45%) at CMR and who had urinary norepinephrine dosage before the CMR acquisition date were included. The acquisitions were performed between March and December 2010. All patients had a 12-lead electrocardiogram and 24h Holter monitoring before CMR. Only asymptomatic patients away from Chagas endemic zones for more than 20 years and using beta-blockers and angiotensin-converting enzyme inhibitors (ACEI) were included. The exclusion criteria were renal dysfunction (estimated creatinine clearance < 30 mL/min), previous cardiac ablation procedure, diabetes or more than two risk factors for coronary heart disease, atrial fibrillation, treadmill test positive for myocardial ischemia, previous myocardial infarction, any previous myocardial or peripheral revascularization procedure, and standard contraindication to CMR (permanent pacemaker, implanted defibrillator, neurosurgical clip, or cochlear implant).

Holter monitoring was considered positive for frequent ventricular arrhythmia in the presence of premature ventricular contractions (PVCs) > 30/hour, or episodes of non-sustained ventricular tachycardia (NSVT) (defined as three or more consecutive ventricular beats with a duration of less than 30 seconds).[21]

Urinary norepinephrine dosages were performed from 2004 to 2006. All patients were instructed to avoid eating food that contained tyramine (a substance that facilitates the release of norepinephrine from storage sites inside neurons), which could interfere with the norepinephrine concentration, at least 24 hours before and during the urine collecting period. The use of beta-blockers was not suspended during collection. Urine collection was performed on Sundays, starting at 6:00 am, during a period of 24 hours, and all samples were cumulatively stored in two polyethylene bottles with a capacity of one liter each. Every bottle contained 1 ml of 6 M HCl (pH 1.0), with the recommendation to keep the samples at 4º C during the collection period (24h). The method used to determine urinary norepinephrine was based on the proposition by Muskiet et al.[22]

CMR was performed on a 1.5 Tesla GE HDX scanner (Wakeusha, Wisconsin), and two pulse sequences were acquired during end-expiratory breath-hold: the first was cine-CMR (Steady-State Free Precession) in the long-axis and short-axis views for assessing mass, volumes, and LVEF. The most basal cut on the short axis was positioned right after the atrioventricular ring, and all subsequent images were acquired with 8 mm thickness and a 2 mm inter-slice gap, up to the LV apex. The parameters used were field of view (FOV) 400 mm, 224 × 224 matrix, 20-24 lines/segment, temporal resolution < 50 ms, repetition time (TR) = 3.9 ms, echo time (TE) = 1.5 ms, flip angle of 50°, and number of excitations (NEX) of 1. Late gadolinium enhancement was performed three minutes after the injection of 0.3 mmol/kg of gadolinium contrast agent (Dotarem®, Guerbet), using inversion-recovery gradient-echo sequence on the long axis and the short axis (delayed enhancement technique) to search for myocardial fibrosis with the following parameters: FOV 360 mm, matrix 224 × 192, 24 lines/segment, TE = 2.9 ms, flip angle 20°, slice thickness of 8 mm with a spacing of 2 mm and NEX of 2. Two blinded independent readers analyzed all CMR images in a dedicated workstation, using specific software (Report CARD®, version 3.6, GE).

Myocardial fibrosis mass was calculated using a specific software solution through semi-quantitative detection of hyperintense areas in short-axis late enhancement sequences. The investigators were free to edit the limits of the fibrosis area.

The study was approved by the research ethics committee of the Clementino Fraga Filho University Hospital, Universidade Federal do Rio de Janeiro, in compliance with national and international guidelines for research on human beings (Resolution No. 466/2012 of the National Health Council).

Statistical Analysis

Based on previous studies, known risk factors for electrical instability were used: > 30 PVCs per hour,[21,23] age,[24] RWMA,[24,25] LVEF, and myocardial fibrosis.[25-27] In addition, urinary norepinephrine dosage was included.

Data normality was verified by the Shapiro-Wilk test as well as with the boxplot and the quartile-quartile plot

methods. Normally distributed variables were presented as mean ± standard deviation. Variables that were not normally distributed were presented as median and interquartile ranges.

For arrhythmia analysis, a cutoff value of 720 PVCs in a 24-hour period or the presence of NSVT was used.[21] RWMA was assessed as the presence or absence by CMR (categorical). To define the cutoff values for LVEF, myocardial fibrosis, urinary norepinephrine level, and age, regression trees were performed using arrhythmia as the outcome.

With the cutoff value already established, a log-linear model was used to measure the dependencies of the variables described above and to confirm the results obtained through the regression tree. The edges of each graph represent the amount of dependence between the variables and outline a number called Cramér's V, which is a digit between 0 and 1 that indicates how strongly two categorical variables are associated. Here is a short statistical explanation: if we want to know if two categorical variables are associated, our first option is the chi-square independence test. A p-value close to zero means that it is very unlikely that the variables will be completely disassociated in a random population. However, this does not mean that the variables are strongly associated. A measure that indicates the strength of the association is Cramér's V.

Then, the correlation coefficient matrix was performed to measure the predictive ability of a continuous variable to predict another variable being analyzed: age, LVEF, fibrosis, arrhythmia, and urinary norepinephrine. The R software was used for data analysis. A p-value < 0.05 was considered significant.

Results

From 328 outpatients screened, a total of 61 (23 male patients) met the inclusion criteria. Two patients were excluded because they could not undergo the post-contrast phase of CMR (delayed enhancement). One of them due to difficult venous access and the other due to gadolinium atopy.

The main data are shown in Table 1. These are patients with chronic heart disease with normal or mildly reduced ejection fraction. Cardiac fibrosis mass (mean 15.02g) was present in nearly half of the patients and significant ventricular arrhythmias in 47% of them. Urinary norepinephrine levels were variable. Table 2 shows the cutoff values found by linear regression trees.

A multivariate analysis using the Loglinear model was used to verify the pattern of interaction (dependence) of the variables shown in Figure 1.

The variables fibrosis, LVEF, and norepinephrine are observed to have a direct pattern of interaction (dependence) with each other, with a high power of association (fibrosis and norepinephrine 0.64, LVEF and norepinephrine 0.63, and fibrosis and LVEF 0.53). These interactions are of second order. Fibrosis is associated with arrhythmia depending on RWMA through a third-order interaction, that is, the three variables must be present. It is also noted that there is no direct interaction between arrhythmia and norepinephrine.

A correlation coefficient matrix was performed, where R demonstrates, in percentage values, how much the five variables are correlated with each other (Figure 2). Variables with the greatest relation (directly or inversely proportional) have the most oval circumference. Asterisks represent the level of significance according to the p-value (*** $p < 0.001$, ** $p < 0.1$, * $p < 0.05$). Fibrosis was inversely proportional to LVEF ($R = -0.61$) and urinary norepinephrine ($R = -0.68$). The variable arrhythmia was shown to have an inverse relationship with LVEF ($R = -0.33$) and urinary norepinephrine ($R = -0.27$). LVEF was directly proportional to norepinephrine ($R = 0.83$).

Discussion

This is the first study on CCC with mild fibrosis and preserved or mildly reduced ejection fraction to show significant dependence between traditional risk factors. More fibrosis was associated with lower norepinephrine levels. Higher LVEF was associated with higher norepinephrine levels, as shown in the correlation matrix (-0.68 and 0.83, respectively). It was also demonstrated that the presence of arrhythmia was not associated with the other variables.

This is a novel publication as it demonstrates for the first time that risk factors for sudden death may already be present, such as sympathetic denervation, myocardial fibrosis, and frequent ventricular arrhythmias, even in patients with preserved or mildly reduced ejection fraction. Furthermore, this finding is of great importance because most Cd patients have normal or mildly reduced ventricular function.

Dependence of higher norepinephrine dosages on higher LVEF in the correlation matrix was also demonstrated by Iosa et al.[28] They demonstrated the inverse relationship between cardiac dysfunction in CCC and norepinephrine levels. In the late phases of Chagas cardioneuropathy, plasma norepinephrine levels remained normal, unlike patients with non-Chagas heart failure, who had higher norepinephrine levels the greater the ventricular dysfunction.

Cd causes autonomous nervous system (ANS) lesions during the acute and chronic phases of the disease. This justifies the correlation between norepinephrine levels, fibrosis, and LVEF observed in this study. These patients seem to have sympathetic denervation caused by progressive neuronal destruction, reflected by the inverse relationship between norepinephrine levels and myocardial fibrosis, as shown in the correlation matrix (Figure 2).

Catecholamine levels are known to vary greatly throughout the circadian cycle, during venipuncture,[29] or even if the patient is hospitalized.[30] Most of the published norepinephrine test results are based on plasma samples and few studies have been conducted in Cd. Ross et al.[31] demonstrated that 24-hour urine norepinephrine dosages reduce false-negative results in patients with pheochromocytoma.

Table 1 – General data

Age		
	Mean ± SD	57.9±10.9
BMI		
	Mean ± SD	26.1±4.8
Gender		
	Female	36
	Male	23
ECG		
	ST repolarization abnormalities	33
	LAFB	5
	RBBB	1
	LBBB	1
	RBBB + LAFB	18
	1st-degree AVB	1
Regional Wall Motion Abnormality		
	Yes	19
	No	40
LVEF		
	45-50%	7
	> 50%	52
	Mean ± SD	66.8 ±11.9
Fibrosis		
	Present	27
	Absent	32
	Median (IQ) (g)	0 (0; 10.9)
24h Holter		
	Without arrhythmias	12
	Between 1 and 719 PVC	19
	> 720 PVC	28
	Median (IQ)	489.0 (3.0; 1813.5)
Norepinephrine (nmol/24h)		
	Median (IQ)	2369.6 (2233.6; 2502.1)
	Without arrhythmia (IQ)	2429.1 (2334.5; 2497.6)
	With arrhythmia (IQ)	2364.1 (2180.1; 2512.3)
	Without fibrosis (IQ)	2437.1 (2342.9; 2759.7)
	With fibrosis (IQ)	2327.4 (1461.1; 2429.1)

BMI: body mass index; ECG: electrocardiogram; LAFB: left anterior fascicular block; RBBB: right bundle branch block; LBBB: left bundle branch block; AVB: atrioventricular block; LVEF: left ventricular ejection fraction; PVC: premature ventricular contraction; IQ: interquartile; SD: standard deviation.

We found only one clinical study using urinary norepinephrine in Cd. Cunha et al.[32] evaluated the involvement of the ANS in the pathogenesis of CCC. They observed decreased urinary norepinephrine levels in CCC with ventricular dysfunction and, conversely, normal or even increased levels in patients with the indeterminate form of Cd.

As previously demonstrated by our group,[25] fibrosis is inversely associated with LVEF. In the current study, fibrosis, RWMA, and norepinephrine have second-order interactions (direct dependence) with LVEF, observed by the Loglinear method. Together or individually, they cause ventricular remodeling, partially justifying the Myerburg model.[33] In the previous study, there was a third-order

Table 2 – Results of the linear regression tree for the cutoff points for the log-linear model

LVEF (n)	RWMA	Arrythmia (n)	Fibrosis (n)	Norepinephrine (n)	Age (n)
≤57% (13)	No (41)	No (31)	≤10.56% (44)	≤2218.97 nmol/24h (15)	≤54 years (20)
>57% (46)	Yes (18)	Yes (28)	>10.56% (15)	>2218.97 nmol/24h (44)	>54 years (39)

LVEF: left ventricular ejection fraction; RWMA: Regional Wall Motion Abnormality.

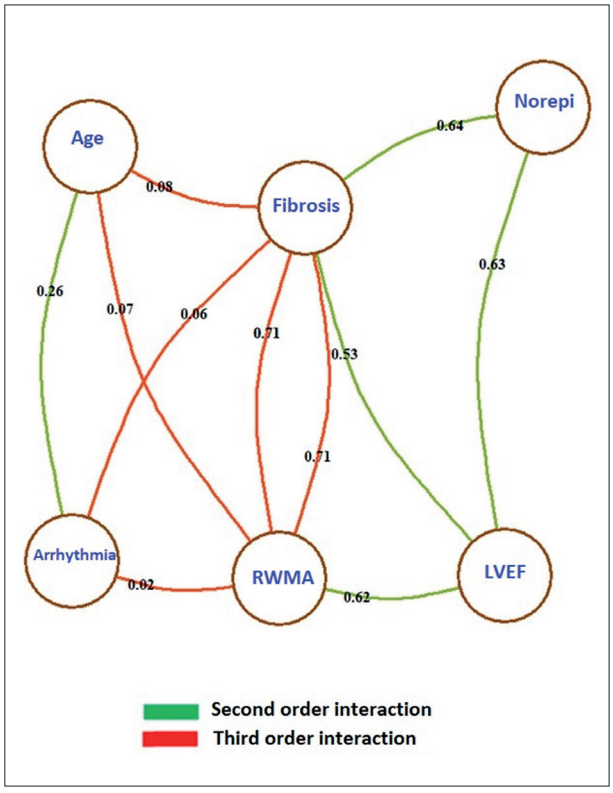

Figure 1 – *Log-Linear Model. Edge weights correspond to the Cramér's V statistic (measure of dependence between discrete variables).*

interaction (the three variables must be present) between fibrosis, arrhythmia, and LVEF, which was not maintained in the current study. This can probably be explained in two different ways: firstly, since sympathetic denervation morphologically occurs before the onset of fibrosis[9,34] this can balance the dependence of the arrhythmia, losing explanatory power; secondly, design, as in the first study the log-linear only considered patients with LVEF above 50% by CMR, that is, seven patients with mild dysfunction (LVEF between 45-50%) were removed, of which six had frequent arrhythmias. This could justify the loss of interaction between the variables.

In our study, the mean myocardial fibrosis weight was 15.02g (Table 1), and the value of 10.56% (10.01g) determined the presence of frequent arrhythmias according to the regression tree. Recently, Senra et al.[26] observed in a retrospective prognostic study that myocardial fibrosis is an independent risk factor (for death, implantable defibrillator triggering, and heart transplantation) in CCC and that each additional gram of fibrosis would increase by 3.1 % the risk of a hard event. They detected an average weight of fibrosis (15.2g or 13.5%) very close to that found in our study. Also, based on a ROC curve analysis, they determined that the cutoff value of 12.3g is a predictor of a major event. In the same year, Volpe et al.[27] in another retrospective prognostic study of about 3 years of follow-up in patients with CCC, detected 10.4g of fibrosis (9.2% of LV mass) and there were 11 deaths, of which 10 had detectable fibrosis.

Gadioli et al.[9] found a proportional relation between arrhythmia severity (SVT and NSVT) and the extension of sympathetic denervation, similar to what was shown in this study, as seen by the presence of arrhythmia with lower levels of norepinephrine, denoting greater denervation. However, they did not find a relation between fibrosis detected by 99mTc-Sestamibi and ventricular arrhythmia, which occurred in this study. This can be explained by the higher spatial resolution of CMR compared to myocardial scintigraphy to detect myocardial fibrosis.

This study has some limitations. The definition of frequent ventricular arrhythmia in the present study may be questionable from a clinical point of view, but not functional in terms of neurogenic modulation. However, when using a low-risk Cd population (LVEF > 45% and mean age 57.9 years) and focusing on the anatomopathological basis of the arrhythmogenic substrate of fibrosis and not on clinical instability due to malignant arrhythmia, it is confirmed that the arrhythmogenic substrate is already present in this population. Likewise, it is evident in this study that the predominant pathogenic mechanism in this population is neurogenic and not cardiac, a fact that has also been published by other authors.[8,35]

Although we cannot definitively rule out the diagnosis of coronary heart disease as an important confounding factor, clinical data and the pattern of fibrosis allow us to infer the absence of functionally significant obstructive coronary disease. Furthermore, this group of patients did not have indications for coronary angiography.[36]

The time interval between urinary norepinephrine dosage and CMR acquisition (about 6 years) may seem long. However, it is important to remember that progression during the early stages of cardiac involvement is very slow, about 1.48 cases/100 patient-years.[37] So, at most, six patients may have changed groups during the study.[38]

The patients were previously using beta-blockers and angiotensin-converting enzyme inhibitors (minimum of 6 months). These drugs were used according to recommendations for Cd[39] with cardiac involvement (stages A and B1). The decision for pharmacological treatment was within the clinical

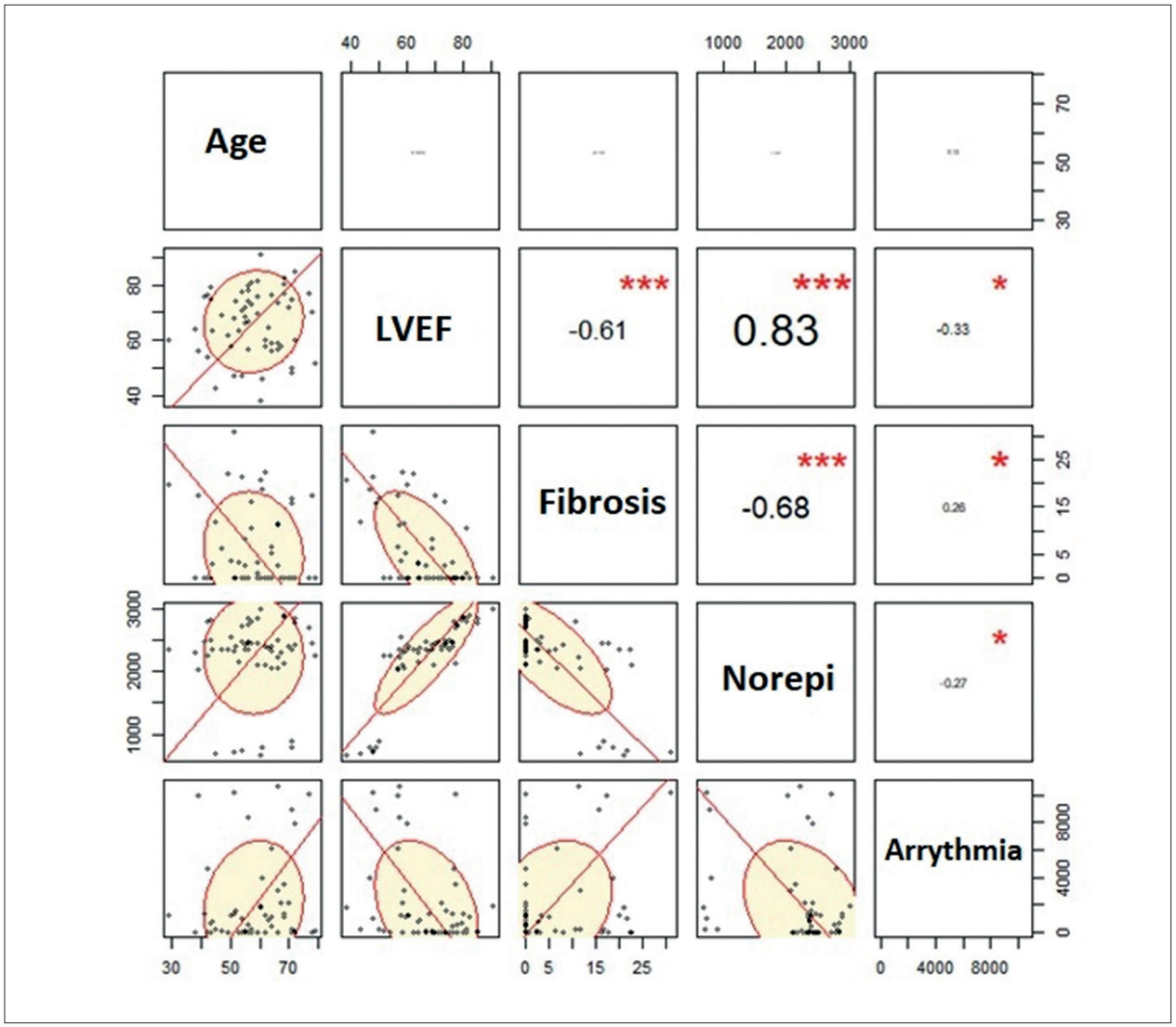

Figure 2 – *Correlation Coefficient Matrix (values in R). The more oval the better the correlation. Asterisks represent the significance according to the p-value. (*** p < 0.001, ** p < 0.1, * p < 0.05).*

context and not intended to control or treat arrhythmias. Therefore, even if these drugs modulate the neurohormonal response, they would not be a limitation of the study since the adrenergic load was established during the chronic use of these drugs.

The Loglinear model shows that arrhythmia quantification is not related to LVEF, fibrosis, and/or norepinephrine dosage, and fibrosis is related to urinary norepinephrine and LVEF with similar explanatory power to each other (Cramér's V statistic of 0.53, 0.63, and 0.64). Indeed, there are data in the Cd literature that the presence of ventricular arrhythmia and/or right bundle branch block (RBBB) are not independent prognostic markers for all-cause mortality. However, they are markers of cardiac involvement.[21] The sudden death mechanism in Cd is due to ventricular tachycardia or fibrillation, not necessarily preceded by complex arrhythmias, which are more intensively associated with LV dysfunction.[4]

Conclusions

In patients with CCC with preserved or mildly reduced ejection fraction, ANS integrity is observed in hearts with little fibrosis and higher LVEF despite the presence of traditional risk factors for sudden cardiac death. There is a correlation between the levels of urinary norepinephrine, LVEF, and myocardial fibrosis, but not with the presence of frequent ventricular arrhythmias.

Author Contributions

Conception and design of the research: Tassi EM, Pereira BB, Pedrosa RC; Acquisition of data: Tassi EM, Continentino MA; Analysis and interpretation of the data: Tassi EM, Nascimento EM, Continentino MA, Pedrosa RC; Statistical analysis: Tassi EM, Nascimento EM, Pereira BB; Writing of the manuscript: Tassi EM, Continentino MA, Pedrosa RC;

Critical revision of the manuscript for intellectual content: Tassi EM, Nascimento EM, Pereira BB, Pedrosa RC.

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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Chagas Heart Disease: The Evolution of the Disease and its Complementary Exams

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Short Editorial related to the article: Relationship between Urinary Norepinephrine, Fibrosis, and Arrhythmias in Chronic Chagas Heart Disease with Preserved or Mildly Reduced Ejection Fraction

As in many areas of Medicine, the scenario that harbors Chagas Disease(CD) has changed substantially. For approximately 50 years, as a Resident Physician, I was on duty at the Emergency Department of the Hospital de Clínicas of the Universidade Federal do Paraná and routinely attended, on each shift, one or more cases of patients with clear Congestive Heart Failure, anasarca, electrocardiogram with conduction disorders and multiple arrhythmias, chest X-ray with cardiomegaly and laboratory diagnosis of CD. There was no echocardiogram. Today this is an unusual situation; when it occurs, students are invited to see an exuberant picture of Chagas' heart disease (CHD), which appears every semester.

In epidemiological surveys, similar findings are observed. In 1984, the prevalence of CD in the State of Paraná, Brazil, was 4% of the population.[1] In 2020, estimates of the prevalence of infections by Trypanosoma cruzi ranged from 1.02% to 2.4% in Brazil.[2] In the period 1975/83, among 291 municipalities in Paraná, 90 (30.9%) had triatomine insects infected by T. cruzi, while in 1990, these were found in only 4 municipalities (1.4%),[3] with subsequent eradication of vector contamination. Vector control strategies have led to a substantial decline in the global prevalence of the disease, estimated at 18 million in 1990 and 6 million in 2018.[4]

Despite the evident progress in the containment of new cases of CD, the sick population is still very large and requires care in their diagnosis and treatment. In the present issue of Arquivos Brasileiros de Cardiologia, Tassi et al. study the findings of complementary exams concerning arrhythmias in CHD.[5]

Laboratory techniques for the diagnosis of chronic CD have not changed for years. The old Machado-Guerreiro reaction (complement fixation) is no longer used due to its low sensitivity, low specificity and complexity of execution. Indirect immunofluorescence, hemagglutination and ELISA (enzyme immunoassay) tests are used. Because of the possibility of false positives (leishmaniasis, malaria, syphilis, toxoplasmosis, leprosy, collagen diseases, hepatitis), it is recommended that the serum be tested in at least two of these methods to confirm the positivity of the serology. In the acute phase of the disease, the preferred test is PCR (Polymerase Chain Reaction).[6]

Cardiovascular assessment of patients with definite or suspected CD is essential to detect eventual cardiac damage. The electrocardiogram is the most important test in the initial evaluation and can indicate whether there is already established cardiomyopathy, presence of arrhythmias and contribution to the estimation of cardiovascular risk.[7]

Chest radiography contributes to the assessment of cardiac chambers and pulmonary congestion. The finding of cardiomegaly has a significant weight in the risk of death scale proposed by Rassi, adding 5 points to a maximum of 20.[8]

Echocardiography, in general, is the key test used to identify structural and functional abnormalities in CD. It integrates routine investigation in the acute and chronic phases, regardless of symptoms, even in the Indeterminate Form. The study contributes to the assessment of systolic and diastolic ventricular functions, regional and global analysis of the left and right ventricles, presence of ventricular aneurysms, and pericardial effusion mainly in the acute phase, thrombus investigation, mitral and tricuspid regurgitation, analysis of pulmonary hypertension.[9]

Holter monitoring (ambulatory ECG monitoring) is another fundamental test for diagnostic investigation, therapeutic management and prognostic assessment of CD. It allows the study of complex ventricular arrhythmias, atrial fibrillation, sick sinus syndrome and atrioventricular and intraventricular conduction defects.[10]

Selected patients with CHD require additional evaluation with other tests: Exercise Tests, Coronary angiography, MRI (ventricular assessment on suboptimal echocardiograms and fibrosis research), Nuclear Medicine Tests (Radionuclear Ventriculography, SPECT, Myocardial Sympathetic Innervation Imaging with MIBG-I123*, positron emission tomography with 18F-fluorodeoxyglucose*) and endomyocardial biopsy* (* = research applications).[4]

The study by Tassi et al.[5] exemplifies the evolution of research in understanding arrhythmias in CHD.

Keywords

Chagas Disease; Chagas Cardiomyopathy/complications; Clinical Evolution; Diagnostic Imaging/methods; Epidemiology; Heart Failure

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Systemic Immune-Inflammation Index Predicts Major Cardiovascular Adverse Events in Patients with ST-Segment Elevated Myocardial Infarction

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Abstract

Background: **The systemic immune-inflammation index (SII) has been reported as a new prognostic marker in tumors and cardiovascular diseases**

Objective: **To investigate the association of SII with adverse cardiovascular events in patients with ST-segment elevated myocardial infarction (STEMI).**

Methods: **A retrospective observational study was conducted on 843 patients with STEMI. Patients were divided into two groups based on the median value of SII. Major adverse cardiovascular events were compared between SII groups. Cox regression analysis was used for detecting independent predictors of cardiovascular adverse events. The improvement of discrimination ability by adding SII to the traditional risk factors such as age, hypertension, diabetes mellitus, and male gender for major adverse events was calculated by c-statistics, integrated discrimination improvement, and net reclassification improvement. A two-sided p-value <0.05 was considered significant.**

Results: **High SII group was older than the low SII group (61.2±11.2, 59.2±7.9, respectively, p=0.002). The high SII group had higher rates of cardiac death, nonfatal myocardial infarction, nonfatal stroke, hospitalization for heart failure, revascularization, and composite major adverse cardiovascular events than the low SII group. SII was an independent predictor of all events mentioned above. Adding SII to traditional risk factors improved their discrimination ability for cardiovascular events. SII was superior to the neutrophil-to-lymphocyte and platelet-to- lymphocyte ratios for predicting cardiovascular adverse events.**

Conclusion: **SII was an independent predictor of major adverse events in patients with STEMI and may be used to improve the prediction of adverse events, especially when combined with traditional risk factors.**

Keywords: **Myocardial Infarction; Heart Defects, Congenital; Coronary Vessels.**

Introduction

Atherosclerosis is the leading cause of cardiovascular disease, and continues to be the leading cause of death worldwide.[1] The presence of inflammation in the atherosclerotic area has a critical pathophysiological role for plaque formation and rupture.[2] Vulnerable atherosclerotic plaque and thrombus formation that results in the cessation of coronary blood flow is the primary pathophysiologic mechanism in patients with ST-segment elevation myocardial infarction (STEMI).[3] The first choice of treatment for STEMI patients is primary percutaneous coronary intervention (pPCI). Despite advances in antithrombotic treatment and reperfusion techniques, patients with STEMI still have a poor prognosis.

Early risk stratification of patients who are at high risk for future adverse cardiovascular events is very crucial. Previous studies have shown that inflammation and thrombosis have been linked to the initiation, progression, and prognosis of STEMI.[4] So, the discovery of novel inflammatory biomarkers has be of interest to detect high-risk patients and to provide information for prognosis.[5,6] Platelets and leukocytes play crucial roles in the development of atherosclerosis and acute coronary syndromes. Higher platelet counts might reflect destructive inflammatory processes and prothrombotic status.[7] Neutrophils are the first leukocytes to migrate from the blood to the damaged myocardial area, and increased neutrophil counts have been associated with large infarct size, mechanical complications, and mortality.[8,9] In contrast, lymphocytes control the immune

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response, providing less myocardial damage.[10] The systemic immune-inflammation index (SII) is a simple marker, which has been established based on the neutrophil, platelet, and lymphocyte counts [SII= (neutrophil x platelet) / lymphocyte] to determine the inflammatory and immune status. Recently, SII was considered an independent predictor of prognosis in several conditions, including tumors and cardiovascular diseases.[1,11,12] We aimed to investigate the predictive ability of SII for adverse clinical outcomes in patients with STEMI after pPCI.

Materials and Methods

A total of 1,187 consecutive patients admitted to our hospital with STEMI who underwent pPCI between 2012 and 2020 were retrospectively included in this study. Of them, 344 patients with previous coronary revascularization, hematological, oncological, or inflammatory disease, active infection, hepatic or renal insufficiency, severe valvular heart disease, and cardiogenic shock at admission were excluded. Also, patients with missing data and patients whose follow-up data could not be obtained were not included in the study population. Finally, the study was completed with 843 patients. The study was carried out according to the Declaration of Helsinki of 1975, as revised in 2008 and approved by the local ethics committee.

Definitions

The diagnosis of STEMI was made based on the updated guidelines for the universal definition of myocardial infarction (MI).[13,14] Baseline characteristics, clinical histories, laboratory measurements, and angiographic images of patients were obtained from the hospital database. All blood samples of patients were obtained at admission to the emergency department. Blood measurements were analyzed using a Beckman Coulter LH 780 hematology analyzer (Beckman Coulter, FL, USA) for hematologic parameters and a Roche Cobas 6000 c501 (Roche, Mannheim, Germany) for biochemical parameters. The SII was calculated with the formula SII= (P x N) / L, where P = total peripheral platelet count; N = neutrophil count (N), and L = lymphocyte count. Creatinine clearance was calculated using the Cockcroft- Gault equation: Creatinine clearance = ([140 - age in years] x weight[kg]) / (72 x serum creatinine [mg/dL]) for men and was corrected by multiplying with 0.85 for women. Hypertension (HT) was diagnosed as systolic blood pressure 140 mm Hg and/or diastolic blood pressure ≥ 90 mm Hg at least two times or the use of current antihypertensive drugs. Diabetes mellitus (DM) was diagnosed based on fasting glucose ≥ 126 mg/dL or postprandial glucose ≥ 200 mg/dL or the use of antidiabetic drugs. Cigarette smoking was defined as patients who had smoked for at least six months continuously during the past year. A family history of coronary artery disease (CAD) was defined as a history of CAD in first-degree relatives less than 55 years for women and 65 years for men.

Angiographic definitions

At the operator's discretion, the standard coronary angiography (CAG) was performed through the transradial or transfemoral approach using the Seldinger technique. Acetylsalicylic acid (300 mg), a loading dose of P_2Y_{12} inhibitors (Clopidogrel), and a standard dose of unfractionated heparin (70-100 U/kg) were given to all patients before the CAG procedure. The use of glycoprotein IIb/IIIa receptor blockers (tirofiban) was left to the operator's discretion. The angiographic images of patients were carefully reviewed by two experienced investigators who were blinded to all clinical data. Thrombolysis in myocardial infarction (TIMI) flow and TIMI myocardial perfusion grade (TMPG) were assessed as previously defined.[15-17] No-reflow was defined TIMI 0, I, and II in the final angiogram. Distal embolization was determined as a new distal filling defect of one or more peripheral coronary artery branches of the infarct-related artery, with an abrupt occlusion distal to the coronary intervention site.

Follow-up

Clinical follow-up data were gathered from the hospital and pharmacy database or through telephone calls with the patients and/or their relatives. Hospital records or death certificates were used to determine the cause of death.

Endpoints

The primary composite endpoint was major cardiovascular adverse events (MACE), which is a combination of cardiovascular death, nonfatal MI, and nonfatal ischemic stroke. Deaths due to MI, life-threatening arrhythmias, cardiac arrest, and deaths attributed to heart failure or other cardiac conditions were all classified as cardiovascular death. Non-fatal MI was defined as the recurrence of chest pain and/or new electrocardiographic ST-segment change with a new dynamic elevation in troponin I and CKMB levels (>20% increase from baseline). Nonfatal ischemic stroke was characterized as a blockage in a blood vessel supplying blood to the brain, as evidenced by magnetic resonance imaging (MRI) or computed tomography (CT) scans, and a recent neurologic deficit that lasted for more than 24 hours.

Statistical Analyses

All statistical analyses were carried out on SAS University Edition (SAS/STAT, SAS Institute Inc, NC, USA). Because there were more than one endpoint and different cut-off points, patients were divided into two groups as high (≥554.9) and low (<554.9) SII based on median SII value. The normality of data was tested using the Kolmogorov-Smirnov test. Continuous variables with a normal distribution were expressed as mean (standard deviation), while those without a normal distribution were presented as median (interquartile range), and categorical variables were expressed as numbers (percentages). The independent Student's t-test or Mann-Whitney U test was used for comparing continuous variables between groups as appropriate. The Pearson Chi-square test or Fisher exact test was used for comparison of categorical variables. Hazard ratios (HR) for Cox proportional hazards regression, adjusted with covariates were used to detect predictors of adverse events in patients with STEMI. We included variables into models according to the event sizes in multivariable Cox regression analysis to avoid overestimation.

To assess the improvement in discrimination ability for long-term adverse events of the baseline model (with traditional risk factors – age, male gender, DM, and HT), with the addition of SII, the Harrell's concordance statistics (c-statistics) with DeLong test,[18] integrated discrimination improvement (IDI), and net reclassification improvement (NRI) were calculated.[19] The receiver operating characteristic (ROC) curve analysis was performed to determine the optimal cutoff value of the SII using the Youden index, and the area under the curve (AUC) was obtained. The Akaike information criterion (AIC),[20] the Bayesian information criterion (BIC),[21] -2 Log likelihood (-2LL), and NagelkarkeR^2 were used to assess the comparisons of the abilities of variables – neutrophil-to-lymphocyte (NLR), platelet-to-lymphocyte ratio (PLR), and SII – to predict MACE. Lower levels of AIC, BIC, and -2LL and higher levels of NagelkarkeR^2 indicate a better model fit.[22] The difference in event-free survival rates between SII groups was analyzed using the Kaplan-Meier survival curve, and the log-rank test was used to evaluate the statistical significance. A p-value of $<.05$ was considered significant in all statistical analyses.

Results

Baseline characteristics, laboratory data, and angiographic features of 843 patients of the high and low SII groups are described in Table 1. The high SII group was older than the low SII group (p=0.002). The presence of familial CAD was more frequent in the high SII group than in the low SII group (p=0.005). White blood cell (WBC) count, platelet count, neutrophil count, and LDL cholesterol levels were more elevated in the high SII group, whereas lymphocyte count was lower. Regarding angiographic data, there was a higher frequency of implanted stents > II, multivessel disease, distal embolization, and no-reflow in the high SII group compared to the low SII group. TMPG and TIMI flow were worse in the high SII group than in the low SII group. The high SII group had higher rates of percutaneous transluminal coronary angioplasty (PTCA) (p=0.002) and lower rates of direct stenting (p=0.008) rates than the low SII.

Clinical outcomes

The median follow-up was 34.2 months (IQR: 8.6- 63.9). The clinical adverse events were compared between the high and the low SII groups (Table 2). In the follow-up, cardiac death, nonfatal MI, nonfatal stroke, hospitalization for congestive heart failure (CHF), revascularization, and frequency of MACE were higher in the high SII group. Results of the Cox regression analysis results are shown in Table 2. High SII was linked to a 3.06-fold increased risk of cardiac death, 2.79-fold increased risk of nonfatal MI, 2.98-fold-increased risk of nonfatal stroke, 11.1-fold increased risk of hospitalization for CHF, 4.11-fold increased risk of revascularization (PCI or coronary artery by-pass graft [CABG]), and 8.52-fold increased risk of MACE. In ROC analysis, a cutoff value of 951.7 for SII had 64.6% sensitivity and 73.6% specificity for discrimination of MACE (AUC=0.741, p<0.0001). In ROC comparison, SII had a better discrimination ability for MACE than NLR and PLR (p<0.0001 for both, Figure 1). Diagnostic performance comparisons between NLR, PLR, and SII showed that SII had a higher prediction ability for MACE than NLR and PLR (Table 3). The Kaplan-Meier survival curve showed that the high SII group had a higher occurrence of MACE compared to the low SII group (Figure 2).

Additional predictive value of SII

Adding SII to the baseline model with traditional risk factors (age, DM, HT, and male gender) improved the prediction of cardiac death, nonfatal MI, nonfatal stroke, hospitalization for CHF, revascularization, and MACE, as demonstrated by the significant increase in the C-statistics (Table 4). Discrimination improvement by adding SII was also confirmed by an IDI of 0.0857, with 49% improvement in NRI for cardiac death, nonfatal MI (NRI:0.4936, IDI:0.0743), nonfatal stroke (NRI:0.4655, IDI:0.0307), hospitalization for CHF (NRI:0.7183, IDI:0.1448), revascularization (NRI:0.2971, IDI:0.0231), and MACE (NRI:0.4539, IDI:0.1073) (Table 4), suggesting that adding SII may provide a significantly better prediction of adverse events than traditional risk factors alone in patients with STEMI.

Discussion

This study has shown that patients with high SII values had higher frequencies of cardiac death, nonfatal MI, nonfatal stroke, hospitalization for CHF, revascularization, and MACE than patients with low SII values. Furthermore, SII was an independent predictor of these adverse outcomes. Adding SII to traditional risk factors such as age, HT, DM, and male gender improved the prediction ability for adverse cardiovascular events in STEMI patients after pPCI. Finally, SII was superior to other conventional biomarkers such as NLR and PLR in predicting MACE.

MI is caused by thrombus formation in the coronary arteries as a result of coronary plaque rupture or erosion of the atheromatous plaque.[3] The inflammatory process and thrombosis were found to play significant roles in the initiation and progression of this condition.[23] Neutrophils release neutrophil extracellular traps (NETs), which have been detected in atheromatous plaque and might play a causative role in atherosclerotic plaque formation and increased thrombus stability.[24] Zhang et al.[25] found that neutrophil counts were independently associated with MACE in STEMI patients.[25] In contrast, lymphocytes reflect a calm and regulated inflammatory process that causes suppressed immune response and less myocardial damage.[26] Lower lymphocyte counts have been linked to a higher risk of cardiovascular disease and mortality.[27] Upon activation, platelets release considerable quantities of proinflammatory chemokines and cytokines from alfa granules, which lead to destructive immune and prothrombotic status. Previous studies have shown that platelet count was associated with MACE.[7,28] Biomarkers derived from these three cell types mentioned above were widely researched and reported as prognostic markers in the literature due to their relatively low cost and easiness for acquisition and calculation. Also, studies with STEMI patients have reported that both NLR and PLR are useful and powerful independent predictors of MACE.[6,29]

Recently, SII has been emerged as a potential marker based on inflammatory cells, including neutrophils, lymphocytes, and platelets, and has been reported to be

Table 1 – Baseline and angiographic characteristics of the study population by SII*

Variables	SII<554.9 (N=421)	SII≥554.9 (N=422)	p value
Age, years	59.2(7.9)	61.2(11.2)	0.002
Male gender, n (%)	277(65.8)	288(68.3)	0.449
Diabetes, n (%)	90(21.4)	111(26.3)	0.093
Hypertension, n (%)	131(31.1)	148(35.1)	0.222
Smoking, n (%)	129(30.6)	156(36.9)	0.052
Hyperlipidemia, n (%)	154(36.6)	171(40.5)	0.239
Family history of CAD, n (%)	74(17.6)	108(25.6)	**0.005**
BMI, kg/m^2	23.8(22-25.3)	23.7(21.4-26.6)	0.589
Previous Medication			
ASA, n (%)	98(23.3)	123(29.2)	0.053
ACEi/ARB, n (%)	154(36.6)	176(41.7)	0.127
Beta blocker, n (%)	147(34.9)	165(39.1)	0.209
Diuretic, n (%)	37(8.8)	52(12.3)	0.096
Statin, n (%)	75(17.8)	94(22.3)	0.106
LVEF, %	42.3(7)	41.6(10.5)	0.256
WBC, 10^3 mL	7.6(6-8.9)	7.9(6.4-9.7)	**0.007**
Haemoglobin, mg/dL	14.2(1.1)	14.2(1.7)	0.651
Platelet, /mm^3	204.1(173.6-228.7)	243.7(189-279)	**<0.0001**
Neutrophil, 10^3 mL	6.3(5.4-7)	6.5(5.4-7.8)	**0.004**
Lymphocyte, 10^3/mL	2.7(2-3.3)	2.1(1.3-3.4)	**<0.0001**
Serum Creatinine, mg/dL	0.9(0.2)	0.9(0.3)	0.825
Total cholesterol, mg/dL	171.3(147.1-191.6)	163.4(129.8-204.6)	0.120
LDL cholesterol, mg/dL	111.9(102.8-121.5)	117.5(99.7-135.9)	**0.006**
HDL cholesterol, mg/dL	43(36.3-48.5)	40.4(31.5-51.8)	0.057
Triglyceride, mg/dL	137.2(98.6-177.7)	129.8(87.9-204.1)	0.858
Glucose, mg/dL	116(29.5)	114.5(37.6)	0.534
Angiographic Characteristics			
Pain to balloon time, hours	4.3(2.8-5.5)	4.4(2.5-6.5)	0.152
Total number of stents > II	27(6.4)	82(19.4)	**<0.0001**
Multivessel disease, n (%)	86(20.4)	123(29.2)	**0.0034**
Total stent length, mm	23.7(4.1)	23.9(6)	0.598
Procedure, n (%)			**0.0008**
Direct stenting	135(32.1)	101(23.9)	0.008
PTCA+stenting	274(65.1)	289(68.5)	NS
Only PTCA	12(2.8)	32(7.6)	0.002
TMPG>II, n (%)	272(64.6)	228(54)	**0.0018**
Postprocedural TIMI flow >III, n (%)	410(97.4)	374(89.6)	**<0.0001**
Use of GpIIb/IIIa inhibitor, n (%)	41(9.7)	77(18.3)	**0.0004**
Distal embolization, n (%)	2(0.5)	15(3.6)	**0.002**
No reflow, n (%)	11(2.6)	48(11.4)	**<0.0001**
DAPT interruption <30 days	6(1.4)	11(2.6)	0.224
DAPT interruption <6 months	22(5.3)	29(6.9)	0.316
Adherence for DAPT for 12 months	399(94.8)	393(93.1)	0.317

SII: systemic immune-inflammation index, CAD: coronary artery disease, BMI: body mass index, ASA: acetylsalicylic acid, ACEi: angiotensin converting enzyme inhibitors, ARB: angiotensin receptor blocker, LVEF: left ventricular ejection fraction, WBC: White blood cell, LDL: low density cholesterol, HDL: high density cholesterol, PTCA: percutaneous transluminal coronary angioplasty, TIMI: thrombolysis in myocardial infarction, TMPG: TIMI myocardial perfusion grade, DAPT: dual antiplatelet therapy; values shown as mean (standard deviation), median (interquartile range), n (%).

Table 2 – Clinical outcomes in ST-segment elevated myocardial infarction (STEMI) patients stratified by systemic-immmune inflammation index (SII) and Cox regression analysis

Clinical Outcomes	SII< 554.9 N=421	SII≥554.9 N=422	p value	Cox regression analysis HR (IC95%)	p value
Cardiac death	17(4)	46(10.9)	0.0002	3.064(1.754-5.353)	<0.0001[a]
Nonfatal myocardial infarction	20(4.8)	54(12.8)	<0.0001	2.787(1.658-4.684)	0.0001[b]
Nonfatal stroke	6(1.4)	16(3.8)	0.0312	2.984(1.163-7.654)	0.023[c]
Hospitalization for CHF	15(3.6)	70(16.6)	<0.0001	11.114(4.137-29.858)	<0.0001[d]
Revascularization (PCI or CABG)	57(13.5)	94(22.3)	0.0009	4.113(1.887-8.966)	0.0004[e]
MACE	41(9.7)	92(21.8)	<0.0001	8.516(4.458-16.268)	<0.0001[e]

a Adjusted for age, gender, hypertension, diabetes mellitus, low-density lipoprotein (LDL) cholesterol
b Adjusted for age, gender, hypertension, diabetes mellitus, LDL cholesterol, family of coronary artery disease
c Adjusted for age
d Adjusted for age, hypertension, diabetes mellitus, LDL cholesterol, gender, family coronary artery disease (CAD),EF (ejection fraction)
e Adjusted for age, hypertension, diabetes mellitus, LDL cholesterol, gender, family of CAD, EF (ejection fraction), body mass index, creatinine, glucose
HR: hazard ratio; CHF: congestive heart failure; PCI: percutaneous coronary intervention; CABG: coronary artery by-pass graft; MACE: major adverse cardiovascular events.

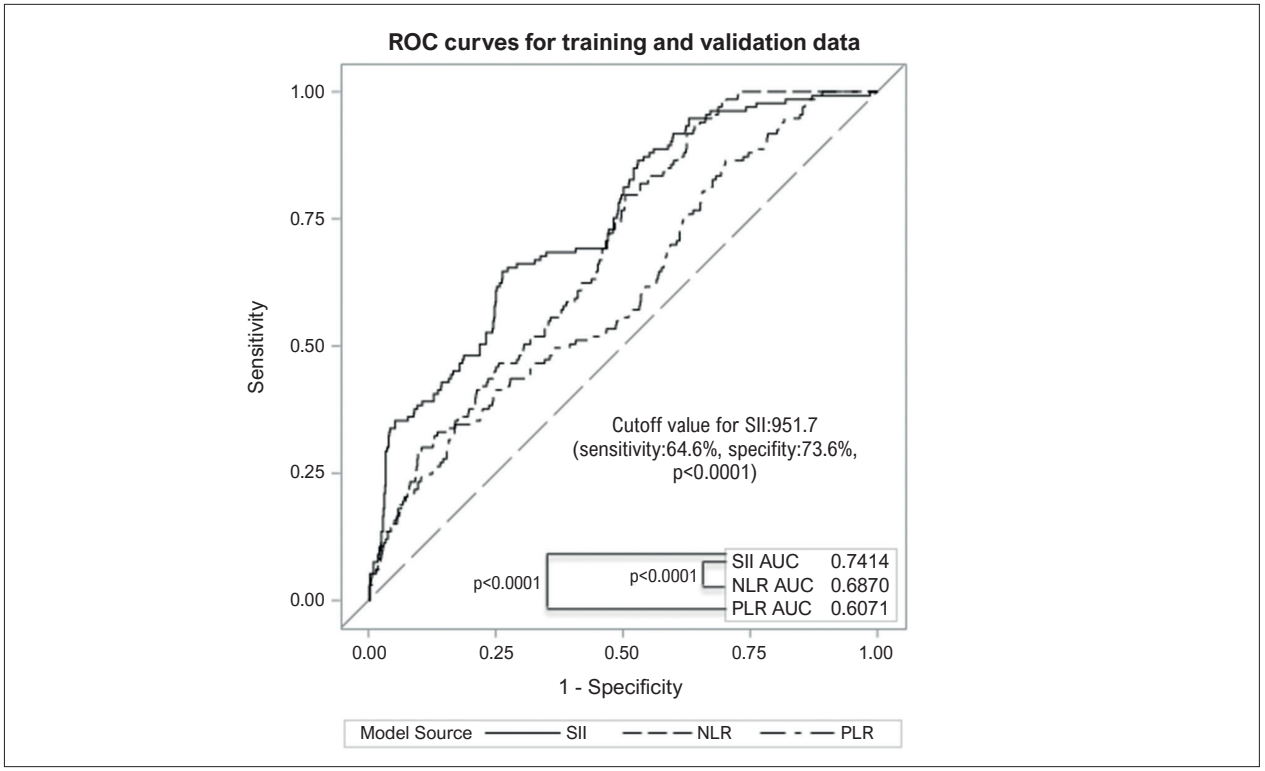

Figure 1 – *Comparisons of Receiver-operating characteristics (ROC) curves of systemic immune-inflammation index (SII), neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR) for major adverse cardiovascular events (MACE) in patients with ST-segment elevated myocardial infarction.*

associated with worse outcomes in several conditions.[1,11,12] Gok et al.[30] reported that SII was associated with massive acute pulmonary embolism and was superior to other inflammation-based indexes, similarly to what we observed in the present study. A previous study by Erdogan et al.[31] showed a significant association between SII and CAD severity. SII was found to be associated with poor postoperative outcomes after elective off-pump coronary artery bypass surgery.[12] Agus et al.[32] reported that SII was independently related to in-hospital mortality in patients with infective endocarditis. In addition, SII has been associated with adverse clinical outcomes in acute coronary syndrome in patients aged between 65 and 85.[33] Although this study[33] had similar results to ours,

in our study, we included adult patients of all ages, and with STEMI only. Another study conducted by Yang et al.[1] proposed that SII was an independent predictor of adverse events in CAD patients, including stable angina pectoris, non-STEMI, and STEMI patients.[1] In recent studies, the prognostic value of SII was reported to be better than PLR and NLR.[3,4] To avoid multicollinearity and interaction, we did not put NLR and PLR in the Cox regression models with SII. However, in concordance with the abovementioned studies, AUC calculated from ROC analysis and model fit comparisons including -2LL, AIC, BIC, and NagelkarkeR^2 demonstrated that SII might fit better than NLR and PLR for risk stratification of STEMI patients undergoing pPCI.

Because the early prediction of adverse events in high-risk patients with STEMI undergoing pPCI is crucial for treatment and follow-up strategies, high SII might serve a role in the risk classification and treatment assignment for these patients.

The relatively small sample size and retrospective and single-center design were the major limitations of this study. In addition, we collected data from an eight-year period, from hospital records, so there might be selection bias due to unmeasured confounding variables affecting adverse events and exclusion of patients with missing variables. The platelet, neutrophil, and lymphocyte counts were recorded only once upon admission. The in-hospital or follow-up measurements were not recorded, and the impacts of changes of these variables on adverse cardiovascular events remained uncertain. Large randomized controlled trials could provide more definitive evidence about the predictive ability of SII for clinical adverse events in patients with STEMI.

Table 3 – Comparison of diagnostic performance of predictors for major adverse cardiovascular events

Variables	-2LL	AIC	BIC	Nagelkarke R^2
SII	665.1	669.1	678.6	0.1367
NLR	707.6	711.6	721.1	0.0551
PLR	713.4	717.4	726.9	0.0434

LL: log likelihood, AIC: akaike criterion index, BIC: bayesian criterion index, SII: systemic immune-inflammation index, NLR: neutrophil-to-lymphocyte ratio, PLR: platelet-to-lymphocyte ratio.

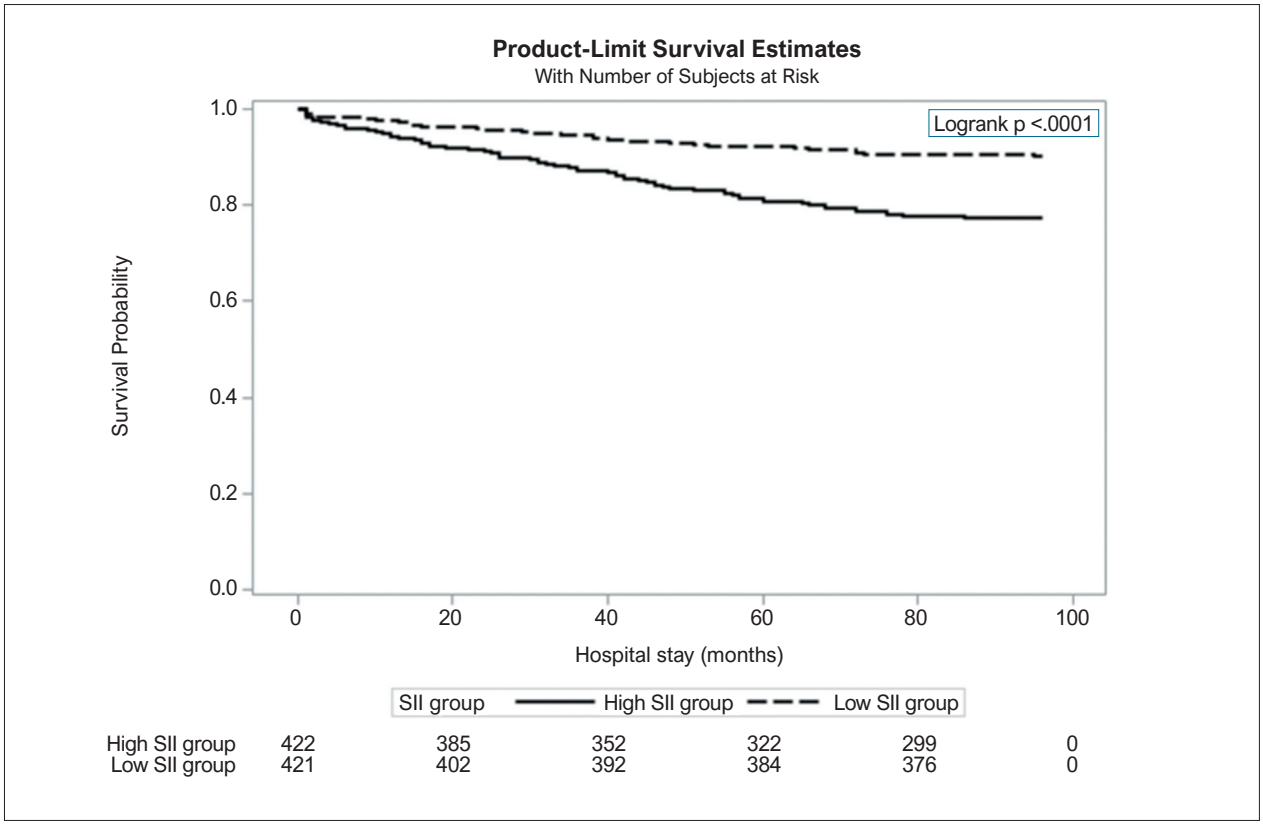

Figure 2 – *Kaplan-Meier survival curves of high and low SII groups for MACE. SII: Systemic immune-inflammation index; MACE: Major adverse cardiovascular events.*

Conclusion

This study identified that high SII was independently related to adverse cardiovascular events, including cardiac death, nonfatal MI, nonfatal stroke, hospitalization for heart failure, revascularization, and composite MACE in patients with STEMI after pPCI. Furthermore, the risk prediction of MACE was improved by adding SII to traditional risk factors. SII was superior to NLR and PLR in the prediction of adverse events in STEMI patients after pPCI. Finally, SII is an easily calculable predictor that could be used to detect high-risk patients with STEMI undergoing pPCI.

Author Contributions

Conception and design of the research, Acquisition of data and Critical revision of the manuscript for intellectual contente: Saylik F, Akbulut T; Analysis and interpretation of the data, Statistical analysis and Writing of the manuscript: Saylik F.

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.

Table 4 – Evaluation of predictive models for cardiac adverse events**

	C-statistics (95% CI)*	NRI (95% CI)	IDI (95% CI)
Cardiac death			
Traditional risk factors	0.704(0.633-0.776)	Ref	Ref
Traditional risk factors +SII	0.780(0.713-0.847)	0.4962(0.2661.0.7264)	0.0857(0.058.0.1133)
p value	0.02	0.0002	<0.0001
Nonfatal myocardial infarction			
Traditional risk factors	0.641(0.571-0.710)	Ref	Ref
Traditional risk factors +SII	0.757(0.688-0.826)	0.4936(0.2772.0.7101)	0.0743(0.054.0.0946)
p value	0.0006	<0.0001	<0.0001
Nonfatal stroke			
Traditional risk factors	0.615(0.481-0.750)	Ref	Ref
Traditional risk factors +SII	0.756(0.631-0.881)	0.4655(0.0871.0.844)	0.0307(0.0158.0.0457)
p value	0.043	0.031	<0.0001
Hospitalization for CHF			
Traditional risk factors	0.884(0.852-0.914)	Ref	Ref
Traditional risk factors +SII	0.939(0.918-0.961)	0.7183(0.5413.0.8953)	0.1448(0.1031.0.1865)
p value	<0.0001	<0.0001	<0.0001
Revascularization (PCI or CABG)			
Traditional risk factors	0.923(0.904-0.942)	Ref	Ref
Traditional risk factors +SII	0.931(0.915-0.949)	0.2971(0.1254.0.4687)	0.0231(0.0089.0.0371)
p value	0.036	0.0009	0.0014
MACE			
Traditional risk factors	0.644(0.592-0.696)	Ref	Ref
Traditional risk factors +SII	0.754(0.703-0.804)	0.4539(0.2806.0.6271)	0.1073(0.0834.0.1311)
p value	<0.0001	<0.0001	<0.0001

*NRI: net reclassification improvement, IDI: integrated discrimination improvement, SII: systemic immune-inflammation index, CHF: congestive heart failure, PCI: percutaneous coronary intervention, CABG: coronary artery by-pass graft, MACE: major adverse cardiovascular events. * p values for c-statistics: DeLong test. ** Traditional risk factors: age, hypertension, diabetes mellitus, and male gender.*

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A New Risk Predictor in Acute Myocardial Infarction. Is There Still Room for One More?

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Short Editorial related to the article: Systemic Immune-Inflammation Index Predicts Major Cardiovascular Adverse Events in Patients with ST-Segment Elevated Myocardial Infarction

Cardiology is one of the specialties that traditionally uses scientific evidence in daily practice, both in risk stratification and diagnosis, therapy and prognosis. One of the most discussed topics is atherosclerosis and inflammation, arousing great interest in the continuous knowledge acquired over the last two centuries. Several authors stand out in this historical context, for example, Rudolf Virchow in the 19th century who described the association of atherosclerosis with inflammation; Marchand in 1904, who suggested the relationship between atherosclerosis and the process of clogging of the arteries and in 1908, Ignatowski who observed the relationship between dietary cholesterol and atherosclerosis. Over the last 100 years, many articles have elucidated the pathophysiological sequence that we know today. Understanding atherosclerotic plaque formation and evolution through complex molecular mechanisms and innate and adaptive immunity, which culminate in acute myocardial infarction (AMI), is well established.[1-4] In 1974, Friedman GD et al., described the role of leukocyte count in the prognosis of AMI,[5] and subsequently, other studies highlighted the importance of these cells in the deterioration and recovery of infarcted myocardium.[6-8] In the same line of investigation, Coste MER et al. investigated cytokines in patients with ST-segment elevation myocardial infarction (STEMI) and the relationship with ventricular function. They observed a balance of pro-inflammatory and anti-inflammatory cytokines, except for IL-6, suggesting a residual inflammatory risk.[9]

In addition to these aspects related to atherosclerotic plaque and inflammatory activity in AMI, another process related to these so-called immuno-inflammatory cells, such as platelets, leukocytes, neutrophils, and lymphocytes, initially gained prominence in the field of oncology when described as a reliable prognostic marker in the progression of various malignant tumors, by the so-called "systemic immuno-inflammation index" (IIIS). The systematic review and meta-analysis by Zhong et al.[10] emphasize the importance of this index in predicting survival since high rates were associated with a worse prognosis in solid tumors.[10] In addition to neoplasms, other factors alter IIIS, such as age, obesity, type 2 diabetes, emotional stress, exogenous steroids, endogenous sex hormones, hematological disorders, stroke, pulmonary embolism, and trauma.[11]

White cells, such as leukocytes and neutrophils, are abundant and the first to act as pro-inflammatory in the infarcted area. On the other hand, platelets participate in the pro-inflammatory and prothrombotic processes and other long-term actions in atherosclerosis. Lymphocytes are cells with immune characteristics whose anti-inflammatory action promotes the protection and recovery of infarcted tissue or cells that have already deteriorated. Due to these cellular functions, mainly in the acute phase of infarction, in recent years, many authors have reported these cellular elements as a prognostic value in acute coronary syndromes (ACS). Takahashi et al. in 2007, studied 116 cases of anterior wall AMI, within the first 12 hours, submitted to primary angioplasty to verify the degree of microvascular involvement of the left ventricle (LV). Multivariate analysis showed that neutrophil grade was an independent predictor of microvascular involvement after angioplasty.[12]

In addition to the importance of these prognostic indices, recently, some studies have demonstrated the role of anti-inflammatory therapy in reducing cardiovascular outcomes. The Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS) demonstrated the reduction of major outcomes by anti-inflammatory treatment with this monoclonal substance with action on interleukin-1 Beta, decreasing levels of ultrasensitive C-reactive protein.[13] Another important study, the Colchicine Cardiovascular Outcomes Trial (COLCOT), demonstrated a 23% reduction in major outcomes using colchicine in chronic coronary heart disease.[14]

In a study analyzing these three cellular elements by the relationship between platelets (P), neutrophils (N) and lymphocytes (L) - (IIIS: PxN/L), Yang et al. described this index as an independent risk predictor, being superior to traditional risk factors.[15]

In this issue of *Arquivos Brasileiros de Cardiologia*, Saylik and Akbulut,[16] list the IIIS, using the same criteria as Yang et al., studying 843 patients with STEMI who underwent primary angioplasty. The high index was associated with older age, higher cardiovascular mortality rates, non-fatal myocardial infarction, non-fatal stroke, hospitalization for heart failure, myocardial revascularization, and major cardiovascular events. They concluded that IIIS is an independent predictor. This study emphasizes that the use of the ratio of platelets, neutrophils and lymphocytes is superior in predicting risk

Keywords

Cardiovascular Diseases; Risk Factors; Myocardial Infarction/complications; Atherosclerosis; Inflammation Mediators; Plaque,Atherosclertic; Cholesterol

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than the neutrophil-lymphocyte ratio and the platelet-lymphocyte ratio used in other studies.[17,18] This is probably due to the combination of mechanisms composed of the immuno-inflammatory response in response to aggression mainly by neutrophils in the first days and cell regeneration by the immune and apoptotic response of lymphocytes in the sequence.[19]

We must consider some methodological aspects, as the study was retrospective, single center, with follow-up by telephone or hospital records and death certificates for the cause of death. In addition, previous medications used, such as statins, colchicine, steroids, chemotherapy drugs and others that could influence the results, were not reported. Another fact that could interfere in the analysis of the results was the collection of mortality data by telephone, medical records and death certificates. However, with the results based on hospital entrance exams and the method used, the study showed that this index of immuno-inflammation has great prognostic importance, being easily incorporated into daily practice due to its low cost and ease of access.

We conclude that the topic reminds us of "one more" tool for stratifying the risk of myocardial infarction in a practical and low-cost way, which can easily be incorporated into our practice.

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Impact of Patient Unawareness and Socioeconomic Factors on Patient Presentation to Primary Percutaneous Coronary Intervention

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Abstract

Background: Patient unawareness about acute myocardial infarction, its complications and the benefits of early revascularization is a crucial point that determines the outcomes. Moreover, the relationship between socioeconomic factors and patient presentation to primary percutaneous coronary intervention (PPCI) has not been fully studied.

Objectives: Our objective was to investigate whether or not patient unawareness and other socioeconomic factors impact patient presentation to PPCI.

Methods: The study comprised 570 patients with ST-segment elevation myocardial infarction (STEMI) revascularized by PPCI. The patients were classified into two groups according to the total ischemia time (the time from STEMI symptom onset to balloon dilatation); group I: Patients with early presentation (1-12 hours). Group II: Patients with late presentation (>12-24 hours). Socioeconomic factors, clinical outcomes including mortality and major adverse cardiac events (MACE) were evaluated in each group. A p-value < 0.05 was considered statistically significant.

Results: There are different socioeconomic factors affecting patient presentation to PPCI. Multivariate regression analysis identified the independent socioeconomic predictors as following: low educational level - OR 4.357 (CI95% 1.087–17.47, p=0.038), social isolation - OR 4.390 (CI95% 1.158–16.64, p=0.030) and unawareness about the benefits of early revascularization - OR 4.396 (CI95% 1.652–11.69, p=0.003). Mortality and MACE were higher in group II.

Conclusion: Patient unawareness and low socioeconomic status were associated with late presentation to PPCI with more adverse outcomes.

Keywords: Socioeconomic Factors; Percutaneous Coronary Intervention; Myocardial Infarction.

Introduction

Acute myocardial infarction (AMI) is a leading cause of morbidity and mortality worldwide. However, advances in thrombolytic therapy and primary percutaneous coronary intervention (PPCI) have enabled the vast majority of patients to survive.[1] Patients with AMI experience various impediments, which may influence their ability to manage their condition optimally. First of all, the patient unawareness about the nature of the disease, its complications and the benefits of early revascularization. Moreover, socioeconomic factors such as education, employment and housing can affect a person's health. Similarly, financial barriers may lead to non-adherence to essential medical therapies and recommendations.[2] Social deprivation impacts the incidence of cardiovascular diseases; furthermore, survival is reduced following AMI in patients from deprived social backgrounds.[3] People who are deprived of one or more of these factors may have difficulty accessing health care, and this may influence their overall health status and wellbeing.

Acute myocardial infarction is an emergency situation that requires rapid decisions and intervention. PPCI is a highly recommended method to restore blood flow rapidly for patients with AMI, aiming to minimize myocardial necrosis and improve survival.[4] The outcomes of PPCI do not depend only on the experience of the operators or the capability of PCI centers, which represents only a small percentage of PPCI outcomes. However, there are many forgotten factors affecting the outcomes related to patient unawareness and socioeconomic factors that determine patient presentation, either early or late, after AMI symptom onset. In the current study, our objective was to investigate the impact of patient unawareness about the nature of AMI and the different socioeconomic factors that may impact patient presentation to PPCI.

Methods

The current study is a prospective cohort study, aiming to investigate the impact of different socioeconomic factors on patient presentation to PPCI. The study was conducted on a convenience sample of adult patients with ST-segment elevation myocardial infarction (STEMI), submitted to revascularization by PPCI at the Cardiovascular Department of Tanta University Hospital, which is a tertiary center for people

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from all over the governorate, with emergency capabilities and a high flow rate. The profile of the local population is a mixture of a small percentage of highly educated individuals and the majority of the population countrywide, who has a low educational level. The patients were classified into two groups according to the total ischemia time (the time from AMI symptom onset to balloon dilatation); group I: Patients with early presentation (1-12 hours). Group II: Patients with late presentation (>12-24 hours). Informed consent was obtained from all participants in this research. Every patient had a code number assigned to his telephone number and address. The study was approved by the local ethical committee and was carried out in agreement with the principles of the Declaration of Helsinki II. STEMI was defined by the characteristic symptoms of typical chest pain, as well as by a 1-mm ST-segment elevation in the inferior leads, or 2-mm ST-segment elevation in the anterior chest leads in two contiguous leads, or a new or presumably new left bundle branch block.[5] Patients with STEMI who received thrombolytic therapy or underwent CABG or presented later than 24 hours and patients with non-STEMI were excluded from the study.

All patients were submitted to full history taking, especially regarding the presence of diabetes mellitus, dyslipidemia, hypertension and current smoking. History of prior myocardial infarction, previous stroke and peripheral arterial diseases was assessed. The onset of chest pain before admission was determined, then the time interval between chest pain onset to balloon dilatation was calculated. History of medication use and compliance with it was questioned, including antihypertensive, cholesterol-lowering and antiplatelet medications. The socioeconomic status of the patients was assessed, including level of schooling, patients' income, social isolation, marital and employment status. The Beck Depression Inventory was used, which consists in a 21-question self-reported measure for the severity of depressive symptoms with a score ranging from 0 to 64, where normal scores range from 0 to 10 and scores of 11 or higher indicate potential clinical depression.[6] Furthermore, other factors that may affect the outcomes were assessed, including whether the patient had health insurance, chest pain onset during the night hours, living away from health care providers and, finally, awareness about the benefits of early revascularization.

A full clinical examination, twelve-lead surface ECG and transthoracic echocardiography were performed in all patients. Routine laboratory investigations including serum hemoglobin, random blood glucose, serum creatinine and CK-MB levels were measured in all patients. On admission, patients received four 300 mg chewable acetylsalicylic acid tablets, 600 mg clopidogrel or 180 mg ticagrelor, in addition to intravenous unfractionated heparin. PPCI was performed via the transfemoral or transradial route consistent with operator preference. Two experienced interventionists evaluated a set of parameters including the culprit vessel, target lesion length, TIMI flow grade before and after the PPCI, and thrombus burden (mild, moderate or high). The use of aspiration catheter and glycoprotein IIb/IIIa inhibitors were recorded. TIMI flow score was defined by the degree of flow into the epicardial coronary artery. TIMI grades were assessed as (grade 0) = complete absence of flow beyond the point of obstruction, (grade 1) = some contrast material flows distal to the obstruction, but complete arterial opacification is not achieved, (grade 2) = delayed opacification of the entire artery and (grade 3) = full prompt visualization of the entire artery.[7]

The outcomes of interest in this study were the occurrence of mortality or major cardiovascular events including cardiac arrest, heart failure, and cardiogenic shock, which is defined as persistent hypotension with systolic blood pressure less than 90 mmHg for at least thirty minutes, with characteristics of tissue hypoperfusion despite adequate fluid administration.[8] Contrast-induced nephropathy is defined as a relative (≥25%) or absolute (≥0.5 mg/dl) increase in serum creatinine from baseline to 3 days after contrast media exposure.[9] The occurrence of cerebral stroke, repeat revascularization and re-infarction, which is defined as recurrence of ischemic symptoms with new ECG changes suggestive of re-infarction were assessed. Major bleeding (bleeding that required prolonged hospital stay or drop of hemoglobin of at least 3 gm/dL) was recorded.[10] No-reflow phenomenon occurs if TIMI flow in the artery is ≤ 2, despite the successful dilation and absence of dissection, spasm or distal embolization seen angiographically after completing the procedure.[11]

Statistical analysis

Statistical analysis was performed using SPSS 23, (SPSS Inc. Released 2015. IBM SPSS statistics for windows, version 23, Armonk, NY; IBM Corp.). The normality of each variable was tested by Shapiro-Wilk test. Quantitative data were expressed as mean ± standard deviation. Qualitative data were expressed as frequency and percentage. Independent-samples Student's t-test was used to compare normally distributed quantitative variables. The Chi-square test (χ^2) was used to study the association between qualitative variables. Whenever any of the expected cells were less than five, Fisher's exact test was used. Survival analysis was performed using Kaplan-Meier statistics with log-rank test to express the significance. Multivariate logistic regression analysis was performed to detect the independent socioeconomic predictors affecting patient presentation to PPCI. A two-sided p-value <0.05 was considered statistically significant.

Results

The current study was carried out with 570 patients presenting with STEMI and submitted to PPCI revascularization. Patients were divided into 2 groups according to total ischemia time; group I: 280 Patients (49.1 %) with early presentation (1-12 hours). Group II: 290 Patients (50.9 %) with late presentation (>12-24 hours). There was no statistically significant difference between the two groups regarding age, sex distribution, presence of hypertension, dyslipidemia and current smoking status. The number of patients with atrial fibrillation in group II was significantly higher than ingroup I. Left ventricular ejection fraction was significantly higher in group I than in group II. Regarding the laboratory results, CK-MB and serum creatinine levels were significantly lower in group I than in group II, as shown in Table 1.

The patients' socioeconomic status, medical follow up, compliance with medication and awareness about the benefits of early revascularization were compared. There

Table 1 – Basal characteristics, echocardiographic data and laboratory data of all patients in both groups

	Group I (n=280) (1-12 hours)	Group II (n=290) (>12-24 hours)	p-value
Age, years	57.16±12.01	56.60±12.06	0.574
Male gender, n (%)	139 (49.6%)	146 (50.3%)	0.867
Smoking, n (%)	74 (26.4%)	79 (27.2%)	0.827
Hypertension, n (%)	94 (33.6%)	91 (31.4%)	0.576
Diabetes mellitus, n (%)	84 (30.0%)	91 (31.4%)	0.721
Dyslipidemia, n (%)	97 (34.6%)	106 (36.6%)	0.634
Prior MI, n (%)	22 (7.9%)	27 (9.3%)	0.536
Previous stroke, n (%)	9 (3.2%)	8 (2.8%)	0.749
Peripheral vascular disease, n (%)	36 (12.9%)	35 (12.1%)	0.776
Atrial fibrillation, n (%)	24 (8.6%)	41 (14.1%)	0.037*
BMI, (kg/m^2)	25.26±4.01	25.42±4.36	0.638
Anti-hypertensive medication use, n (%)	84 (30.0%)	76 (26.2%)	0.314
Cholesterol lowering medication use, n (%)	76 (27.1%)	77 (26.6%)	0.873
Anti-platelet medication use, n (%)	97 (34.6%)	89 (30.7%)	0.314
Systolic BP, mmHg	125.3±17.85	124.1±20.9	0.462
Diastolic BP, mmHg	77.50±8.20	76.26±9.50	0.096
LVEF, (%)	47.50±4.65	45.86±6.46	0.001*
Hemoglobin, g/dL	11.56±1.48	11.61±1.46	0.646
Random blood glucose, mg/dL	162.5±43.8	160.6±49.9	0.621
Serum creatinine, mg/dL	1.036±0.23	1.093±0.24	0.006*
CK-MB, U/L	72.53±33.07	81.98±43.47	0.004*
Volume of contrast agent,(mL)	184.2±69.9	182.2±65.3	0.728

*MI: myocardial infarction; BMI: body mass index; LVEF: left ventricular ejection fraction; CK-MB: Creatine kinase myocardial band; *: significant p-value.*

was a statistically significant difference between the two groups regarding the number of patients seen by medical specialist in the previous year, which was higher in group I. Moreover, the number of patients compliant with medical treatment was also significantly higher in this group. The number of patients who suffered from social isolation was higher in group II than in group I. The number of patients with low level of schooling was significantly higher in group II than in group I. Regarding patient awareness about the benefits of early revascularization, the number of patients who was aware was significantly higher in group I than in group II. The number of patients experiencing symptom onset during the night hours was higher in group II, and the number of patients living away from health care providers was also higher in group II, as shown in Table 2.

Regarding the angiographic results, the lesion thrombus burden in the culprit vessel was significantly higher in group II than in I group. Moreover, the need for aspiration catheter and glycoprotein IIb/IIIa inhibitor use was also higher in group II. There was no statistically significant difference between the two groups regarding initial TIMI flow, the length of the lesion or the culprit vessel, although post-procedural TIMI flow showed a statistically significant difference with a higher incidence of no-reflow in group II, as shown in Table 3.

Concerning the outcomes, mortality was significantly higher in group II than in group I. The incidence of cardiogenic shock was significantly higher in group II than in group I. The number of patients with heart failure was higher in group II than in group I. Moreover, the occurrence of the no-reflow phenomenon was significantly higher in group II than in group I, as shown in Table 4 and Figure 1.

Multivariate regression analysis was performed to identify the independent socioeconomic predictors affecting patient presentation to PPCI as depicted in Table 5, with the following results: level of schooling OR 4.357 (CI95% 1.087–17.47, p=0.038), social isolation - OR 4.390 (CI95% 1.158–16.64, p=0.030) and patient awareness about the benefits of early revascularization - OR 4.396 (CI95% 1.652–11.69, p=0.003). The Kaplan Meier curve was performed showing cumulative survival in patients from both groups, as shown in Figure 2.

Discussion

Acute myocardial infarction is an emergency condition that requires rapid decision to seek medical advice for early revascularization and salvage of cardiac muscle from

Table 2 – Socioeconomic factors of all patients in both groups

	Group I (n=280) (1-12 hours)	Group II (n=290) (>12-24 hours)	p-value
Has seen a medical specialist in the previous year, n (%)	193 (68.9%)	113 (39.0%)	0.001*
Compliance with medical treatment, n (%)	159 (56.8%)	121 (41.7%)	0.001*
Income category			
High income, n (%)	88 (31.4%)	77 (26.6%)	0.199
Low income, n (%)	192 (68.6%)	213(73.4%)	
Level of schooling			
Bachelor's degree or higher, n (%)	119 (42.5%)	88 (30.3%)	0.003*
High school or less, n (%)	161 (57.5%)	202 (69.7%)	
Social isolation			
Lives with others, n (%)	248 (88.6%)	228 (78.6%)	0.001*
Lives alone, n (%)	32 (11.4%)	62 (21.4%)	
Beck Depression Inventory			
Normal, n (%)	247 (88.2%)	250 (86.2%)	0.473
Abnormal, n (%)	33 (11.8%)	40 (13.8%)	
Marital Status			
Married, n (%)	188 (67.1%)	177 (61.0%)	0.129
Separated/Divorced/ Single/ Widow/Widower, n (%)	92 (32.9%)	113 (39.0%)	
Employment status			
Employed, n (%)	173 (61.8%)	170 (58.6%)	0.718
Retired, n (%)	50 (17.9%)	54 (18.6%)	
Unemployed, n (%)	57 (20.4%)	66 (22.8%)	
Awareness about the benefits of early revascularization, n (%)	179(63.9%)	103 (35.5%)	0.001*
Onset of chest pain during night hours, n (%)	112 (40.0%)	148 (51.0%)	0.008*
Health insurance, n (%)	89 (31.8%)	81 (27.9%)	0.315
Living away from health care providers, n (%)	33 (11.8%)	52 (17.9%)	0.039*

**: significant p value.*

necrosis. Although the PPCI is the gold standard for treating patients with STEMI, its main limitation is the time delay. Contemporary management of STEMI is built around early reperfusion therapies to reduce infarction size and optimize outcomes.[12] Ischemia duration is a key determinant of infarction size, as myocyte death is directly proportionate to the duration of coronary artery occlusion.[13] Therefore, the survival benefit from the opening up of the occluded coronary artery is crucially related to the time in the very early course of STEMI presentation.[14] Therefore, in the current study, we divided the patients into two groups according to the total ischemia time, which is considered the cornerstone for PPCI outcomes. Although it is highly recommended that total ischemia time be shortened in patients with STEMI, it can vary according to the knowledge of the patient about the disease and other different socioeconomic factors that determine the early or late presentation to health care providers. Although the health policy of the state has been enhanced in previous years with the integration of different health policy models, including the program ('stent for life') in which PPCI is available freely for all patients with AMI, regardless of their socioeconomic status, as well as by the integration of the Emergency Care Network-CATH-LAB, we decided to investigate the different socioeconomic factors and other related factors that may impact patient presentation to PPCI.

In this study, patients with late presentation (group II) showed an increase in CK-MB enzyme levels, which indicates an increase in myocardial necrosis due to the long duration of ischemia and also reflected on left ventricular ejection fraction, which was significantly lower in this group than in group I. This decrease in ejection fraction can lead to adverse outcomes as reported by Ng et al.,[15] who studied 2648 patients with STEMI, divided into three groups according to left ventricular function: (1) severely impaired LVEF <40%, (2) moderately impaired LVEF 40–50% and

Table 3 – Angiographic results of all patients in both groups

	Group I (n=280) (1-12 hours)	Group II (n=290) (>12-24 hours)	p-value
Interval from symptom onset to FMC, (hours)	7.61±2.71	18.34±3.41	0.001*
Interval from FMC to balloon dilation, (minutes)	63.98±19.50	64.04±19.45	0.971
Initial TIMI flow			
0-2	246 (87.9%)	265 (91.4%)	0.168
3	34 (12.1%)	25 (8.6%)	
Post-procedural TIMI flow			
0	2 (0.7%)	7 (2.4%)	0.027*
1	8 (2.9%)	18 (6.2%)	
2	13 (4.6%)	22 (7.6%)	
3	257 (91.8%)	243(83.8%)	
Thrombus burden			
Low	147 (52.5%)	116 (40.0%)	0.010*
Moderate	85 (30.4%)	106 (36.6%)	
High	48 (17.1%)	68 (23.4%)	
Aspiration catheter	22 (7.9%)	39 (13.4%)	0.031*
Glycoprotein IIb/IIIa inhibitors	26 (9.3%)	48 (16.6%)	0.010*
Reperfusion type			
Balloon angioplasty	8 (2.9%)	14 (4.8%)	0.466
Direct stenting	56 (20.0%)	55 (19.0%)	
Stenting after pre-dilation	216 (77.1%)	221 (76.2%)	
Length of the lesion, mm	21.39±5.40	20.73±5.25	0.143
Culprit vessel			
LM coronary artery, n (%)	6 (2.1%)	7 (2.4%)	0.829
LAD coronary artery, n (%)	111 (39.6%)	121 (41.7%)	0.613
CX coronary artery, n (%)	85 (30.4%)	90 (31.0%)	0.861
Right coronary artery, n (%)	78 (27.9%)	72 (24.8%)	0.412

*FMC: first medical contact; TIMI: thrombolysis in myocardial infarction; LM: left main; LAD: left anterior descending; CX: circumflex; *: significant p value.*

Table 4 – Outcomes of primary percutaneous coronary intervention

	Group I (n=280) (1-12 hours)	Group II (n=290) (>12-24 hours)	p-value
Mortality, n (%)	7 (2.5%)	17 (5.9%)	0.046*
Cardiogenic shock, n (%)	15 (5.4%)	30 (10.3%)	0.027*
Cardiac arrest, n (%)	16 (5.7%)	12 (4.1%)	0.384
Contrast-induced nephropathy, n (%)	26 (9.3%)	34 (11.7%)	0.343
Heart failure, n (%)	23 (8.2%)	42 (14.5%)	0.019*
Major bleeding, n (%)	2 (0.7%)	5 (1.7%)	0.274
Reinfarction, n (%)	4 (1.4%)	6 (2.1%)	0.560
Repeat revascularization, n (%)	4 (1.4%)	7 (2.4%)	0.393
Cerebral stroke, n (%)	2 (0.7%)	3 (1.0%)	0.682
No-reflow phenomenon, n (%)	25 (8.9%)	47 (16.2%)	0.009*

**: significant p value.*

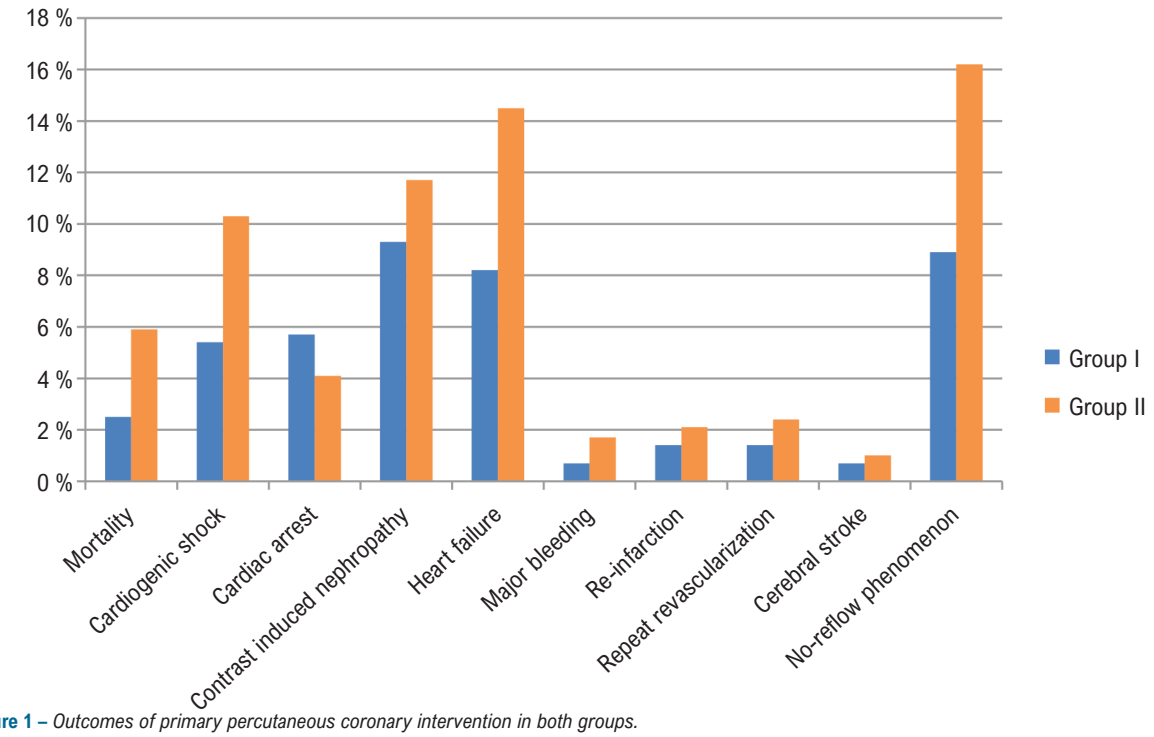

Figure 1 – *Outcomes of primary percutaneous coronary intervention in both groups.*

Table 5 – Multivariate regression analysis for socioeconomic independent predictors affecting patient presentation to PPCI

	Multivariate analysis		value- p
	OR	(95% CI)	
Has seen a medical specialist in the previous year	2.364	0.866–6.450	0.093
Compliance with medical treatment	1.237	0.436–3.511	0.689
Level of schooling	4.357	1.087–17.47	0.038*
Social isolation	4.390	1.158–16.64	0.030*
Awareness about the benefit of early revascularization	4.396	1.652–11.69	0.003*
Chest pain onset during the night hours	1.707	0.493–5.909	0.398
Living away from health care providers	1.001	0.279–3.598	0.999

**: significant p value.*

(3) normal LVEF ≥50% and concluded that adverse events are markedly increased in those with LVEF <40%.

The analysis of different socioeconomic factors in the present study showed that the number of patients with low educational level was significantly higher ingroup II, and also the number of patients that suffered from social isolation and lived alone were higher in this group. Moreover, the patients' awareness about the benefits of early revascularization was significantly lower in this group, implying the consequences of the delayed seeking of medical advice. In addition, the number of patients in group II that was seen by a medical specialist in the previous year and those compliant with medical treatment was significantly lower in this group. In agreement with our results, Schröder et al.,[16] observed that patients with higher socioeconomic status had greater knowledge about medical treatment and could use medical records to obtain more information, while patients with low socioeconomic status seem to lack knowledge about treatment and have problems in understanding the information provided to them. Moreover, the study by Roth et al.,[17] who studied the role of the socioeconomic environment on medical

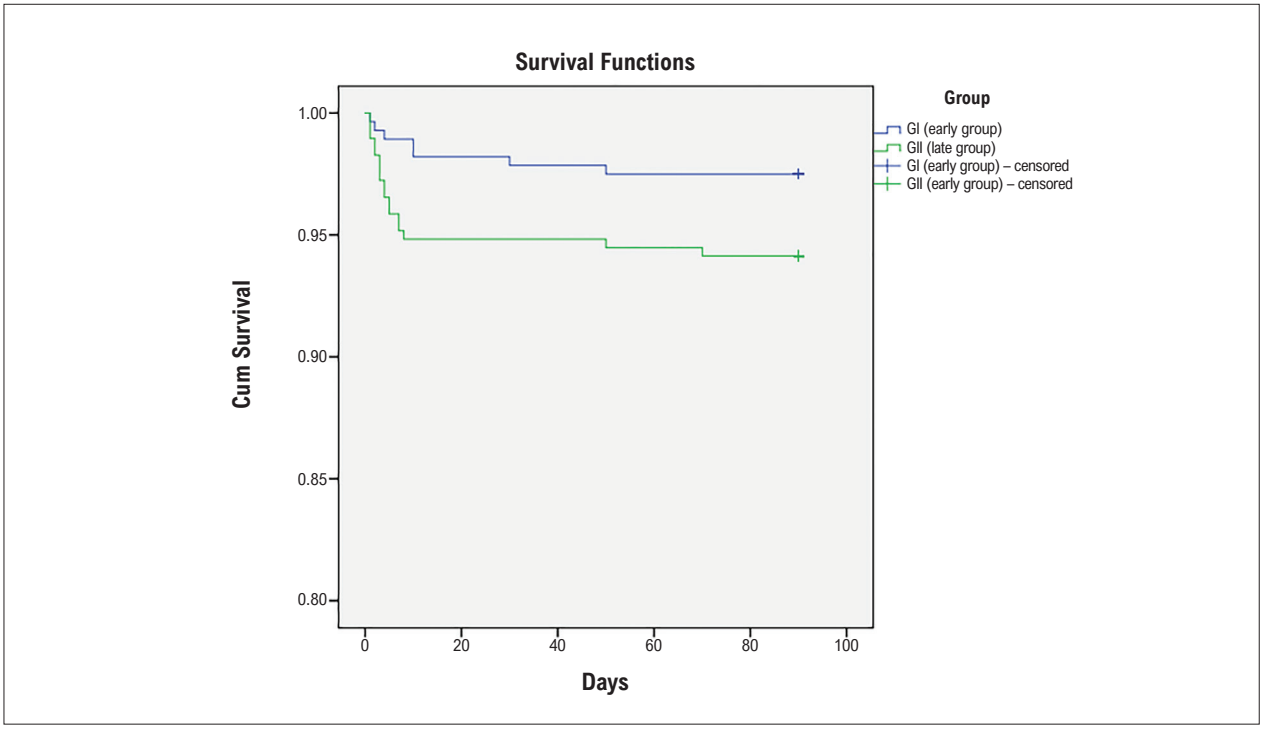

Figure 2 – *Kaplan-Meier curve showing cumulative survival in patients from the early and late presentation groups.*

outcomes after AMI and included 870 patients with STEMI submitted to PPCI at the General Hospital of Vienna, demonstrated an association between the socioeconomic status distribution and conventional risk factors, which in turn, showed a significant impact on survival for patients with STEMI. In agreement to our results, Jones et al.,[18] studied 13,770 consecutive patients who underwent PPCI at a single center between 2005 and 2011 and reported several possible reasons why socioeconomic status might influence PPCI outcomes and observed that social isolation was increasingly seen in those of low socioeconomic status and has been associated with poorer outcomes following AMI. Furthermore, Kareem et al.,[19] who investigated the impact of socioeconomic status on adverse cardiac events after coronary angioplasty concluded that low socioeconomic status, was associated with lower adherence to medication and higher mortality after PCI. Another important factor observed in the present study is that the number of patients who experienced chest pain onset during the night hours was significantly higher in group II. By further analyzing this group, it was found that if patients were aware of the nature of AMI, they would call the ambulance center during the night hours for referral to the hospital and early revascularization by PPCI, rather than staying at home and wait to go to the hospital in the morning. This reflects the patients' reluctance to seek medical care during the night hours due to their unawareness.

In the current study, patients in group II had a higher incidence of no-reflow phenomenon than patients in group I. Brosh et al.[20] also reported a significant difference in the door-to-balloon time in patients with and without the no-reflow phenomenon ($p=0.000$). Moreover, Yip et al.[21] demonstrated that the rate of no-reflow was lower in patients who were reperfused within less than 4 hours and Kirma et al.[22] found that delayed reperfusion > 6 hours was correlated with no-reflow ($p<0.05$), which is in agreement with our results. In the early stages of AMI, the thrombus is rich in thrombocytes and is easier to be treated with adjunctive pharmacotherapy. Furthermore, delayed reperfusion results in a well-organized intracoronary thrombus, thus reducing the likelihood of achieving TIMI 3 flow.[22, 23]

The outcomes after PPCI were worse in group II, as mortality and major adverse cardiac events were significantly higher in this group than in group I. Cardiogenic shock remains the most common cause of death in patients hospitalized with STEMI. The incidence of patients with cardiogenic shock was significantly higher in group II (10.3%) than (5.4%) in group I. The underlying reason may be the fact that more cell necrosis occurs in patients with STEMI that had a later presentation. Thus, the highest CK-MB levels were found in group II. Cardiogenic shock has a frequency of around 7-10%.[24,25] It is associated with clinical signs of hypoperfusion, which include decreased urine output and peripheral vasoconstriction. Moreover, the occurrence of atrial fibrillation was significantly higher in group II. Atrial fibrillation can lead to a decrease in cardiac output, with more hemodynamic compromise.[26,27] Furthermore, serum creatinine levels were significantly higher in group II; all of these factors increase the possibility of contrast-induced nephropathy, which in

turn worsen the outcomes and increase mortality, despite advances in pharmacological, mechanical and reperfusion strategies.[28-31]

Conclusions

Patient unawareness about the nature of AMI, its complications and the benefits of early revascularization and the patients' low socioeconomic status were associated with a late presentation to PPCI. The independent socioeconomic predictors affecting the presentation to PPCI in the current study were low educational level, social isolation and unawareness about the benefits of early revascularization.

Author Contributions

Conception and design of the research and Statistical analysis: Khalfallah M; Acquisition of data, Analysis and interpretation of the data, Writing of the manuscript and Critical revision of the manuscript for intellectual content: Khalfallah M, Allaithy A, Maria DA.

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 Faculty of Medicine, Tanta University. 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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If "Time Is Muscle," Then the Patient's Knowledge Must Save Time

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Short Editorial related to the article: Impact of Patient Unawareness and Socioeconomic Factors on Patient Presentation to Primary Percutaneous Coronary Intervention

More than half a century ago, Eugene Braunwald's group experimental work on the factors influencing infarct size following coronary artery occlusions led to the concept of "Time is Muscle" in what relates to acute myocardial infarction management.[1]

Timely reperfusion of the occluded coronary arteries is critical to saving at-risk ischemic myocardial cells in acute ST-elevation myocardial infarction (STEMI).

In the last decades, the focus has been put on the efforts to shorten the door-to-needle or door-to-balloon times and look for better and safer modalities of reperfusion therapies.

When different reperfusion modalities are to be considered, the duration of symptoms and the expected time to reach reperfusion are key to choosing the best therapy for each patient. This concept has led to the comparison of lytic pharmacologic therapy, initiated in the pre-hospital phase or at hospitals without cath lab facilities, and percutaneous coronary intervention – PCI.[2]

Independently of what reperfusion strategy is chosen (lytics or PCI), the time from symptom onset to successful reperfusion is critical to the short- and long-term patients' prognosis.[3,4]

To quote Elliott M. Antman's landmark paper: "*In the future, advances in the care of patients with ST-segment elevation myocardial infarction (STEMI) will not come from the analysis of trials that do not reflect current practice in an effort to rationalize extending the percutaneous coronary intervention (PCI)-related delay time. We must move beyond such arguments and find ways to shorten the total ischemic time.*"[5]

Terkelsen et al. [6] divided the total ischaemic time into 'patient delay' and 'system delay,' suggesting that the latter, but not the former, can be influenced by the healthcare provider.

The 2017 European Society of Cardiology STEMI guidelines[7] indicates that all components of the system delay (determined as the interval from first medical contact (FMC) to reperfusion) represent the quality of care, and it is recommended to measure them as quality indicators.

Keywords

Myocardial Infarction; Percutaneous Coronary Intervention/methods; Awareness; Myocardial Reperfusion; Comprehensive Health Care/economics; Myocardial Ischemia/therapy

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Nevertheless, as mentioned above, total ischemic time is the major determinant of infarct size in STEMI. Emphasis has been placed on reducing the door-to-reperfusion therapy time component (the so-called system delay), whereas the symptom-to-FMC (the patient delay) is often overlooked.

Patient delay can be attributed to several individuals and societal characteristics of the patients presenting with STEMI. Several papers have addressed this issue and found that the decision to seek medical help by calling the emergency services or self-presenting to a medical facility can vary from person to person. However, some common characteristics have been identified that justify the late presentation of patients to first medical contact.[8-11]

In this issue of Arquivos Brasileiros de Cardiologia, Khalfallah et al.[12] present a very interesting evaluation of two factors that influence patient delay in PCI reperfusion.[12]

Patient awareness of myocardial ischemia-related symptoms and that those symptoms might alert to a serious (even life-threatening) disease is a major determinant of the timely decision to seek medical care. Campaigns directed to increase patient awareness have shown mixed results, mostly due to different approaches seeking to improve the health literacy of the at-risk populations.[8,12]

Another relevant aspect of patient awareness is the patient's knowledge of early reperfusion benefits. Khalfallah et al.[12] found that awareness of the patients about the benefits of early revascularization was significantly lower in late presenting patients, which they suggest might be another reason for late seeking medical advice.[12]

The other relevant finding of this paper is the relationship between patients' socioeconomic factors and the timing of patient presentation to medical care. The authors performed a multivariate regression analysis to identify the independent socioeconomic predictors affecting patient presentation to PCI and found that the proportion of patients with low educational levels was significantly higher in the late presenting group.[13] Also, patients who suffered from social isolation and those that lived alone were more prevalent in this group. As the authors discuss, these findings are in line with other studies on this topic,[14,15] but this is another area of conflicting reports, with other authors reporting no relationship between socioeconomic factors and timing of presentation.[13]

We can thus conclude that this is a matter of great interest and ongoing research and that more studies seeking to evaluate the impact of health literacy on the prognosis of STEMI patients are welcome. Nevertheless, evidence shows that healthcare providers must continue giving the best care possible (including timely reperfusion) to early and late presenters.[16]

Healthcare professionals, particularly those responsible for caring for high-risk patients, must grab any opportunity to improve their patients' health literacy concerning myocardial ischemia-related symptoms, the risks of later presentation to medical care, and the benefits of early reperfusion in the case of suspected myocardial infarction.

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In-Hospital Mortality from Cardiovascular Diseases in Brazil during the First Year of The COVID-19 Pandemic

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Abstract

Background: **The COVID-19 pandemic has had an impact on mortality from several diseases worldwide, especially cardiovascular diseases (CVD). Brazil is a continent-sized country with significant differences in the health care structure between its federative units.**

Objective: **Analyze in-hospital mortality from CVDs in the Brazilian public health system during the first year of the COVID-19 pandemic (2020).**

Methods: **This is an ecological study analyzing the absolute number of in-hospital deaths and the rate of in-hospital mortality in Brazil, its macro-regions, and federative units. Data were obtained from the Hospital Information System of the Brazilian Ministry of Health. To analyze excess mortality, the P-score was used. It compares the events observed with those expected for a given place and period. The P-score was corrected by the joinpoint regression model, with a 95% confidence interval and 5% significance level.**

Results: **There were 93,104 in-hospital deaths due to CVD in Brazil in 2020, representing 1,495 fewer deaths (P score: −1.58) than expected. The central-west region had a positive P-score, with a 15.1% increase in the number of deaths. Ten federative units showed a greater number of deaths in 2020. There was also a 13.3% excess in-hospital mortality at the country level, and an excess in-hospital mortality in all macro-regions.**

Conclusions: **There was a decrease in the absolute number of in-hospital deaths, as well as an increase in in-hospital mortality from CVD in Brazil, in 2020, after the COVID-19 pandemic onset.**

Keywords: **COVID-19; Cardiovascular Diseases; Mortality.**

Introduction

The first cases of coronavirus disease 2019 (COVID-19) were registered in December 2019 in China, and the disease quickly spread throughout the world. In March 2020, COVID-19 was declared a pandemic by the World Health Organization.[1,2] Transmission may be person-to-person or due to contact with contaminated surfaces, thus favoring the rapid spread of the virus. COVID-19 can potentially lead to death, according to age, immune status, and pre-existing chronic diseases of infected patients.[3,4]

In Brazil, the first case was confirmed on 26 February 2020, and the first death was registered on 17 March 2020.[5] On 18 April 2021, almost one year and two months after the start of the pandemic, there were 13.9 million confirmed cases and approximately 373,000 deaths in Brazil, with a case-fatality rate of 2.7%.[6] Besides, since the onset of the pandemic, the country has been facing an economic and political crisis, which has made it even more difficult for the country to handle the disease.[7,8]

COVID-19 may be asymptomatic, or manifest a wide spectrum of symptoms, including fever, dyspnea, cough, myalgia, anosmia, and chest pain.[6] In addition, patients may also present cardiovascular symptoms, either due to indirect cardiac involvement (from systemic inflammation, thrombogenesis, and increased metabolic demand associated with decreased cardiac reserve) or direct action of the pathogen in cardiac tissue.[9] Thus, the novel coronavirus can result in myocardial injury, arrhythmia, heart failure, myocarditis, and shock, especially in the presence of pre-existing cardiovascular disease (CVD).[10-12]

Furthermore, non-pharmacological measures aimed at reducing COVID-19 transmission at the community level have affected the organization of healthcare services, for instance, by reducing the number of face-to-face consultations and hours of operation of the services. Non-pharmacological measures

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also included restricted urban mobility and recommendations to seek medical attention only when strictly necessary.[13-15] Population's behavior has also changed, primarily due to concerns regarding contamination by the novel coronavirus.[14,16]

Several studies worldwide have demonstrated a significant reduction in hospital admissions due to CVD, in parallel to increased mortality and complication rates, in comparison with rates before the pandemic or previous years.[17-22] In Brazil, a study reported reduced hospital admissions and increased in-hospital mortality from CVD during the first months of the pandemic.[23] However, there are no studies with official data from the entire year of 2020.

Moreover, in a continent-sized country like Brazil, it is crucial to understand the situation in each region to help policy decision-making. Therefore, the objective of this study was to investigate in-hospital mortality from CVD within the realm of the Brazilian public health system during the first year of the COVID-19 pandemic (2020).

Methods

This is an ecological study analyzing the number of in-hospital deaths, rate of in-hospital mortality, and cause of deaths according to chapter IX of the International Classification of Diseases (ICD-10). The following were considered as units of analysis: Brazil, its macro-regions, and its federative units. Data were obtained from the Hospital Information System (SIH, acronym in Portuguese) of the Brazilian Ministry of Health (http://tabnet.datasus.gov.br/cgi/deftohtm.exe?sih/cnv/nruf.def). The SIH registers all hospital admissions financed by the SUS.

The in-hospital mortality rate was calculated using the following equation:

$$\text{In-hospital mortality rate} = \frac{\text{Number of in – hospital deaths due to CVD}}{\text{Number of hospital admissions due to CVD}} \times 100$$

The P-score calculates "excess mortality" as the percentage difference between the number of deaths during a given period and the average number of deaths during the same period in previous years. The recommended P-score (using the absolute number of in-hospital deaths) and the adapted P-score (using in-hospital mortality rates) were used for analysis of in-hospital mortality, as per the following equations:

P-score of the absolute number of in-hospital deaths:

$$\text{P score} = \frac{\text{Number of in-hospital deaths due to CVD (2020) – Expected number of in – hospital deaths due to CVD.}}{\text{Expected number of in – hospital deaths due to CVD}} \times 100$$

For the adapted P score of in-hospital mortality rate:

$$\text{P Score} = \frac{\text{In – hospital mortality rate due to CVD (2020) – Expected value of in – hospital mortality due to CVD}}{\text{Expected value of in – hospital mortality due to CVD}} \times 100$$

In these equations, the 'expected value' refers to the average from the previous five years (2015 to 2019).[24-]

Since the calculation of the expected value for the year 2020 does not consider the time trend of the phenomenon, it can be overestimated (if the trend indicator is descending) or underestimated (if the time trend is increasing). For this reason, we also analyzed the period trend by theho joinpoint regression model with Monte Carlo permutation test (4,499 permutations). The model allows the classification of trends as increasing, decreasing or stationary and the calculation of the average percent change (APC). A confidence interval of 95% and a significance level of 5% were adopted.

The APC was used to correct the number of in-hospital deaths expected for 2020, as well as the in-hospital mortality rate (%). In this process, a monthly time series of the five years (2015-2019) was adopted, totaling 60 months. To obtain the expected values, the following rules were adopted:

If increasing trend: mean value of 2015-2019 + APC

If decreasing trend: mean value of 2015-2019 - APC

If stationary trend: only the mean value was used.

Subsequently, the study proceeded to descriptive analysis (absolute and relative frequency) of in-hospital mortality and the P scores for the country, its macro-regions, and federative units. The results were presented considering the whole year of 2020 and the period from March to December of the same year, considering that COVID-19 was confirmed in Brazil at the end of February and the disease spread from March onwards.

The software Microsoft Office Excel® (©2008 Microsoft Corporation), SPSS statistics v.21 (©IBM corporation) e Joinpoint Regression 4.5.0.1 (National Cancer Institute – EUA) were used.

This study used public domain data, which do not allow for identification of individuals. For this reason, approval by the Research Ethics Committee was waived.

Results

In 2020, there were 93,104 in-hospital deaths due to CVD in Brazil, which is less than that expected for that year, given that the average from the previous 5 years (2015 to 2019) was 94,599, expressing a difference of 1,495 in-hospital deaths (P score: -1.58). When considering only the months from March to December 2020, there was a decrease of 3.85% (73,061 expected in-hospital deaths and 70,246 observed). Regarding the macro-regions, only the Central-West Region showed a positive P score, with a 15.12% increase in the number of deaths from January to

December, and 13.42% from March to December. There were 999 more deaths considering the whole year of 2020, 666 more considering only the pandemic period (March-December) (Figures 1 A and B).

Ten federative units showed a higher number of deaths in 2020 in relation to what was expected, as follows: two in the north region (Amazonas and Roraima), four in the northeast (Maranhão, Rio Grande do Norte, Paraíba, and Bahia), one in the south (Paraná), and three in the central-west (Mato Grosso do Sul, Goiás, and the Federal District). When considering the March-December period, this number was reduced to six (Amazonas, Roraima, Paraíba, Mato Grosso do Sul, Goiás and Federal District) (Figures 1 A-B).

When analyzing the in-hospital mortality rate from January to December 2020, an excess of 13.34% was observed in Brazil in 2020 (expected rate for 2020: 8.28%; observed rate for 2020: 9.38%). Regarding the period from March to December, the rate increased from 8.12% to 9.64% (P Score 18.76). Excess in-hospital mortality was also observed in all macro-regions. The highest P-scores were observed in the central-west region (24.10% from January to December and 28.78% from March to December), followed by the south region (15.23% from January to December and 20.92% from March to December). In addition, six federative units showed negative P-score when analyzing the entire year of 2020 (Rondônia, Amapá, Piauí, Alagoas, Sergipe and Mato Grosso) and three when considering the March-December period (Rondônia, Piauí and Mato Grosso) (Figures 1 C-D).

During January and February, the P-scores for in-hospital deaths due to CVD in Brazil and its regions were positive. In January, for example, the nationwide P-score was 4.4; the highest score was in the central-west region (17.0) and the lowest in the southeast (1.5). In March, the nationwide P-score (-1.7) and regional (except for the central-west) P-scores became negative. At the nationwide level, the P-score was observed to become positive from September to November 2020. The northeast region maintained a negative P-score for every month of the year. In the southeast region, the P score became positive in August (1.5), September (0.4), and November (10.7), and, in the South, it became positive in the months of August (1.2) and September (4.7). In the central-west, a peculiar pattern was observed, where the score became negative only in April (-3.7) (Figures 2 A-E).

In January 2020, negative P-scores for in-hospital mortality rate were observed on the nationwide level (-0.1) and in the southeast (-2.9) and south (-2.5) regions. On the other hand, the central-west showed a higher P-score (12.7). For all the following months (February to December), there was excess mortality in all five macro-regions of Brazil. It is noteworthy that, in March, after the pandemic was established in Brazil, the national P-score was almost three times higher (from 2.9 to 8.9) than in February. When analyzing the data by region, it was observed that excess mortality differed between macro-regions. While the P-score increased from 1.5 in February to 10.2 in March (6.6 times greater) in the southeast, it increased from 1.6 to 2.1 (1.3 times greater) in the northeast and from 4.4 to 6.1 (1.4 times greater) in the north. In the central-west, this increase occurred later, only in May (Figures 3 A-E).

Discussion

This study analyzed in-hospital mortality from CVD in public health in Brazil during the year of 2020. A decrease was observed in the absolute number of in-hospital deaths, in addition to an increase in the in-hospital mortality rate in all Brazilian macro-regions and in most federative units during the period analyzed.

The decrease in the absolute number of deaths due to CVD in Brazil in 2020 may be explained by the lower number of patients seeking health services during the pandemic, and adoption of non-pharmacological measures to contain the pandemic.[13] Different investigations[17-22] throughout the world have reported reduced numbers of hospital admissions in 2020, when compared to periods before the pandemic, as was shown in our study.

In a multicenter study in the state of Massachusetts, USA, in March 2020, a 43% reduction was observed in hospitalization rates due to acute CVDs, including heart failure, acute coronary syndrome, and stroke.[17]Another study observed a sharp decline in the number of hospital admissions due to other causes, such as acute appendicitis, acute coronary syndrome, stroke, bone fractures, cancer, and live births, in a network of hospitals in Qatar.[25]

Concerns about contracting COVID-19 in hospital centers,[24] social-distancing recommendations,[26] and difficulties in locomotion by means of public transportation,[27] may have contributed to the decrease in hospital admissions and, consequently, to the decrease in the absolute number of deaths due to CVD registered in 2020. Brazilian studies have indicated that this epidemiological scenario is in contrast with the increase in out-of-hospital deaths due to cardiorespiratory arrest,[28-30] as observed in the city of Belo Horizonte, where there was a 33% increase in the first month of the pandemic (March 2020), in comparison to March of the previous year.[28] Furthermore, a study conducted in Italy reported a 58% increase in out-of-hospital cardiac arrest, which was strongly associated with the cumulative incidence of COVID-19.[31] Therefore, what has been observed is the occurrence of hidden mortality,[29] mostly at the homes of individuals who adhered to and respected sanitary recommendations.

In Brazil, a continent-sized country, characterized by demographic and epidemiological polarization,[32] the pandemic has not spread homogenously throughout the territory. Consequently, the pandemic has had a different impact across regions. In our study, except for the central-west, there was a decrease in the number of in-hospital deaths due to CVD in relation to what was expected in all the regions. When analyzing by month, while a decline in P-score was seen in the north, northeast, south, and southeast regions in March, in the central-west, this decrease was observed later, in April, and it remained negative only during this month. This result is in line with the course of the pandemic in this region; in March, for instance, the region registered only 460 cases of the disease, in contrast with 3,400 cases registered in the southeast.[32]

Two factors should be considered with respect to the central-west region. It is likely that the slower advance of COVID-19 in this region is associated with the lower migratory flow of people, as compared with other regions like the northeast

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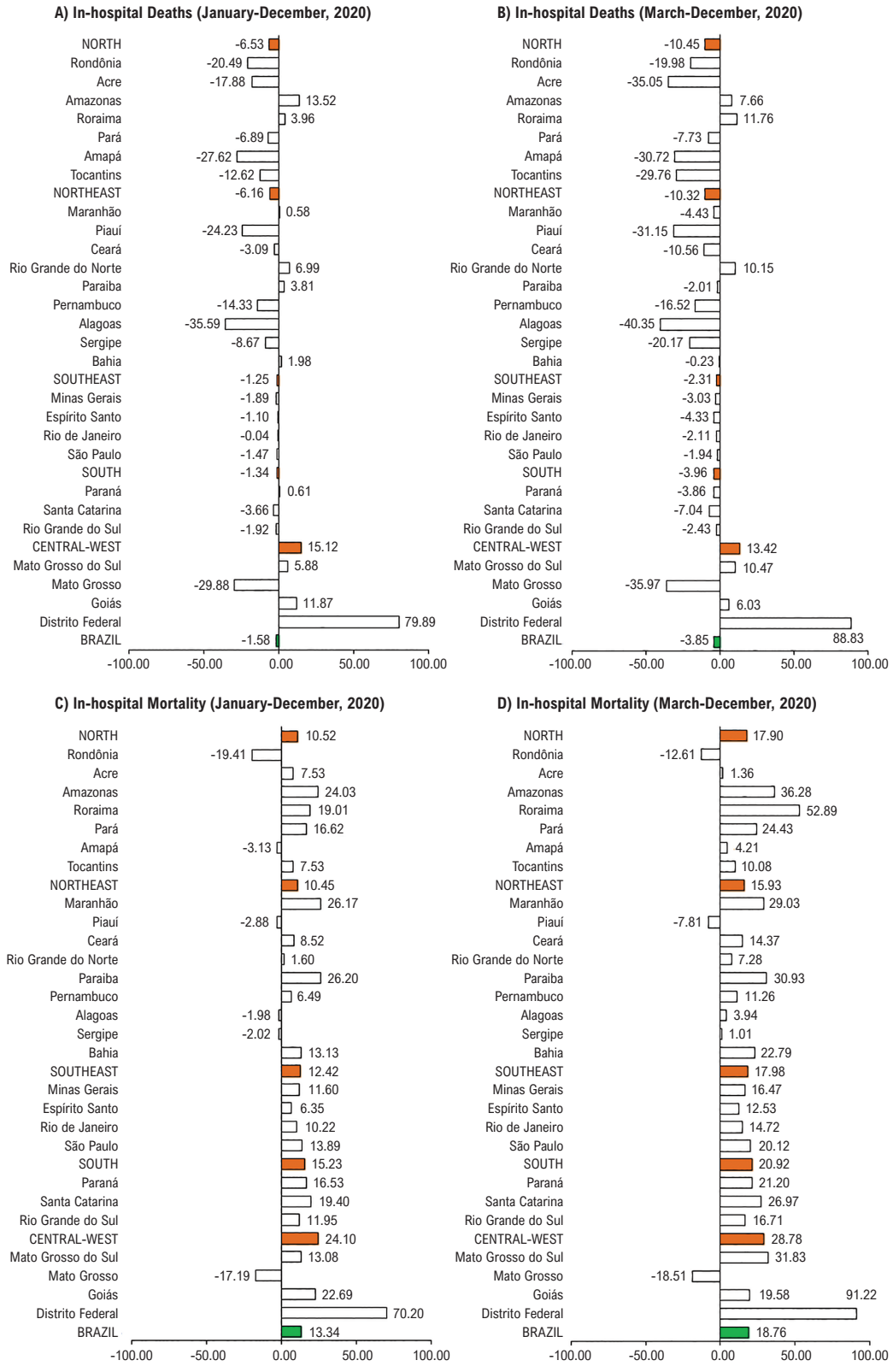

Figure 1 – *P-score of the absolute number of in-hospital deaths (A and B) and in-hospital mortality rate (C and D) due to cardiovascular diseases in Brazil, its regions, and federative units during the first year of the COVID-19 pandemic, Brazil, 2020.*

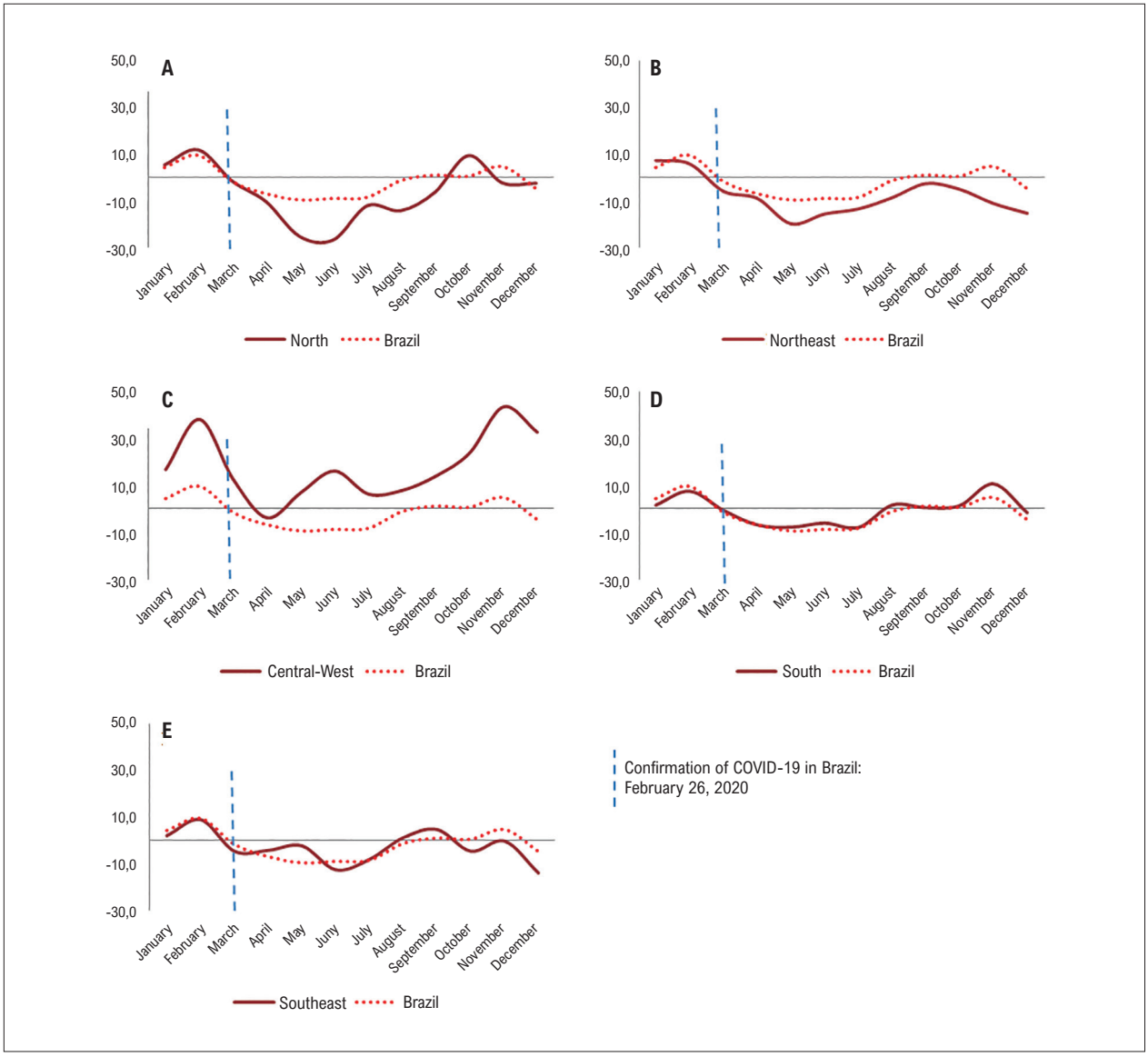

Figure 2 – *P score for absolute number of in-hospital deaths due to cardiovascular diseases, by macro-region, during the first year of the COVID-19 pandemic. Brazil, 2020.*

and the southeast.[33] This fact may have led to a delayed increase in the number of cases of COVID-19, and consequently a delayed impact on health services in comparison to other regions.[33,34]

In addition to this, the central-west may have been influenced by the Federal District, where P-score of deaths was 81.5, much higher than the expected. Even though it is not possible to give a clear explanation about this high score in the Federal District, it may be related to the singularities regarding its political role in the country, given that it is the national capital of Brazil.[33] Also, there are local characteristics related to the health system, including the high availability of intensive care unit beds – 4.5 per 10,000 inhabitants (overall), 1.6/10,000 in the public sector, and 11.6/10,000 in the private one.[35] This high availability of beds in the Federal District also moves the central-west region to second place in availability of beds by Brazilian macro-region (2.5 per 10,000).[35] Discrepancies between federative units regarding the operational capacity of their local health services to handle COVID-19 have been a point of criticism.[36] In line with this, a study conducted in six Brazilian capitals, showed a higher excess mortality from CVD in less developed cities during the pandemic, possibly associated with the collapse of the health system in these regions.[37]

If, on one hand, as previously discussed, there was a reduction in the absolute number of in-hospital deaths, on the other hand, an excess was observed in the in-hospital mortality rate at the country level and in all macro-regions, which is in agreement with what has been observed in previous studies[17-20,22,23] It is unlikely that this increase in in-hospital mortality is merely related to the effects of COVID-19 on the cardiovascular system. In Austria, for instance, only 6.2% of patients urgently admitted due to

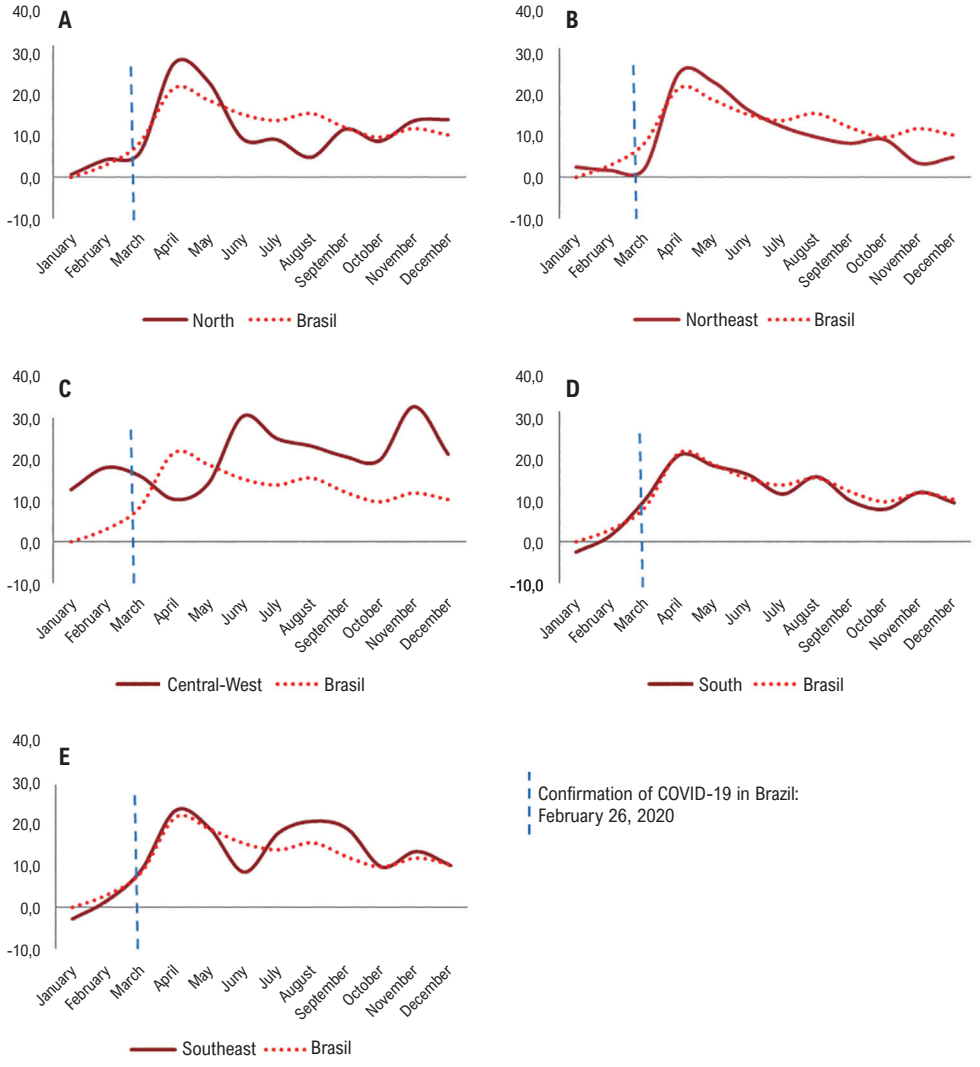

Figure 3 – *P score for in-hospital mortality rate due to cardiovascular diseases, by macro-region, during the first year of the COVID-19 pandemic. Brazil, 2020.*

cardiovascular conditions tested positive for COVID-19, which would not explain the 65% increase in in-hospital mortality observed in hospitals in that country.[18]

Also, the increase in in-hospital mortality may be the result of multiple factors, such as changes in the health system during the pandemic. In Germany, a study showed a reduction in hospital admissions accompanied by a significant increase in mortality due to acute myocardial infarction during the pandemic. They also observed a greater delay in seeking medical assistance from the onset of symptoms and worse clinical condition upon admission.[22] Health teams have been redirected to provide care for patients with COVID-19, and elective surgeries and outpatient care have been interrupted.[11,23] Therefore, the delay in seeking medical assistance[38-40] and the harmful effects of SARS-CoV-2 on the cardiovascular system[10,12] may have contributed to increased clinical decompensation and in-hospital mortality during the pandemic.[11,23] A study conducted in the Brazilian state of Pernambuco showed that prior existence of CVD accelerated mortality from COVID-19 by approximately four days.[41]

Regarding Brazilian macro-regions, the highest excess in-hospital mortality (P-score 18.2) was found in the south, which may be explained by demographic and epidemiological characteristics of the population. In 2020, 16.4% of the region's population was 60 years or older, and the aging index was 86% (86 individuals aged 60 years or older for each group of 100 individuals under 15 years of age), which is the highest in the country.[42] Furthermore, the elderly population has the highest prevalence of CVD.[43,44]

Study limitations

Even considering the methodological robustness of this study, it has some limitations. The first concerns the use of secondary data from the SIH. The quality of these data depends on records inserted into the system. The quality of the P-score depends directly on the accuracy of available data, which means that a delay between occurrence and registration of death can affect its accuracy. The lack of data on overall mortality from cardiovascular diseases in Brazil, in addition to the assessment of in-hospital mortality restricted to the public health network are important limitations that deserve to be mentioned.

Conclusions

This study has demonstrated a decrease in the absolute number of in-hospital deaths, as well as an increase in in-hospital mortality due to CVD in Brazil in 2020, after the onset of the COVID-19 pandemic, with differences between macro-regions and federative units. The impact of the COVID-19 pandemic has been vast, including a profound effect on health services and existing diseases. Strengthening the national public health system seems to be the most important measure in handling the pandemic and its consequences in Brazil.

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Author Contributions

Conception and design of the research: Armstrong AC, Santos M, Souza CDF, Carmo RF; Acquisition of data: Santos LG, Leal TC, Paiva JPS, Silva LF, Santana G, Rocha C, Santos M, Souza CDF; Analysis and interpretation of the data: Armstrong AC, Santos LG, Leal TC, Paiva JPS, Silva LF, Santana G, Rocha C, Alves T, Araujo S, Santos M, Souza CDF, Carmo RF; Statistical analysis: Souza CDF; Writing of the manuscript: Santos LG, Leal TC, Paiva JPS, Silva LF, Santana G, Rocha C, Santos M, Souza CDF, Carmo RF; Critical revision of the manuscript for intellectual contente: Armstrong AC, Souza CDF.

Potential Conflict of Interest

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

Sources of Funding

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Study Association

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

Ethics approval and consent to participate

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

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The COVID-19 Pandemic and Cardiovascular Disease in Brazil: Learning from the Data

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Short Editorial related to the article: In-Hospital Mortality from Cardiovascular Diseases in Brazil during the First Year of The COVID-19 Pandemic

The World Health Organization (WHO) estimates nearly 15 million excess deaths associated with COVID-19 in the world in 2020 and 2021, defined as the difference between the total number of deaths (from all causes) and the number of expected deaths if there was no pandemic.[1]

In Brazil, the WHO estimates 99 and 220 excess deaths associated with the COVID-19 pandemic per 100,000 inhabitants in 2020 and 2021, respectively.[1] This would translate into around 680,000 excess deaths in the first two years of the pandemic, *i.e.*, tens of thousands higher than the officially reported COVID-19 deaths in the period. Many of these excess deaths are related to sub notification due to lack of testing or misdiagnosis (true deaths from COVID-19 assigned to other conditions). Other fatal events were from other causes and somehow indirectly associated with the pandemic, such as the deaths from illnesses not properly treated due to the overwhelmed health system. Considering that cardiovascular disease (CVD) is the main cause of death in Brazil,[2] it is crucial to unravel the impact of COVID-19 on CVD statistics.

In this context, Armstrong et al.,[3] analyzing data from public hospitals in Brazil, report that the number of in-hospital deaths due to CVD in 2020 was only 1.58% lower than expected based on the average of previous years. However, the in-hospital case fatality rate due to CVD increased by 13.3% in the whole year and by 18.8% from March to December.[3]

These findings are in agreement with other studies that reported, during the pandemic, a reduction in the number of patients seeking medical care, a decrease in CVD hospitalizations and procedures, more severely diseased hospitalized patients, and consequently an increase in hospital lethality due to CVD.[4-10] Importantly, a repeatedly reported finding is an uncomfortable increase in home deaths.[11-13] Therefore, it is now clear that the pandemic has substantially impacted CVD care in Brazil.

Keywords

COVID-19; Cardiovascular Diseases; Mortality; Hospital Mortality

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What are the takeaways from this diagnosis? First, physicians are expected to have learned that there are cases where the investigation, intervention, or hospitalization cannot be postponed. Second, there is a large room to educate patients about warning signs of severe conditions, such as acute coronary syndrome and stroke, minimizing the home deaths due to patient fear of going to the hospital. Third, smoothing the consequences of the pandemic is only possible with a well-prepared health system that can rapidly respond to the outbreak's demands while not compromising the care of other deadly diseases. Brazil is not used to natural disasters or pandemics, and many underestimated the potential damage of the virus. Now we have the opportunity to learn from the experience as Asian countries did from the SARS epidemic in 2003 and better prepare ourselves for future catastrophic events.

After the most critical, pre-vaccination phase of the pandemic, the attention now shifts to another concern: to which extent will the cancellation of medical consultations and procedures forced by the pandemic affect CVD? Suboptimal risk factor control and interventions carried out late may add another layer to the impact of the COVID-19 pandemic on CVD outcomes. Continuous monitoring of the situation is needed and will probably be addressed by future studies.

Another relevant aspect is to acknowledge that the effects of the pandemic are not uniform in the community. Marinho et al.[14] found an excess mortality rate of 26.3% (23.3%-29.3%) among blacks/browns in Brazil in 2020, while this number was 15.1% (14.1%-16.1%) in whites.[14] In Belo Horizonte-MG, the excess mortality in 2020 increased as the Health Vulnerability Index worsened.[15] Also, Brant et al. reported that the increase in CVD home deaths in Belo Horizonte-MG in 2020 was more pronounced in more socially vulnerable individuals.[13] Identifying the most affected subgroups is strategic for defining priority targets for public health interventions and avoiding the dangerous path of increasing health inequalities.

In the last decades, we have observed a continuous decline in the age-adjusted CVD mortality in Brazil, although this decrease has attenuated in the last years.[2] It is not yet clear whether the pandemic will substantially modify this trend. Nevertheless, the change in the pattern of hospitalizations for CVD and the unacceptable increase in home deaths cannot be passively watched without perplexity. It is time to learn from the data and act to minimize the impacts of the pandemic on CVD outcomes.

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Left Atrial Appendage Closure with the LAmbre Device – Initial Multicentre Experience in Brazil

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Abstract

Background: **Left atrial appendage (LAA) closure has been an alternative to oral anticoagulation (OAC) for stroke prevention in patients with non-valvular atrial fibrillation (NVAF).**

Objectives: **To report the first results of an initial multicenter experience in Brazil and to investigate the feasibility, safety, and efficacy of LAA closure with the new LAmbre device.**

Methods: **We collected procedural and follow-up data of 51 consecutive patients with non-valvular atrial fibrillation, restrictions for long-term OAC and suitable anatomy that underwent LAA closure with the LAmbre device in 18 centers in Brazil. Procedural indications were significant bleeding under OAC (47.1%), stroke or persistent LAA thrombus despite OAC (27.5%), bleeding plus stroke (17.6%), other clinical contraindications for OAC (5.9%), and patient's choice due to sports practice (1.9%).**

Results: **Twenty-five men (49%) and 26 women (51%), with a mean age of 76±7.7 years, mean CHA2DS2-VASc score of 4.6± 1.7 and mean HAS-BLED score of 3.4± 1.1 were studied. Procedural success rate was 100%. Procedure-related immediate complications were pericardial effusion in two patients, and immediate device embolization in one case. No large residual shunts (> 5 mm) were observed, and small shunts (<5mm) were detected in four patients by color Doppler at the end of the procedure. After a mean follow-up of 18 ± 12 months, there were no deaths, strokes nor any other major complications.**

Conclusion: **LAA occlusion with the LAmbre device was safe and effective in this small case series. Despite these encouraging initial results, the small number of cases warrants further studies with longer-term follow-up.**

Keywords: **Atrial Fibrillation; Atrial Appendage; Coronary Occlusion.**

Introduction

Transcatheter left atrial appendage (LAA) occlusion has become increasingly popular as an alternative option to anticoagulation for thromboembolic event prophylaxis in non-valvular atrial fibrillation (NVAF) patients.[1] Oral anticoagulant therapy (OAC), either with Vitamin K Antagonists (VKA) or Direct Oral Anticoagulants (DOACs) has proven to be an effective therapy for preventing stroke in AF patients.[2] Unfortunately, long-term OAC compliance, underprescription, and complications make this therapy not applicable for a significant number of patients.[3] Thus, the need for a non-pharmacological form of prophylaxis has increased over the years.

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Considering that over 90% of the intra-atrial thrombi formed as a consequence of NVAF are located inside the trabecular portion of the atrial appendage, LAA occlusion seemed to be a reasonable option.[4] Initially proposed as a surgical procedure, percutaneous occlusion is now performed all over the world. Different devices and techniques are available for LAA occlusion. Randomized trials have shown that LAA occlusion is non-inferior to Warfarin and DOACs in terms of reduction of stroke and systemic embolism, and superior to warfarin regarding late mortality.[5-10]

LAmbre device is a LAA occluder released in Brazil in 2018, after the Amplatzer Cardiac Plug (ACP) and the Watchman Filter devices. This paper intends to report the results of the first multicenter Brazilian Registry of the use of the LAmbre device for percutaneous closure of the LAA for stroke prevention in patients with NVAF.

Methods

Between May 2018 and November 2020 consecutive patients who underwent percutaneous LAA closure with the LAmbre device in 18 different centers in Brazil were prospectively studied. Many of these procedures were performed under the

supervision of a proctor. All patients had NVAF and an absolute or relative contraindication for long-term OAC therapy – the only exception was one patient who refused OAC due to personal preferences. All of them had been submitted to transesophageal echocardiogram (TEE) or cardiac computed tomography (CT) for assessment of LAA size and morphology, intended landing zone diameters and the presence of thrombus.

The procedures were performed under general anesthesia and orotracheal intubation. Non-fractioned heparin (100 mg/kg or 10,000 International Units) and antibiotic prophylaxis (intravenous Cefazolin 2g) were administered to all patients, followed by Cefazolin 1g IV as single dose 6 h after procedure, in the intensive care unit (ICU). Procedures were monitored by TEE and fluoroscopy.

After femoral venous access was obtained, transseptal puncture with Brockenbrough needle was done targeting the inferior and posterior fossa ovalis. Left atrial (LA) pressure was recorded immediately after the left atrium was accessed; if values were lower than 10 mmHg, saline was rapidly infused for restoration of true LAA diameters. A 5F Pigtail catheter was positioned inside the LAA to obtain angiographies and measurements in right anterior oblique (RAO) caudal and cranial views. After angiography, a Super-Stiff guidewire J-Tip 0.035″/260 cm was cautiously introduced inside the LAA through the Pigtail catheter. The device size was confirmed by intraoperative angiography and TEE and should be 2 to 8 mm larger than the intended landing zone. The device was implanted through the long sheath indicated for the size of the chosen device. Implant technique was described elsewhere.[11]

Patients were kept in ICU overnight and discharged from hospital the next day after another TTE, provided no complications occurred.

Aspirin (100 mg) and Clopidogrel (75 mg) were prescribed after procedure. Clopidogrel was discontinued after three months, and lifelong Aspirin prescribed thereafter. Follow-up TEE was performed three and six-months after the procedure.

The Lambre Device

The LAmbre™ device (Lifetech Scientific, Shenzhen, China) is a self-expanding Titanium Nitride (TiN)-covered nitinol mesh occlusion device. It comprises three parts: a disc designed to cover the LAA ostium, a connector pin, and an eight-armed umbrella with small attachment hooks, that anchors the device to the body of the LAA, increasing stability. The umbrella is designed with a forward movement of the arms whose atraumatic tips, when fully opened, engage the trabeculae of the LAA, and the small distal hooks connect to the LAA wall, enhancing the stability of the device. The disk is configured to totally cover the LAA ostium. Both umbrella and disk have polyethylene terephthalate fabric sewn inside (Figure 1). In addition, LAmbre™ device comes in two versions: the standard type and the special type device.

In the standard type device, the umbrella sizes range from 16 to 36 mm in two-millimeter increments, with disks that are 6 mm larger than 16-30mm umbrellas or 4 mm larger than 32-36mm umbrellas. In the special type device, the umbrella sizes range from 16 to 26 mm, also in two-millimeter increments, with disks 14 mm larger than 16-18 mm and 12 mm larger than 20-26 mm umbrellas.

The delivery system is composed of a double curve (45 and 30 degrees), sheath of 8F to 10F, and a delivery cable with screwing mechanism. Its noteworthy that the screw on the disk surface is recessed, to prevent thrombus formation over the device.

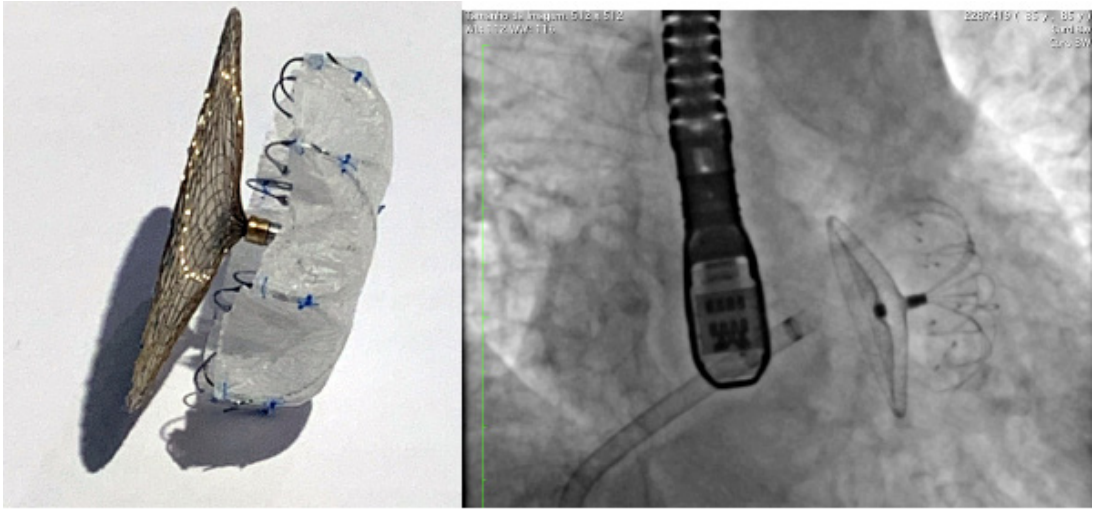

Figure 1 – *LAmbre™ device. Left panel shows umbrella and disk connected through a central pin. The arms have atraumatic round tips that engage the trabecular portion of the left atrial appendage (LAA) and small hooks that attach to the LAA wall. The disk covers the LAA ostium and is connected to the umbrella by a pin, with no screw protruding on the external surface of the disk. Right panel: fluoroscopy after implantation.*

Statistical analysis

Events are expressed as absolute numbers and percentages. Continuous variables were expressed as mean ± standard deviation (SD). A descriptive analysis of the data was carried out. Data were analyzed using the software SPSS / PASW (IBM Corp, NY, USA).

Results

A total of 51 patients (25 men) were consecutively selected for LAA occlusion with the LAmbre device in 18 different centers in Brazil. Mean age was 76±7.7 years. Mean CHA2DS2-VASc and HAS-BLED were 4.6±1.7 and 3.4±1.1, respectively. AF was paroxistic in 24, persistent in 1 and permanent in 26 patients. Indications for the procedure were significant bleeding (mostly cerebral or gastrointestinal) in 24 patients (47.0%), stroke despite adequate OAC in 13 (25.5%) and bleeding and stroke in nine (17.6%) patients. Other indications for LAA occlusion were contraindication to OAC in three cases, persistent LAA thrombus despite OAC in one case and patient's choice (due to sports practice) in another (Table 1).

Procedural data are presented in Table 2. Mean landing zone size was 23.84±4.5 mm and mean size of the implanted device was 27±5.1 mm – thus the size of the implant was 3.7mm (mean) larger than the measured LAA orifice. Standard type device was used in the majority (94.1%) of patients and the special type in the remainder (5.9%). The sizes of the implanted devices were 28-34mm (n=9), 24-30mm (n=7), 30-34mm (n=6), 26-32mm (n=5), 34-38mm (n=5), 22-28mm (n=4), 32-36mm (n=4), 36-40mm (n=4), 18-24mm (n=2), e 20-26mm (n=2). Special device sizes used were 16-30mm, 22-34mm and 24-36mm.

The first chosen device was implanted in 45 patients (88.2%). A second device was necessary in six patients (11.8%): In two cases the first chosen device was damaged during loading by inexperienced operators and needed to be replaced. Incorrect measurements determined device retrieval and replacement for another one more compatible with LAA dimensions in three patients. In another case with challenging anatomy due to a retroflexed chicken wing appendage, a second lower transeptal puncture and smaller device implantation was deemed necessary to achieve total occlusion.

In addition, three patients had patent foramen ovale (PFO). In two of them, access to left atrium was obtained through the PFO tunnel. The third one had a retroflex chicken wing appendage and access via PFO tunnel prevented delivery sheath coaxiality. Transseptal puncture was performed, and the procedure was carried out without further difficulty. The PFO was closed in two of these cases with a dedicated device (25-18 mm CERA PFO device in one case and 25-25 mm CERA MF ASD device in the other) (Figure 2). Another patient had an ostium secundum atrial septal defect that was closed in the same procedure with a 33mm Occlutech ASD device.

Two patients developed pericardial effusions. In one of them the appendage was perforated by the stiff guidewire. Percutaneous pericardial drainage was immediately carried out and was followed by a LAmbre 20-26mm device implantation, which was immediately embolized. A second 34-38mm device was implanted and the effusion subsided. The first device was snared out from the descending aorta the next day. In a second patient pericardial effusion with cardiac tamponade occurred few hours after the procedure, due to perforation of the main pulmonary artery by the hooks of the device. Surgical drainage was performed, and the patient recovered uneventfully.

One patient underwent previous LAA closure with a Watchman device, but suffered a recurrent stroke few months thereafter due to a second large lobe that was inadvertently left uncovered in the first procedure. A LAmbre device was implanted in a second procedure months later with total occlusion of LAA (Figure 3).

An 86-year-old male patient had been previously submitted to coronary bypass graft surgery with pacemaker implantation. He also had severe aortic stenosis, which was treated with transcatheter aortic valve implantation (TAVI). One week after TAVI, the patient presented with important cardiac dysfunction due to significant mitral regurgitation and had Mitraclip and LAmbre implanted during the same surgical procedure (Figure 4).

Device implantation was possible in all cases. There were no large residual shunts (> 5 mm) and minor shunts (<5mm) were detected by color Doppler in four patients (7.8%) at the end of the procedure. No patient had significant bleeding during hospitalization. During a mean follow-up of 18±12 months, none of the patients suffered further significant bleeding or thromboembolic events, and no deaths or late complications were reported by any center.

Discussion

Initially described by Lam in 2013,[12] the LAmbre was described as an easy-to-use, safe and effective device. Potential advantages of LAmbre over other devices were pointed out by the author and included smaller delivery sheaths, the ability to be fully retrieved and repositioned many times and enhanced stability after implantation. Moreover, the possibility of shallow device deployment and the use of less maneuvers for positioning helps to prevent LAA perforation and enables the use of the device for treatment of LAAs with distal thrombus using the no-touch technique, in which the occluder is implanted without advancing neither the delivery sheath nor the guidewire into the appendage.[12-15] The design of the standard and special LAmbre devices makes it more suitable in case of difficult anatomies, mainly when there are shallow landing zones or a mismatch between a large ostium and narrow landing zone[16,17] (Figures 5 and 6).

Although more than 7,000 implants have already been made worldwide, literature on LAmbre™ is still scarce. The publication with the largest number of patients (n=153) showed a 3.3% procedural complication rate, with no case of device embolization, and a yearly stroke rate of only 1.3% (vs. 6.4% predicted by the CHA_2DS_2-vasc score) at follow up.[11] The initial European experience with 60 cases had similar results (procedural complication rate of 3.3%, annual stroke rate at follow-up of 1.6%).[18]

Table 1 – Clinical characteristics of the patients (n=51)

Variable	Result*
Age (years)	76 ± 7.7
Female sex	26 (51)
Atrial fibrillation	
Permanent	26 (51)
Persistent	1 (2)
Paroxystic	24 (47)
CHA_2DS_2-VASc Score	4.6 ± 1.7
HASBLED Score	3.4 ± 1.1
Indications for LAA closure	62 (68,1)
Significant bleeding	24 (47)
Stroke despite adequate OAC	13 (25.5)
Bleeding + stroke	9 (17.6)
Contraindication for OAC	3 (5.9)
Persistent thrombus in LAA despite OAC	1 (2)
Patient's choice	1 (2)

**Mean ± SD or absolute numbers (percentage). LAA: left atrial appendage; OAC: oral anticoagulation.*

Table 2 – Procedural data

Variable	Result*
Access	
Transeptal	48 (94.1)
PFO / ASD	3 (5.9)
Landing zone (mm)	23.8 ± 4.5
Device implanted	
Size (mm)	27 ± 5.1
Standard design	48 (94.1)
Special design	3 (5.9)
Devices per procedure (n)	
1	45 (88.2)
2	6 (11.8)
Success	51 (100)
Residual leak	
None	47 (92.2)
Minor (< 5mm)	4 (7.8)
Major (> 5mm)	0
Complications	
Death	0
Stroke	0
Major bleeding	0
Pericardial effusion	2 (3.9)
Embolization (snared)	1 (2)

**Mean ± SD or absolute numbers (percentage). PFO: patent foramen ovale; ASD: atrial septal defect.*

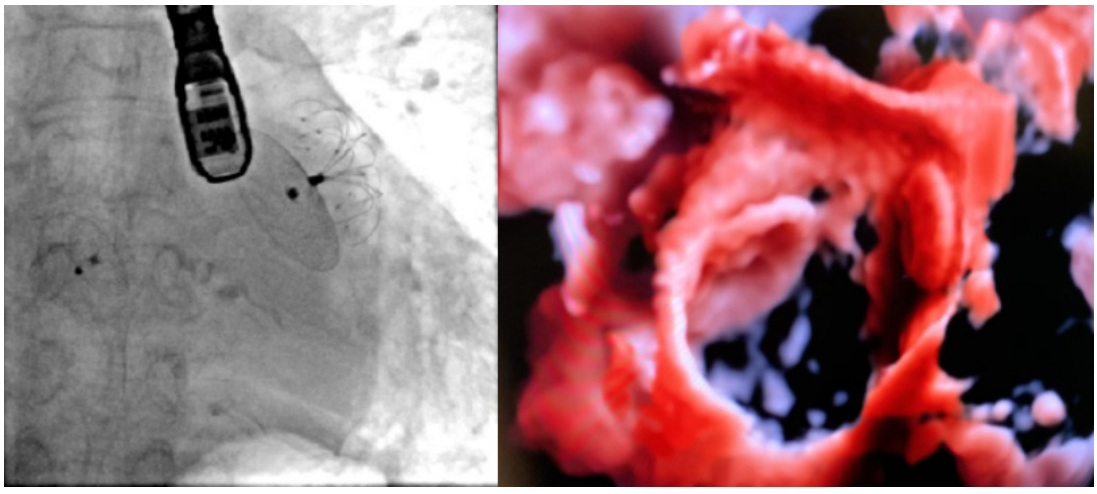

Figure 2 – *Left atrial appendage (LAAE) closed through a patent foramen ovale (PFO). Left: LAmbre device occluding the LAA and a second dedicated device occluding the PFO; right: the same image seen by 3D transesophageal echocardiogram .*

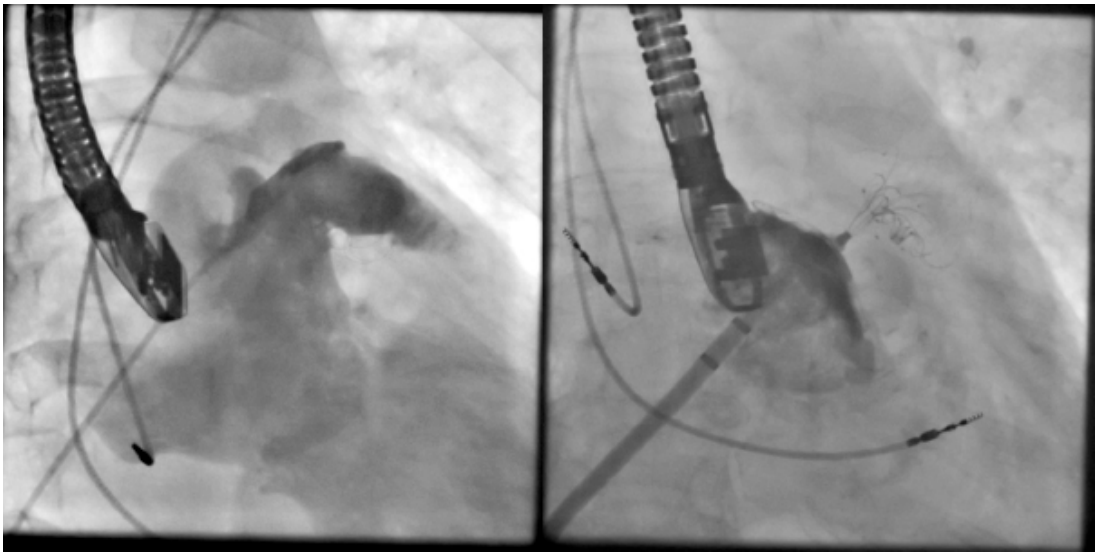

Figure 3 – *Left: Watchman device implanted in a lower lobe of the left atrial appendage (LAA); the upper lobe was left uncovered. Right: Watchman device inside the lower lobe and the LAmbre device implanted in the upper lobe with the disk totally occluding the ostium of the LAA. No residual shunt was seen immediately after the procedure.*

A systematic review of 10 publications encompassing 403 NVAF patients treated with LAmbre showed a procedural success rate of 99.7% and an overall complication rate of 2.9% (0.3% mortality, 1.7% pericardial tamponade, 0.3% stroke and major bleeding complications) with no device embolization. At follow-up, major adverse cardiovascular events were reported in 3.3%; stroke or transient ischemic attack in 1.7%, thrombus formation on the device in 0.7% and residual flow > 5mm in 1%.[19]

An ongoing trial (Lifetech LAmbre™ Left Atrial Appendage Closure System Post-Market Clinical Follow-Up – LISA Study; NCT03122028) aims to enroll 500 patients in 22 study sites in eight different countries in Europe and China, with the purpose to examine the safety and feasibility of LAmbre device implantations in patients with NVAF that cannot use OAC. Comparison between LAmbre and Amplatzer devices showed similar long-term efficacy and safety in patients with NVAF.[20,21]

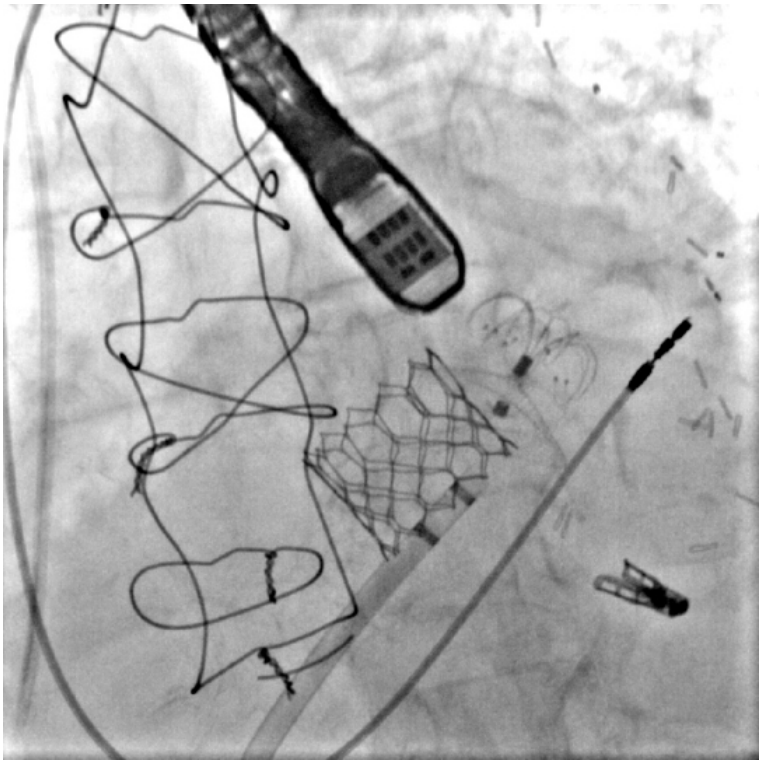

Figure 4 – *Eighty-six-year-old patient with multiple interventions: coronary artery bypass graft, pacemaker implantation, transcatheter aortic valve implantation (TAVI), Mitraclip and LAmbre device occluding the atrial appendage. Both Mitraclip implantation and the left atrial appendage occlusion were performed during the same surgical procedure.*

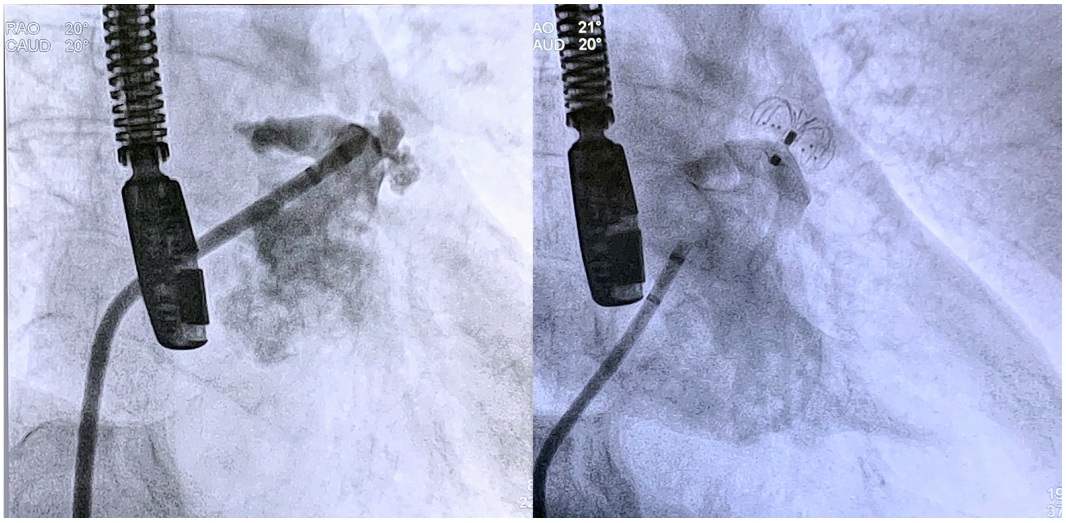

Figure 5 – *Left: retroflexed chicken wing left atrial appendage (LAA); right: LAA totally occluded after implantation of a standard-type LAmbre device.*

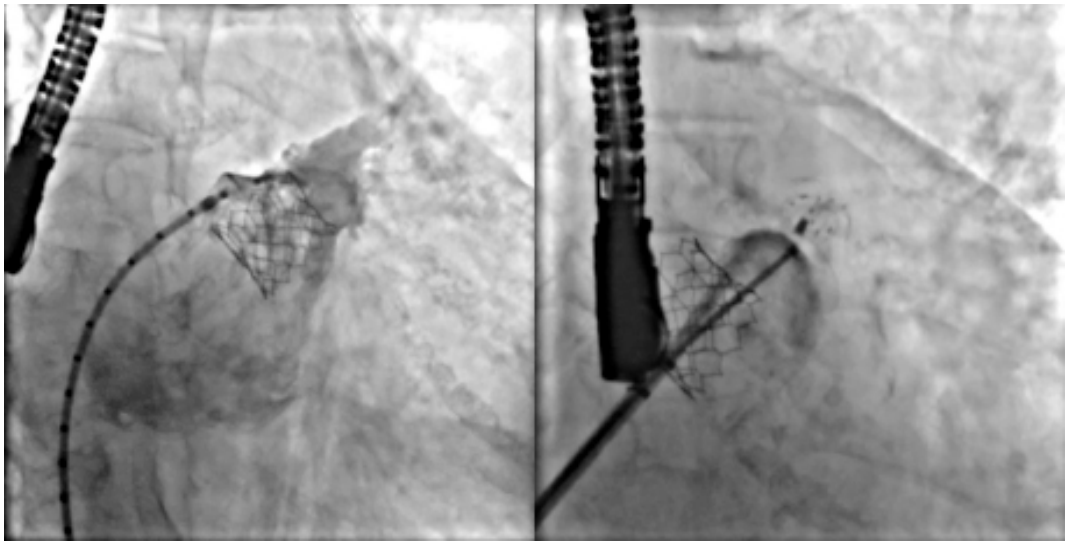

Figure 6 – *Left: very shallow left atrial appendage (LAA); right: LAA occluded by a special-type LAmbre device. Additionally, this patient was previously submitted to percutaneous coronary intervention and transcatheter aortic valve implantation.*

The immediate and late results presented in this study are well in accordance with available literature. The acceptable rate of procedural complications and the favorable follow-up of this high-risk and complex cohort of patients is encouraging. The unique features of the LAmbre™ device, most particularly in its special configuration, rendered very challenging procedures safely feasible. This prosthesis brings advances in both device design and implantation technique and may be a valuable addition to the armamentarium of LAA closure.

Limitations

This study has several limitations. As an inherent limitation to a non-randomized study, there is no control group. As in every observational study, there may be flaws in patient selection. However, this registry was designed to include all patients eligible for the procedure (intention-to-treat), reflecting a real-world practice. Although the data have been prospectively collected, this is a retrospective analysis, without independent monitoring, or a core lab analysis. Especially due to reimbursement difficulties in Brazil, basically all centers included in this Registry are centers with low volume of LAA closure and, thus, the learning curve of the operators is flattened, which has a direct impact on complication rates. And, finally, all the data collected were spontaneously reported by investigators, without independent adjudication.

Conclusions

Initial experience with the LAmbre device in 18 different centers in Brazil was safe and effective, in this small number of patients. As with all devices used for LAA closure, the learning curve with LAmbre had an impact on complications, but even so at rates that are acceptable and comparable to the literature. Be it as it may, a larger number of patients and a longer- term follow-up is warranted for obtaining a fair comparison between LAmbre and the other devices currently used for percutaneous LAA closure in Brazil.

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Authors Contribution

Conception and design of the research, Analysis and interpretation of the data, Statistical analysis and Writing of the manuscript: Chamie F, Guerios E; Acquisition of data and Critical revision of the manuscript for intellectual content: Chamie F, Guerios E, Silva DP, Fuks V, Torres R.

Potential Conflict of Interest

Dr. Francisco Chamie – left atrial appendage occlusion proctor for Lifetech Scientific.

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Tackling Bleeding – One Appendage at a Time

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Short Editorial related to the article: Left Atrial Appendage Closure with the LAmbre Device – Initial Multicentre Experience in Brazil

Atrial fibrillation (AF) is the most common cardiac arrhythmia,[1] affecting approximately 80% of the population aged 80 years or older.[2] It increases the risk of cardioembolic stroke 5-fold across all ages[3] and is related to more than 20% of strokes in patients above 80 years. Embolic strokes are often more severe than other strokes,[4] and anticoagulants are the cornerstone of the treatment, paramount to reducing cardioembolic risk in this population. However, the decision to start oral anticoagulants is not always straightforward and requires assessing both embolic and bleeding risks.[5] Embolic risk in patients with AF is usually assessed using standardized scoring systems such as the CHA_2DS_2-VASc score,[6] but it can be further refined using other clinical data such as left atrial size[7] and duration of AF.[8] Bleeding risk is usually assessed using the HAS-BLED score,[9] with severe bleedings being more common in older patients.[10] For that reason, physicians are often fearful of starting anticoagulation in older patients, even though current evidence shows that it is usually safe to use oral anticoagulants in most of these patients.[11] However, major bleeding can occur in up to 3% of patients using oral anticoagulants,[12] requiring the interruption of the treatment.

Over 90% of all left atrial thrombi originate in the LAA,[13] and the risk reduction with LAA occlusion is comparable to anticoagulation.[14] For this reason, percutaneous LAA occlusion has emerged as an alternative treatment for patients with either contra-indications to oral anticoagulation or an embolic event while using oral anticoagulants. There is growing evidence that LAA occlusion is safe and feasible in most patients,[15-17] and this initial multi-centric experience of LAA occlusion using the plug-based device LAmbre in Brazil[18] shows similar results to current medical literature. In this study, 74.6% of all patients have had either a major bleeding episode using oral anticoagulants or a stroke despite oral anticoagulation. Patients were at high embolic and bleeding risks, with a mean CHA_2DS_2-VASc score of 4.6 ± 1.7 and a mean HAS-BLED score of 3.4 ± 1.1. The procedure's success rate was 100%, with no deaths or strokes at a mean follow-up of 18 ± 12 months.

In the United States, in the first three years of the NCDR Left Atrial Appendage Occlusion Registry,[17] 38,158 patients underwent LAA occlusion. Regardless of regional differences, there seems to be a striking difference with Brazil. Naturally, the present article[18] does not encompass the entirety of cases performed in the country, but it gathered cases from 18 centers across Brazil, with 51 cases being performed in 2 and a half years. Brazilians are aging and getting frailer,[19] similar to their counterparts elsewhere. It is reasonable to assume that older age and increasing frailty also increase AF and bleeding risks in this population. The question that remains to be answered is: why LAA occlusion is so rarely performed in Brazil? Is it the cost? Or is there a lack of awareness and, therefore, fewer indications? Where should we act to deliver better care to these patients?

In conclusion, percutaneous LAA occlusion is a proven technology. It is a safe, feasible and effective alternative to oral anticoagulants in patients with AF and at high risk of both embolic and bleeding events. Hopefully, the present study[18] will help spread the word about a procedure that is not common in Brazil, unlike the patients who are likely to benefit from it.

Keywords

Anticoagulants/therapeutic use; Hemorrhage; Arrhythmias, Cardiac; Atrial Appendage; Stroke; Atrial Fibrillation

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Longitudinal Changes in Physical Activity Levels and Cardiovascular Risk Parameters in Patients with Symptomatic Peripheral Artery Disease

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Abstract

Background: Previous cross-sectional studies have demonstrated that physical activity is associated with lower cardiovascular risk in patients with peripheral artery disease (PAD). However, it is not possible to establish causality, and longitudinal design studies are required.

Objective: To analyze the changes in cardiovascular risk parameters and physical activity levels after a 2-year follow-up in patients with symptomatic PAD.

Methods: This study started in 2015. In the first phase, 268 patients were included. In the second phase, after 2 years (median = 26 months), 72 patients were re-evaluated. Cardiovascular risk parameters, such as blood pressure, cardiac autonomic modulation, and arterial stiffness, and physical activity levels were measured at baseline and after 2 years of follow-up. Association among delta changes (values from follow-up – baseline) in physical activity and cardiovascular parameters were analyzed by multiple linear regression. The significance level was set at $p < 0.05$.

Results: Patients reduced their total physical activity levels compared to baseline (baseline = 2257.6 ± 774.5 versus follow-up = 2041 ± 676.2 min/week, $p = 0.001$). After follow-up, ankle-brachial index (0.62 ± 0.20 versus 0.54 ± 0.20, $p = 0.003$), and standard deviation of all RR intervals (43.4 ± 27.0 versus 25.1 ± 13.4 ms, $p < 0.001$) were lower, whereas carotid-femoral pulse wave velocity was higher (9.0 ± 3.0 versus 10.7 ± 3.4 m/s, $p = 0.002$) compared to baseline values. We did not observe any association among delta values of physical activity levels and cardiovascular risk parameters.

Conclusion: Patients with PAD had reduced physical activity levels and impaired cardiovascular risk parameters during 2-year follow-up.

Keywords: Peripheral Arterial Disease. Cardiovascular System. Arterial Pressure. Exercise.

Introduction

Intermittent claudication is the main symptom of peripheral artery disease (PAD), and it is characterized by pain, cramps, or a burning sensation that affects lower limbs during physical activity, especially while walking.[1] Patients with PAD and intermittent claudication symptoms present limited mobility, poor control of cardiovascular parameters,[2,3] and impaired quality of life.[4,5]

Physical activity has been recommended to improve functional capacity and cardiovascular function in these patients.[6-8] In fact, patients with symptomatic PAD and higher levels of physical activity present better functional capacity and a lower risk of cardiovascular mortality compared to sedentary patients.[9,10] However, due to the cross-sectional design of these studies, it is not possible to establish causality, and longitudinal design studies are required. Also, it is unknown whether alterations in these parameters occur during follow-up in PAD patients.

Therefore, this study aimed to analyze the longitudinal changes in physical activity and cardiovascular risk parameters after a 2-year follow-up in patients with PAD. We also analyzed whether changes in physical activity levels are associated with changes in cardiovascular risk parameters after a 2-year follow-up. We hypothesized that changes in physical activity levels would be associated with better cardiovascular risk parameters.

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Methods

This is a longitudinal study that started in 2015, consisting of 2 phases. In the first phase of the study, 268 patients were included and submitted to measurements of physical activity (accelerometry), functional capacity, and cardiovascular risk parameters (clinical blood pressure, central blood pressure, cardiac autonomic modulation, and arterial stiffness). After 2 years, all patients included in the first phase were invited to phase 2.

Sample recruitment, screening, and sizing

Patients were recruited at hospitals in Sao Paulo, Brazil. The inclusion criteria were: age > 45 years of both sexes, ankle-brachial index (ABI) < 0.90 in one or both limbs, and presence of intermittent claudication symptoms. This study was approved by the Institutional Ethics Committee. Before data collection, patients were informed about the procedures involved in the study, and they signed an informed consent form.

Before and after the 2-year follow-up, patients underwent evaluations in 2 visits with an interval of at least 7 days. During the first visit, clinical, socio-demographic, and functional capacity data were obtained, and all patients received a physical activity monitor GT3X+ triaxial accelerometer (Actigraph, Pensacola, FL, USA). During the second visit, measurements of cardiovascular risk parameters such as clinical blood pressure, central blood pressure, cardiac autonomic modulation, and arterial stiffness were obtained. This session started between 1:00 and 2:00 pm, and patients were given the following instructions: eat a light meal, do not exercise at least 24 hours before the day of the evaluation, do not drink any alcoholic or caffeinated drinks, do not smoke 12 hours before the session, and maintain a normal routine of eating and taking their medication.

Physical activity level

Physical activity levels were obtained using a GT3X+ triaxial accelerometer (Actigraph, Pensacola, FL, USA). All patients received instructions to use the accelerometer for 7 consecutive days, removing it only for sleeping or bathing. The device was attached to an elastic belt and fixed to the right side of the hip. For analysis, a minimum of 10 hours of daily physical activity recordings was necessary. They were considered valid if they had at least 4 days of activity: 3 weekdays and 1 weekend day. The data were collected in the frequency of 30 Hz and were analyzed using 60-second epochs. Periods with consecutive values of 0 (with a 2 min spike tolerance) for 60 min or longer were interpreted as "accelerometer not worn" and excluded from the analysis. The average of total time spent at each intensity of physical activity was calculated using the cutoff points specific to older people,[11] adapted by Buman et al.,[12] considering sedentary time as 0 to 99 counts/min; low-light physical activity as 100 to 1040 counts/min, high-light physical activity as 1041 to 1951 counts/min, and moderate to vigorous physical activity as ≥ 1952 counts/min using the vertical axis, analyzed in min/day, adjusting for the time and number of days the device was worn. Additionally, we also calculated the percentage of patients who met the current physical activity recommendations (≥ 150 min/week) at baseline and after 2 years.

Functional capacity

A 6-minute walk test was conducted in a 30-meter long corridor, following the protocol previously described.[13] Two cones were placed 30 meters apart, and patients were instructed to walk as many laps around the cones as possible. They were also instructed to inform when claudication symptoms (pain, discomfort, cramps, and tiredness) occurred in order to determine claudication onset distance. In addition, the total walking distance was defined as the maximum distance completed by the patient at the end of the 6-minute walk test.

Office blood pressure

Office blood pressure was measured using a monitor (HEM-742, Omron Healthcare, Japan), which consists of an electronic and digital arm blood pressure device with automatic deflation and inflation. For this, patients remained in a sitting position for at least 10 minutes. Three consecutive measurements were taken, 1 minute apart, on both arms, with adequate cuff size. The value used was the average of the 3 measurements, as recommended by the Brazilian Society of Cardiology.[14]

Central blood pressure

Central blood pressure was measured by radial artery by pulse wave analysis using the applanation tonometry technique (SphymoCor, AtCor Medical, Australia). After at least 15 minutes of rest in the supine position, 11 seconds of radial central blood pressure wave recording were used. After this procedure, the SphygmoCor ® software derives the ascending aorta pressure wave, equivalent to the pressure wave measured by an invasive catheter, obtaining systolic and diastolic central blood pressure. For better measurement accuracy, only values with indexes greater than 90% were considered valid.

Arterial stiffness

Arterial stiffness was estimated by carotid-femoral aortic pulse wave velocity using the applanation tonometry technique, following the recommendations of the American Heart Association.[15] The carotid-femoral aortic pulse wave velocity was recorded sequentially by transcutaneous transducers positioned above the carotid artery and the right femoral artery, using an applanation tonometry apparatus (Sphygmocor, AtCor Medical, Australia). Electrocardiography recording was obtained simultaneously with carotid-femoral aortic pulse wave measurements as a reference standard for calculating wave transit time. Two surface distances were measured by the investigator: one between the recording point in the carotid artery and the sternal notch (distance 1) and the other between the sternal notch and femoral artery (distance 2). The distance travelled by the pulse wave was calculated as: distance 2 − distance 1. Carotid-femoral aortic pulse wave velocity was calculated as: carotid-femoral aortic pulse wave velocity = ¼ * distance travelled by pulse wave (m) / transit time (s).

Cardiac autonomic modulation

Cardiac autonomic modulation was assessed by the heart rate variability technique. For this, patients remained at rest, lying down for 15 minutes and the RR intervals were recorded using a heart rate monitor (Polar V800, Polar Electro, Finland). For analysis, the first 5 minutes were excluded, and those with at least 10 minutes of steady signal were considered valid signals. After collection, RR intervals were exported to Kubios HRV program (Biosignal Analysis and Medical Imaging Group, Finland) and then analyzed in time and frequency domains. Time-domain parameters were: standard deviation of all RR intervals (SDNN), root mean square of the squared differences between adjacent normal RR intervals (RMSSD), and percentage of adjacent intervals over 50 ms (PNN50).[16] Frequency domain parameters were obtained by the spectral analysis technique using the autoregressive method. Frequencies between 0.04 and 0.4 Hz were considered physiologically significant; the low-frequency component is represented by oscillations between 0.04 and 0.15 Hz, and the high-frequency component by those between 0.15 and 0.4 Hz. The power of each spectral component was calculated in normalized terms, dividing the power of each band by the total power, from which the very low frequency (< 0.04 Hz) band value was subtracted, and the result was multiplied by 100.[16]

Statistical analysis

All statistical analyses were performed using Statistical Package for the Social Sciences software and SPSS/PASW version 20 (IBM Corp, New York, NY, USA). Normality data were analyzed using the Kolmogorov-Smirnov test. Continuous variables were summarized as mean and standard deviation (normal distribution data) or median and interquartile range (non-normal distribution data), whereas categorical variables were summarized as absolute numbers and percentages, with the respective confidence intervals.

Clinical characteristics at baseline and follow-up were compared using the paired t-test or Wilcoxon signed-rank for continuous variables and the McNemar test for categorical variables. Associations among the delta changes (values from follow-up – baseline) in physical activity and cardiovascular parameters were analyzed by multiple linear regression adjusted for sex, age, changes in antihypertensive medication, ABI, weight, and walking capacity, which are classical confounders in PAD.[17-20]

Residual analysis was performed. Homoscedasticity was analyzed by graphical analysis (scatterplot), and adherence to normal distribution was tested using the Kolmogorov-Smirnov test. Multicollinearity analysis was performed assuming variance inflation factors less than 5 and tolerance below 0.20. For analyses, significance level was set at $p < 0.05$.

Results

The recruitment of the study was conducted between September 2015 and November 2017 (Figure 1). In the first phase of the study, 268 patients underwent baseline measurements. In the second phase of the study, 96 patients agreed to participate, and 24 of those patients were not eligible because of missing data on physical activity. Therefore, the final sample of this study comprises 72 patients.

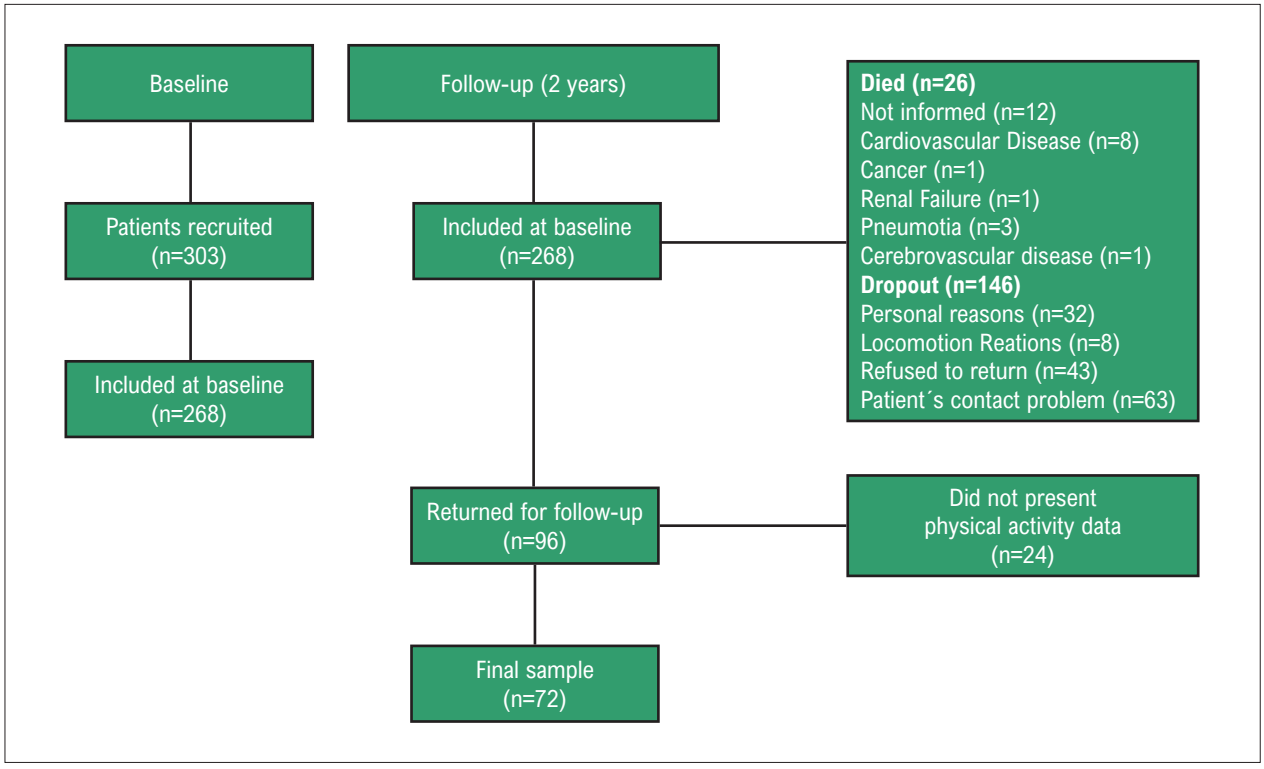

Figure 1 – *Flowchart of the study.*

Table 1 shows the clinical characteristics of patients at baseline and follow-up. After 2 years, we observed a decrease in ABI during follow-up.

Table 2 shows data on total physical activity at the baseline and follow-up period. After 2 years, we observed a significant reduction in time spent in total physical activity and an increase in sedentary time compared to baseline values.

Table 3 shows data on cardiovascular risk parameters at baseline and follow-up. We observed an increase in carotid-femoral pulse wave velocity and a decrease in SDNN in follow-up when compared to baseline values.

We did not observe any association between sedentary time and physical activity with delta values of office and central blood pressure (Table 3), arterial stiffness indicators,

Table 1 – Clinical characteristics of patients with peripheral artery disease (n = 72)

Variables	Baseline	Follow-up	p
Weight (kg)	74.5±13.5	73.7±12.9	0.128
Body mass index (kg/m²)	27.5±4.4	27.3±4.0	0.357
Ankle-brachial index	0.62±0.20	0.53±0.20	0.004
Six-minute walk test	350±90	364±105	0.257
Comorbid conditions			
Diabetes mellitus (%)	42.3	47.2	0.375
Hypertension (%)	82.9	86.1	0.500
Dyslipidemia (%)	84.5	91.8	0.063
Obesity (%)	26.3	38.0	0.359
Coronary artery disease (%)	34.8	40.3	0.523
Stroke (%)	15.7	21.9	0.125
Heart failure (%)	13.2	15.9	0.607
Cancer (%)	11.8	9.9	0.998
Medication			
Antiplatelet (%)	89.7	84.5	0.549
ACE inhibitor (%)	23.9	2.8	0.001
Angiotensin-receptor antagonist (%)	27.9	28.2	0.727
Calcium-channel blocker (%)	22.1	26.8	0.508
Diuretic (%)	41.2	32.4	0.648
Beta-blockers (%)	50.0	26.8	0.007
Statins (%)	92.6	90.1	0.774
Hypoglycemics (%)	47.1	42.3	0.727
Peripheral vasodilator (%)	29.4	47.9	0.004

Data presented as mean ± standard deviation or relative frequency. ACE: angiotensin-converting enzyme.

Table 2 – Physical activity level of patients at baseline and follow-up (n = 72)

Variables	Baseline	Follow-up	p
Sedentary time	4178 (962)	4442 (809)	0.001
Low-light PA (min/week)	2055 (904)	1851 (662)	0.001
High-light PA (min/week)	2257.6 ± 774.5	2041 ± 676.2	0.001
Moderate to vigorous PA (min/week)	85 (177)	41 (79)	0.001
Total PA (min/week)	2257.6 ± 774.5	2041 ± 676.2	0.001
Met PA recommendations (n, %)	6 (7.8)	3 (3.9)	0.250

Data presented as median (interquartile range) or as mean ± standard deviation. PA: physical activity.

Table 3 – Cardiovascular risk parameters at baseline and follow-up (n = 72)

Variables	n	Baseline	n	Follow-up	p
Resting HR (bpm)	72	64.4± 11.5	72	67.7 ± 17.2	0.12
Brachial SBP (mmHg)	72	133.3 ± 21.0	73	132.5 ± 21.0	0.69
Brachial DBP (mmHg)	72	73.0 ± 10.2	73	72.7 ± 10.6	0.74
Central BP (mmHg)	62	130.9 ± 22.3	62	128.0 ± 21.4	0.43
Central DBP (mmHg)	62	75.2 ± 9.9	62	74.6 ± 9.8	0.79
PP (mmHg)	62	55.7 ± 182	62	52.5 ± 18.3	0.09
AIx (%)	60	32.3 ± 11.1	60	30.6 ± 13.2	0.59
AIx 75 bpm (%)	60	26.6 ± 9.6	60	26.9 ± 10.6	0.42
Cf-PWV (m/s)	43	8.4 (3.21)	43	11.5 (6.2)	0.01
SDNN (ms)	39	45.6 ± 31.4	39	24.3 ± 13.3	0.01
RMSSD (ms)	39	31.7 (29.2)	39	21.1 (33.8)	0.18
PNN50 (%)	39	5.8 (16.8)	39	3.1 (18.5)	0.23
LF (un)	39	63.2 (32.4)	39	61.4 (24.6)	0.97
HF (un)	39	36.8 (32.4)	39	38.6 (24.6)	0.98
LF/HF	39	1.71 (3.11)	39	1.56 (1.69)	0.69

Data presented as mean ± standard deviation or as median (interquartile range). AIx: augmentation index; BP: blood pressure; Cf-PWV: carotid-femoral pulse wave velocity; DBP: diastolic blood pressure; HF: high frequency; HR: heart rate; LF: low frequency; PNN50: percentage of adjacent intervals over 50 ms; PP: pulse pressure; RMSSD: root mean square of the squared differences between adjacent normal RR intervals; SBP: systolic blood pressure; SDNN: standard deviation of all RR intervals.

and heart rate variability parameters after 2-year follow-up in patients with symptomatic PAD (Tables 4 and 5).

Discussion

The results of this study indicate that important changes in cardiovascular risk parameters and physical activity occurs after 2 years in patients with symptomatic PAD. These changes include increases in the prevalence of comorbid conditions, decreases in lower limb hemodynamic (ABI), increases in arterial stiffness, and reductions in physical activity levels with a concomitant increase in time spent in sedentary behavior.

The results also indicate a marked worsening in the clinical profile in our sample, with an increase in the prevalence of cardiovascular risk factors after a 2-year follow-up. Reduced ABI and heart rate variability and increased arterial stiffness were also observed. As these factors are highly related to cardiovascular mortality,[21-23] the alterations in clinical profile and cardiovascular parameters observed over time in patients with PAD may potentially explain the severe prognosis of these patients. Thus, these results highlight the importance of aggressive secondary prevention strategies, including risk factor modification, antiplatelet therapy, lipid-lowering therapy, antihypertensive treatment, and especially increased physical activity levels.[24,25] In fact, previous studies have shown that regular physical activity improved different health parameters in PAD, such as walking ability, vascular function, inflammation, and calf muscle hemoglobin oxygen saturation.[26-28]

Physical activity guidelines for the general and PAD population recommend engaging in at least 150 minutes of moderate physical activity, 75 minutes of vigorous physical activity, or an equivalent combination of moderate to vigorous physical activity weekly to promote overall health benefits.[24-26] In the present study, during the 2-year follow-up, patients increased their sedentary time 7% while in low-light, high-light, moderate to vigorous, and total physical activity, they decreased 7%, 10%, 38%, and 10%, respectively. In addition, a reduction of 50% of patients who met the recommendations for physical activity guidelines was observed after a 2-year follow-up (7.8% versus 3.9%). These results are alarming since the guidelines for patients with PAD are clear in recommending regular physical activity as an initial clinical treatment.[29,30] Thus, as most of our patients did not modify or even worsened their physical activity levels, this raises the need to explore strategies to understand the barrier and create new strategies to promote engagement in physical activity in these patients.

We did not observe an association between changes in physical activity with any of the cardiovascular parameters during the 2-year follow-up. These results contrast with our initial hypothesis that changes in physical activity would be associated with cardiovascular risk parameters. A possible explanation is that most of our patients were already physically inactive at baseline, and only 3.9% met the minimum physical activity recommendations during the follow-up. Thus, these lower levels of physical activity were not enough to promote changes in cardiovascular risk parameters in patients with PAD during the follow-up period.

This study is an analysis of a 2-year follow-up, and the results are preliminary and require further investigations at a longer follow-up period and in a larger sample size.

Table 4 – Relationship between sedentary and physical activity with changes in office and central blood pressure after 2-year follow-up in patients with symptomatic peripheral artery disease (n = 72)

Independent variables	Models	Δ Office SBP N=72		Δ Office DBP N=72		Δ Central SBP N=62		Δ Central DBP N=62	
		b	p	b	p	b	p	b	p
Δ Sedentary time (min/week)	Crude	0.045	0.707	-0.079	0.512	0.085	0.518	0.113	0.391
	Adjusted	0.172	0.254	-0.117	0.907	0.235	0.183	0.211	0.230
Δ Low-light PA (min/week)	Crude	-0.075	0.531	0.055	0.646	-0.109	0.407	-0.106	0.419
	Adjusted	-0.193	0.202	0.010	0.947	-0.256	0.146	-0.196	0.275
Δ High-light PA (min/week)	Crude	-0.001	0.933	-0.005	0.274	0.001	0.906	0.002	0.726
	Adjusted	-0.002	0.895	-0.005	0.357	-0.003	0.843	0.002	0.784
Δ MVPA (min/week)	Crude	0.054	0.653	0.039	0.746	-0.042	0.749	-0.122	0.352
	Adjusted	0.250	0.098	0.227	0.120	0.194	0.270	-0.044	0.806

All analyses were adjusted for sex, age, changes in antihypertensive medication, ankle-brachial index, weight, and walking capacity. b: standardized coefficients; DBP: diastolic blood pressure; MVPA: moderate to vigorous physical activity; PA: physical activity; SBP: systolic blood pressure.

Table 5 – Relationship between sedentary and physical activity with changes arterial stiffness indicators and heart rate variability parameters after 2-year follow-up in patients with symptomatic peripheral artery disease (n = 72)

Independent variables	Models	Δ Cf-PWV N=43		Δ AIx N=60		Δ SDNN N=39		Δ LF/HF N=39		Δ LF N=39		Δ HF N=39	
		b	p	b	p	b	p	b	p	b	p	b	p
Δ Sedentary time (min/week)	Crude	-0.148	0.349	0.129	0.331	-0.004	0.557	0.087	0.608	0.001	0.923	-0.001	0.923
	Adjusted	-0.003	0.989	0.100	0.568	-0.007	0.458	-0.061	0.842	-0.002	0.841	0.002	0.841
Δ Low-light PA (min/week)	Crude	0.154	0.330	-0.168	0.203	-0.003	0.596	-0.081	0.634	-0.001	0.837	0.001	0.837
	Adjusted	-0.018	0.936	-0.188	0.279	0.010	0.416	0.066	0.829	0.001	0.911	-0.001	0.911
Δ High-light PA (min/week)	Crude	0.001	0.002	-0.008	0.245	-0.023	0.179	-0.001	0.506	-0.003	0.814	0.003	0.814
	Adjusted	0.002	0.477	-0.006	0.443	-0.019	0.359	-0.002	0.444	-0.021	0.286	0.021	0.286
Δ MVPA (min/week)	Crude	-0.070	0.660	0.150	0.256	0.007	0.901	-0.240	0.153	-0.042	0.352	0.042	0.352
	Adjusted	-0.028	0.897	0.038	0.194	-0.019	0.773	-0.196	0.415	-0.015	0.814	0.015	0.814

All analyses were adjusted for sex, age, changes in antihypertensive medication, ankle-brachial index, weight, and walking capacity. AIx: augmentation index; b: standardized coefficients; Cf-PWV: carotid-femoral pulse wave velocity; HF: high frequency; LF: low frequency; MVPA: moderate to vigorous physical activity; PA: physical activity; SDNN: standard deviation of all RR intervals.

The clinical significance of the present study is that these patients presented impaired cardiovascular profile and reduced physical activity after 2 years, and these results highlight the importance of developing and delivering clinical strategies to tackle these risk factors with the aim of reducing cardiovascular risk in the PAD population.

This study has some limitations that should be mentioned. We had a significant loss of heart rate variability data due to the presence of cardiac arrhythmias or pacemakers, which may have affected the power to infer cause and effect for these variables. In some patients, it was not possible to collect the applanation tonometry data because of a non-detectable femoral pulse (weak or nonexistent pulse). We had high dropout rates during the follow-up period, which may incur a selection bias. On the other hand, strong aspects of our study include the 2-year longitudinal design, more robust analysis of cardiovascular risk parameters, and the objective measurement of physical activity levels.

Conclusion

Patients with PAD had reduced physical activity levels and impaired cardiovascular risk parameters after 2 years. In addition, there was no association of changes in physical activity with cardiovascular risk parameters over the 2-year follow-up.

Authors Contribution

Conception and design of the research, Obtaining financing and Critical revision of the manuscript for intellectual content: Ritti-Dias RM, Cucato GG; Acquisition of data: Monteiro F, Correia MA, Oliveira PML; Analysis and interpretation of the data: Monteiro F, Correia MA, Farah BQ, Ritti-Dias RM, Cucato

GG; Statistical analysis: Monteiro F, Correia MA, Farah BQ, Oliveira PML; Writing of the manuscript: Monteiro F, Farah BQ, Christofaro DGD.

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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Physical Activity Levels Change Over Time in Individuals with Peripheral Arterial Disease

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Short Editorial related to the article: Longitudinal Changes in Physical Activity Levels and Cardiovascular Risk Parameters in Patients with Symptomatic Peripheral Artery Disease

Physical activity plays a key role in improving functional capacity and cardiovascular function in peripheral arterial disease (PAD).[1] There is a direct relationship between the improvement in peak oxygen consumption (VO_2peak) and the reduction in the risk of mortality; in addition, improving symptoms related to intermittent claudication provides a better quality of life (QoL).[2,3] However, the assessment of the level of physical activity is often carried out in transversal studies, showing that a higher level of physical activity is correlated with a greater functional capacity, for example. However, the studies do not consider exposure over a given period, leaving open whether there are changes in cardiovascular risk parameters and physical activity levels in these individuals after a follow-up. This is what Cucato et al.,[4] analyzed in this edition of the *Arquivos Brasileiros de Cardiologia*.

Initially, we will bring the methodological study issues, which began in 2015 and included, in the first phase, 268 patients. After 2 years of follow-up, 72 patients were reassessed in the second phase. Different cardiovascular risk parameters and physical activity levels were evaluated using a GT3X+ triaxial accelerometer (Actigraph, Pensacola, FL, USA). Here it is important to highlight the first positive point, which was to use an accelerometer to control physical activity levels, since many studies use a questionnaire to control the level of physical activity.[5] All patients were instructed to use the accelerometer for 7 consecutive days, removing it only to sleep or shower. The device was fixed to the right side of the hip, and for analysis, a minimum of 10 hours of daily physical activity recording was required. Those who had at least 4 days of activity, 3 weekdays and 1 weekend day were considered valid. We highly value this part, as it is a simple method that provides us with extremely high-quality information.

Keywords

Physical Activity; Peripheral Arterial Disease; Acceleration; Velocity; Walking Speed; Exercise

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Among the different parameters of cardiovascular risk, we can highlight blood pressure, cardiac autonomic modulation and arterial stiffness. While the functional capacity was evaluated through the 6-minute walk test. Despite being an extremely safe, effective and reproducible test, it has limitations, and here is a suggestion for future studies to evaluate VO_2peak and its variables through a specific test using the Gardner protocol.[6-8]

Regarding the results, we can highlight that the patients reduced their total physical activity levels during these 2 years (2.257 ± 774.5 min/week pre versus 2.041 ± 676.2 min/week post, $p = 0.001$). Something important and worrying is that the ankle-brachial index (ABI) was also significantly reduced after the two-year follow-up (0.62 ± 0.20 pre versus 0.54 ± 0.20, $p = 0.003$). Why is this result worrying? Some studies show that the ABI is a prognostic marker in individuals with PAD; combining this with a reduction in physical activity levels, we will have an alarming scenario for this population. In the present study, QoL was not evaluated; however, in a worsening scenario of different parameters, we can speculate that these individuals probably worsened their QoL. From the perspective of cardiovascular parameters, we will highlight the worsening of heart rate variability measured by the standard deviation of RR intervals ($p < 0.001$).

One of the points that draws much attention is that it was not mentioned whether the individuals in the baseline participated in any physical training program since Dr. Cucato's research group is the reference in Brazil and one of the references in the world on PAD rehabilitation.[9] Often, when individuals participate in a rehabilitation program, they increase their daily physical activity levels. However, at the end of the program, the tendency is to reduce their physical activity levels.[10] The article's message is very clear, and it makes us think about the importance of monitoring these individuals over time. PAD ends up being an underdiagnosed disease; that is, individuals have symptoms but often do not care, reaching a critical level that generates several negative consequences, such as reduced functional capacity, worsening of QOL and worsening of cardiovascular parameters. New studies must be designed a priori for a long follow-up of these individuals so that we will have more information about the evolution of the disease and what benefits a higher level of physical activity can provide.

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Relationship between Systemic Immune-Inflammation Index and Coronary Collateral Circulation in Patients with Chronic Total Occlusion

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Abstract

Background: **Inflammation plays a key role in the initiation and progression of coronary artery disease (CAD). The systemic immune-inflammation index (SII) is a novel inflammatory parameter that has been shown to be associated with CAD.**

Objective: **This study aimed to investigate the relationship between SII and coronary collateral circulation (CCC) in patients with stable CAD and chronic total occlusion (CTO).**

Methods: **The patients were divided into two groups, with poor CCC and good CCC, according to the Rentrop Classification. Ninety-four patients had poor CCC, and 81 patients had good CCC. Inflammation parameters were calculated from the laboratory results. The statistical significance level applied was 0.05.**

Results: **High SII level (OR: 1.003, 95% CI: 1.001-1.004, p<0,001), absence of CTO in RCA (OR: 0.204, 95% CI: 0.096-0.436, p<0,001) and low Gensini score (OR: 0.980, 95% CI: 0.962-0.998, p=0,028) were significantly associated with poor CCC. The cutoff value of SII was 679.96 for the highest predictive power of poor CCC, with a sensitivity of 74.5% and specificity of 43.2%. Mortality rates were similar between the two groups during a mean follow-up of 21.5±10.8 months (p=0.107).**

Conclusions: **High SII level, the absence of CTO in the right coronary artery, and low Gensini score were significantly related to poor CCC. The rapid and cost-effective use of new inflammatory markers in clinical practice guides the prognosis of CAD.**

Keywords: **Collateral Circulation; Coronary Occlusion; Coronary Vessels.**

Introduction

Chronic total occlusion (CTO) is a type of coronary artery disease (CAD) characterized by complete or near-complete occlusion of the epicardial coronary arteries for at least three months and has worse clinical outcomes. CTO has an incidence ranging from 18% to 52% in the cohort obtained from the examination of coronary angiographies.[1] Coronary collateral circulation (CCC) is an adaptive response that develops to maintain perfusion of myocardial tissue in patients with stenotic or occlusive coronary lesions. In a meta-analysis by Meier et al., it was reported that patients with good CCC had 36% less mortality than patients with poor CCC.[2]

The degree of coronary stenosis, presence of diabetes mellitus, exercise status, anginal attacks, mediators that affect angiogenesis such as vascular endothelial growth factor (VEGF), and the levels of inflammatory cells affect coronary collateral development.[2-6] Because of the inflammatory processes that affect CAD on a large scale, inflammatory parameters obtained from routine tests such as complete blood count (CBC) and blood biochemistry are frequently used in a wide variety of clinical studies as predictors of both coronary collateral development and CAD severity.[7-9]

Systemic immune-inflammation index (SII), a novel inflammatory parameter, was found to be an independent predictor of cardiovascular events in CAD patients undergoing percutaneous coronary intervention (PCI).[10] Although many inflammatory parameters have been studied in CAD patients with CTO, monocyte to high-density lipoprotein ratio (MHR) and SII have not been previously studied in the literature in this clinical situation. Therefore, we aimed to investigate the predictor value of SII on coronary collateral development in patients with stable CAD with CTO.

Methods

Study population and design

After the approval of the local ethics committee, 2576 coronary angiography procedure results were assessed between January 2018 and July 2020, obtained from the institute records. The flowchart of patient enrollment is seen in Figure 1. One hundred

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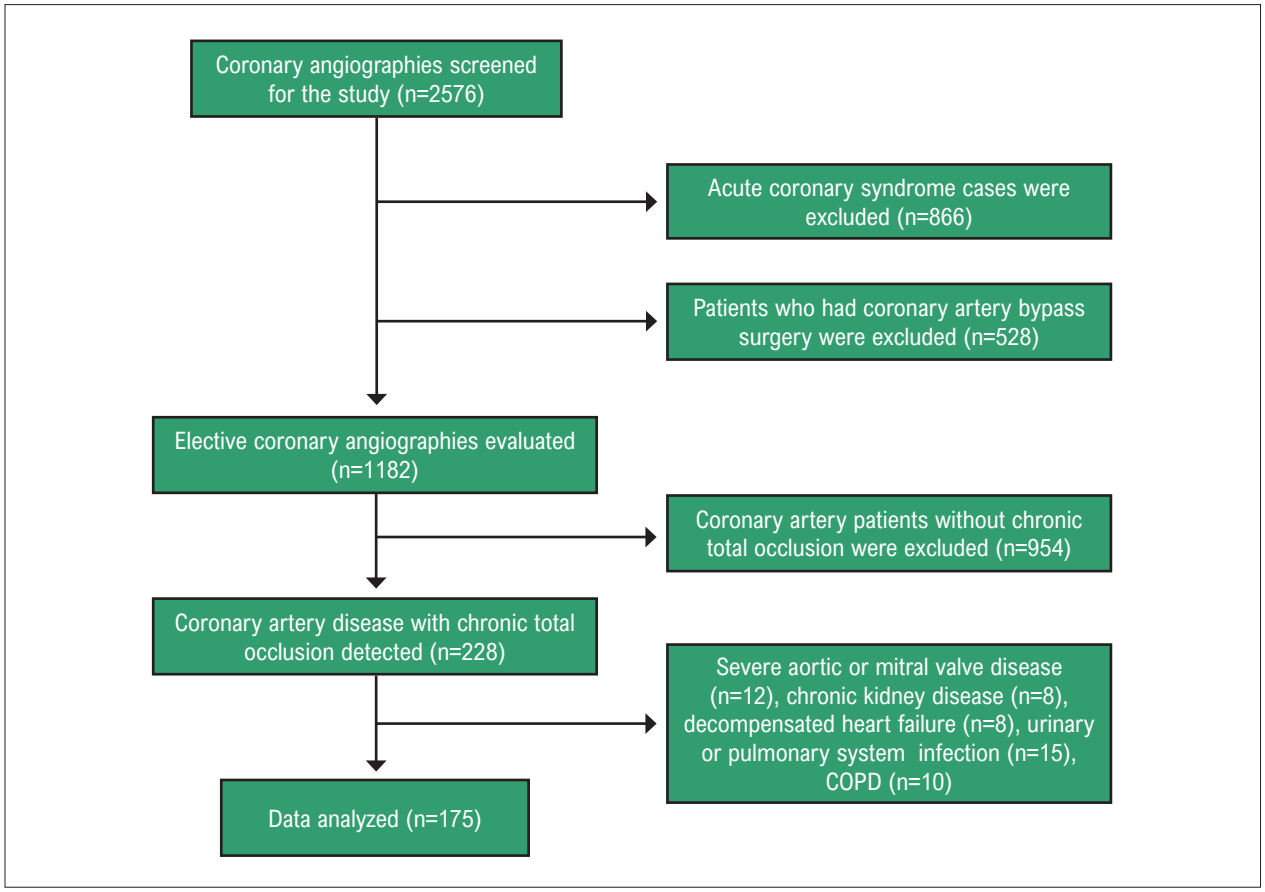

Figure 1 – *Flowchart of patient enrollment.*

and seventy-five stable CAD patients with CTO were included in the study and were grouped according to the Rentrop classification,[11] in terms of coronary collateral development in CTO. The patients were divided into two groups, with poor CCC (Grades 0 and 1) and with good CCC (Grades 2 and 3). Ninety-four patients had poor CCC, and 81 patients had good CCC. Clinical and demographic characteristics, CAD risk factors, medications, laboratory results, electrocardiogram (ECG), and mortality recordings of the patients were obtained from the hospital database. SII, MHR, platelet to lymphocyte ratio (PLR), and neutrophil-lymphocyte ratio (NLR) were calculated from the CBC and biochemical parameters laboratory results. The SII value was calculated with the formula SII = (P × N) / L. In the formula, P, N, and L symbolize platelets, neutrophils, and lymphocytes, respectively. Hypertension was defined as the previous documentation of a systolic blood pressure of 140 mm Hg and/or a diastolic blood pressure of 90 mm Hg in at least two measurements or active use of any antihypertensive agent. Diabetes mellitus was defined as a fasting plasma glucose level > 126 mg/dL, a glucose level > 200 mg/dL, or a glycated hemoglobin level over 6.5% in any measurement, or the active use of an antidiabetic agent. Total cholesterol >200 mg/dL and triglyceride levels >150 mg/dL were considered as hyperlipidemia, or the active use of an antihyperlipidemic drug.

Patients with moderate to severe heart valve pathology, acute coronary syndrome in last three months, decompensated heart failure (NHYA class III or IV), chronic obstructive pulmonary disease, clinical signs of active infection, acute or chronic renal, hepatic insufficiency, and those with a history of malignancy, coronary artery bypass grafting (CABG) surgery, pulmonary embolism, chronic inflammatory or autoimmune diseases, and those undergoing renal-hepatic transplantation were excluded from the study.

This study complies with the principles outlined in the Declaration of Helsinki.

Coronary collateral circulation assessment

Coronary angiography was indicated in patients with chest pain or those submitted to non-invasive tests that showed myocardial ischemia. The coronary angiography was performed by transfemoral or transradial access using the routine Judkins technique. CTO was defined as a total occlusion of a coronary artery with a distally TIMI 0 flow for at least 3 months. Patients who had at least one coronary artery with CTO were included in the study. CCC was evaluated by two cardiologists who were blinded to the study. CCC was graded using the scoring system developed by Cohen et al. (the Rentrop classification).[11] According to the classification system: Grade 0, no visible filling from any coronary collateral; Grade 1, filling of side branches of the artery to be dilated via collateral channels without visualization of the epicardial

part; Grade 2, partial filling of the epicardial part via collateral channels; Grade 3, complete filling of the epicardial artery, being dilated via collateral channels.

Statistical analysis

All data were analyzed using the SPSS 22.0 statistics package (SPSS Inc., Chicago, IL, USA). Continuous variables were reported as mean ± standard deviation, and categorical variables as absolute and relative frequencies. The Kolmogorov-Smirnov test was used to determine the normality of the data. The independent Student's t-test was used to compare normally-distributed variables. Categorical variables were compared with the χ^2 test or Fisher's exact test. A p-value < 0.05 was considered statistically significant. The effects of different variables on poor CCC were assessed by backward logistic regression analysis. The inclusion of covariates in the multivariate model was first determined by selecting those that exhibited 2-sided $p < 0.10$ in the unadjusted analyses. The inclusion of additional covariates was determined by performing a stepwise-backward selection process until all the other variables in the model exhibited $p < 0.10$. The receiver-operating characteristic (ROC) curve analysis was used to determine the best cutoff value of the SII level in predicting poor CCC.

Results

In total, 175 stable CAD patients with CTO were enrolled in the study. The mean age of the patients was 68.2±10.9 and 80.6% of the patients were male. There were two groups; one that had 94 patients in the poor CCC (Rentrop Grade 0 or 1) and 81 patients in the good CCC (Rentrop Grade 2 or 3) groups. Age, gender, presence of hypertension, diabetes hyperlipidemia, family history of cardiovascular disease (CVD), prior MI, and medications were similar between the two groups. In all patients, the CTO location was higher in the right coronary artery (RCA) and statistically higher in the good CCC group. Multivessel disease (≥ 2 CAD) rate was slightly and Gensini score was significantly higher in the good CCC. Mortality rates were similar between the two groups, during a mean follow-up of 21.5±10.8 months. Baseline demographic, clinical characteristics, CAD risk factors, and previous medication of the patients are shown in Table 1.

The laboratory results and the inflammatory parameters of both groups are shown in Table 2. Platelet levels, WBC and neutrophil counts were remarkably higher in the poor CCC group. Lymphocyte count was higher in the good CCC group. Hemoglobin, monocyte count, glomerular filtration rate, and cholesterol levels were similar between the two groups. Among the inflammatory parameters, C-reactive protein (CRP) and MHR showed no significant difference between groups, but NLR, PLR, and SII values were found to be statistically lower in the good CCC group.

The multivariate Backward-Regression analysis of risk factors for poor CCC was performed. The model included age, gender, hypertension, diabetes, hyperlipidemia, current smoking, prior MI, multivessel disease, heart rate, ejection fraction, acetylsalicylic-acid use, statin use, presence of CTO in the RCA, collateral state, Gensini score, NLR, PLR, and SII. The analysis showed that the absence of CTO in RCA and low Gensini score were related to poor CCC. In addition, a high SII level was significantly associated with poor CCC (Table 3).

We assessed the predictor value of the SII for poor CCC in a ROC curve analysis. When the cutoff value of the SII was set at 679.96, the predictive power of poor CCC was the highest, with a sensitivity of 74.5% and specificity of 43.2% (AUC: 0.732; 95% CI, 0.659–0.804, $p<0.001$) (Figure 2).

Discussion

To the best of our knowledge, this is the first study that evaluates the relationship between SII and CCC in patients with stable CAD and CTO. In the current study, we found that a high SII, the absence of CTO in RCA, and low Gensini score were related to poor CCC.

Coronary collateral vessels are an adaptive mechanism that is activated by chronic or recurrent myocardial ischemic events; they progress gradually, and protect from myocardial ischemia and its associated complications.[2,12] Hypoxia, increased redox potential or shear stress, and some genomic expressions cause endothelial cell activation and initiation of the inflammatory cascades.[13] Because of the central role of the inflammation on the initiation and progression of CAD, various studies have been carried out to identify the effect of inflammatory processes on CCC. High CRP, NLR, PLR, CRP to albumin ratio (CAR), and fibrinogen to albumin ratio (FAR) have been used for this purpose.[7,8,14-16]

Acar et al. found that PLR was a predictor of poor collateral flow in patients with stable angina pectoris and CTO.[7] In another study, NLR was found to be associated with reduced coronary collateral flow in CAD with CTO.[8] We also found the PLR and NLR levels were high in the poor CCC group ($p<0.001$), but this significance was not found in the regression analysis.

Increased MHR level has been identified as a predictor of the high SYNTAX score in stable CAD patients.[9] In the current study, we also aimed to investigate the effect of this inflammatory parameter on CCC development, but there was no significant difference in terms of MHR.

SII has been developed from inflammatory cells including platelet, neutrophil, and lymphocyte counts. Firstly, it has been associated with poor prognosis in many types of cancer.[17,18] Using The Dongfeng-Tongji cohort, Xu et al. have found that SII was associated with thrombocytosis, inflammation, and the development of cerebrovascular disease in 13,929 middle-aged and older adults without CVD and cancer, over a mean follow-up of 8.28 years.[19] Yang et al. have demonstrated that high SII level is independently associated with increased risk of cardiovascular death, nonfatal MI, nonfatal stroke, and admission for heart failure in 5206 CAD patients who underwent PCI.[10] In this study, an optimal SII cutoff point (≥694.3) was identified for major adverse cardiovascular events (MACE) in the CAD cohort. Similarly, in our study, we found an optimal SII cutoff point of 679.96 for the best prediction of poor CCC, with a sensitivity of 74.5% and a specificity of 43.2%.

The effect of the CCC on mortality is debatable. In a meta-analysis that included over 3000 patients, Allahwala

Table 1 – Baseline demographic and clinical characteristics of the study population

Characteristics	All patients (n = 175)	Coronary collateral circulation		p-value
		Poor (n = 94)	Good (n = 81)	
Age (years), mean±SD	68.2±10.9	69.1±11.2	67.3±10.5	0.275
Male, n (%)	141 (80.6)	74 (78.7)	67 (82.7)	0.568
SBP, mm Hg	138.4±20.44	127.8±16	129.7±18.6	0.478
DBP, mm Hg	74.19±12.79	76.1±11.6	76.7±13	0.742
Current smoker, n (%)	36 (20.6)	18 (19.1)	18 (22.2)	0.708
Hypertension, n (%)	103 (58.9)	59 (62.8)	44 (54.3)	0.283
Diabetes mellitus, n (%)	69 (39.4)	38 (40.4)	31 (38.2)	0.877
Hyperlipidemia, n (%)	15 (8.6)	10 (10.6)	5 (6.1)	0.418
Family history of CVD, n (%)	15 (8.6)	10 (10.6)	5 (6.1)	0.418
Prior MI, n (%)	77 (44)	44 (46.8)	37 (45.7)	0.448
Medication, n (%)				
ASA	92 (52.6)	56 (59.6)	36 (44.4)	0.050
P2Y12 inhibitor	42 (24)	27 (28.7)	15 (18.5)	0.155
Statin	52 (29.7)	29 (30.8)	23 (28.4)	0.743
ACEI/ARB	71 (40.6)	40 (42.5)	31 (38.2)	0.644
Beta blocker	83 (47.4)	48 (51)	35 (43.2)	0.363
Calcium channel blocker	31 (17.7)	18 (19.1)	13 (16)	0.692
EF, %, mean±SD	47.1±12.2	46.1±12.2	48.3±12.2	0.224
Multivessel disease, n (%)	121 (69.1)	59 (62.8)	62 (76.5)	0.071
CTO location, n (%)				
LAD	46 (26.3)	30 (31.9)	16 (19.7)	0.085
Cx	25 (14.3)	16 (17)	9 (11.1)	0.287
RCA	96 (54.9)	38 (40.4)	58 (71.6)	<0.001
Other	22 (12.6)	13 (13.8)	9 (11.1)	0.652
Gensini score, mean±SD	58.6±23.2	55±18.6	62.8±27.1	0.025
Mortality, n (%)	41 (23.4)	27 (28.7)	14 (17.3)	0.107

ACEI: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin receptor blocker; ASA: Acetyl salicylic acid; CTO: Chronic total occlusion; CVD: Cardiovascular disease; Cx: Circumflex coronary artery; DBP: Diastolic blood pressure; EF: Ejection fraction; LAD: Left anterior descending coronary artery; MI: Myocardial infarction; RCA: Right coronary artery; SBP: Systolic blood pressure.

et al. have indicated that robust CCC is not associated with lower rates of acute myocardial infarction or all-cause mortality but increases the chance of PCI success.[1] On the other hand, Meier et al. demonstrated that high collateralization had a protective effect and a 36% decreased mortality risk compared with patients with low collateralization.[2] However, in our study, there was no significant difference in mortality rates during 21.5±10.8 months of follow-up.

This study has some limitations. First, there was quite a small number of patients and the study was a cross-sectional, single-center one, with a retrospective design. Hence, the selected sample population may not reflect the whole cohort, and thus further studies are warranted. Second, all measurements and laboratory parameters were evaluated only once during follow-up. Finally, specific gene expressions, inflammatory parameters such as VEGF and TNF-α were not measured, so these measurements could be supportive in demonstrating the association of poor CCC with SII.

Conclusion

In this study, we found that a high SII, the absence of CTO in RCA, and low Gensini score were significantly related to poor CCC. It is important to quickly determine the inflammation status from the blood laboratory results and to determine the poor CCC and high-risk patients that result in high mortality in CAD patients. SII is an inflammatory parameter, which is easy to calculate from CBC and may be very useful to identify high-risk patients with poor CCC.

Table 2 – Laboratory results and inflammatory parameters of the patients

Characteristics	All patients (n = 175)	Coronary collateral circulation		p-value
		Poor (n = 94)	Good (n = 81)	
Laboratory results, mean±SD				
Hemoglobin, g/L	13.2±2	13±2.2	13.5±1.8	0.139
Platelet count, 10^3/μL	253.8±60.4	267.5±65.2	237.9±50.1	0.001
WBC count, 10^3/μL	9.4±2.8	10.1±3.1	8.7±2	0.001
Neutrophil count, 10^3/μL	6.5±2.5	7.3±2.9	5.6±1.6	<0.001
Lymphocyte count, 10^3/μL	2.1±0.9	1.9±0.85	2.2±0.88	0.028
Monocyte count, 10^3/μL	0.62±0.25	0.62±0.26	0.62±0.25	0.251
Creatinine, mg/dL	1.04±0.28	1.04±0.27	1.04±0.29	0.895
GFR, mL/min	74.1±20.1	73.2±19.9	75.1±20.5	0.526
Total cholesterol, mg/dL	180.9±46.3	126±70.3	113±46.3	0.583
HDL-C, mg/dL	40.8±12.3	42±11.4	39.5±13.2	0.174
LDL-C, mg/dL	107.4±42.8	104.3±43.2	110.8±42.3	0.319
Triglycerides, mg/dL	171±112	167.9±99.8	174.6±125.2	0.694
CRP, mg/L	13.2±22	14.2±23.4	12.1±20.2	0.533
MHR	17.1±10.1	15.9±8	18.4±12	0.112
NLR	4.1±3.7	5.1±4.7	2.9±1.3	<0.001
PLR	152.5±108.7	179.5±136.7	121.2±46	<0.001
SII	1030.6±1008.9	1335.3±1275.4	679.9±295.3	<0.001

CRP: C-reactive protein; GFR: Glomerular filtration rate; HDL-C: High density lipoprotein cholesterol; LDL-C: Low density lipoprotein cholesterol; MHR: monocyte to high-density lipoprotein ratio; NLR: neutrophil to lymphocyte ratio; PLR: platelet to lymphocyte ratio; SII: systemic immune-inflammation index; WBC: total white blood cells.

Table 3 – Multivariate Backward-Regression analysis of risk factors for poor CCC

Variables *,**,***	OR (95% CI)	p value
Hyperlipidemia	0.313 (0.091-1.071)	0.064
RCA CTO	0.204 (0.096-0.436)	<0.001
Gensini score	0.980 (0.962-0.998)	0.028
ASA use	0.526 (0.249-1.111)	0.092
SII	1.003 (1.001-1.004)	<0.001

*ASA: Acetyl salicylic acid; CCC: Coronary collateral circulation; CI: Confidence interval; RCA: Right coronary artery; OR: Odds ratio; SII: systemic immune-inflammation index. *Nagelkerke R square: 0.432. **The model included age, gender, hypertension, diabetes, hyperlipidemia, current smoking status, prior MI, multivessel disease, heart rate, ejection fraction, acetylsalicylic-acid usage, statin use, presence of chronic total obstruction in the right coronary artery, collateral grade, Gensini score, NLR, PLR, and SII. ***Selection of the covariates for the multivariate models is explained in the Methods section. Unless otherwise indicated, odds ratio is interpreted as the presence (vs. absence) of each categorical variable or an increase of one (1) unit of each continuous variable.*

Author contributions

Conception and design of the research: Mehmet Koray Adali, Ipek Buber, Samet Yilmaz. Acquisition of data: Mehmet Koray Adali, Ipek Buber, Gursel Sen. Analysis and interpretation of the data: Mehmet Koray Adali, Ipek Buber, Gursel Sen, Samet Yilmaz. Statistical analysis: Mehmet Koray Adali, Samet Yilmaz. Writing of the manuscript: Mehmet Koray Adali, Gursel Sen, Samet Yilmaz. Critical revision of the manuscript for intellectual content: Mehmet Koray Adali, Ipek Buber, Samet Yilmaz.

Potential Conflict of Interest

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

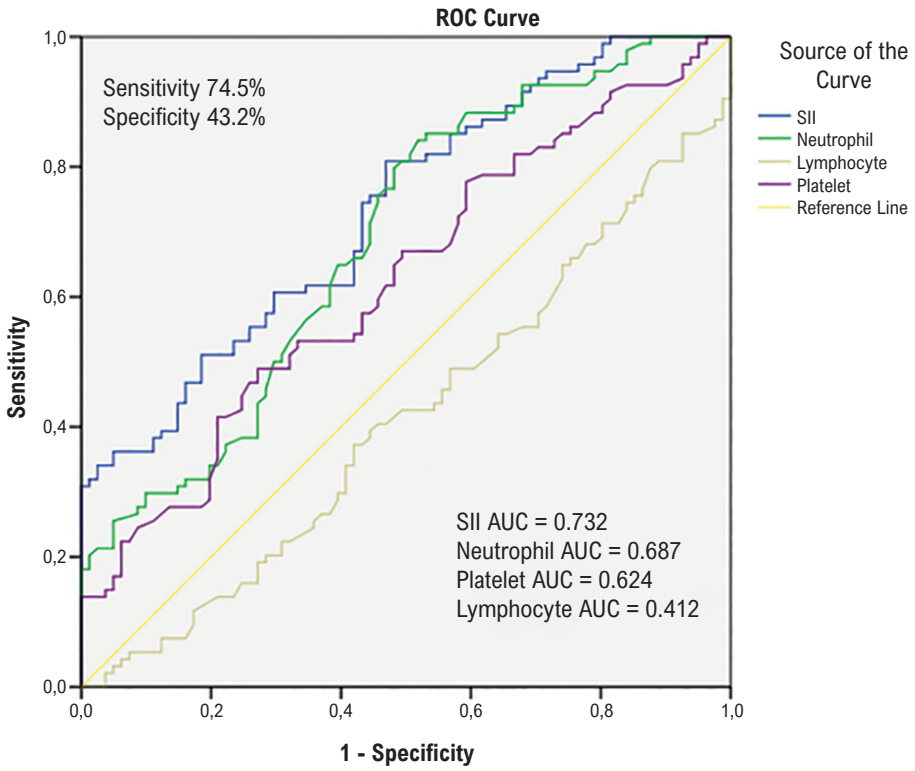

Figure 2 – *ROC curves of patients with poor CCC predicted by SII.*
AUC: Area under curve; CCC: coronary collateral circulation; ROC: Receiver-Operating characteristics; SII: Systemic imune-inflammation index

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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 Pamukkale University under the protocol number E-60116787-020-4313. 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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Abnormal Circadian Blood Pressure Variation is Associated with SYNTAX Scores in Hospitalized Patients with Acute Coronary Syndrome

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Abstract

Background: Blunted nocturnal blood pressure (BP) reduction, referred to as non-dipper hypertension, is a strong predictor of cardiovascular morbidity and mortality.

Objectives: This study aimed to investigate the relationship between non-dipper hypertension and the severity and complexity of coronary artery disease using SYNTAX score in hospitalized patients with acute coronary syndrome.

Methods: A total of 306 consecutive patients with acute coronary syndrome were screened. Patients who were clinically stable and admitted to the intermediate intensive care unit at least 24 hours after angiography and/or successful revascularization. After the exclusion criteria, 141 patients (34 female and 107 male; mean age 61 ± 11 years) were included. Non-dipper hypertension has been defined as a 0% to 10% decrease in average systolic BP at nighttime compared to daytime, measured at hourly intervals using the same automatic BP measuring device on bedside monitors (Vismo PVM-2701; Nihon Kohden Corp., Tokyo, Japan). SYNTAX score was calculated with an online calculator. The independent predictors of SYNTAX score were assessed using multivariable logistic regression analysis. $P < 0.05$ was considered statistically significant.

Results: The patients with non-dipper hypertension had higher SYNTAX score than the patients with dipper hypertension (11.12 ± 6.41 versus 6.74 ± 6.45, $p < 0.0001$). In a multivariable logistic regression model, non-dipper hypertension status (odds ratio: 5.159; 95% confidence interval: 2.246 to 11.852, $p < 0.001$), sex ($p = 0.012$) and low-density lipoprotein cholesterol ($p = 0.008$) emerged as independent predictors of high SYNTAX score.

Conclusions: The results of our study provide a possible additional mechanism linking abnormal circadian BP profile with coronary artery disease severity and complexity in patients with acute coronary syndrome.

Keywords: Hypertension; Blood Pressure Monitoring Ambulatory; Acute Coronary Syndrome; Inpatients; Coronary Artery Disease.

Introduction

Physiological blood pressure (BP) exhibits a circadian pattern with a decrease of 10% to 20% during sleep in relation to daytime BP. This decrease during sleep is defined as extreme dipping if ≥ 20%, normal dipping if 10% to 20%, non-dipping if < 10%, and reverse dipping if there is any increase (night to day ratio: ≤ 0.8, < 0.8 to ≤ 0.9, < 0.9 to ≤ 1, and > 1, respectively).[1] Blunted nocturnal BP reduction is a strong predictor of cardiovascular morbidity and mortality for patients with and without hypertension.[2-7] The standard method for determining non-dipper and dipper patterns in patients is 24-hour non-invasive ambulatory blood pressure monitoring (ABPM), which is generally performed out of the office. On the other hand, alternatively, clinical blood pressure monitoring (CBPM) in hospitalized patients and home blood pressure monitoring (HBPM) in outpatients are performed with infrequent manual or automatic BP measurements. CBPM and HBPM have previously shown to have daytime and nighttime BP measurements similar to ABPM in hospitalized patients and outpatients and to be consistent with ABPM in demonstrating non-dipper hypertension.[8-10]

Although diurnal BP disorders are linked to damage of several organs and cardiovascular events, the underlying mechanism is unclear.[11-13] However, the clinical significance of abnormal circadian BP variation in patients admitted to the hospital with a recent cardiovascular event has not yet been studied. The Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery Study (SYNTAX) score (SX score) is one of the most accepted detailed coronary angiographic scoring systems for determining the severity and complexity of coronary artery disease (CAD), depending on coronary anatomy and lesion characteristics.[14-16] This

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study aimed to evaluate the relationship between SX score and blunted nighttime BP dipping using frequent CBPM (hourly intervals) in hospitalized patients with acute coronary syndrome (ACS).

Methods

Study population

This single-center, cross-sectional, prospective study was held between January and April 2020 at the Ahi Evren Thoracic and Cardiovascular Centre, Trabzon, Turkey. The study participants were prospectively enrolled from a total of 306 patients who had undergone coronary angiography with ACS (ST-elevation myocardial infarction [STEMI], non-STEMI [NSTEMI], unstable angina pectoris [USAP]). Biochemistry parameters, including total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglycerides, and renal function tests, were measured. Hematological parameters were measured as a part of the automated complete blood count (Mindray BC-5800 auto hematology analyzer, Mindray Medical Electronics Co. Shenzhen, China). Hypertension was diagnosed and stratified based on recent guidelines.[17] Patients who had previously received antihypertensive treatment continued the same treatments throughout the follow-up period. We gave antihypertensive medicines to all patients in the morning hours without changing their usage. Hypercholesterolemia was defined as total cholesterol > 200 mg/dl. The estimated glomerular filtration rate was calculated using the Cockcroft-Gault formula.[18] We excluded patients with any of the following: presenting with cardiogenic shock or arrest, receiving intravenous nitroglycerine or inotrope therapy for any reason, history of coronary artery bypass grafting, valvular heart disease, malignancy, renal or hepatic disease, symptomatic heart failure, secondary hypertension, uncontrolled arrhythmia, ongoing angina or anxiety, obstructive sleep apnea syndrome or sleep disorder, and morbid obesity (body mass index > 35). Finally, the study population consisted of 141 clinically stable patients, including 85 with NSTEMI, 15 with USAP, and 41 with STEMI (Figure 1). Patient ages ranged from 32 to 91 years. The study protocol conformed to the principles of the Declaration of Helsinki and received approval from the local Institutional Review Board. Informed consent was obtained from each study participant.

Coronary angiography

All patients underwent coronary angiography within 24 hours. The average time from symptoms to coronary angiography was approximately 2 to 6 hours. Coronary angiography was performed by the standard Judkins technique using 6 or 7 French catheters (Expo, Boston Scientific Corporation, Massachusetts, USA) through the femoral artery. When necessary, percutaneous coronary intervention for the culprit lesion was successfully performed on eligible patients in the same session (120/141 patients, 85%). SX score was calculated with an online calculator as described in the literature according to the basal angiographic findings by 2 experienced operators who were blind to other parameters.[16]

Blood pressure measurement and study protocol

In our clinic, patients with ACS are followed up in the intensive care unit for at least the first 24 hours after percutaneous coronary intervention. However, low-risk stable patients (patients with successful revascularization, no malignant arrhythmia, relieved pain, and no signs of heart failure) are mobilized and followed up in the intermediate intensive care unit at the end of 24 hours. Our study population was selected from these patients, and hourly BP measurements were made in the intermediate intensive care unit with an automatic BP measurement device on bedside monitors for all patients (Vismo PVM-2701, Nihon Kohden Corp., Tokyo, Japan). Measurements were made in the upper limb using 2 inflatable cuffs (22 × 12 and 30 × 14 cm) to cover at least 80% of the patient's arm circumference. Measurement accuracy was ensured by optimizing all patient monitors before the first measurements and comparing them with calibrated standard sphygmomanometer measurements. By enabling the patients to sleep in their beds at 23:00 and wake up at 7:00, nighttime BP values were obtained by hourly measurement. We informed all patients before the procedure and took all nighttime BP measurements while the patients were sleeping.

We excluded measurement if the patient awoke for any reason, and the measurement was repeated immediately after the patient slept. Coffee drinking, smoking, and exercise were not allowed before measurement; after sitting and resting for 5 minutes, daytime BP was obtained by measuring BP hourly between 08:00 and 22:00 with the same device in the supine position. For all measurements, patient monitors were set to measure at 1-hour intervals. The same experienced healthcare personnel checked the patients in terms of sleep-wake status, cuff appropriateness, and patient position during measurement; nighttime BP measurements were recorded under dim light, without fully turning on the intermediate intensive care unit lights. If the patient was transferred to the intermediate intensive care unit at a time that did not correspond to the beginning of the measurement periods, we started the measurements in the first following period (23:00 at night-time or 7:00 the daytime). Patients were followed up in the intermediate intensive care unit for at least 24 hours. Extreme BP values (systolic BP > 200 mmHg or < 90 mmHg; diastolic BP > 110 mmHg or < 40 mmHg) were considered as erroneous measurement and were not included in the analysis. By averaging the hourly BP values for 9 nighttime periods (23:00 to 07:00) and 15 daytime periods (8:00 to 22:00), a single daytime and nighttime mean BP value was obtained. Nighttime to daytime systolic BP dip was calculated as 100 × ([day-time systolic BP mean – nighttime systolic BP mean]/daytime systolic BP mean]). Decrease in BP at nighttime compared to daytime was defined in the following manner: normal dipping if 10% to 20%, non-dipping if < 10%, and reverse dipping if there was any increase (night to day ratio: ≤ 0.8, < 0.8 to ≤ 0.9, < 0.9 to ≤ 1, and > 1, respectively).

Echocardiographic evaluation

Echocardiographic examination was performed with a commercially available cardiovascular ultrasound system (Vivid 5, GE Vingmed, Horten, Norway). Data acquisition

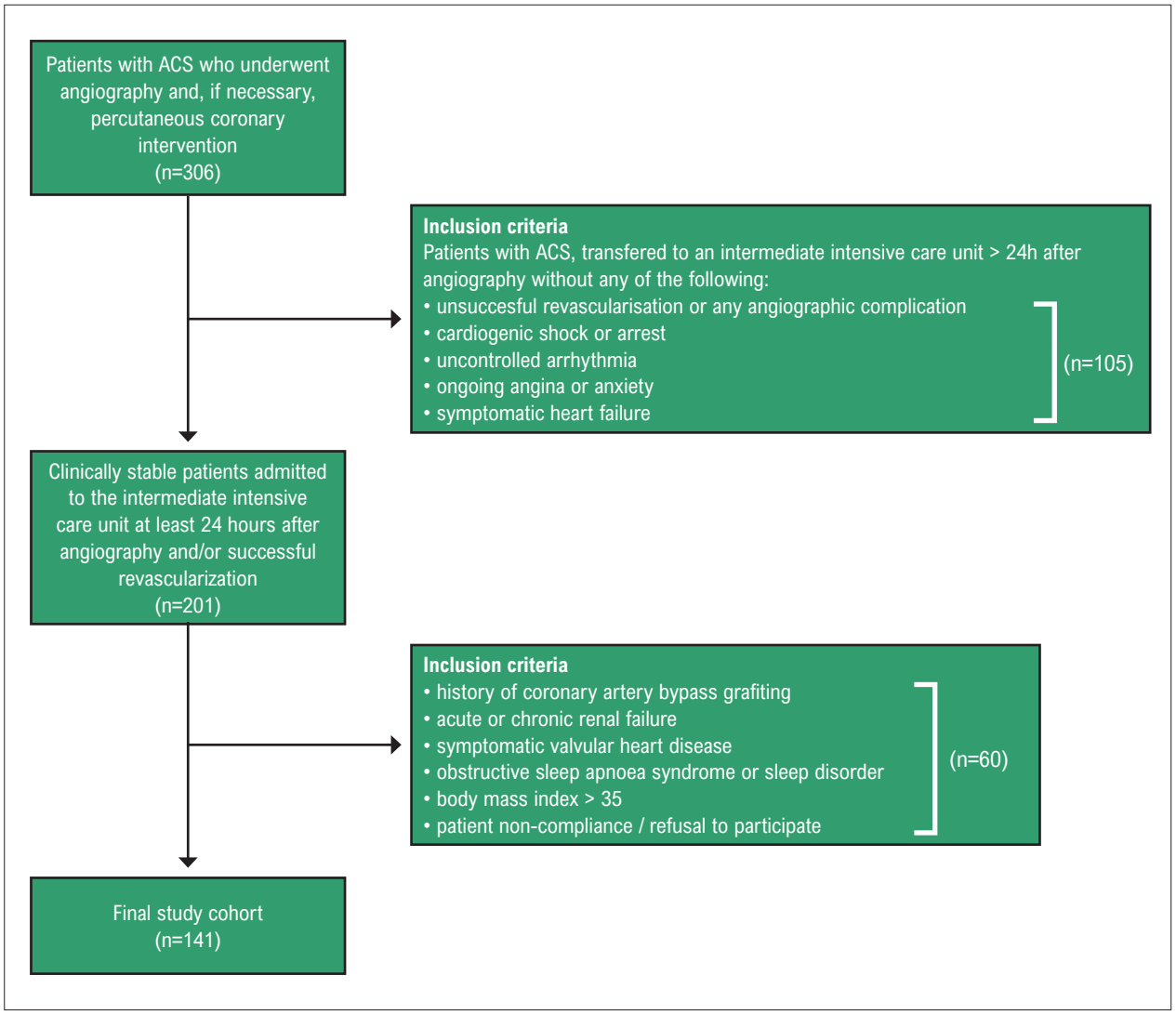

Figure 1 – *Flowchart of the study. ACS: acute coronary syndrome.*

was performed with a 1.5 to 2.6 MHz transducer in the parasternal and apical views (standard 2- and 4-chamber views). Two-dimensional and Doppler images were obtained during breath-hold and stored in cine-loop format from 3 consecutive beats; average values were reported, and electrocardiograms were simultaneously recorded. Left ventricle ejection fraction was derived by the apical biplane modified Simpson rule. Doppler measurements included peak early mitral filling velocity (E wave), peak late mitral filling velocity (A wave), and the ratio of peak early and late mitral filling velocities (E/A). For myocardial tissue velocities, tissue Doppler imaging sample volume was placed at the lateral mitral annulus at the junction between the left ventricular lateral wall and mitral annulus apical 4-chamber view. Tissue Doppler imaging included the following parameters: early diastolic myocardial velocity (Em), late diastolic myocardial velocity (Am), and Em/Am. All echocardiograms were interpreted by two experienced cardiologists who were blind to patient status.

Statistical analysis

SPSS 21.0 for Windows (SPSS Inc., Chicago, IL, USA) was used for statistical analyses. Quantitative data were expressed as mean ± standard deviation. Categorical data were presented as number and frequency (%). For the suitable analysis technique, Kolmogorov–Smirnov and homogeneity of variance tests were applied. Independent sample t-tests were used for two-group comparison of the normally distributed variables, and Mann–Whitney U-test was used for two-group comparison of the variables without normal distribution. Non-normally distributed variables were expressed as medians (interquartile ranges). Normally distributed continuous variables were expressed as mean ± standard deviation. Categorical variables were compared using the chi-square test. Independent predictors of SX score were assessed using multivariable logistic regression analysis. In the multivariate procedure, age, sex, body mass index, history of hypertension and diabetes mellitus, smoking, glomerular filtration rate,

LDL cholesterol levels, and non-dipper hypertension were the clinical variables considered. $P < 0.05$ was considered statistically significant.

Results

In this study, a total of 306 consecutive patients with ACS were screened. After excluding patients who met the exclusion criteria, the remaining 141 patients (34 female and 107 male; mean age 61 ± 11 years) were included in the study (Figure 1). STEMI, NSTEMI, and USAP were observed in 41 (29%), 85 (60%), and 15 (11%) patients, respectively. Among all patients with ACS, non-dipper hypertension was observed in 95 (67%) patients. The clinical characteristics of patients are displayed in Table 1. There were noticeable significant clinical differences between the groups. Patients with non-dipper hypertension had higher STEMI and lower USAP percentage than patients with dipper hypertension. Patients with non-dipper hypertension also had higher SX score, higher peak high-sensitivity troponin I levels, higher left ventricular dimensions, and lower ejection fraction than the patients with dipper hypertension (Tables 1 and 2 and Figure 2).

Patients were grouped according to median SX score tertiles defined as: low SX score < 8 (n = 61, 43%) and high SX score ≥ 8 (n = 80, 57%). The number of patients with high scores was significantly higher in the non-dipper hypertension group compared to the dipper hypertension group (Table 1). In a multivariable logistic regression model, non-dipper

Table 1 – Baseline clinical characteristics of the study population

	Dipper group (n=46)	Non-dipper group (n=95)	p
Age (years)	61±12	61±11	0.868[a]
Male sex (n) (%)	35 (76)	72 (76)	0.969[a]
BMI (kg/m^2)	27.4±3.8	28.0±3.7	0.395[a]
HT (n, %)	23 (50)	48 (51)	0.953[b]
DM (n, %)	12 (26)	29 (31)	0.586[b]
Smoking (n, %)	14 (30)	36 (38)	0.385[b]
Mean daytime BP (mmHg, systolic/diastolic)	121.3±13.9/ 73.4±9.2	118.2±15.4/ 69.5±10.3	0.251[a] 0.035[a]
Mean nighttime BP (mmHg, systolic/diastolic)	103.5±12.3/ 63.0±8.2	118.2±15.4/ 70.5±9.8	<0.001[a] <0.001[a]
ACS type:			
STEMI (n, %)	7 (15)	34 (36)	0.012[b]
NSTEMI (n, %)	29 (63)	56 (59)	0.641[b]
USAP (n, %)	10 (22)	5 (5)	0.030[b]
SYNTAX Score*	5 (0-21)	9.5 (0-29)	<0.00'c
High SYNTAX Score (n, %)[#]	16 (35)	64 (67)	<0.001[b]
Medications			
ACE inhibitor or ARB (n, %)	16 (35)	30 (32)	0.704[b]
Calcium antagonist (n, %)	6 (13)	21 (22)	0.200[b]
Diuretics (n, %)	8 (17)	17 (18)	0.942[b]
MRA (n, %)	1 (2)	2 (2)	0.979[b]
B-blocker (n, %)	10 (22)	27 (28)	0.398[b]
α-blocker (n, %)	1 (2)	0 (0)	0.149[b]
Clopidogrel	35(76.1)	84(88)	0.082[b]
Ticagrelol	8 (17)	9 (9.5)	0.180[b]
Prasugrel	3 (6.5)	2(2.1)	0.330[b]
Acetylsalicylic acid	46 (100)	95 (100)	1[b]
Statin	46 (100)	93 (98)	1[b]

*[a] Independent t test, [b] Chi-square test, [c] Mann–Whitney U test, * Data are expressed as median (interquartile range) for continuous variables. [#]Above the median value. ACE: angiotensin converting enzyme; ACS: acute coronary syndrome; ARB: angiotensin receptor blocker; BMI: body mass index; BP: blood pressure; DM: diabetes mellitus; HT: hypertension; MRA: mineralocorticoid receptor antagonist; NSTEMI: non-ST-elevation myocardial infarction; STEMI: ST-elevation myocardial infarction; USAP: unstable angina pectoris.*

Table 2 – Biochemical values and echocardiographic parameters of the study population

	Dipper group n=46	Non-dipper group n=95	p
Peak hs-troponin I (ng/L) *	2413 (13.9-50000)	9036 (1.01-150050)	0.021[c]
Creatinine (mg/dL) *	0.94 (0.56-1.66)	0.87 (0.63-1.86)	0.361[c]
eGFR (ml/dk/1,73 m^2) *	83.5 (34-114)	89.6 (32.9-118)	0.737[c]
Sodium (mmol/L)	137±2	137±2	0.549[a]
Potassium (mmol/L)	4.3±0.3	4.3±0.4	0.930[a]
Calcium (mg/dL)	9.0±0.4	8.8±0.5	0.058[a]
ALT (IU/L) *	24 (9-94)	24 (6-150)	0.418[c]
AST (IU/L) *	35.5 (15-291)	38 (10-472)	0.809[c]
CRP (mg/L) *	2.65 (0-79)	2.4 (0-93)	0.974[c]
FBG (mg/dL) *	122.5 (74-367)	127 (59-316)	0.427[c]
LDL-C (mg/dL)	137±39	134±39	0.709[a]
HDL-C (mg/dL)	48±18	45±12	0.301[a]
TC (mg/dL)	204±48	203±43	0.880[a]
TG (mg/dL)	174±143	166±147	0.541[a]
LV-EDD (mm)	46.1±4.4	47.9±4.6	0.037[a]
LV-ESD (mm)	30.9±5.8	33.3±5.6	0.025[a]
IVS (mm) *	11 (8-14)	12 (9-15)	0.000[c]
PW (mm) *	11 (8-14)	11 (9-14)	0.045[c]
LA (mm) *	36 (24-47)	36 (30-57)	0.286[c]
EF (%)*	55 (35-65)	55 (25-65)	0.009[c]
DD (n, %)	31 (67)	62 (65)	0.669[b]

*[a] Independent t test, [b] Chi-square test, [c] Mann–Whitney U test * Data are expressed as median (interquartile range) for continuous variables. ALT: alanine aminotransferase; AST: aspartate aminotransferase; CRP: C-reactive protein; DD: diastolic dysfunction; EF: ejection fraction; eGFR: estimated glomerular filtration rate; FBG: fasting blood glucose; HDL-C: high-density lipoprotein cholesterol; hs-troponin I: high-sensitivity troponin I; IVS: interventricular septum; LA: left atrium; LDL-C: low-density lipoprotein cholesterol; LV-EDD: left ventricular end-diastolic diameter; LV-ESD: left ventricular end-systolic diameter; PW: posterior wall; TC: total cholesterol; TG: triglycerides.*

hypertension status emerged as and independent predictor of high SX score. Other independent predictors of high SX score included sex and LDL cholesterol (Table 3).

Discussion

Our results suggested a significant association between blunted nocturnal systolic BP reduction (non-dipper hypertension) on frequent CBPM and the severity and complexity of CAD calculated by SX score among patients hospitalized for ACS. Also, we found that non-dipper hypertension was an independent indicator of higher SX score in these patient populations.

For the first time, O'Brien et al.[19] reported that the blunted decrease in nighttime BP was associated with a higher prevalence of stroke. They described this circadian BP abnormality as non-dipper hypertension. Since then, a growing number of reports have published that there is a close relationship between non-dipper hypertension and increased cardiovascular morbidity and mortality.[2-7] In a recent meta-analysis, the ABC-H[7] study evaluated the 8-year follow-up of 17,312 hypertension patients. The non-dipping pattern, after adjustment for 24-hour systolic BP, predicted an excess risk ranging from 33% for all-cause mortality to 57% for cardiovascular mortality. Mousa et al.[20] showed a significant association between non-dipper hypertension and significant CAD (≥ 70% coronary artery stenosis on angiography) independent of other clinical parameters in men. Wirtwein et al.[21] reported that extent of significant coronary artery stenosis (≥ 50% stenosis in at least three coronary arteries on angiography) and major adverse cardiovascular events were related to blunted nighttime systolic BP dipping.

Although the close correlation between non-dipper hypertension and major adverse cardiovascular events has been demonstrated in many different studies, the underlying pathophysiological mechanism remains unclear. SX score has been proven to reflect major adverse cardiovascular events as in non-dipper hypertension. Therefore, the results of our study may provide additional evidence for such correlation by revealing more intense and more complex CAD calculated by SX score in patients with ACS and non-dipper hypertension. Among the most emphasized mechanisms in pathogenesis are the shift to sympathetic overactivity in the autonomic

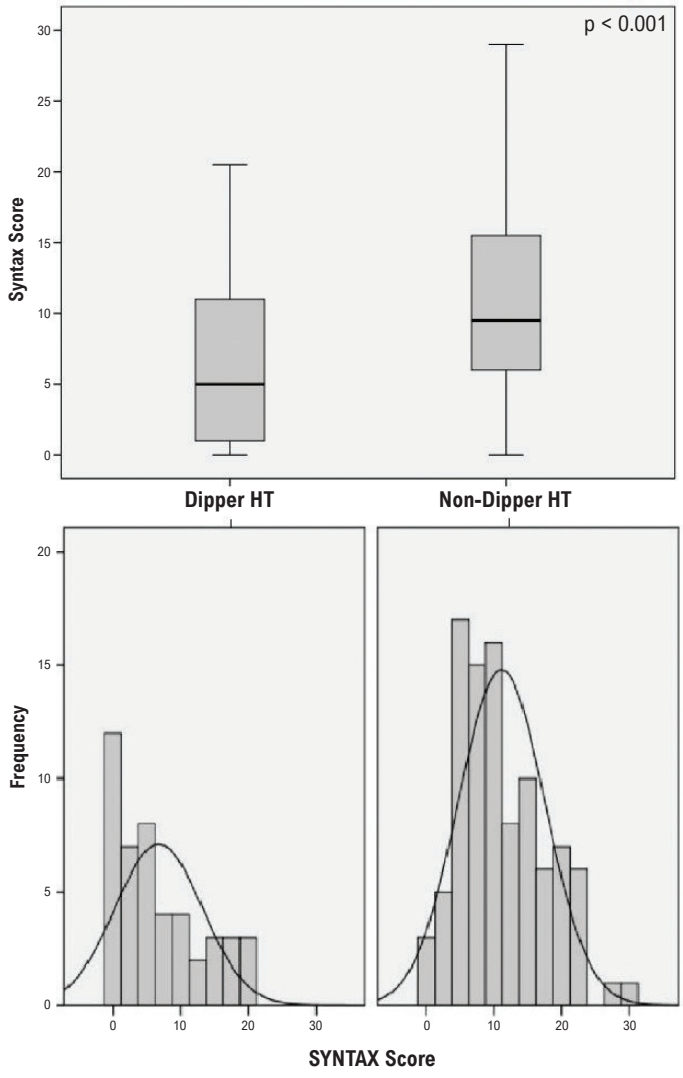

Figure 2 – *Comparison of SYNTAX scores of patients in dipper and non-dipper hypertension groups (11.12 ± 6.41 versus 6.74 ± 6.45, p < 0.001). HT: hypertension.*

Table 3 – Multivariate analysis showing the association between parameters and Syntax score

Variables	β	SE	Wald	OR (95% CI)	p
Age	-0.016	0.024	0.424	0.984 (0.939-1.032)	0.515
Sex	1.406	0.562	6.260	4.081 (1.356-12.282)	0.012
BMI	-0.051	0.054	0.903	0.950 (0.855-1.056)	0.342
HT	0.000	0.445	0.000	1.000 (0.418-2.389)	0.999
DM	-0,030	0.453	0.004	0.970 (0.399-2.357)	0.947
Smoking	0.056	0.456	0.015	1.058 (0.433-2.586)	0.901
eGFR	-0.013	0.014	0.856	0.987 (0.960-1.015)	0.355
LDL-C	0.015	0.005	7.048	1.015 (1.004-1.026)	0.008
Non-dipper HT	1.641	0.424	14.952	5.159 (2.246-11.852)	0.000

BMI: body mass index; DM: diabetes mellitus; eGFR: estimated glomerular filtration rate; HT: hypertension; LDL-C: low-density lipoprotein cholesterol.

nervous system at night, arterial baroreceptor dysfunction, elevated myocardial repolarization lability, increased sodium sensitivity, increased arterial stiffness, chronic low-grade inflammation, and endothelial dysfunction.[22-27] Decreased arterial tone at night causes pulsatile BP to be transmitted to microcirculation more effectively than during the day and disrupts the physiological laminar flow. As a result, arterial endothelial cells are exposed to oscillatory shear stress; nitric oxide bioavailability decreases; oxidative stress increases, and endothelial dysfunction, which is the first step in the development of atherosclerosis, is stimulated.[28,29] Complex coronary lesions assessed by SX score, such as branches, bifurcations, and curvatures, are closely related to oscillating shear stress, supporting this hypothesis.[30] We have previously shown that, in patients with ACS, oxidative stress markers significantly increased in intensive CAD assessed by the Gensini score.[31] Moreover, precursors of thrombogenesis such as von Willebrand factor, D-dimer, fibrinogen, and P-selectin have been shown to be significantly increased in patients with non-dipper hypertension and CAD, supporting the mechanism associated with ACS.[32] We also found a higher percentage of STEMI in patients with non-dipper hypertension, in which thrombosis is more prominent in its pathophysiology than in other ACS types.[33]

ABPM is considered the gold standard for monitoring nighttime BP; however, alternative methods have begun to develop, especially in hospitalized patients, due to the limited clinical use of ABPM, its high cost, and the fact that it disrupts sleep comfort. Xu et al.[8] measured, with a manual sphygmomanometer, 6 times a day at 4-hour intervals in hospitalized patients the values they called CBPM compared with traditional 24-hour ABPM. The investigators reported a strong correlation between clinical and ambulatory BP for both systolic and diastolic BP. Also, they declared that the detection of non-dippers by CBPM was in good agreement with 24-hour ABPM. Moreover, since an automatic home blood pressure monitor was first developed in 2001 and used for nighttime BP monitoring in a study, many studies have confirmed a strong correlation between APBM and HBPM measurements. It has been reported in the literature that HBPM can be a reliable alternative to ABPM to evaluate nighttime BP and detect non-dipper hypertension.[9,10,34] Recently, the J-HOP Nocturnal BP Study data, the largest practice-based HBPM cohort, showed that a 10 mmHg increase in nighttime systolic BP in HBPM was associated with a significant 20.1% increase in major adverse cardiovascular events, similar to those measured by ABPM.[35] Although Xu et al.[8] calculated CBPM in hospitalized patients by taking 3 daytime and 3 night-time BP measurements in a single day, in most HBPM studies, 3 daytime and 3 night-time BP measurements were repeated over 1 to 2 weeks and averaged. To overcome limited stay in the intermediate intensive care unit and the lack of opportunity to measure on repeated days under the same conditions, we performed CBPM at frequent intervals (once an hour) as a combination of both of these methods in our study.

Study limitations

Our study has some limitations:

Reproducibility could not be analyzed, as it was possible to measure BP for only one day. To overcome this problem, we used frequent CBPM, a modified CBPM, in our study.

Although we paid the maximum attention to ensure optimal conditions and sleep-wake levels, sleep quality that could affect nighttime BP was not evaluated in our study.

Even if both groups compared were in the same conditions, the hospitalization period immediately after ACS might affect the patients' stress state and autonomic nervous system, causing different results from the stable condition.

Conclusion

Our study results revealed the relationship between SX score and non-dipper hypertension in patients with ACS, to the best of our knowledge for the first time, providing a possible additional mechanism linking abnormal circadian BP with cardiovascular diseases. Further studies are needed to clarify this association and determine the approaches required for optimal diurnal BP. Longer duration and multiple 24-hour BP measurements may be more informative in this regard.

Authors Contribution

Conception and design of the research: Turan T, Kul S, Akyüz AR, Sayin MR; Acquisition of data: Özderya A, Sahin S, Konuş AH, Kara F, Akyüz AR; Analysis and interpretation of the data: Turan T, Kul S, Konuş AH, Uzun G, Akyüz AR; Statistical analysis: Özderya A, Sahin S, Kara F, Sayin MR; Writing of the manuscript: Turan T, Özderya A, Kara F, Sayin MR; Critical revision of the manuscript for intellectual content: Sahin S, Kul S, Konuş AH, Uzun G,

Potential Conflict of Interest

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

Sources of Funding

There was no external funding source for this study.

Study Association

This study is not associated with any thesis or dissertation.

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Can Attenuated Nocturnal Dipping be a Predictor of the Severity and Complexity of Coronary Artery Disease in Hospitalized Patients with Acute Coronary Syndrome?

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Minieditorial referente ao artigo: A Variação Anormal da Pressão Arterial Circadiana está Associada aos Escores SYNTAX em Pacientes Hospitalizados com Síndrome Coronariana Aguda

It is well established that there are significant prognostic implications resulting from the abnormal behavior of some 24-hour blood pressure (BP) parameters obtained through Ambulatory Blood Pressure Monitoring (ABPM).[1] Among them, the abnormal behavior of the mean systolic blood pressure (SBP) and diastolic (DBP) in 24 hours, wakefulness and sleep, stand out.[2] Specifically regarding the behavior of BP during sleep, it is already well established that the absence of nocturnal dipping has, independently, a significant impact on the increased cardiovascular risk.[3,4] Other parameters that may have prognostic implications are early morning BP elevation and greater 24-hour BP variability.[1,5]

Some recommendations are essential for the success of the ABPM exam, among them, the orientation for the patient to maintain their usual activities during the monitoring day. In this sense, assessing the circadian pattern of BP in hospitalized patients is not one of the indications of the method, even intending to study specific outcomes.

In the present cross-sectional and prospective study, Turan T. et al. aimed to evaluate, in hospitalized patients with the acute coronary syndrome (ACS), the relationship between coronary artery disease (CAD) and lower nocturnal BP dips.[6] To assess CAD, the SYNTAX score was used, which is well established for this purpose. And for BP assessment, clinical monitoring was adopted through an automatic device on monitors at the bedside. Such measurements were performed every hour, during the day and night. The authors established their own protocol, considering the averages of hourly BP values for 9 night periods (11:00 pm to 7:00 am) and 15 daytime shifts (8:00 am to 10:00 pm), obtaining a single mean daytime and nighttime BP value. Regarding the present, absent or reverse dipping definition, the parameters are the same used in the ABPM.

Among the results obtained, it can be highlighted that hospitalized patients with ACS, hypertensive and without nocturnal dipping had a higher SYNTAX score. In addition, the number of patients with high scores was significantly higher in the group of hypertensive patients without nocturnal dipping compared to the group with dipping. Despite not being able to establish causality effects because it is a cross-sectional study, in the multivariate logistic regression analysis, the status of hypertension without nocturnal dipping (non-dipper) was presented as an independent predictor of a high SYNTAX score.

This is the first study to assess the behavior of nocturnal BP in hospitalized patients with ACS. However, another study published by Mousa et al. had already demonstrated an association between hypertension without dipping and significant CAD in men.[7] It was shown that the absence of nocturnal dipping corresponded to an independent risk marker for CAD, with data obtained by ABPM in clinically stable patients, and elective coronary angiography.

Some limitations, duly described by Turan T. et al., are very important in the present study's analysis. Among them, it stands out the lack of verification of the reproducibility of BP measurements and the clinical condition of the evaluated patients, which can be very different from the usual condition in everyday life.[6] In this sense, it is worth reinforcing the mention by the authors of the study by Xu T. et al., who demonstrated a good correlation between the traditional manual BP measurement with a sphygmomanometer and the 24-hour ABPM in the detection of hypertensive patients without nocturnal dipping, also in a hospital.[8]

We know that ABPM is the gold standard for measuring BP, including the assessment of nocturnal dipping.[1,9] However, studies like this are important so that we have other alternatives in the circadian assessment of BP in the hospital environment and the study of its correlation with outcomes. New randomized studies assessing the method's reproducibility may provide greater support for clinical practice in a hospital environment.

Keywords

Blood Pressure; Nocturnal Dipping; Arterial Hypertension; Acute Coronary Syndrome; Coronary Artery Disease

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Catheter Ablation is Superior to Antiarrhythmic Drugs as First-Line Treatment for Atrial Fibrillation: a Systematic Review and Meta-Analysis

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Abstract

Background: **Catheter ablation is a well-established therapy for rhythm control in patients who are refractory or intolerant to anti-arrhythmic drugs (AAD). Less is known about the efficacy of catheter ablation compared with AAD as a first-line strategy for rhythm control in atrial fibrillation (AF).**

Objectives: **We aimed to perform a systematic review and meta-analysis of catheter ablation vs. AAD in patients naïve to prior rhythm control therapies.**

Methods: **PubMed, EMBASE, and Cochrane databases were searched for randomized controlled trials that compared catheter ablation to AAD for initial rhythm control in symptomatic AF and reported the outcomes of (1) recurrent atrial tachyarrhythmias (ATs); (2) symptomatic AF; (3) hospitalizations; and (4) symptomatic bradycardia. Heterogeneity was examined with I^2 statistics. P values of < 0.05 were considered statistically significant.**

Results: **We included five trials with 994 patients, of whom 502 (50.5%) underwent catheter ablation. Mean follow-up ranged from one to five years. Recurrences of AT (OR 0.36; 95% CI 0.25-0.52; p<0.001) and symptomatic AF (OR 0.32; 95% CI 0.18-0.57; p<0.001), and hospitalizations (OR 0.25; 95% CI 0.15-0.42; p<0.001) were significantly less frequent in patients treated with catheter ablation compared with AAD. Symptomatic bradycardia was not significantly different between groups (OR 0.55; 95% CI 0.18-1.65; p=0.28). Significant pericardial effusions or tamponade occurred in eight of 464 (1.7%) patients in the catheter ablation group.**

Conclusion: **These findings suggest that catheter ablation has superior efficacy to AAD as an initial rhythm control strategy in patients with symptomatic AF.**

Keywords: **Catheter Ablation; Anti-Arrhythmia Agents; Atrial Fibrillation.**

Introduction

Atrial fibrillation (AF) is a highly prevalent condition, estimated to affect nearly 50 million people worldwide.[1,2] The global prevalence of AF continues to increase, likely related to population aging and the rising prevalence of obesity and cardiometabolic disease. In the US alone, more than 12 million individuals may have AF by 2030.[1,2] The diagnosis and burden of AF are associated with increased mortality, cerebrovascular events, heart failure, and hospitalizations.[3,4] However, improved survival, quality of life, and freedom from non-fatal events can be achieved with effective strategies of anticoagulation, heart rate control, and/or rhythm control in selected patients.[3-5]

Antiarrhythmic drug (AAD) therapy and catheter ablation with pulmonary vein isolation are two well-established options for rhythm control when maintenance of sinus rhythm is desirable. However, both strategies have drawbacks, including limited efficacy. AAD can lead to side effects, drug-drug interactions, and ventricular arrhythmias, and catheter ablation is an invasive procedure, with the potential for rare but serious complications. In the most recent multi-society guidelines from Europe and North

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America, catheter ablation is recommended as a class I indication for patients who fail a strategy of AAD, whereas its use as a first-line therapy is less recommended.[3,4]

Recently, two large, randomized trials have explored the role of catheter ablation as first-line therapy for rhythm control in patients with symptomatic AF.[6,7] These trials have greatly increased the population of randomized patients who underwent either catheter ablation or AAD as a first-line strategy for rhythm control. Therefore, we sought to perform a systematic review and meta-analysis comparing these two strategies in randomized studies, evaluating efficacy outcomes in a large population, as well as to examine secondary endpoints, for which the individual studies may be underpowered.

Material and methods

Eligibility criteria and data extraction

We restricted our analysis to studies that met all the following inclusion criteria: (1) randomized controlled trials (RCTs) of catheter ablation vs. AADs; (2) inclusion of patients with symptomatic AF who had not received any AAD treatment; and (3) analysis of any of the following outcomes of interest – recurrence of atrial tachyarrhythmias, recurrence of symptomatic AF, hospitalizations, symptomatic bradycardia, and quality of life. The exclusion criteria included non-randomized studies, and trials including patients who had previously failed catheter ablation or AAD therapy. In case of studies with overlapping patient populations, the study with the largest number of patients was included. There were no restrictions for inclusion based on the size of the study population.

Two authors (G.B.J. and L.B.S.) independently extracted data following pre-defined search criteria and quality assessment methods. Disagreements between these authors were resolved by consensus among three authors (R.C., G.B.J., and L.B.S.).

Search strategy

We systematically searched PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials. The search was conducted without date restrictions in December 2020 for studies published in English only. The following medical subject heading terms were included: "atrial fibrillation" AND ("ablation" OR "radiofrequency" OR "cryoablation" OR "cryoballoon") AND ("antiarrhythmic" OR "AAD" OR "amiodarone" OR "sotalol" OR "flecainide" OR "propafenone" OR "dofetilide") AND ("first-line" OR "initial"). In addition, the reference lists of all included studies, meta-analyses and reviews were manually searched.

Quality assessment

Risk of bias and quality assessment of individual studies were analyzed with the Cochrane Collaboration's tool for assessing risk of bias in randomized studies.[8] Each trial was given a score for "high risk", "low risk", or "unclear risk" in each of the five domains: selection, performance, detection, attrition, and reporting biases. Funnel plots of individual study weights against point estimates were used to check for evidence of publication bias.

Statistical analysis

Systematic review and meta-analysis were performed according to the Cochrane Collaboration's tool for assessing risk of bias and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement.[9] Odds ratios (OR) with 95% confidence intervals (CI) were computed to compare the incidence of binary endpoints between the two treatment arms. We used Cochran's Q test and I^2 statistics to evaluate for heterogeneity. Endpoints were considered to have low heterogeneity if $p > 0.10$ and $I^2 < 25\%$. We used a fixed-effect model for endpoints with $I^2 < 25\%$ (low heterogeneity). In outcomes with high heterogeneity, pooled estimates were computed with DerSimonian and Laird random-effects model. P values of < 0.05 were considered statistically significant. Statistical analyses were performed with Review Manager 5.4 (Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark).

Results

As detailed in Figure 1, 1,281 studies were identified using the search strategy in the three databases and manual search of references of pertinent reviews and meta-analyses. After removal of duplicate articles and unrelated studies, 25 were fully reviewed for the inclusion and exclusion criteria. A total of five studies and 994 patients were included, of whom 502 (50.5%) underwent catheter ablation.[6,7,10-12] Population characteristics are presented in Table 1. The studies were heterogeneous with regards to the ablation technique, monitoring of recurrent atrial tachyarrhythmias (ATs), and the follow-up period, which ranged from one to five years.

Recurrence of ATs were significantly less frequent in patients treated with catheter ablation (147/502; 29.2%) as compared with AAD (245/492; 49.8%) (OR 0.36; 95% CI 0.25-0.52; p<0.001; Figure 2). Similarly, symptomatic recurrences of AF were also reduced in patients randomized to catheter ablation (57/398; 14.3%) compared with AADs (118/393; 30%) (OR 0.32; 95% CI 0.18-0.57; p<0.001; Figure 3). Hospitalizations were also less frequent in the catheter ablation group (21/436; 4.8% vs. 66/431; 15.3%) (OR 0.25; 95% CI 0.15-0.42; p<0.001; Figure 4).

Regarding safety endpoints, symptomatic bradycardia (OR 0.55; 95% CI 0.18-1.65; p=0.28; I^2=0%; Figure 5) was not significantly different between patients treated with catheter ablation (3/502; 0.6%) and AAD therapy (7/492; 1.4%). A clinically significant pericardial effusion or pericardial tamponade occurred in 8 of 464 patients in the catheter ablation group (1.7%).

Supplementary Table 1 outlines the quality appraisal of each individual RCT. All studies were considered at risk for performance bias, given the impossibility to perform patient and investigator blinding in the trials. Otherwise, studies were judged to be at low risk of biases. Sensitivity analyses were performed by systematically removing each study from the pooled estimates. After removal of each individual study, the results for recurrences of ATs, symptomatic AF, hospitalizations, and symptomatic bradycardia were unchanged. Although limited by the small number of studies, there was no definitive evidence of publication bias in the funnel plots (Supplementary Figure 1).

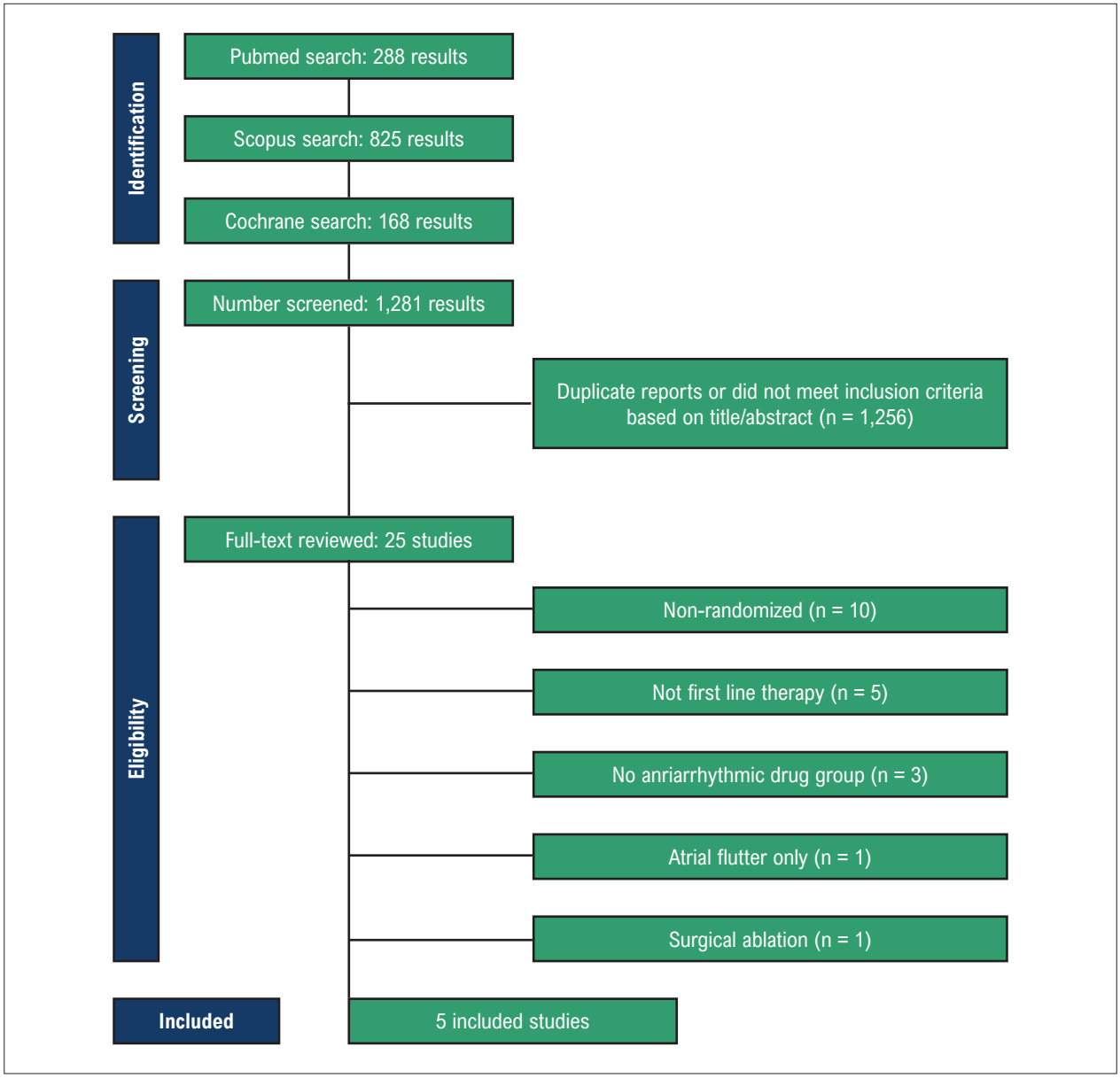

Figure 1 – *PRISMA flow diagram of study screening and selection*

Discussion

In this systematic review and meta-analysis of five studies and 994 patients, we compared catheter ablation with AAD as first-line therapy for rhythm control in patients with AF. The main findings were as follows: (1) the incidence of symptomatic recurrent AF over a follow-up period of one to five years was approximately halved by catheter ablation as compared with AAD (14.3% vs. 30.0%, respectively; OR 0.32; p<0.001); (2) this difference was also statistically significant for reduction of ATs, favoring catheter ablation (OR 0.36; p<0.001); and (3) there was a 3-fold decrease in hospitalizations among those who underwent catheter ablation (4.8% vs. 14.3%).

Catheter ablation has proven to be a superior option to escalation of AAD therapy for rhythm control among patients who have recurrent AF despite an initial attempt of AAD therapy or prior ablation. In the Catheter Ablation vs. Antiarrhythmic Drug Therapy for Atrial Fibrillation (CABANA) trial, 2,204 patients with symptomatic AF with current or past use of ≥1 AAD were randomized to catheter ablation with pulmonary vein isolation or drug therapy. In intention-to-treat analysis, over a median follow-up of 48.5 months, AF recurrence occurred in 49.9% of patients randomized to catheter ablation and 69.5% of those in the drug therapy arm (HR 0.52; 95% CI 0.45-0.60; p<0.001). The primary outcome of death, disabling stroke, serious bleeding or cardiac arrest was not significantly different between ablation and AAD therapy (8% vs. 9.2%, respectively; HR 0.86; p=0.30).[13]

Despite disappointing results with regards to mortality and vascular endpoints, CABANA and other trials unquestionably

Table 1 – Baseline characteristics of included studies

	Number of patients	Male, n(%)	Mean age (years)	Catheter ablation technique	AAD therapy	AT monitoring	Paroxysmal AF, n (%)	Mean time from AF diagnosis (months)	Mean LVEF (%)	Follow-up (years)
RAAFT-1 2005	67	NA	CA: 53 AAD: 54	RF	Flecainide, 77% Sotalol, 23% No AAD reported in ablation group	24-hour Holter before discharge, 3, 6 and 12 months	CA: 32 (97) AAD: 35 (95)	5	CA: 53 AAD: 54	1
MANTRA-PAF 2012	294	CA: 100 (68) AAD: 106 (72)	CA: 56 AAD: 54	RF	Class IC drugs preferred; class III second line; AAD allowed in ablation group for the 3-month blanking period	7-day Holter monitoring at 3, 6, 12, 18 and 24 months	CA: 146 (100) AAD: 148 (100)	NA	LVEF >60%: 237 (80%)	5*
RAAFT-2 2014	127	CA: 51 (77.3) AAD: 45 (73.8)	CA: 56 AAD: 54	RF	During 90-day blanking period: Flecainide, 69%; propafenone 25%; dronedarone 3%. AAD allowed in ablation group	ECG, Holter, transtelephonic monitor, or rhythm strip	CA: 65 (98) AAD: 59 (97)	NA	CA: 61 AAD: 61	2
STOP-AF 2020	203	CA: 63 (61) AAD: 57 (58)	CA: 60 AAD: 62	CB	In AAD group: flecainide 60%; propafenone 7%; dronedarone 12%; sotalol 7%; amiodarone 2%. In ablation group, AAD allowed for 80 days in blanking period.	12-lead ECG conducted at baseline, 1, 3, 6, and 12 months; patient-activated telephone monitoring weekly and when symptomatic at 3-12 months; 24h ambulatory monitoring at 6 and 12 months	CA: 104 (100) AAD: 99 (100)	15.6	CA: 61 AAD: 61	1
EARLY-AF 2020	303	CA: 112 (72.7) AAD: 102 (68.5)	CA: 58 AAD: 59	CB	Flecainide 76%; propafenone 5%; sotalol 15%; dronedarone 3%; AAD allowed in blanking period.	Implantable cardiac monitoring; manual weekly transmissions; visits at 3, 6 and 12 months	CA: 147 (95) AAD: 140 (94)	1	CA: 60 AAD: 60	1

P values < 0.05 were considered statistically significant in all included studies; ‡hypertension and structural heart disease; AAD: antiarrhythmic drugs; AF: atrial fibrillation; AT: atrial tachyarrhythmia; CA: catheter ablation; CB: cryoablation; ECG; electrocardiogram; LVEF: left ventricular ejection fraction; NA: not available; RF: radiofrequency.

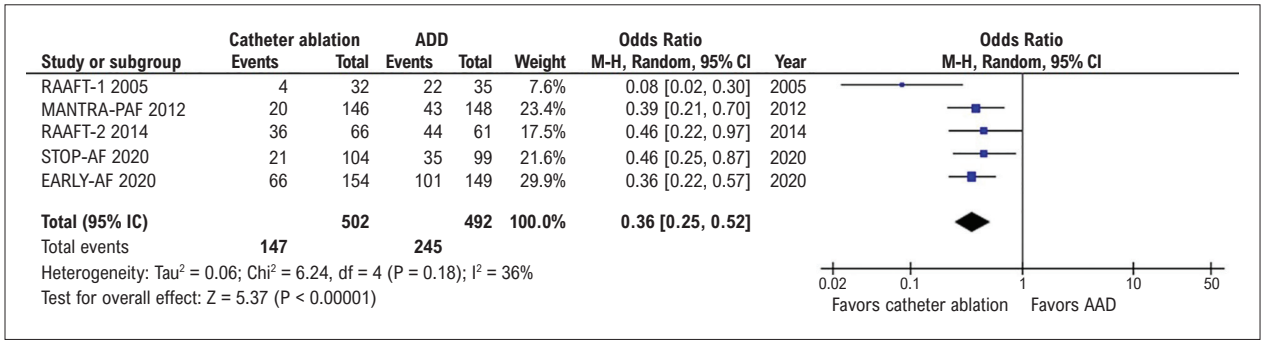

Figure 2 – *Recurrences of atrial tachyarrhythmias were significantly less common with catheter ablation compared to antiarrhythmic drugs (p<0.001). AAD: antiarrhythmic drugs.*

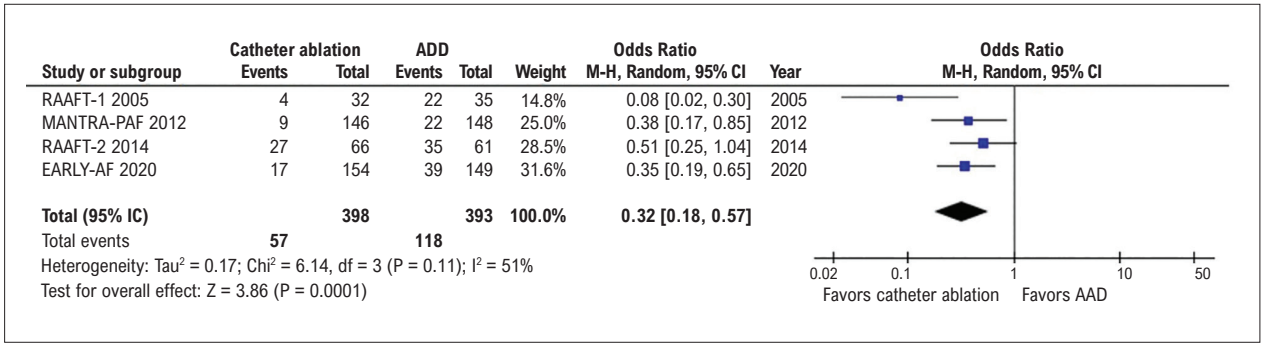

Figure 3 – *Recurrences of symptomatic AF were significantly less common with catheter ablation compared to antiarrhythmic drugs. (p<0.001). AAD: antiarrhythmic drugs.*

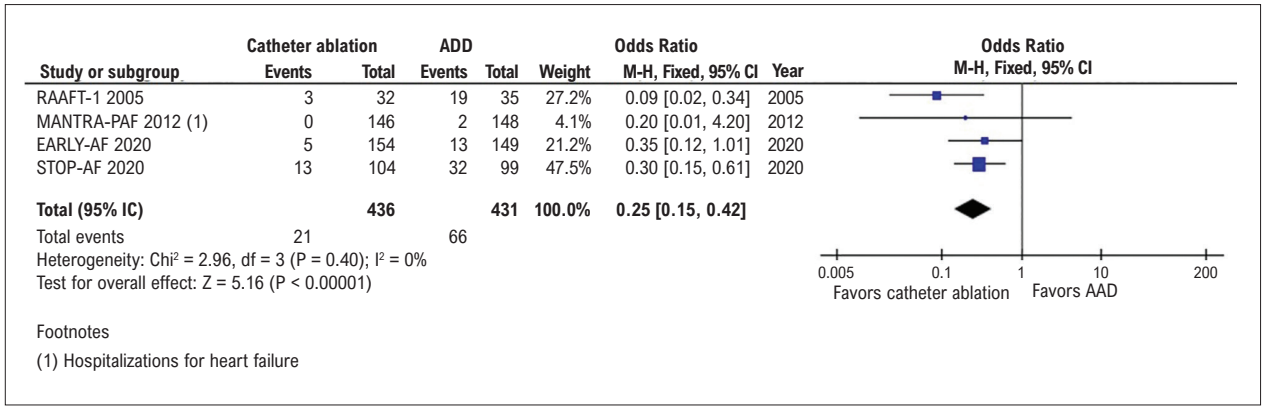

Figure 4 – *Hospitalizations were significantly less common with catheter ablation compared to antiarrhythmic drugs (p<0.001). AAD: antiarrhythmic drugs.*

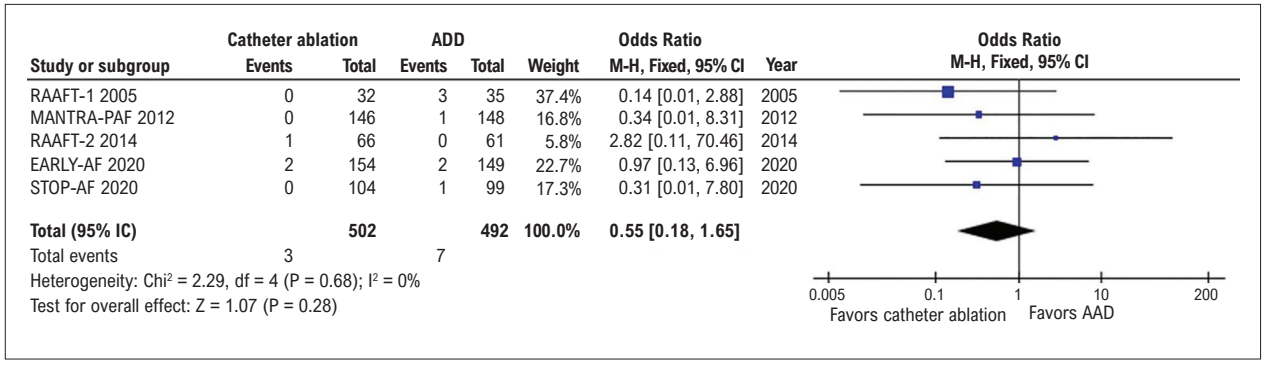

Figure 5 – *The incidence of symptomatic bradycardia was rare and similar between groups (p=0.28). AAD: antiarrhythmic drugs.*

show a higher efficacy of catheter ablation as compared with AAD therapy alone in patients who previously failed rhythm control with AAD.[13-16] Nevertheless, there has been a renewed interest in effective rhythm control early in the natural history of AF. Indeed, the notion that 'AF begets AF', due to atrial fibrosis and adverse remodeling, is well-known for nearly three decades.[17,18] In the recently published Treatment of Atrial Fibrillation for Stroke Prevention Trial (EAST-AFNET 4), 2,789 patients with AF diagnosed within the prior 12 months (27% persistent AF) were randomized to early rhythm control with catheter ablation (8%) or AAD (87%) or to usual care with rate control and rhythm control for refractory symptoms. Over a median follow-up of 5.1 years, there was a significant reduction in the primary endpoint of cardiovascular death, stroke, or hospitalization with heart failure or acute coronary syndrome favoring early rhythm control (3.9 per 100 person-years) over usual care (5.0 per 100 person-years) (HR 0.79; 96% CI 0.66-0.94; p=0.005).[19]

The strategy of early rhythm control with AAD, however, is limited by reduced efficacy of drug therapy alone. A recent systematic review and meta-analysis from the Cochrane

Collaboration examined the efficacy and safety of AADs in 59 RCTs with 20,981 participants, including both paroxysmal and persistent AF. Over a mean follow-up of 10.2 months, AF recurred in 43-67% of patients treated with AADs.[20] The limited efficacy of AAD therapy is quite evident when considering the high cross-over rate from the AAD arm to the catheter ablation arm in randomized trials. In the STOP AF First: Cryoballoon Catheter Ablation in Antiarrhythmic Drug Naïve Paroxysmal Atrial Fibrillation trial, a third of patients in the AAD group underwent an ablation due to drug therapy side effect or recurrence of AF.[6] In the CABANA trial, 27.5% of patients in the AAD group crossed over to catheter ablation during follow-up.[13]

Earlier trials comparing the efficacy of catheter ablation to AAD therapy in patients naïve to any rhythm control strategy were limited by small sample sizes.[10,12] Collectively, these studies did not determine a conclusive superiority of catheter ablation over AAD therapy.[10-12] A meta-analysis of these trials found a significantly lower freedom from AF recurrence with catheter ablation, relative to AAD therapy (risk ratio [RR] 0.63; 95% CI 0.44-0.92; p=0.02); however, the rate of symptomatic AF recurrences was not significantly different between groups (RR 0.57; 95% CI 0.30-1.08; p=0.09).[21] Therefore, the STOP AF First and the Cryoablation or Drug Therapy for Initial Treatment of Atrial Fibrillation (EARLY-AF) trials were designed to further investigate the role of catheter ablation as a first-line rhythm control strategy.

Our findings provide a more accurate understanding of the treatment effect by pooling a large population of patients randomized to catheter ablation or AAD therapy. The magnitude of effect favoring catheter ablation was substantial. The absolute reduction in the frequency of AT and symptomatic AF with catheter ablation as compared with AAD therapy was 20% and 15%, respectively. When considering these findings, safety outcomes of catheter ablation must not be overlooked, to guide shared decision-making. The pooled incidence of significant pericardial effusions and/or pericardial tamponade in these studies was 1.7%. In a meta-analysis of nearly 9,000 patients who underwent cryoablation or radiofrequency ablation, the incidence of pericardial tamponade was 1.1%. Phrenic nerve palsy occurred in 1.6% of patients who underwent cryoablation, but the vast majority resolved during short-term follow-up.[22]

As shown in Table 1, the ablation techniques were heterogeneous between studies. The three earlier studies used radiofrequency ablation, whereas the more recent STOP-AF and EARLY-AF trial used cryoballoon.[6,7,10-12] Although the techniques have important differences in operator learning curves and safety endpoints, the FIRE and ICE randomized trial[23] and a meta-analysis[22] have shown similar efficacy between the two techniques. More importantly, radiofrequency technology has improved substantially in recent years, particularly with the development of contact force sensors, which were not used in the radiofrequency trials included in the present study. A meta-analysis of 22 studies showed that contact force-guided catheter ablation substantially reduced procedure time and improved AF-free survival by 12%.[24] Whether the use of newer technology for radiofrequency catheter ablation would modify the comparative efficacy of catheter ablation vs. AAD for initial rhythm control in symptomatic AF is unknown. However, if so, this would translate into an even more favorable effect of ablation relative to AAD therapy.

Our study has limitations. First, long-term follow-up beyond two years was only possible for two out of five studies. Second, the rhythm monitoring strategy was heterogeneous between studies as outlined in Table 1, varying from periodic Holter monitoring to continuous cardiac monitoring. However, sensitivity analysis removing one study at a time did not alter the significance of efficacy estimates. Third, the absence of patient-level data precluded more granular assessment of outcomes, such as time-to-recurrence of AT/AF. Finally, the small number of studies did not allow for subgroup analyses of different catheter ablation techniques. However, a prior meta-analysis has shown similar efficacy between radiofrequency and cryoballoon ablation.[22]

Conclusion

In summary, catheter ablation significantly reduces the recurrence of AT and symptomatic AF as compared with AAD therapy in patients who are naïve to prior attempts of rhythm control. This study provides evidence supporting catheter ablation as a class I indication for rhythm control in patients with paroxysmal AF.

Data sharing agreement

Because this meta-analysis was based on data extracted from previously published research, all data and study materials are available in the public domain. The authors of this meta-analysis did not have access to patient-level data of the included studies, and researchers interested in these data are encouraged to contact the corresponding authors of each study.

Author Contributions

Conception and design of the research and Statistical analysis: Cardoso R; Acquisition of data: Cardoso R, Justino GB, Graffunder FP, Benevides L; Analysis and interpretation of the data: Cardoso R, Justino GB, Graffunder FP, Benevides L, Knijnik L, Sanchez LMF; Writing of the manuscript: Cardoso R, Justino GB, Graffunder FP, Knijnik L, Sanchez LMF, d'Avila A; Critical revision of the manuscript for intellectual contente: Cardoso R, Justino GB, Benevides L, Knijnik L, Sanchez LMF, d'Avila A.

Potential Conflict of Interest

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

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Study Association

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

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*Supplemental Materials

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Catheter Ablation as First-Line Therapy in the Treatment of Atrial Fibrillation – Should We Always Indicate it?

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Short Editorial related to the article: Catheter Ablation is Superior to Antiarrhythmic Drugs as First-Line Treatment for Atrial Fibrillation: a Systematic Review and Meta-Analysis

Atrial fibrillation (AF) is the most common cardiac arrhythmia in clinical practice, affecting approximately 1 to 2% of the general population and is associated with an increased risk of cardioembolic events and a negative impact on quality of life. The cardiovascular mortality rate described is approximately 5% per year,[1] and it is estimated that the risk of cardiovascular complications is higher in the first year after the diagnosis of arrhythmia.[2] The recurrence rate of AF without adequate preventive treatment is around 90%, which expresses the magnitude of the problem.[3]

Thus, it seems quite reasonable to postulate the concept that an early approach to AF brings relevant clinical benefits to these patients. Recent data obtained from the EAST-AFNET4[4] study clearly demonstrated that this approach is a valid and effective strategy. The study involved 2789 patients diagnosed with AF for at least 12 months who were randomized to early treatment of AF (ablation: 8% and AAD: 87%) or conservative treatment. At a median follow-up period of 5.1 years, the early treatment group demonstrated a significant reduction in the primary endpoint of cardiovascular death compared to the conservative group. The risk of stroke, hospitalization for HF or acute coronary syndrome was also lower in the early approach group. The study design was not primarily intended to assess the safety and effectiveness of early treatment components (ablation vs. antiarrhythmic drugs - AAD). Therefore, the authors concluded that an early heart rhythm control strategy was associated with a lower risk of unfavorable outcomes than usual care in patients with AF and associated cardiovascular conditions.

Catheter ablation has proved to be a superior alternative to pharmacological treatment in rhythm control and improved quality of life.[5-7] Several previous trials have also demonstrated the clear benefit of catheter ablation of AF as first-line therapy, reinforcing the concept that a shorter time from diagnosis to ablation is associated with a lower rate of recurrence and fewer repeat procedures and a reduction in hospitalization.[8,9] Similarly, the shorter time from the first diagnosis of persistent AF to ablation reduces the occurrence of extrapulmonary vein triggers and recurrence of atrial tachyarrhythmias.[10]

In this journal, Carddoso et al.[11] presented an elegant systematic review and meta-analysis on the superiority of catheter ablation as first-line therapy over AADs for AF.

Trials selected should meet all of the following inclusion criteria: randomized controlled trials of catheter ablation vs. AAD; AF patients who did not receive AAD treatment; analysis of any of the following outcomes of interest: recurrence of atrial tachycardia, recurrence of symptomatic AF, hospitalizations, symptomatic bradycardia, and quality of life. Exclusion criteria were non-randomized studies and trials, including patients who had previously undergone catheter ablation or AAD therapy without success.

Initially, 1281 studies were identified by the search strategy, and, in the end, 5 studies were included, with 994 patients, of which 502 (50.5%) underwent catheter ablation, with a follow-up time that ranged from one to five years old.

The recurrence of AT was significantly less frequent in patients treated with catheter ablation (147/502; 29.2%) compared to AAD (245/492; 49.8%) (OR 0.36; 95%CI 0.25 -0.52; p<0.001). Recurrence of symptomatic AF was also lower in the catheter ablation group (57/398; 14.3%) compared to the AAD group (118/393; 30%), as was the rate of hospital admissions (21/436; 4.8% vs. 66/431; 15.3%) (OT 0.25; 95% CI 0.15-0.42; p<0.001). Symptomatic bradycardia was not different between the two groups (OR 0.55; 95%CI 0.18-1.65; p=0.28). Effusion or cardiac tamponade occurred in 8/464 patients in the ablation group (1.7%).

The authors then conclude that the findings obtained from this systematic review suggest greater efficacy of catheter ablation as an initial strategy to control heart rhythm in patients with symptomatic AF.

Two recent and important studies shed light on this topic, the EARLY-AF and the STOP-AF.[12,13] Both used the cryoablation technique and clearly demonstrated the superiority of catheter ablation over AADs as first-line therapy in managing these patients.

As can be seen, the benefit of this strategy has extensive scientific evidence. However, the question of systematically indicating catheter ablation as initial therapy before AAD encounters some limitations in the real world: patients' limited access to this type of intervention; the costs involved and the sources of payment; patient acceptance; and, above all, the acceptance and incorporation of this conduct as a clinical practice proven to be beneficial and safe for our patients.

Keywords

Arrhythmias,Cardiac/complications; Atrial,Fibrillation/complications; Thromboembolism/mortality; Thrombolytic Therapy/adverse effects; Catheter Ablation/methods.

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Prognostic Value of Adenosine Stress Perfusion Cardiac Magnetic Resonance Imaging in Older Adults with Known or Suspected Coronary Artery Disease

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Abstract

Background: **There is limited data on the prognostic value of stress cardiac magnetic resonance (CMR) in older adults.**

Objective: **To determine the prognostic value of adenosine stress CMR in older individuals with known or suspected coronary artery disease (CAD).**

Methods: **Between 2010 and 2015, consecutive patients aged 65 years or older referred for adenosine stress CMR were followed for the occurrence of severe cardiac events (cardiac death and nonfatal myocardial infarction) and major adverse cardiovascular events (MACE) that also included hospitalization for heart failure and ischemic stroke. Univariate and multivariate analyses were performed to determine the prognostic value of myocardial ischemia, with p-value <0.05 considered statistically significant.**

Results: **After a mean follow-up period of 50.4 months in 324 patients (48% male, 73±7 years), 21 severe cardiac events and 52 MACE occurred. Patients with myocardial ischemia (n=99) had significantly higher rates of severe cardiac events (HR 5.25 [95% CI 2.11-13.04], p<0.001) and MACE (HR 3.01 [95% CI 1.75-5.20], p<0.001) than those without ischemia. Multivariable analysis determined ischemia as an independent predictor of severe cardiac events (HR 3.14 [95% CI 1.22-8.07], p=0.02) and MACE (HR 1.91 [95%CI 1.02-3.59], p=0.04). Ischemia provided an incremental prognostic value over clinical factors and left ventricular ejection fraction for predicting severe cardiac events and MACE (p<0.01 for both). No severe adverse events occurred during or immediately after CMR examinations.**

Conclusion: **Adenosine stress CMR is safe and has prognostic value in older adults with known or suspected CAD.**

Keywords: **Adenosine; Cardiac Magnetic Resonance Imaging; Coronary Artery Disease; Elderly; Stress Test.**

Introduction

Aging is associated with diffuse changes throughout the cardiovascular system. The prevalence and severity of coronary artery disease (CAD) increase progressively with age in both men and women.[1] In developed countries, approximately two-thirds of all myocardial infarctions (MI) occur in people over 65 years old.[2] The elderly are more likely to present with atypical symptoms such as exertional shortness of breath or fatigue rather than typical angina.[3] The prevalence of silent myocardial ischemia and unrecognized myocardial infarction (MI) is also significantly higher in the elderly and has prognostic value.[4] Older patients also tend to be at increased risk for complications including heart failure, arrhythmias, bleeding, and death in the setting of cardiac procedures, such as percutaneous coronary intervention or cardiac surgery. Therefore, diagnosis and risk stratification of CAD in elderly patients are critically important.

Testing for ischemia in elderly patients is challenging. Exercise testing is less feasible in older adults due to lower exercise capacity and comorbidities, as well as baseline electrocardiographic (ECG) abnormalities that limit ischemic assessments. Cardiac magnetic resonance (CMR) provides a comprehensive assessment of CAD with very high accuracy. CMR can assess global and regional ventricular function, myocardial ischemia, and infarction in a single study. Moreover, pharmacological stress CMR offer strong evidence for the prognosis, including mortality in patients with known or suspected CAD.[5-8]

Previous data have shown that stress perfusion CMR performed in elderly patients is safe and well-tolerated.[9,10] A recent study reported the prognostic value of dipyridamole stress perfusion CMR in elderly patients with suspected CAD.[10] Adenosine is most often used for stress perfusion CMR in clinical practice. However, prognostic data of adenosine stress CMR in elderly patients remain limited.

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The objective of this study was to determine the prognostic value of adenosine stress CMR in older adults with known or suspected CAD.

Methods

Study population

Consecutive patients older than 65 years with known or suspected CAD, who were referred for adenosine stress CMR from January 2010 to December 2015 at our outpatient center were enrolled. Detailed medical history was collected on the same day of CMR examination. History of hypertension, diabetes mellitus, hyperlipidemia, CAD, and stroke was defined by recent guidelines.[11-14]

Exclusion criteria included (i) known non-ischemic cardiomyopathy (e.g., hypertrophic, dilated, or infiltrative), (ii) incomplete CMR examination, (iii) poor CMR images, and (v) lack of follow-up data. The institutional ethics committee approved this retrospective study and waived the need for additional written informed consent.

Concern has been expressed regarding the association of gadolinium use with the development of nephrogenic systemic fibrosis in patients with severe kidney injury, especially in the elderly. Patients who had glomerular filtration rate <30 mL/min/1.73m^2 did not undergo a contrast-enhanced CMR examination and were not included in this study.[15]

CMR protocol

The CMR study was performed to assess cardiac function, myocardial perfusion, and late gadolinium enhancement (LGE) using a 1.5 Tesla Philips Achieva XR scanner (Philips Medical Systems, Best, The Netherlands).

The cardiac functional study was performed by acquiring the images using the steady-state free precession (SSFP) technique in a vertical long axis, 2-chamber, 4-chamber, and multiple slice short-axis views. Parameters for cardiac function were echo time (TE) 1.8 milliseconds (ms), repetitive time (TR) 3.7 ms, number of excitations 2, field of view (FOV) 390 x 312 mm, matrix 256 x 240, reconstruction pixels 1.52 x 1.21, slide thickness 8 mm, and flip angle of 70 degrees.

The myocardial first-pass perfusion study was performed by injecting 0.05 mmol/kg of gadolinium contrast agent (Magnevist, Bayer Schering Pharma, Berlin, Germany) at a rate of 4 mL/s immediately after a 4-minute infusion of 140 mcg/kg/min of adenosine.[16] If after 3 minutes of continuous infusion at the standard rate, the hemodynamic response to adenosine was inadequate (heart rate increase <10 beats/min or systolic blood pressure decrease <10 mmHg, with minimal or no reported side effects from the patient), then the infusion rate was increased up to 210 mcg/kg/min for a further 2 minutes.[16] Three short-axis slices of basal, mid, and apical left ventricular (LV) levels were acquired using an ECG-triggered, SSFP, inversion-recovery, single-shot, turbo gradient-echo sequence. Image parameters were TE 1.32 ms, TR 2.6 ms, flip angle 50 degrees, slide thickness 8 mm, FOV 270 mm, and reconstructed FOV 320 mm.

LGE images were acquired approximately 10 minutes after an additional bolus of gadolinium (0.1 mmol/kg, rate 4 mL/s) by the 3D segmented-gradient-echo inversion-recovery sequence. LGE images were acquired in multiple short-axis slices at levels similar to the functional images, long axis, 2-chamber and 4-chamber view. Parameters for LGE study were TE 1.25 ms, TR 4.1 ms, flip angle 15 degrees, FOV 303 x 384 mm, matrix 240 x 256, in-plane resolution 1.26 x 1.5 mm, slice thickness 8 mm and 1.5 sensitivity-encoding factor.

Image analysis

Standard LV volumes, mass, and ejection fraction (EF) were quantitatively measured from the stack of short-axis SSFP cine images.

The perfusion and LGE images were analyzed using visual assessment and consensus by two CMR-trained physicians blinded to the clinical and follow-up data. Perfusion images were read, and each of the 16 segments was visualized (segment-17 at the apex was not visualized). Inducible ischemia was defined as a subendocardial perfusion defect that (i) persisted beyond peak myocardial enhancement and for several RR intervals, (ii) was more than two pixels wide, (iii) followed one or more coronary arteries, and (iv) showed absence of LGE in the same segment.[10,17] Dark-banding artefacts were recorded if an endocardial dark band appeared at the arrival of contrast in the LV cavity before contrast arrival in the myocardium.[17] LGE images were also analyzed using visual assessment. LGE was considered present only if confirmed on both the short-axis and at least one other orthogonal plane.[17] The total number of LGE segments was calculated using the American Heart Association 17-segment model.[18]

Clinical follow-up

Follow-up data were collected from clinical visits and medical records. Clinical event adjudication was completely blinded to clinical and CMR data. Patients were followed for severe cardiac events and major adverse cardiovascular events (MACE). Severe cardiac events were defined as the composite outcomes of cardiac mortality and nonfatal MI.[19] MACE was defined as the composite outcomes of cardiac mortality, nonfatal MI, hospitalization for heart failure, and ischemic stroke.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 20.0 (IBM Corp., Armonk, NY, USA). Continuous variables with normal distribution were presented as mean ± standard deviation (SD). The normality of variable distribution was assessed by the Kolmogorov-Smirnov test. Categorical variables were presented as absolute numbers and percentages. Differences between patients with and without myocardial ischemia in terms of clinical baseline and CMR characteristics were compared using the Student's unpaired t-test for continuous variables, and the chi-square test or Fisher's exact test for categorical variables, as appropriate.

Composite outcomes between patients with and without myocardial ischemia were estimated using the Kaplan-Meier method and compared with the log-rank test. To analyze the predictors of severe cardiac events and MACE, a Cox-regression analysis was performed to assess univariable predictors from baseline characteristics and CMR parameters. Variables with p-value <0.05 in the univariable analysis were entered into the multivariable analysis. Two multivariable models were developed to assess the prognostic value of myocardial ischemia. First, ischemia was included as a categorical variable (presence or absence). Second, ischemia was included as a continuous variable (per-segment extent).

To assess the incremental prognostic values of significant predictors, global chi-square values were calculated after adding predictors in the following order: clinical, LVEF, ischemia, and LGE.

The hazard ratios (HRs) and 95% confidence intervals (CIs) of the outcomes were calculated, with a p-value <0.05 considered statistically significant.

Results

A total of 327 patients were enrolled, with three excluded due to loss of follow-up data. No patients were excluded because of poor image quality, and 324 were included in the final analysis. Table 1 summarizes the clinical data of the patient population. The average age was 73±7 years. Forty-six patients had known CAD, and 6 had previous MI. The overall study cohort had mean LVEF of 68.8±13.8%.

Myocardial ischemia was detected in 99 patients (31%), with the average number of ischemic segments of 6.9±3.9. Sixty-seven had LGE, and all showed a CAD pattern (subendocardial or transmural LGE). Among 67 patients that had LGE, 3 had a history of MI. Thus, 64 patients (19.7%) had LGE without a history of MI ('unrecognized MI').

Patients with myocardial ischemia had a greater LV mass index, lower LVEF, and higher prevalence of LGE than those without ischemia. Patients with ischemia were also more likely to have a history of CAD or MI and be on antiplatelet and nitrate therapy.

No patient died during or shortly after CMR, while one patient had mild heart failure requiring adjustment of diuretics without hospital admission. Two patients experienced angina that rapidly resolved with sublingual nitrate use. No cases of acute MI or strokes were recorded during or immediately after CMR. The main minor adverse events included headache, nausea, chest discomfort, dyspnea, and transient blood pressure drop.

During the average follow-up period of 50.4±19.2 months, 21 severe cardiac events and 52 MACE occurred. Table 2 depicts the cardiovascular events in patients with and without ischemia. The Kaplan-Meier curves of both groups are shown in Figure 1. Patients with myocardial ischemia had significantly higher rates of severe cardiac events (annual events rate 3.8% *versus* 0.7%, p<0.001) and MACE (annual event rate 7.9% *versus* 2.7%, p<0.001) than those without ischemia.

Univariable and multivariable analyses for the prediction of severe cardiac events and MACE are shown in Tables 3 and 4, respectively. The number of patients and events were limited; therefore, to avoid the potential for overfitting, only the most significant predictors from univariable analysis were included in any multivariable model.

The most significant predictors identified by the univariable analysis for severe cardiac events were previous MI, LV mass index, LV end-diastolic volume index, myocardial ischemia, and LGE (p<0.001 for all). A history of heart failure, left atrial diameter, LV mass index, LVEF, myocardial ischemia, and LGE were the most significant predictors of MACE (p<0.001 for all).

Multivariable analyses showed that previous MI, LV mass index, and myocardial ischemia were independent predictors of severe cardiac events. For MACE, history of heart failure, myocardial ischemia, and LGE were independent predictors. Note that both the presence of myocardial ischemia (model 1) and the number of ischemic segments (model 2) were independent predictors for severe cardiac events and MACE.

Figure 2 shows the incremental prognostic values of clinical and CMR data for the prediction of severe cardiac events and MACE. When the prognosis was assessed in a hierarchical manner (clinical variables only, clinical+LVEF, clinical+LVEF+ischemia, and clinical+LVEF+ischemia+LGE), the presence of myocardial ischemia demonstrated an incremental prognostic value over clinical variables and LVEF for both severe cardiac events (Figure 2A) and MACE (Figure 2B). Adding LGE provided a further incremental prognostic value for MACE (Figure 2B). However, LGE did not show an incremental prognostic value over ischemia for severe cardiac events (Figure 2A).

Eighteen patients died during the follow-up. Ten patients died from non-cardiac causes (e.g., malignancy). Patients with myocardial ischemia had a significantly higher rate of all-cause mortality than those without ischemia (Table 2). However, there was no significant difference between patients with and without ischemia regarding the non-cardiac mortality rate (HR 1.66, 95% CI 0.47-5.88, p=0.44).

Discussion

Our results demonstrated that myocardial ischemia using adenosine stress perfusion CMR was a strong and independent predictor of severe cardiac events and MACE in older adults with known or suspected CAD. Adenosine stress CMR was also feasible and safe in this population.

Most cardiovascular diseases, including CAD, increase in prevalence and severity with age. Diagnosis, risk stratification, and treatment of CAD in older patients remain challenging. Stable CAD manifests differently in the elderly, with exertional dyspnea, fatigue, and abdominal discomfort as the most common presentations.[3] Aging

Table 1 – Clinical characteristics of patients with and without myocardial ischemia

	Total	Ischemia Present	Ischemia Absent	p-value
	(n=324)	(n=99)	(n=225)	
Male gender	156 (48.1)	55 (55.6)	101 (44.9)	0.08
Age, years	72.7 ± 7.4	72.9 ± 7.7	72.6 ± 7.3	0.73
Body mass index, kg/m^2	26.5 ± 4.2	25.8 ± 3.9	26.9 ± 4.2	**0.03**
Systolic blood pressure, mmHg	138.8 ± 18.9	142.2 ± 19.3	137.3 ± 18.7	**0.03**
Diastolic blood pressure, mmHg	72.8 ± 11.5	71.9 ± 12.1	73.2 ± 11.2	0.33
Heart rate, bpm	76.9 ± 13.1	76.2 ± 12.8	77.2 ± 13.3	0.52
Hypertension	289 (89.2)	87 (87.8)	202 (89.8)	0.61
Diabetes mellitus	188 (58.0)	57 (57.6)	131 (58.2)	0.91
Hyperlipidemia	231 (71.3)	74 (74.8)	157 (69.8)	0.36
Stable coronary artery disease	46 (14.2)	28 (28.3)	18 (8.0)	**<0.001**
Previous myocardial infarction	6 (1.9)	5 (5.1)	1 (0.4)	**0.01**
Prior revascularization	14 (4.3)	8 (8.1)	6 (2.7)	**0.04**
History of typical angina	31 (9.6)	15 (15.2)	16 (7.1)	**0.02**
History of heart failure	23 (7.1)	9 (9.1)	14 (6.2)	0.35
Stroke	16 (4.9)	4 (4.0)	12 (5.3)	0.78
Current smoking	37 (11.4)	22 (22.2)	15 (6.7)	**<0.001**
Medications				
ACEI or ARB	148 (45.7)	50 (50.5)	98 (43.6)	0.25
Antiplatelet	153 (47.2)	60 (60.6)	93 (41.3)	**0.001**
Beta-blocker	151 (46.6)	47 (47.5)	104 (46.2)	0.84
Calcium channel blocker	111 (34.3)	35 (35.4)	76 (33.8)	0.78
Nitrate	49 (15.1)	25 (25.3)	24 (10.7)	**0.001**
Statin	156 (48.2)	51 (51.5)	105 (46.7)	0.42
CMR				
Left atrial diameter, mm	32.9 ± 4.0	33.6 ± 4.1	32.6 ± 3.9	0.05
LV mass index, g/m^2	51.9 ± 16.8	59.0 ± 18.8	48.9 ± 14.8	**<0.001**
LVEDV index, ml/m^2	74.7 ± 24.4	82.1 ± 29.0	71.5 ± 21.4	**<0.001**
LVESV index, ml/m^2	25.7 ± 22.9	32.2 ± 29.9	22.8 ± 18.3	**<0.001**
LVEF, %	68.8 ± 13.8	65.1 ± 17.5	70.5 ± 11.5	**0.001**
Presence of LGE	67 (20.7)	45 (45.5)	22 (9.8)	**<0.001**
Average numbers of segments with LGE	4.1 ± 2.5	4.3 ± 2.6	3.6 ± 2.4	0.16

*Values are number (percentages) or mean ± SD. **Bold** values are <0.05. ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blocker; CMR: cardiac magnetic resonance; EDV: end diastolic volume; ESV: end systolic volume; EF: ejection fraction; LGE: late gadolinium enhancement; LV: left ventricular.*

and comorbidities limit exercise capacity; therefore, the ECG treadmill testing, and exercise echocardiography are impractical for this population. Pharmacological stress cardiac imaging, such as nuclear perfusion imaging and CMR are the preferred modalities; however, recent data has revealed limited accuracy of nuclear perfusion imaging compared to CMR. Data from large multicenter studies suggested that CMR had greater sensitivity than nuclear perfusion imaging for CAD detection in both males and females.[20,21] Unlike nuclear perfusion imaging, CMR does not expose patients to ionizing radiation and offers both accuracy and safety.

Global and regional myocardial function is a well-known predictor of disease severity and prognosis.[22] CMR is considered the gold standard for the assessment of global ventricular function and a good tool for the assessment of regional ventricular function.[23,24] The elderly have a higher prevalence of lung diseases, such as chronic obstructive

Table 2 – Patients' outcomes

	Total	Ischemia Present	Ischemia Absent	HR (95% CI)	p Value
All-cause mortality	18 (5.6)	10 (10.1)	8 (3.6)	3.13 (1.23, 7.94)	**0.02**
Cardiac mortality	8 (2.5)	6 (6.1)	2 (0.9)	7.59 (1.53, 37.66)	**0.01**
Nonfatal myocardial infarction	18 (5.6)	12 (12.1)	6 (2.7)	5.22 (1.95, 13.94)	**0.001**
Hospitalization for heart failure	31 (9.6)	16 (16.2)	15 (6.7)	2.81(1.38, 5.70)	**0.004**
Ischemic stroke	9 (2.8)	3 (3.0)	6 (2.7)	1.31 (0.32, 5.25)	0.70
Severe cardiac events[a]	21 (6.5)	14 (14.1)	7 (3.1)	5.25 (2.11, 13.04)	**<0.001**
MACE[b]	52 (16.0)	27 (27.3)	25 (11.1)	3.01 (1.75, 5.20)	**<0.001**

Severe cardiac events=composite outcomes of cardiac mortality and nonfatal myocardial infarction. MACE: composite outcomes of cardiac mortality, nonfatal myocardial infarction, hospitalized for heart failure, and ischemic stroke. [a]Five patients had two events (nonfatal myocardial infarction and cardiac mortality). [b]Nine patients had more than one event (six patients had two events, one patient had three events, and two patients had four events). Values represent the number of patients (percentages). ***Bold*** *values are <0.05. CI: confidence interval; HR: hazard ratio; MACE: major adverse cardiovascular events.*

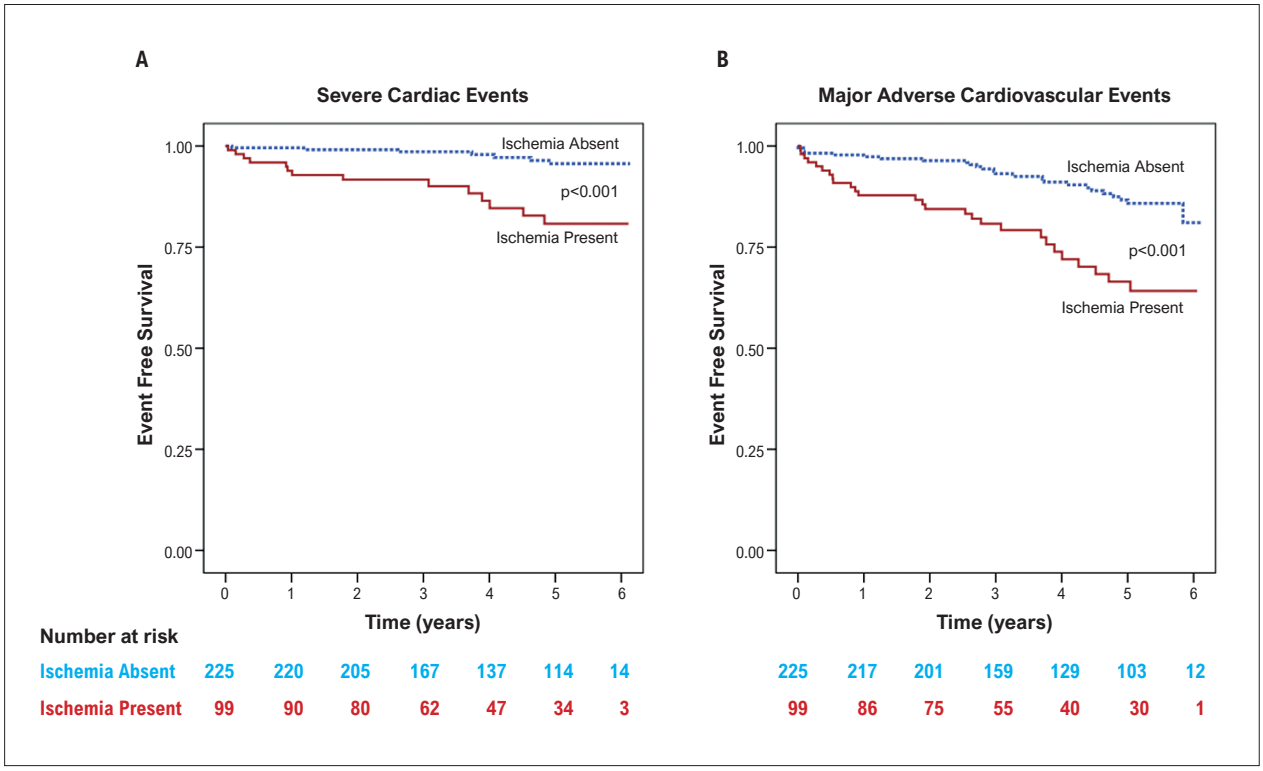

Figure 1 – *Kaplan-Meier curves for the incidence of severe cardiac events (A) and MACE (B). HR: hazard ratio; MACE: major adverse cardiovascular events.*

pulmonary disease and this may limit the assessment by echocardiography due to a poor echocardiographic window. CMR can assess cardiac function without the limitation of the cardiac plane, and also assess endocardial and epicardial borders without geometrical assumptions. Elderly patients may be more vulnerable to adverse events during or after CMR (e.g., arrhythmia or hypotension) due to the high prevalence of comorbidities. The applicability and safety of stress CMR were determined in patients older than 70 years, with results showing that stress CMR performed in elderly patients was safe and well-tolerated.[9,10] Our results confirmed that adenosine stress CMR was safe in older adults without serious adverse events such as death, acute MI, or stroke during or immediately after CMR examinations.

Numerous studies have demonstrated the prognostic value of CMR in patients with known or suspected CAD.[5-8] However, the mean age of patients in these studies was

Table 3 – Predictors of severe cardiac events

	Univariable Analysis		Multivariable Analysis			
			Model 1[a]		Model 2[b]	
	HR (95% CI)	P-Value	HR (95% CI)	p Value	HR (95% CI)	p-value
Male gender	1.26 (0.53, 2.97)	0.59				
Age, years	1.01 (0.95, 1.07)	0.70				
Body mass index, kg/m^2	0 .90 (0.81, 1.01)	0.08				
Systolic blood pressure	0.99 (0.97, 1.02)	0.63				
Diastolic blood pressure	0.98 (0.94, 1.02)	0.33				
Heart rate, bpm	1.01 (0.97, 1.04)	0.71				
Hypertension	2.57 (0.34, 19.17)	0.36				
Diabetes mellitus	1.21 (0.51, 2.89)	0.67				
Hyperlipidemia	1.06 (0.39, 2.92)	0.90				
Stable coronary artery disease	2.26 (0.82, 6.19)	0.11				
Previous myocardial infarction	9.36 (2.75, 31.81)	**<0.001**	6.70 (1.83, 24.49)	**0.004**	5.90 (1.52, 22.93)	**0.01**
History of typical angina	2.80 (1.02, 7.65)	**0.04**				
History of heart failure	2.78 (0.93, 8.30)	0.07				
Stroke	0.05 (0.00-177.4)	0.46				
Current smoking	1.82 (0.61, 5.41)	0.28				
ACEI or ARB	1.11 (0.46, 2.60)	0.82				
Antiplatelet	2.09 (0.84, 5.20)	0.11				
Beta-blocker	1.15 (0.48, 2.71)	0.75				
Calcium channel blocker	0.96 (0.38, 2.38)	0.94				
Nitrate	3.03 (1.25, 7.33)	**0.01**				
Statin	1.46 (0.61, 3.47)	0.39				
Left atrial diameter, mm	1.16 (1.06, 1.27)	**0.002**				
LV mass index, g/m^2	1.03 (1.02, 1.05)	**<0.001**	1.04 (1.02, 1.05)	**0.001**	1.03 (1.02, 1.05)	**0.001**
LVEDV index, ml/m^2	1.02 (1.01, 1.03)	**<0.001**				
LVESV index, ml/m^2	1.02 (1.01, 1.03)	**0.001**				
LVEF, %	0.96 (0.94, 0.99)	**0.01**				
Presence of myocardial ischemia	5.25 (2.11, 13.04)	**<0.001**	3.14 (1.22, 8.07)	**0.02**	-	-
Ischemia extent, per 1 segment	1.17 (1.09, 1.26)	**<0.001**	-	-	1.11 (1.02, 1.20)	**0.01**
Presence of LGE	4.97 (2.11, 11.73)	**<0.001**				

*[a]Myocardial ischemia was included as a categorical variable (presence or absence). [b]Myocardial ischemia was included as a continuous variable (per-segment extent). **Bold** values are <0.05. ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blocker; CMR: cardiac magnetic resonance; EDV: end diastolic volume; ESV: end systolic volume; EF: ejection fraction; LGE: late gadolinium enhancement; LV: left ventricular.*

60-65 years, with no specific assessment of the elderly. Pezel et al. reported on the prognostic value of dipyridamole stress perfusion CMR in 754 elderly patients aged over 75 with suspected CAD.[10] In their study, 20% of the patients showed evidence of inducible ischemia, while 9.4% had LGE. The authors determined that the presence of myocardial ischemia was associated with the occurrence of MACE, including cardiac death and nonfatal MI.[10] Our study, which included patients with known stable CAD and previous MI, found that 30.5% had inducible ischemia and 20.7% had LGE. The prevalence of myocardial ischemia in our study was comparable with previous reports that included patients with known CAD.[5,7] Similarly, patients with inducible ischemia in our study demonstrated lower LVEF and higher prevalence of LGE than those without myocardial ischemia.[5-7]

Our results indicated that patients with inducible ischemia had significantly higher rates of severe cardiac

Table 4 – Predictors of major adverse cardiovascular events

	Univariable Analysis		Multivariable Analysis			
			Model 1[a]		Model 2[b]	
	HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p-value
Male gender	1.15 (0.67, 1.99)	0.61				
Age, years	1.05 (1.01, 1.08)	**0.02**				
Body mass index, kg/m^2	0.98 (0.92, 1.05)	0.60				
Systolic blood pressure	0.99 (0.98, 1.01)	0.43				
Diastolic blood pressure	0.97 (0.95, 0.99)	**0.02**				
Heart rate, bpm	1.01 (0.99, 1.03)	0.30				
Hypertension	2.11 (0.66, 6.78)	0.21				
Diabetes mellitus	1.21 (0.70, 2.11)	0.50				
Hyperlipidemia	1.17 (0.61, 2.23)	0.64				
Stable coronary artery disease	1.58 (0.77, 3.24)	0.22				
Previous myocardial infarction	6.13 (2.21, 17.06)	**0.001**				
History of typical angina	1.43 (0.64, 3.17)	0.38				
History of heart failure	3.70 (1.90, 7.20)	**<0.001**	3.50 (1.79, 6.82)	**0.001**	3.32 (1.70, 6.50)	**0.001**
Stroke	1.15 (0.36, 3.70)	0.81				
Current smoking	1.62 (0.79, 3.33)	0.19				
ACEI or ARB	1.23 (0.71, 2.11)	0.46				
Antiplatelet	1.57 (0.90, 2.73)	0.11				
Beta blocker	1.02 (0.59, 1.77)	0.93				
Calcium channel blocker	0.69 (0.37, 1.27)	0.24				
Nitrate	1.87 (1.01, 3.45)	**0.04**				
Statin	1.19 (0.69, 2.05)	0.53				
Left atrial diameter, mm	1.13 (1.06, 1.20)	**<0.001**				
LV mass index, g/m^2	1.03 (1.02, 1.04)	**<0.001**				
LVEDV index, ml/m^2	1.02 (1.01, 1.03)	**<0.001**				
LVESV index, ml/m^2	1.02 (1.01, 1.03)	**<0.001**				
LVEF, %	0.97 (0.95, 0.98)	**<0.001**				
Presence of myocardial ischemia	3.01 (1.75, 5.20)	**<0.001**	1.91 (1.02, 3.59)	**0.04**	-	-
Ischemia extent, per 1 segment	1.11 (1.06, 1.17)	**<0.001**	-	-	1.08 (1.01, 1.14)	**0.02**
Presence of LGE	3.70 (2.13, 6.43)	**<0.001**	2.64 (1.39, 4.99)	**0.003**	2.86 (1.58, 5.17)	**0.001**

*[a]Myocardial ischemia was included as a categorical variable (present or absent). [b]Myocardial ischemia was included as a continuous variable (per-segment extent). **Bold** values are <0.05. ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blocker; CMR: cardiac magnetic resonance; EDV: end diastolic volume; ESV: end systolic volume; EF: ejection fraction; MACE: major adverse cardiovascular events; LGE: late gadolinium enhancement; LV: left ventricular.*

events and MACE than those without ischemia. Myocardial ischemia was also an independent predictor of severe cardiac events and MACE. In contrast, patients without myocardial ischemia had a significantly lower risk for cumulative events (<1% per year for severe cardiac events). These findings agreed with those by Pezel et al.[10]

LGE is a well-validated method for detecting myocardial scars and fibrosis.[25] Specific scar patterns corresponding to MI and various non-ischemic cardiomyopathy are diagnostically useful.[25,26] Recent guidelines have highlighted the importance of myocardial fibrosis imaging by CMR.[14,27] A significant proportion of patients with stable CAD have normal LV systolic function. The presence of LGE also demonstrated its prognostic value in patients with normal LVEF and wall motion.[28] Similarly to our study, LV systolic function was preserved. LGE was detected in 20.7% of patients and was an independent predictor of MACE.

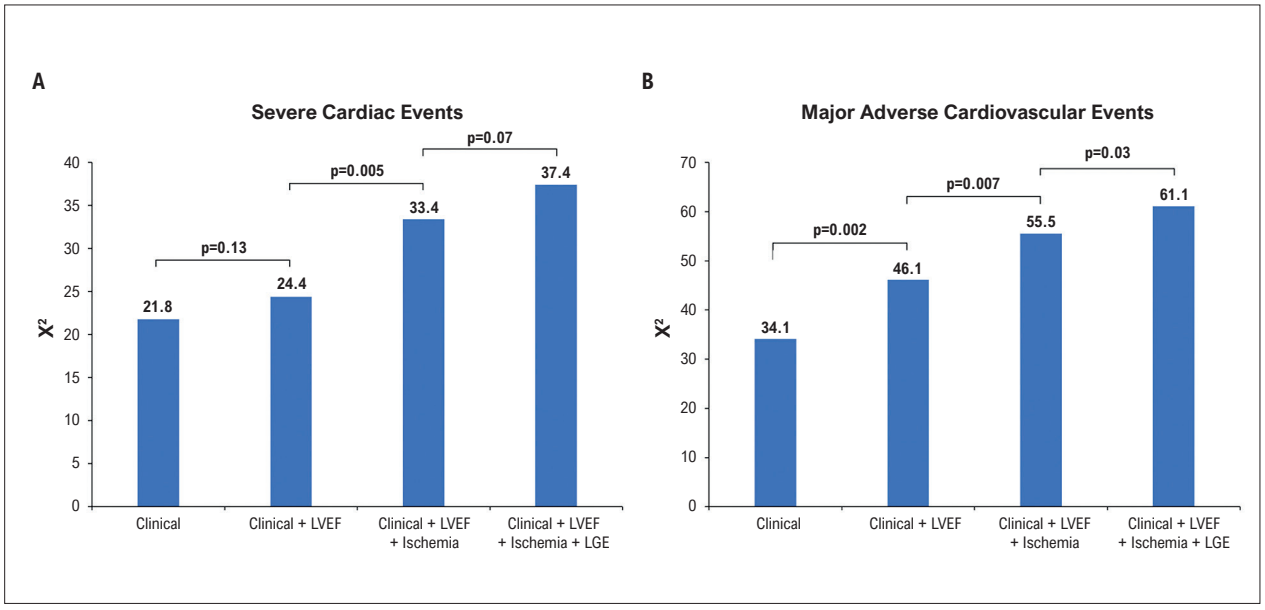

Figure 2 – *Incremental prognostic value of LVEF, myocardial ischemia, and LGE for severe cardiac events (A) and MACE (B). Clinical=age, male gender, previous myocardial infarction, and history of heart failure. LGE: late gadolinium enhancement; LVEF: left ventricular ejection fraction; MACE: major adverse cardiovascular events.*

Moreover, given the very small proportion of patients with a history of MI (< 2%), our data also demonstrated a compatible prevalence of 'unrecognized MI' (19.7%) when compared to previous data.[3,29-33] Unrecognized MI is not an uncommon condition, with a prevalence of approximately 10-40% of patients with known or suspected CAD.[3,29-33] LGE-CMR has improved the detection of small lesions due to MI (as little as 1 g), which do not give rise to Q-waves on the ECG.[29,30,33] Additionally, recent studies consistently demonstrated that unrecognized MI using LGE-CMR was independently associated with an increased risk of cardiovascular events.[29,30,33]

Limitations

Several limitations of our study should be considered. Firstly, the study methodology was retrospective and, therefore, some confounding factors could not be totally eliminated. Secondly, our stress protocol acquired only three short-axis slices to detect myocardial ischemia and may have underestimated perfusion defects in some small areas (compared to four or five short-axis slices). Thirdly, our study had a relatively low event rate, while some degree of overfitting may have occurred in the multivariable analyses. Finally, we did not provide the information regarding the adequacy of medical therapy after stress CMR that might affect the prognosis.

Conclusions

Adenosine stress CMR is safe and shows prognostic value in older adults with known or suspected CAD.

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Author Contributions

Conception and design of the research, Analysis and interpretation of the data, Writing of the manuscript and Critical revision of the manuscript for intellectual content: Yodying Kaolawanich, Thananya Boonyasirinant; Acquisition of data and Statistical analysis: Yodying Kaolawanich.

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Study Association

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Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Siriraj Institutional Review Board under the protocol number 778/2559 (EC3) COA no. Si 782/2016.. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013.

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Stress CMR in the Elderly: Does It Provide the Answers?

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Short Editorial related to the article: Prognostic Value of Adenosine Stress Perfusion Cardiac Magnetic Resonance Imaging in Older Adults with Known or Suspected Coronary Artery Disease

`Life is the art of drawing sufficient conclusions from insufficient premises´

Samuel Butler

After the ISCHEMIA clinical trial, despite the ongoing debate, clinicians need to contemplate all strategies for patients with chronic stable ischemic heart disease (SIHD).[1] The management of SIHD has two aims – improve prognosis and/or relieve symptoms. Most studies have shown that revascularisation provides greater symptom benefits than optimal medical therapy (OMT) alone, but data on hard outcomes have been elusive. Therefore, improving our clinical decision-making tools in selecting patients for revascularization is important. This becomes particularly important when we select elderly patients for revascularisation because the risk-benefit ratio is probably more tenuous than a younger cohort. The elderly present difficulties in the evaluation of SIHD due to multiple reasons. One refinement is the adequate selection of the method to evaluate SIHD. A panoply of non-invasive techniques exists for imaging, including cardiac computed tomography, echocardiography, nuclear medicine techniques and cardiac magnetic resonance (CMR). Combining the right patient and the right method of evaluation followed by the right therapeutic strategy improves outcomes. In clinical medicine, what is important is not how much we do but how well our patients do after what we do.

CMR stress perfusion is a valuable resource with a high negative predictive value in those who do not have perfusion defects irrespective of the presence or absence of coronary artery disease.[2] Few studies exist on the prognostic value of adenosine stress perfusion CMR in elderly patients with or without established SIHD. The study by Boonyasirinant and Kaolawanich,[3] although not the first, is a welcome addition to the repository of existing literature that provides a cogent reason for using stress CMR for the evaluation of ischemia now addressing the elderly age group.[3] Their findings demonstrate that while clinical data were combined with information on left ventricular function, no incremental value was seen compared to clinical data alone in predicting serious cardiac events. The presence of ischemia as detected by CMR helped predict events significantly better. The predictive power was not increased with the addition of information on late gadolinium enhancement. Esteban-Fernandez et al. found that elderly patients with a moderate or severe degree of ischemia on stress CMR have a higher risk of having an event during follow-up.[4] Taken together, these two studies provide evidence for the use of adenosine stress CMR in predicting outcomes in elderly patients. A notable feature of both studies is the absence of significant adverse events of adenosine. However, the ISCHEMIA clinical trial reflected the limited availability of both equipment and expertise, where CMR was the least chosen method to evaluate for ischemia (5%), reflecting real-world practice.

Like almost every significant study in cardiovascular medicine, the choice of endpoints is debatable. This study defined serious cardiac events as non-fatal myocardial infarction and cardiac mortality. With current therapy, most myocardial infarctions are non-fatal, and the evolving definitions of myocardial infarction make it a moving target. Secondly, although we all try to use evidence-based medicine as the foundation of our clinical practice, we need to remember that medicine is essentially a retail business, as noted eloquently by Atul Gawande.[5] As we treat each patient one at a time and not the population *per se*, statistical significance is not always synonymous with clinical relevance for the individual patient.

Another important point to remember is that the risk of adverse cardiac events, inherent in the presence of markers such as ischemia, can be mitigated by adequate OMT. No clear information on therapy used in the two groups is provided. A very significant difference in smoking rates between those with and without ischemia was noted. Although not statistically significant to be entered into the model, clinicians know how continued smoking contributes to clinical events. In real-world clinical practice, imaging is usually requested when revascularisation is contemplated in those with known SIHD and not necessarily to risk stratify patients. No technique in imaging to evaluate SIHD is the holy grail, and all are essentially complementary. With the worldwide population aging, we should seek out the best ways to evaluate and manage SIHD, and the study is a worthwhile step in this endeavour.

Dr. Thomas served as a Consultant for the ISCHEMIA study´s Clinical Coordinating Center at NYU Langone Medical Center.

Keywords

Magnetic Resonance Spectroscopy/methods; Coronary Artery Disease/surgery; Aged; Diagnostic,Imaging; Exercise Test

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Precision Medicine: Can 18F-FDG PET Detect Cardiotoxicity Phenotypes?

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Short Editorial related to the article: Chemotherapy-induced Cardiac 18F-FDG Uptake in Patients with Lymphoma: An Early Metabolic Index of Cardiotoxicity?

The publication of the article by Dourado et al.[1] in the *Arquivos Brasileiros de Cardiologia* should be carefully considered by cardiologists engaged in Precision Medicine. In this study,[1] the authors investigated the intensity of 2-deoxy-2[18F] fluoro-D-glucose (18F-FDG) myocardial uptake in 70 patients with lymphoma by positron emission tomography associated with computed tomography (PET/CT) scans before, during and after chemotherapy. They observed a progressive increase in glucose metabolism in the left ventricle from baseline PET/CT to interim PET/CT, and from interim PET/CT to post-therapy PET/CT. More than half of patients showed an increase of ≥ 30% in cardiac 18F-FDG uptake measured by left ventricular SUV max. The authors inferred that PET/CT is a reliable method to assess the intensity of 18F-FDG uptake in patients with lymphoma during and after chemotherapy. More importantly, the authors could identify a group of patients in which the metabolic effects of chemotherapy on the left ventricle were the greatest.[1] These findings can contribute to a strategy for the early identification of patients who are more sensitive to cardiotoxicity of chemotherapeutic agents and for the definition of individualized preventive measures of irreversible myocardial damage.

Precision Medicine is commonly defined as an approach for disease treatment and prevention that takes into account individual variability and disease manifestation for each person. For this purpose, it is fundamental to clarify specific mechanisms of disease and key points for the implementation of effective interventions.[2] This process is known as deep phenotyping, where endotypes, *i.e.*, phenotypes underlying the common phenotype are identified, allowing a more effective guidance of therapeutic approaches.[3]

Keywords

Radionuclide Imaging; Positron-Emission Tomography; Toxicity

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18F-FDG is a sensitive molecular probe that can evaluate not only an increased expression of glucose uptake by viable tumor cells but also monitor the effectiveness of therapeutic response to cancer treatment. Borde et al.[4] were one of the first to demonstrate the impact of anthracycline toxicity on FGD uptake in a group of patients who showed a considerable increase in the tracer uptake after treatment. The authors speculated that the dose of adriamycin may have reached the individual limit, leading to activation of the NRG-erbB pathway and increased glucose utilization by the myocytes. Experimental studies with cardiac radiotherapy have shown that the increased FDG uptake in an irradiated field may be associated with microvascular damage related to the direct injury of the mitochondria by radiation.[5]

In the recent Brazilian position statement on the use of multimodality imaging in cardio-oncology,[6] 18F-FDG PET/CT is mentioned in the diagnosis of cardiotoxicity induced by immune checkpoint inhibitors, as the method allows to detect, assess and even quantify the extent of inflammation in several cardiovascular disorders, including myocarditis, pericarditis and vasculitis.[6] In addition to 18F-FDG PET/CT, other nuclear medicine techniques can be used to assess cardiac toxicity induced by cancer. Figure 1 illustrates that the list of the nuclear medicine applications has been progressively increasing, including not only tests for evaluation of systolic and diastolic functions (which become abnormal in advanced stages of cardiac damage only), but also tests that evaluate more sensitive processes in the heart, such as perfusion, innervation, and cell metabolism.

In summary, Precision Medicine is very important for current medicine. As in the study by Dourado et al.[1] who found a profile of molecular response to chemotherapy treatment in a group of patients, we believe that, in the future, preventive and therapeutic approach in cardio-oncology will also be individualized. Some experimental studies have suggested that non-pharmacological approaches, like regular exercise, can be useful to prevent chemotherapy-induced cardiotoxicity, and are more precisely prescribed with the identification of patients at higher risk.[7] Therefore, the stratification of patients and the understanding of their cellular and biochemical responses to treatments will allow a tailored approach, reducing morbidity and increasing the chances of successful treatment outcomes.

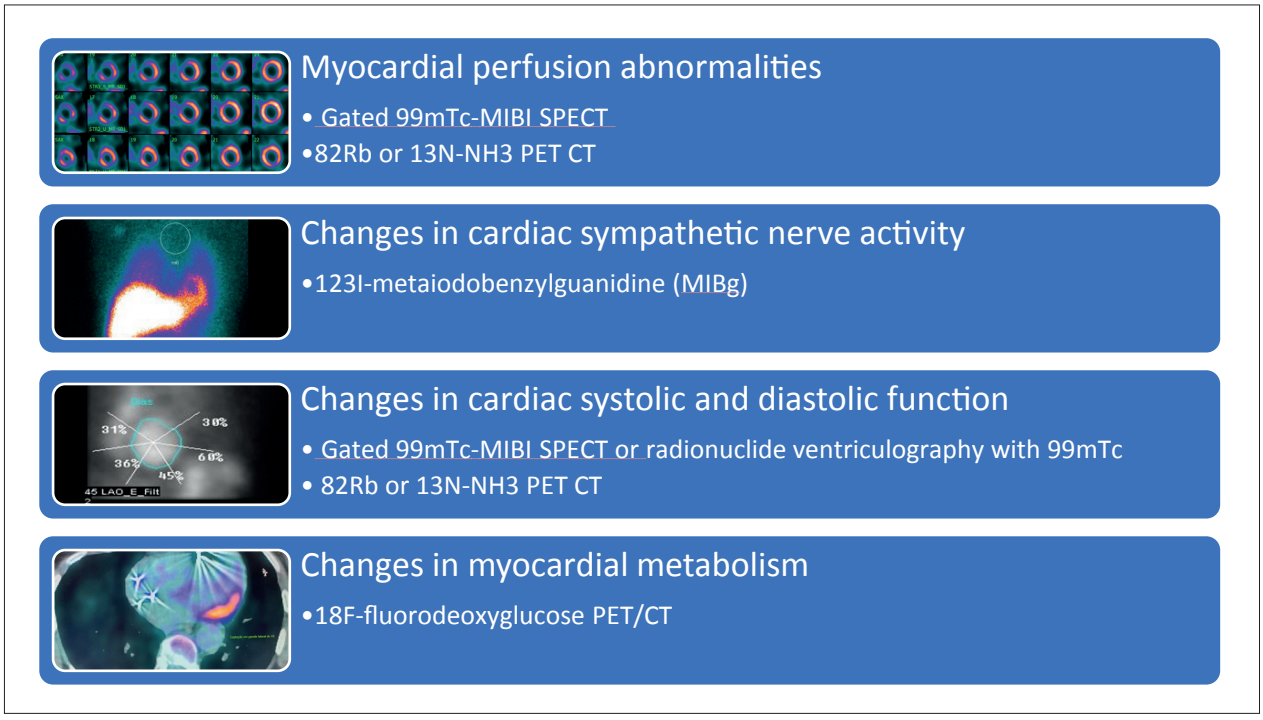

Figure 1 – *Main applications of nuclear medicine for detection and monitoring of cardiotoxicity in cancer treatment. MIBI: sestamibi; Rb: Rubidium; PET CT: positron emission tomography-computed tomography; SPECT: single-photon emission computed tomography; NH3: ammonia; Tc: Technetium.*

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Riociguat: An Alternative to Treat Pulmonary Hypertension

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Short Editorial related to the article: Soluble Guanylate Cyclase Stimulators (Riociguat) in Pulmonary Hypertension: Data from Real-Life Clinical Practice in a 3-Year Follow-Up

In recent years, significant progress has been achieved regarding the knowledge of the pathobiology of pulmonary hypertension (PH), which was conducted in a research effort to identify new treatment strategies. Among the 5 clinical subgroups of PH, the most common is idiopathic pulmonary arterial hypertension (PAH), associated with increased morbidity and mortality rate.[1] Exercise capacity, WHO functional class, hemodynamic values, findings on imaging, and biomarkers of myocardial dysfunction are parameters used to predict the survival of patients with PH.[2] This is a great clinical challenge; the improvement of patients' quality of life and the variability between therapies worsens because a proper care provider decision is expected since it might affect the outcome. Rapid diagnosis is essential and could justify that all patients with suspected diagnoses should be referred to an expert center. Treatment depends on the classification of PH, including primarily the specific drugs alone or in combination which target the phosphodiesterase type 5 inhibitors (PDE5i),[3] soluble guanylate cyclase (GCs) stimulators, endothelin receptor antagonists, prostacyclin analogs, and prostacyclin receptor agonists which interfere with the vascular dysfunction of pulmonary arteries.[4] Since PAH is a disease that includes vasoconstriction of pre-capillary arterioles and obstructive, hyperproliferative and vascular lesions, these drugs do not target vascular remodeling and certainly do not improve cardiac function. Thus, it is essential to search for pulmonary vasodilators that interfere with this relevant molecular pathways.[5]

In issue of the *Arquivos Brasileiros de Cardiologia*, Spilimbergo et al.[6] report a follow-up study in which patients with PH were treated with an GCs stimulant, riociguat, which is approved for treating PAH because it augments the nitric oxide (NO)-cyclic GMP pathway. The authors describe live cases outcome spanning 3 years, focusing on PAH (type 1) and chronic thromboembolic PH (CTEPH, type 4). Riociguat increases the activity of GCs, which is the intracellular receptor for NO, that has vasodilatory and antiproliferative effects on blood vessels, including the pulmonary arteries. Considering the cohort of 31 patients, 32% were in WHO functional class II and this value increased to 71% after 3 years of treatment with riociguat. The authors highlighted that riociguat interfered with the disease process because most patients treated with riociguat demonstrated stable or better risk parameters at 3 years of follow-up. Previously, Ghofrani et al.[7] demonstrated that riociguat, through the direct activation of GCs, promoted an increase in cyclic GMP and consequently pulmonary vasodilation, and its administration 3 times daily in patients with PAH improved serum N terminal pro B type natriuretic peptide (NT-proBNP) concentrations, time to clinical worsening, and WHO functional class.[7] Reduction of NT-proBNP levels was not observed by Spilimbergo et al.,[6] possibly explained by the small number of patients included in the study. Similarly, in 2015, the CHEST-2 study described that long-term administration of riociguat in patients with CTEPH improved exercise and functional capacity.[8,9] All classes of PH-specific agents are expensive and will not provide the cure but reduce hospital admission and improve functional capacity. Riociguat might be an alternative option for patients with PAH who do not respond sufficiently to treatment with PDE5i[9] since it can stimulate GCs independently of NO.[10]

There is strong evidence to suggest that riociguat is a promising intervention to improve the prognosis of patients with PH.

Keywords

Hypertension Pulmonary/therapy; Hypertension Pulmonary/physiopathology; Enzyme Activators/therapeutic use; Riociguat/therapeutic use; Pyrazoles/therapeutic use; Pyrimidines/therapeutic use

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2021 Top 10 Articles in the *Arquivos Brasileiros de Cardiologia* and the *Revista Portuguesa de Cardiologia*

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Introduction

Annually the *Revista Portuguesa de Cardiologia* (RPC) and the *Arquivos Brasileiros de Cardiologia* (ABC) have gathered to elaborate a special article with the selection of their best original publications.[1-3] Over the years, the high quality of their papers has become clear, evidencing the dynamism of cardiovascular investigation in Portuguese-speaking countries.

Following tradition, the editorial bodies of the RPC and the ABC met once again to select the ten best articles published in 2021 by each of those journals (Tables 1 and 2). Although the year 2021 was marked again by the impact of the COVID-19 pandemic, both journals had excellent publications in all areas of Cardiovascular Medicine, from cardiovascular prevention to heart failure (HF), including an excellent selection of papers on the COVID-19 pandemic in the Brazilian and Portuguese populations. The high quality of the publications in both journals makes the selection of the best articles a complex task.

We provide a list of the ten best articles in each journal and their brief description, as well as their major implications for cardiovascular disease diagnosis, treatment, and understanding. Aiming to improve their understanding, the articles were grouped and presented according to four general themes.

COVID-19 and its consequences

The years 2020 and 2021 were marked by the huge impact of the COVID-19 pandemic on health care worldwide. In a study published in the RPC, Mesquita et al.[4] have analyzed the prevalence and prognostic impact of cardiac arrhythmias on patients hospitalized with COVID-19. They used the national registry from the Portuguese Association of Arrhythmology, Pacing, and Electrophysiology with data from 20 Portuguese hospitals relative to 692 patients admitted due to COVID-19. Of those patients, 11.7% had arrhythmic events. The most frequent arrhythmias were atrial fibrillation and flutter (AFF – 62.5%). Two patients (3.1%) had ventricular tachycardia, and 17 (26.6%) had paroxysmal supraventricular tachycardia. Those patients had neither important complications from the arrhythmic event or death from arrhythmic cause, despite their more severe COVID-19 and many comorbidities, nor higher frequency of hemodynamic instability and/or multiple organ failure. Although 76.6% of the patients with arrhythmic events were on medication that increases the QT interval (ritonavir/lopinavir, hydroxychloroquine or azithromycin), only seven patients (10.9%) had a prolonged QT interval (ranging from 480ms to 596 ms).[4] Those authors concluded that the incidence of cardiac arrhythmias is high in patients hospitalized due to COVID-19, but they did not associate with increased cardiac mortality, although they often occurred in patients with more severe disease and multiple organ failure. The incidence of ventricular arrhythmias was low although the patients were on medications that prolong the QT interval.

An observational study has assessed the mortality rate from cardiac arrest (CA) relative to the total number of household visits reported by the mobile urgent healthcare service (in Portuguese, SAMU) in the city of Belo Horizonte, Minas Gerais state, Brazil, in March 2018, 2019, and 2020. There was a gradual increase in the number of household deaths due to CA relative to the total number of visits provided by the SAMU, as well as a proportional 33% increase in household deaths in March 2020, when the COVID-19 pandemic began. Most patients (63.8%) were at least 60 years of age, and 87% of the reported CAs were associated with clinical comorbidities, such as systemic arterial hypertension (22.87%), HF (13.03%), and diabetes mellitus (11.0%). It is worth noting that, although the families knew the patients had comorbidities, in 38.4% of the cases reported, the families did not know which those comorbidities were.[5] The Brazilian health system needs to

Keywords

Brazil; Technical Cooperation/trends; Dissemination of Information; Cardiovascular Diseases; Impact Factor.

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Table 1 – List of the ten best articles published in the *Arquivos Brasileiros de Cardiologia* in 2021

Link	Authors and titles of the articles
https://abccardiol.org/wp-content/uploads/articles_xml/0066-782X-abc-117-01-0091/0066-782X-abc-117-01-0091.x44344.pdf	Alves P et al. Relação entre Resposta Imune Inata do Receptor Toll-Like-4 (TLR-4) e o Processo Fisiopatológico da Cardiomiopatia da Obesidade Relationship between Innate Immune Response Toll-Like Receptor 4 (TLR-4) and the Pathophysiological Process of Obesity Cardiomyopathy
https://abccardiol.org/wp-content/uploads/articles_xml/0066-782X-abc-116-06-1091/0066-782X-abc-116-06-1091.x44344.pdf	Morais TC et al. Performance Diagnóstica da FFR por Angiotomografia de Coronárias através de Software Baseado em Inteligência Artificial Diagnostic Performance of a Machine Learning-Based CT-Derived FFR in Detecting Flow-Limiting Stenosis
https://abccardiol.org/wp-content/uploads/articles_xml/0066-782X-abc-116-03-0466/0066-782X-abc-116-03-0466.x44344.pdf	Matos LCV et al. O Escore Gensini e a Carga Trombótica Adicionam Valor Preditivo ao Escore SYNTAX na Detecção de No-Reflow após Infarto do Miocárdio Gensini Score and Thrombus Burden Add Predictive Value to the SYNTAX Score in Detecting No-Reflow after Myocardial Infarction
https://abccardiol.org/wp-content/uploads/articles_xml/0066-782X-abc-117-05-0944/0066-782X-abc-117-05-0944.x44344.pdf	Santos SC et al. Mortalidade por Insuficiência Cardíaca e Desenvolvimento Socioeconômico no Brasil, 1980 a 2018 Mortality Due to Heart Failure and Socioeconomic Development in Brazil between 1980 and 2018
https://abccardiol.org/wp-content/uploads/articles_xml/0066-782X-abc-117-03-0426/0066-782X-abc-117-03-0426.x44344.pdf	Santos IS et al. Diagnóstico de Fibrilação Atrial na Comunidade Utilizando Eletrocardiograma e Autorrelato: Análise Transversal do ELSA-Brasil Atrial Fibrillation Diagnosis using ECG Records and Self-Report in the Community: Cross-Sectional Analysis from ELSA-Brasil
https://abccardiol.org/wp-content/uploads/articles_xml/0066-782X-abc-116-02-0219/0066-782X-abc-116-02-0219.x44344.pdf	Mendes SL et al. Resultados Clínicos e Hemodinâmicos de Longo Prazo após o Transplante de Coração em Pacientes Pré-Tratados com Sildenafil Long-Term Clinical and Hemodynamic Outcomes after Heart Transplantation in Patients Pre-Treated with Sildenafil.
https://abccardiol.org/wp-content/uploads/articles_xml/1678-4170-abc-116-04-0695/1678-4170-abc-116-04-0695.x44344.pdf	Oliveira JC et al. Acesso à Terapia de Reperfusão e Mortalidade em Mulheres com Infarto Agudo do Miocárdio com Supradesnivelamento do Segmento ST: Registro VICTIM Access to Reperfusion Therapy and Mortality in Women with ST-Segment–Elevation Myocardial Infarction: VICTIM Register
https://abccardiol.org/wp-content/uploads/articles_xml/1678-4170-abc-116-04-0795/1678-4170-abc-116-04-0795.pdf	Hussid MF et al. Obesidade Visceral e Hipertensão Sistólica como Substratos da Disfunção Endotelial em Adolescentes Obesos Visceral Obesity and High Systolic Blood Pressure as the Substrate of Endothelial Dysfunction in Obese Adolescents

https://abccardiol.org/wp-content/uploads/articles_xml/0066-782X-abc-116-01-0004/0066-782X-abc-116-01-0004.x44344.pdf	Miguel-dos-Santos R et al. Treino de Força Reduz Stress Oxidativo Cardíaco e Renal em Ratos com Hipertensão Renovascular Strength Training Reduces Cardiac and Renal Oxidative Stress in Rats with Renovascular Hypertension
https://abccardiol.org/wp-content/uploads/articles_xml/0066-782X-abc-117-02-0309/0066-782X-abc-117-02-0309.x44344.pdf	Chehuen M et al. Respostas Fisiológicas à Caminhada Máxima e Submáxima em Pacientes com Doença Arterial Periférica Sintomática Physiological Responses to Maximal and Submaximal Walking in Patients with Symptomatic Peripheral Artery Disease
https://abccardiol.org/wp-content/uploads/articles_xml/0066-782X-abc-116-02-0266/0066-782X-abc-116-02-0266.x27815.pdf	Guimarães et al. Aumento de Óbitos Domiciliares devido a Parada Cardiorrespiratória em Tempos de Pandemia de COVID-19 Increased Home Death Due to Cardiopulmonary Arrest in Times of COVID-19 Pandemic

better the patients' and families' knowledge about their diseases, emphasizing and improving access to the hospital system to reduce the impact of out-of-hospital CA, whose chance of survival is low.

Fernandes et al.[6] have conducted a retrospective study with 187 patients admitted to an intensive care unit (ICU) after CA over a 5-year period. The median patients' age was 67 years. In-hospital CA occurred in 61% of the cases, and 87% had an initial non-shockable rhythm. The mean time until return of spontaneous circulation (ROSC) was 10 minutes. Presumed cardiac causes accounted for only 31% of the cases, which is explained by the exclusion of patients with CA due to ST-elevation myocardial infarction (STEMI), who were directly admitted to the coronary ICU in the same hospital. Those authors reported in-hospital mortality of 63% (45% of which related to withdrawal of life-support measures) and 1-year mortality of 72%. The prevalence of favorable neurologic status at hospital discharge [cerebral performance category (CPC) = 1] was only 25%. The independent predictors of in-hospital mortality were time until initiating basic life support (BLS), high SAPS II score, non-shockable initial rhythm, and vasopressor support duration. Although the time until initiating BLS and the time until ROSC were longer for patients with out-of-hospital CA, the clinical results did not differ significantly in the two populations of patients. Survival with a favorable neurologic status (CPC = 1 or 2) was associated with less frequent epileptic activity and shorter ventilatory support, but not with assisted CA, initial rhythm, time until ROSC, or implementation of the normothermia protocol. Finally, the neurologic outcomes and mortality were similar in both sexes. That study emphasizes the importance of improving all chain of survival components to optimize those patients' prognosis. In addition, it reinforces the need for clinical trials in the area, ideally multicenter and duly framed within the ethical context.[6]

Cardiac arrhythmia and its impact on society

Atrial fibrillation and flutter are the most common arrhythmias in both the general population and the patients with COVID-19, although they do not associate with the presence of CA.[4-7] Aiming to study the incidence of factors associated with cardiovascular diseases and diabetes, a longitudinal study of adult health in Brazil (ELSA-Brasil) was conducted. That study is a large multicenter cohort of individuals aged 35 to 74 years in six Brazilian cities. A substudy[8] of the ELSA-Brasil, with 13 260 participants, investigated the presence of AFF, which was defined by use of electrocardiogram or self-report. That substudy aimed to assess whether age and sex were associated with the use of anticoagulants to prevent stroke. The authors reported predominance of the female sex (54.4%), median age of 51 years, and AFF detection in 333 (2.5%) participants. The authors reported the association of AFF with age (OR: 1.05; 95% CI: 1.04-1.07), arterial hypertension (OR: 1.44; 95% CI: 1.14-1.81), coronary artery disease (CAD - OR: 5.11; 95% CI: 3.85-6.79), HF (OR: 7.37; 95% CI: 5.00-10.87), and rheumatic fever (OR: 3.38; 95% CI: 2.28-5.02). Only 20 patients with CHA_2DS_2-VASc score ≥2 (10.8%) were on anticoagulants, whose use was smaller in women. Those findings represent a great challenge to the AFF treatment.

In 2018, the CASTLE-AF study[9] showed that atrial fibrillation (AF) ablation could improve the prognosis of a selected population of patients with HF. In another study, Ribeiro et al.[10] have retrospectively assessed the impact of AF ablation in 22 patients with HF (32% with NYHA functional class II and 58% with NYHA functional class III) and left ventricular ejection fraction (LVEF) <50%. The procedure was successful in 100% of the patients, with no complication reported. The recurrence of AF after the blanking period was 18%. After a median 11-month follow-up, those authors reported an improvement in functional capacity, with mean pre-procedure and post-procedure NYHA functional classes

Table 2 – List of the ten best articles published in the *Revista Portuguesa de Cardiologia* in 2021

Authors	Titles of the articles
Dinis Mesquita et al.	Cardiac arrhythmias in patients presenting with COVID-19 treated in Portuguese hospitals: A national registry from the Portuguese Association of Arrhythmology, Pacing and Electrophysiology
Ana Manuel et al.	Long-term outcomes after radiofrequency catheter ablation of the atrioventricular node: The experience of a Portuguese tertiary center
Joana Ribeiro et al.	Impact of catheter ablation for atrial fibrillation in patients with heart failure and left ventricular systolic dysfunction
Jesús Velásquez-Rodríguez et al.	Influence of left ventricular systolic function on the long-term benefit of beta-blockers after ST-segment elevation myocardial infarction
Luis Raposo et al.	Adoption and patterns of use of invasive physiological assessment of coronary artery disease in a large cohort of 40 821 real-world procedures over a 12-year period
João Costa et al.	Atherosclerosis: The cost of illness in Portugal
Carina Silva et al.	Prognostic impact of iron deficiency in acute coronary syndromes
Luis Paiva et al.	Non-vitamin K antagonist oral anticoagulation versus left atrial appendage occlusion for primary and secondary stroke prevention after cardioembolic stroke
Catarina de Sousa et al.	The burden of infective endocarditis in Portugal in the last 30 years: a systematic review of observational studies
Felipa de Mello Sampayo et al.	Cost-effectiveness of cardio-oncology clinical assessment for prevention of chemotherapy-induced cardiotoxicity

of 2.35±0.49 and 1.3±0.47, respectively, ($p<0.001$). In addition, the mean LVEF improved from 40% to 58% ($p<0.01$), and there was favorable remodeling of left cardiac chambers. The authors concluded that, in patients carefully selected with AF, HF and LVEF <50%, AF ablation results in significant functional class improvement, LVEF improvement, and favorable structural remodeling of left cardiac chambers. Similarly to large scale clinical trials recently published,[11] those authors proposed AF ablation be early considered in those patients, because of its high safety profile as compared to pharmacological rhythm control strategies.

Regarding invasive electrophysiology, Manuel et al.[12] have published an interesting study with long-term follow-up of patients submitted to radiofrequency catheter ablation of the atrioventricular node. They assessed data from 123 patients (mean age, 69±9 years) of a Portuguese tertiary center, with a median 8.5-year follow-up. The indications for that procedure were low percentage of biventricular pacing (8%), presence of tachycardiomyopathy (80%, and 65% of which related to AF of rapid ventricular response despite pharmacological therapy), the occurrence of inappropriate shocks of implantable cardiac defibrillator (2%) or uncontrollable supraventricular tachycardia (10%). In 89% of the cases, a device was implanted during ablation, 14% of which were of cardiac resynchronization, while the remaining patients already carried such devices. The procedure was successfully performed in all patients, with no periprocedural major complication. It is worth noting that, during follow-up, no major complication was documented in association with implantable cardiac devices. In addition, the authors reported improvement of the NYHA functional class, fewer hospitalizations, and a reduction in the number of unplanned visits due to HF decompensation. All-cause mortality was 3.5% by the end of the first year and 23% throughout the entire follow-up, in accordance with that reported in the literature. That study shows the high efficacy and safety of the atrioventricular node ablation procedure in selected patients, a technique that can be especially important to treat complex patients, allowing symptom improvement and a reduction in hospitalization from HF, as reported in the European guidelines.[13]

Left atrial appendage occlusion (LAAO) is a current controversial theme in cardiology. In a study published in the RPC, Paiva et al.[14] have analyzed the safety and efficacy of that procedure in patients with nonvalvular AF for primary and secondary stroke prevention. Those authors have conducted a prospective observational study involving 91 patients submitted to LAAO and 149 patients treated with nonvitamin K antagonist oral anticoagulants (DOACs) in a mean 13-month follow-up. The mean age of the patients undergoing LAAO was 74.7±8.7 years (vs. 77.8±8.0 years of the patients on DOACs), 59% were of the male sex. Their mean CHA_2DS_2-VASc score was 4.3±1.4 (vs. 5.3±1.3) and their mean HAS-BLED score was 3.0±0.9 (vs. 4.0±0.7). The devices ACP/Amulet™ and

Watchman™ were used, and the procedural rate of success was 96.3%, with no major complication reported. The study showed a nonsignificant trend towards a reduction in the composite endpoint of death, stroke, and major bleeding in patients submitted to LAAO (11.0% vs. 20.9%; HR: 0.42, 95% CI: 0.17-1.05, p=0.06). Approximately 20% of the patients submitted to LAAO stopped antiplatelet treatment six months after device implantation due to recurrent minor bleeding, but neither cardiovascular events nor severe bleedings occurred. The authors concluded that LAAO was not inferior to DOACs to prevent the primary composite endpoint of death, stroke, and major bleeding in patients with nonvalvular AF. The scientific community awaits the results of several ongoing randomized clinical trials on this subject, which might provide definitive responses regarding the role of LAAO in the treatment of patients at high risk for stroke (for example, patients with history of intracranial bleeding).[15-18]

The major question regarding LAAO is its cost-effectiveness, yet to be answered in the literature available. In fact, health economics has become one of the most relevant themes, especially in countries that provide universal access to the health system, such as Brazil. A good example is the cost associated with atherosclerosis, which is the pathological denominator common to the major causes of morbidity and mortality in developed countries, such as acute and chronic coronary syndromes, ischemic stroke, and peripheral artery disease. In an article published in the RPC, Costa et al.[19] tried to quantify the economic impact of atherosclerosis in Portugal, using prevalence data and recurring to multiple national databases. The total costs of atherosclerosis in 2016 reached 1.9 billion euros, which correspond to 11% of all health expenditure and to approximately 1% of the gross domestic product in 2016. Of those costs, 58% represented direct costs with the disease, 55% of which related to primary health care, and 42% were indirect costs, 91% of which related to labor absenteeism. Of the manifestations of atherosclerosis, ischemic heart disease had a higher cost per patient, mainly due to medication cost. One may conclude that, considering its high prevalence (9% of the adult population in Portugal) and economic impact, atherosclerosis remains a clinical, social, and financial challenge to the health systems around the world, which may be compounded in the future by population aging.

Current challenges in coronary artery disease

The higher cost of atherosclerotic disease per patient relates to ischemic heart disease and its approach, mainly because of the different therapies available.[19] Several studies have shown that invasive coronary functional assessment with fractional flow reserve (FFR or iFFR) can be cost-effective[20] and improve the prognosis.[21-23] However, its use in clinical practice is still residual in most interventional cardiology laboratories. In an interesting study, Raposo et al.[24] have assessed the pattern of use of those techniques of invasive functional assessment of CAD in two reference centers over a period of 12 years, with a total of 40 821 patients submitted to invasive coronary angiography. Those techniques were applied to only 0.6% of the patients undergoing coronary angiography for valve disease and to 6.0% of those undergoing coronary angiography for stable CAD. In 42.9% of the stable CAD patients undergoing percutaneous coronary intervention (PCI), neither there was evidence of previous ischemia on imaging tests nor physiological assessment was performed. The age of the operators and the time of procedure associated significantly with the use of invasive physiology. The publication timing of reference clinical trials and of relevant international recommendations associated with a higher rate of adoption of those techniques. The scientific evidence on non-hyperemic indices (iFFR), of easy and rapid use, increased the proportion of their use as compared to hyperemic indices (FFR), however without increasing the overall rate of use. The authors concluded that the suboptimal rate of use of the invasive functional assessment of CAD is an opportunity to improve the prognosis of patients with angiographically moderate CAD through dedicated strategies aimed at increasing adherence to scientific recommendations and reducing clinical inertia.

Noninvasive quantification of myocardial FFR can be particularly useful in moderate stenoses (50% to 69%), helping discriminate lesions associated with significant ischemia.[25] Recent studies have shown the high accuracy of noninvasive FFR computed from coronary computed tomography angiography (FFR_{CT}) to identify myocardial ischemia as compared to FFR or iFFR, considered the gold-standard method.[26,27] A retrospective study with patients referred for coronary computed tomography angiography and coronary angiography has assessed the diagnostic performance of FFR_{CT} in detecting significant CAD as compared to FFR, defining obstructive CAD as lumen reduction ≥50% on coronary computed tomography angiography and functionally obstructive CAD as FFR ≤0.8. The study included 93 consecutive patients (152 vessels) and assessed FFR_{CT} by using a machine-learning-based software. Good agreement regarding the FFR measure was observed, with a post-processing time of 10 minutes. Regarding diagnostic performance, even in previous generation CT scanners, there was good agreement between FFR_{CT} and FFR, with minimal FFR_{CT} overestimation (bias: -0.02; limits of agreement: 0.14-0.09). The FFR_{CT} *performance was* significantly superior as compared to the visual classification of coronary stenosis, reducing the number of false-positive cases. The authors have concluded that artificial-intelligence-based FFR_{CT}, even using previous generation CT scanners, shows good diagnostic *performance for* CAD detection, which can be used to reduce invasive procedures.[28]

According to data from the Brazilian Unified Public Health System (SUS), the number of hospitalizations from MI in the public health system adjusted to population increased by 54% from 2008 to 2019. The number of nonprimary PCI procedures per inhabitant doubled, while that of primary PCI increased by 31%. The in-hospital mortality from MI decreased from 15.9% in 2008 to 12.9% in 2019, which is still very high as compared to the world rates.[7] It is worth noting that access to myocardial

reperfusion, which is the therapeutic basis of MI, is not widely available, especially for women, increasing mortality and impacting on the total costs of atherothrombotic disease. A cross-sectional study with data from the VICTIM Registry has assessed patients diagnosed with STEMI from four hospitals (one public and three private) that offer primary PCI in the state of Sergipe, from December 2014 to June 2018. The study included 878 patients with STEMI, 33.4% of whom were women. Slightly more than half of the patients underwent myocardial reperfusion (53.3%, 134 women and 334 men). Women had lower rates of fibrinolysis (2.3% of the total, 1.7% in women and 2.6% in men) and of primary PCI (44% in women and 54.5% in men), resulting in higher in-hospital mortality for women as compared to that for men (16.1% vs. 6.7%). It is worth noting that women, as compared to men, had higher rates of diabetes mellitus (42% vs. 28.5%), systemic arterial hypertension (75.1% vs. 59%), and dyslipidemia (50.2% vs. 33.3%). The authors have emphasized the worst results for the public health system users, mainly for women, and pointed to the need to improve the access of women with STEMI to effective treatment strategies to reduce in-hospital mortality.[29]

Primary PCI is aimed at restoring arterial lumen patency to promote blood flow in coronary microcirculation. However, one in every three patients remains with reduced microvascular flow even with restored macrovascular flow, a phenomenon known as no-reflow. Those patients are at higher risk for HF, cardiogenic shock, and cardiovascular death.[30] Although the SYNTAX score is a good predictor of microvascular dysfunction, the atherosclerotic and thrombus burdens are not considered in the algorithm, because of the exclusion of obstructive lesions with stenoses <50% and the attribution of a low score to the presence or absence of a thrombus, respectively. To assess whether the atherosclerotic burden (through the Gensini score) and the thrombus burden in the culprit coronary artery improved the ability of the SYNTAX score to detect no-reflow, Matos et al.[31] have assessed 481 consecutive patients with STEMI, who presented within 12 hours from symptom onset. No-reflow was defined as TIMI flow <3 or TIMI flow =3, but myocardial blush grade <2. Thrombus burden was quantified according to the TIMI thrombus grade scale (0 to 5). Patients' mean age was 61±11 years, and no-reflow occurred in 32.8% of the patients. The independent predictors of no-reflow were SYNTAX score (OR=1.05, 95% CI: 1.01–1.08, p<0.01), thrombus burden (OR=1.17, 95% CI: 1.06–1.31, p<0.01), and Gensini score (OR=1.37, 95% CI: 1.13–1.65, p<0.01). The combined scores had a larger area under the curve as compared to the SYNTAX score alone (0.78 [0.73–0.82] vs. 0.73 [0.68–0.78], p=0.03). Those authors have concluded that the atherosclerotic and thrombus burdens in the culprit artery add predictive value to the SYNTAX score to detect no-reflow. The major limitation of that study is its cross-sectional and single-center character.

One strategy to improve mortality from MI would be the use of beta-blockers (BB) and acetylsalicylic acid. Recently the long-term prognostic benefit of BB use after acute coronary syndrome has been questioned. In a retrospective study published in the RPC, Velásquez-Rodríguez et al.[32] have tried to respond that question analyzing 972 consecutive patients admitted with STEMI, 99.7% of whom submitted to PCI, with a mean age of 62.6±13.5 years, and 21.8% of the female sex. At discharge, 85.9% of the patients were on BB. As expected, those who did not receive BB had more comorbidities (neoplasia, anemia, chronic obstructive pulmonary disease), and higher prevalence of inferior STEMI and of high-grade atrioventricular block. After a mean follow-up of 49.6±24.9 months, the use of BB was an independent predictor of survival in the general population (HR 0.61, 95% CI: 0.38-0.96), but, when stratified according to LVEF, only those with LVEF ≤40% seemed to have a survival benefit with that therapy. The authors have concluded that the study results raise reasonable doubts regarding the real benefit of the long-term systematic use of BB after STEMI in patients with LVEF >40%. In another observational study including 1520 patients, published in the RPC in 2018, Timóteo AT et al.[33] concluded that the systematic use of BB after acute coronary syndrome was beneficial regardless of the LVEF value. Briefly, in 2022 it seems reasonable to state that, in the absence of scientific evidence from randomized clinical trials with proper sample sizes, there is still room for BB therapeutic individualization after MI in patients with LVEF >40% that considers the patients' mean life expectancy, their preferences, functional and cognitive status, comorbidities, frailties, drug interactions, and adverse reactions.[34]

New strategies to minimize adverse outcomes from MI are welcome, one of them being the extrapolation of data from patients with HF of ischemic etiology.[35] In the literature, data relative to the prognostic impact of iron deficiency in acute coronary syndromes are scarce. A study published in the RPC by Silva et al.[36] has aimed to fill that gap. That study assessed data from 817 patients admitted due to acute coronary syndrome to a Portuguese tertiary hospital. The patients were assigned to two study groups according to the presence (n=298, 36%) or absence (n=519) of iron deficiency on admission. Those with iron deficiency more frequently had moderate and severe left ventricular dysfunction, right ventricular dysfunction, and higher Killip classes. In the middle-term follow-up (mean of 738 days), those patients showed higher all-cause mortality (12.6% vs. 6.3%, p=0.04), NYHA functional class III/IV HF (10.5% vs. 5.3%, p=0.011), as well as higher rate of hospital readmission (9.8% vs. 13.7%, p=0.048). Iron deficiency was an independent predictor of death or HF during follow-up and enabled the prognostic stratification, regarding the occurrence of death or HF, of patients without anemia and/or with lower Killip classes (≤2). The authors concluded that iron deficiency is not only a prevalent condition among patients with acute coronary syndrome but also an independent predictor of death or severe HF in the middle-term follow-up. In addition, iron deficiency can be an interesting complement in the prognostic stratification of patients with acute coronary syndrome without anemia, as well as in those with Killip classes ≤2.

Heart failure: from causes to prevention

Heart failure affects approximately 26 million people around the world and these figures tend to increase with population aging, high prevalence of cardiovascular risk factors, patients' survival from MI, and improvement in HF therapies. In addition, worse outcomes from HF and social determinants seem to be associated.[37] Santos et al.[38] have assessed the temporal progression of the mortality rates from HF according to sex and age group in Brazil, its geographic regions, and federative units, from 1980 to 2018, and their association with the Municipal Human Development Index (MHDI). Mortality from HF decreased in Brazil over the 29 years studied, with a trend towards progressive reduction since 2008, reaching, by the end of 2018, similar levels in the geographic regions and federative units. The mortality rates from HF in the male sex were higher almost in all periods and age ranges assessed, probably because of the relation with the ischemic etiology of HF. An inverse trend was observed between the variation in the mortality rates of the federative units from 1990 to 2018 and the variation in their respective MHDI from 1991 to 2010. The authors suggested that, regarding mortality from HF, more important than the increase in the MHDI is the final level of that index (MHDI $\geq$0.7). The authors concluded that the access to health care should be expanded and encouraged a more effective control of the cardiovascular risk factors (dyslipidemia, obesity, sedentary lifestyle, diabetes) and of the social determinants, which contribute significantly to mortality from ischemic heart disease and HF.

Considering the increasing population at risk for developing HF after exposure to cardiotoxic chemotherapy (CTX), in addition to the scarce scientific evidence to support different strategies of cardioprotection in those patients, Mello et al.[39] have published a cost-effectiveness study to provide some answers. Those authors have calculated and compared the QALYs of two cardioprotective strategies: a universal cardioprotective strategy (all patients receiving BB and angiotensin-converting-enzyme inhibitor); and another guided by LVEF imaging assessment (in which the cardioprotective medication was initiated upon diagnosis of HF due to CTX, defined by a symptomatic LVEF decrease >10% to a final value $\leq$55%). For that calculation, a Monte Carlo simulation of a Markov model was used. The authors concluded that, from a cost-effectiveness perspective, the imaging-assessment-guided cardioprotective strategy was superior to the universal cardioprotective strategy, providing more QALYs at a lower cost. In the reference case of a 63-year-old female with breast cancer undergoing CTX with anthracyclines and trastuzumab over 5 years, the imaging-assessment-guided cardioprotective strategy resulted in 4.22 QALYs at a cost of €2594, while the universal cardioprotective strategy resulted in 3.42 QALYs at a cost of €3758. Further large-scale clinical trials are needed to better define the population of patients who benefit from cardioprotective strategies in cardiotoxicity primary prevention.

The obesity-related disorders, such as insulin resistance, diabetes, and dyslipidemia, are considered HF predictors and associate with adipose tissue dysfunction, promoting maladaptive cardiac responses, such as myocyte hypertrophy, contractile dysfunction, and cardiac remodeling, which contribute to their development and chronic HF progression.[40] Alves et al.,[41] in an elegant study with Wistar rats, have hypothesized that the activation of the toll-like receptor 4 (TLR-4) participates in the obesity-related cardiac disease by triggering cytokine production via nuclear factor-κB (NF-κB). The 'obese' group, which was fed a high sugar-fat diet and water plus 25% of sucrose for 30 weeks, showed: obesity, high levels of glucose, triglycerides and uric acid, insulin resistance, high systolic blood pressure, high levels of tumor necrosis factor alpha (TNF-α) in the adipose tissue, in addition to cardiac remodeling and diastolic dysfunction. In the obese group of Wistar rats, the TLR-4 and NF-κB expression, the levels of cytokines, and the TLR-4 gene and protein expression were higher, and the NF-κB phosphorylation was increased, confirming the activation of that pathway as an inflammation mediator. The authors concluded that the innate immune response via TLR-4 activation is one of the mechanisms that can contribute to the myocardial inflammatory process of obesity, and that the inflammation derived from cardiac TLR-4 activation is a new mechanism that can lead to cardiac remodeling and dysfunction.

Obesity in adolescence can lead to metabolic syndrome (MS) and endothelial dysfunction, being a predictor of adult obesity, in addition to an early marker of cardiovascular risk. It is worth noting that sleep respiratory diseases, such as obstructive sleep apnea (OSA), are some of the consequences of obesity.[42] To investigate whether obesity in adolescence is associated with MS and/or OSA, in addition to its relation to endothelial dysfunction, Hussid et al.[43] have studied 20 sedentary obese adolescents (14.2±1.6 years, 100.9±20.3 kg) and 10 normal-weight adolescents (15.2±1.2 years, 54.4±5.3 kg) paired by sex. The authors assessed the risk factors for MS, vascular function (flow-mediated dilation), functional capacity (VO_2peak), and the presence of OSA (apnea-hypopnea index > 1 event/hour on polysomnography). In the sample studied, obesity was an important risk factor for the MS development and led to endothelial dysfunction. Increased waist circumference and systolic blood pressure were predictors of endothelial dysfunction in adolescents. Most adolescents had OSA, regardless of obesity. The reduced sample size, girls' menstrual cycle hormones affecting the endothelial function, and absence of patterns for the variables studied in the Brazilian adolescents might have influenced the study's findings.[43]

Heart transplantation (HT) is the gold-standard care of terminal HF and there is a strong association between pulmonary artery systolic pressure (PASP) and lethality from that procedure, severe pulmonary hypertension (PH) being one of the major contraindications for transplantation because of post-operative right heart dysfunction.[44] Mendes et at.[45] have studied 300 consecutive candidates for HT treated between 2003 and 2013, dividing them into two groups according to the presence of PH. Of those patients, 95 had fixed PH, 30 of whom were pre-treated with

sildenafil and received a HT, constituting group A. Group B included 205 patients without PH who also received a HT. The PASP decreased after HT in both groups but remained significantly high in group A as compared to that in group B (40.3 ± 8.0 mm Hg vs. 36.5 ± 11.5 mm Hg, p=0.022). One year after HT, PASP was 32.4 ± 6.3 mm Hg in group A *versus* 30.5 ± 8.2 mm Hg in group B (p=0.274). The authors concluded that, in patients with PH pre-treated with sildenafil, early post-operative hemodynamics and prognosis are numerically worse as compared to those in patients without PH. However, after 1 year, middle- and long-term mortalities are similar. They emphasized that the use of sildenafil to reduce PASP can be considered a valuable 'rescue therapy' in the group of patients with terminal HF.

Physical exercises minimize the major HF determinants, such as obesity, hypertension, and myocardial ischemia, and help both primary and secondary prevention of atherothrombotic disease. Patients with symptomatic peripheral artery disease (PAD), especially with intermittent claudication, have arterial hypertension, autonomic cardiac dysfunction, endothelial dysfunction, and increased oxidative stress and inflammation. In addition, PAD is a marker of atherosclerotic burden and associates with multisite atherothrombotic disease. Exercise training is considered the best treatment for patients with symptomatic PAD because it improves those patients' locomotion ability, claudication symptoms, quality of life, and cardiovascular health.[46] Cheuen et al.[47] have conducted a study to compare the acute effects of maximal and submaximal walking on cardiovascular function and to assess the post-exercise regulation and associated pathophysiological processes in patients with symptomatic PAD. The authors recruited 30 men who underwent two sessions: maximal walking (Gardner's protocol) and submaximal walking (15 bouts of 2 minutes of walking separated by 2 minutes of upright rest). In each session, the following parameters were assessed before and after walking: vital signs, heart rate variability, forearm and calf blood flows, reactive hyperemia, lipid peroxidation, and plasma levels of nitric oxide, C-reactive protein, TNF-α, and vascular and intercellular adhesion molecules (VCAM and ICAM, respectively). They reported that submaximal, but not maximal, walking reduced post-exercise blood pressure, while maximal walking maintained cardiac overload elevated during the recovery period. The maximal and submaximal walking sessions increased heart rate, cardiac sympathovagal balance, and post-exercise inflammation similarly, but did not change post-exercise nitric oxide bioavailability and oxidative stress. New longitudinal studies with larger and diverse populations need to be conducted to measure the long-term effects and to establish the best approach to patients with symptomatic PAD.

Still regarding physical exercise, Santos et al.[48] have studied male Wistar rats, aged 10 to 12 weeks, to assess whether strength training reduces oxidative damage to the heart and contralateral kidney caused by renovascular hypertension induction surgery. In addition, they assessed the changes in the activity of endogenous antioxidant enzymes (superoxide dismutase, catalase, and glutathione peroxidase). The strength training was initiated four weeks after renovascular hypertension induction, was performed at 70% of 1RM, and lasted for 12 weeks. After the training period, there was a reduction in oxidative damage to lipids and proteins, with reduction in the hydroperoxides and total sulfhydryl levels, respectively, as well as an increase in the activities of superoxide dismutase, catalase, and glutathione peroxidase. Those authors concluded that the strength training can reduce oxidative damage by increasing the activities of antioxidant enzymes and suggested that strength training can be a nonpharmacological tool to treat renovascular hypertension, with the potential to prevent the damage advance to the heart and the kidney without renal artery stenosis. Studies on human beings need to be performed to confirm the hypothesis.

Sousa et al.[49] have published a study on the epidemiology of infective endocarditis in Portugal, a systematic review of observational studies, including data from 1872 patients and enabling the assessment of important trends in diagnosis, treatment, and prognosis of those patients over the past three decades. The mean age was 55.5 ± 12.1 years, and there was a significant prevalence of males. Over time, the series reported a trend towards an increase in the patients' mean age, which was 61.6 ± 16.3 years in 2008. The percentage of patients with endocarditis of a prosthetic valve or of an implantable cardiac device has also increased over the past decades, being 22.6% and 6.0%, respectively, in the most recent series. The prevalence of enterococcal infection was 10.2%, in accordance with data from the EURO-ENDO European registry[50] and once again reflecting the patients' growing aging. The use of non-ultrasonographic cardiac imaging techniques (FDG-PET and cardiac computed tomography angiography) was globally low because most patients were treated before the 2015 European guidelines,[51] in which assessment with those techniques played a major role for the first time in the diagnosis and prognostic stratification. The rate of cardiac surgery varied substantially (3.1% to 52%), being higher in the most recent series. Short-term mortality ranged from 3.0% to 37.2%. That study provides important epidemiological information on a pathology of growing prevalence and complexity. This information can encourage clinical trials about the subject, on which scientific evidence regarding the best diagnostic and therapeutic strategies is still scarce.

Conclusions

Despite the COVID-19 pandemic, 2021 was a year of intense activity for scientific publication in the *Arquivos Brasileiros de Cardiologia* and the *Revista Portuguesa de Cardiologia*. In this review of the ten best articles of 2021 in each of those journals, we aimed to review in a clear and practical way the findings of those papers and to emphasize their clinical importance for the understanding of cardiovascular disease. It is paramount to acknowledge how we advanced last year so we can progress even more in the coming years.

The 2021 highlights were for the thematic areas as follows: COVID-19 and its consequences, cardiac arrhythmia and its impact on society, current challenges in coronary artery disease, and heart failure: from causes to prevention. The articles approached new technologies, epidemiology of diseases, experimental studies for pathophysiological understanding, and fight of risk factors through a healthy lifestyle, particularly with studies on physical exercise and its role in cardiovascular diseases.

It was a true honor and pleasure for the editors of the two most important scientific journals in Portuguese to comment on such high-quality articles. We are very grateful to all authors who continue to submit their best science to our journals. We hope our readers enjoy this review and be encouraged to have their own articles in the list of the 2022 Top Ten. It is not too late! Submit your best science!

Author Contributions

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Heart Failure with Mildly Reduced Ejection Fraction: Therapeutical Considerations and Reasons for This Renaming

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Introduction

Heart failure (HF) has been classically divided into HF with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction (HFpEF). However, to better classify HF patients with a left ventricular ejection fraction (LVEF) between 41 and 49%, previous guidelines have introduced the term HF with mid-range ejection fraction.[1] Nonetheless, shortly after its formal introduction, HF with mid-range ejection fraction is now called HF with mildly reduced ejection fraction (HFmrEF).[2] In this letter, we explore the reasons behind this renaming and why this change is more important than it may seem.

Prevalence, Characteristics and Prognosis

HFmrEF comprises 13-24% of the HF population.[1] Specifically in Brazil, 19.6% of HF patients were classified as HFmrEF in the community.[3] While previous guidelines indicated that HFmrEF resembled more HFpEF,[1] extensive evidence published since its introduction showed this group is more similar to HFrEF or have intermediate characteristics.[1] On the other hand, prognostically, HFmrEF has better outcomes than HFrEF.[1] Importantly, HFmrEF comprehends individuals with different LVEF trajectories (e.g. HFpEF with a deteriorated LVEF; HFrEF with an improved LVEF or HFmrEF with an unchanged LVEF) that have different prognosis.[1] This highlights the heterogeneity of HFmrEF compared with HFrEF and HFpEF. HF phenotypes according to LVEF are described in Figure 1.

Therapeutical Considerations for Heart Failure with Mildly Reduced Ejection Fraction

Angiotensin-converting-enzyme inhibitors (ACEi), Angiotensin receptor blockers (ARBs) and Angiotensin Receptor-Neprilysin Inhibitors (ARNI)

Evidence for the effectiveness of ARBs in HFmrEF is controversial. In a post-hoc analysis of the CHARM-Preserved trial, candesartan was shown to be effective compared to placebo in reducing the composite end-point of cardiovascular (CV) death or HF hospitalization (HR: 0.76, 95%CI: 0.61-0.96) and HF hospitalization alone (HR: 0.72; 95%CI: 0.55-0.95).[4] However, in a prespecified analysis of the I-PRESERVE trial, irbesartan had no effect on CV death or HF hospitalization (HR: 0.98; 95%CI: 0.85-1.12) in patients with a LVEF between 45 and 59%.[5] Evidence on the effect of ACEi in HFmrEF is limited. In the PEP-CHF trial observed perindopril had no effect on reducing all-cause mortality, CV death or HF hospitalization.[6] Nevertheless, this trial included a large proportion of HFpEF patients. Regarding ARNI, in a prespecified analysis of the PARAGON-HF trial, sacubitril/valsartan significantly reduced CV death or HF hospitalization compared with valsartan alone in patients with a LVEF <57%.[7] A further post-hoc analysis that combined data from the PARAGON-HF and PARADIGM-HF trials, showed that individuals with HFrEF and HFmrEF had a significant risk reduction in the composite endpoint of HF hospitalization or CV death.[8] For this reason, the FDA extended the indication of sacubitril/valsartan in the package insert to include HFrEF and HFmrEF. Therefore, although this evidence is hypothesis-generating only, patients with HFmrEF probably benefit from sacubitril/valsartan.

Mineralocorticoid receptor antagonists (MRA)

A post-hoc analysis of the TOPCAT trial showed that, although spironolactone had greater benefits at lower LVEF, it did not improve outcomes in patients with LVEF between 44 and 50%.[9] Nonetheless, a significant regional difference was observed in the TOPCAT trial. While patients enrolled in the Americas had a significant 18% risk reduction in the primary outcome, in Russia and Georgia, spironolactone did not improve prognosis.[10] Further analysis showed that a substantial proportion of patients enrolled in Russia and Georgia did not receive or take spironolactone,[11] which can explain this difference. Also, data from a meta-analysis that included 11 randomized controlled trials (RCTs) showed spironolactone significantly reduced the risk of hospitalizations, improved New York Heart Association functional class and decreased levels of b-type natriuretic peptide in HFmrEF and HFpEF patients.[12] Thus, spironolactone is probably effective in HFmrEF.

Sodium–glucose cotransporter 2 inhibitors

In the EMPEROR-PRESERVED trial, empagliflozin significantly reduced the combined risk of CV death or HF hospitalization compared with placebo in patients with a LVEF >40%, although this benefit came from the reduction in HF hospitalizations.[13] In a prespecified subgroup analysis,

Keywords

Cardiovascular Diseases; Heart Failure; Stroke Volume; Prognosis; Mineralocortical Receptor Antagonists; Angiotensin Converting Enzyme Inhibitors; Digoxin.

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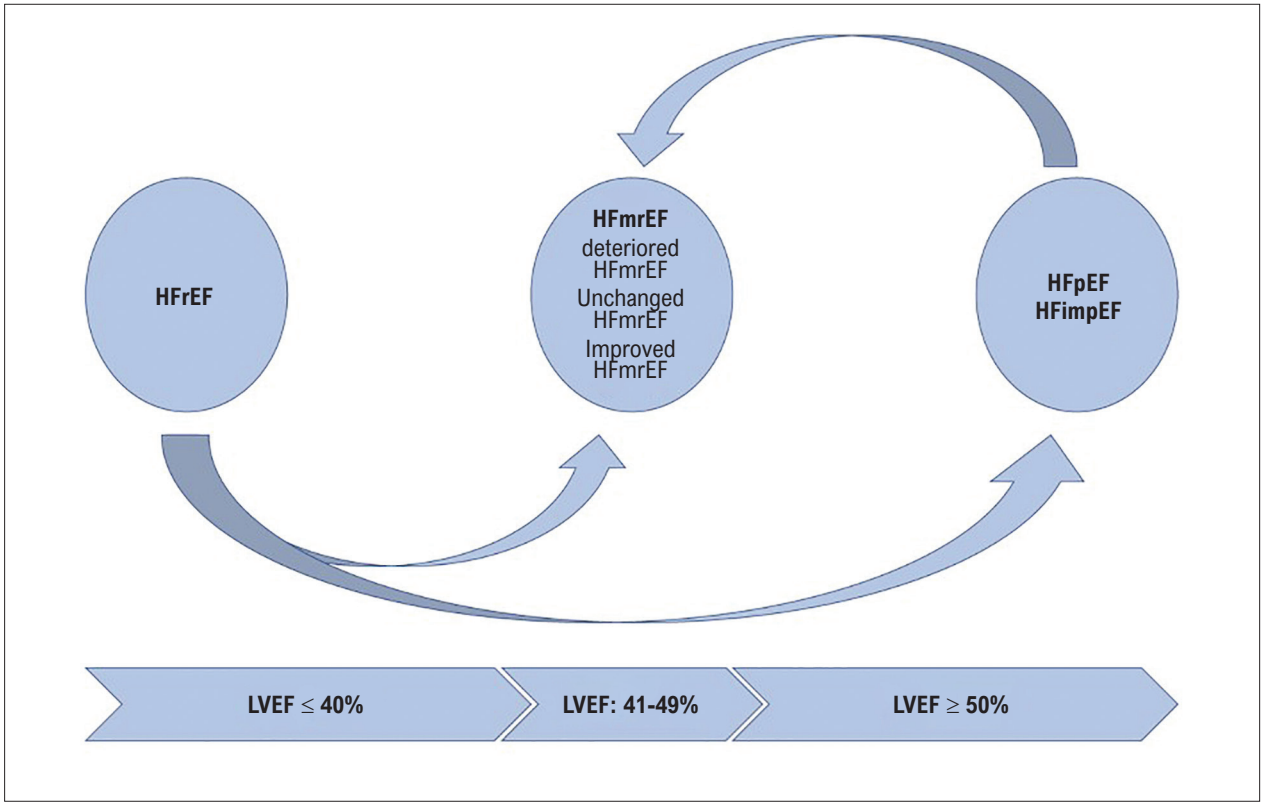

Figure 1 – *Heart Failure Phenotypes according to Left Ventricular Ejection Fraction. HFmrEF – heart failure with mildly reduced ejection fraction; HFimpEF – heart failure with improved ejection fraction; HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction; LVEF> left ventricular ejection fraction. HFrEF covers patients with a LVEF ≤ 40%. Nonetheless, some of these patients can have a 10-point increase from baseline LVEF and become HFimpEF. HFmrEF comprises patients with LVEF from 41-49%, which could be patients with an unchanged LVEF; patients with a deteriorate LVEF and patients with an improved LVEF before reaching HFimpEF criteria. Finally, patients with a LVEF ≥ 50% are classified as HFpEF.*

empagliflozin was even more effective in HFmrEF, and significantly reduced the risk of the composite outcome by 29% compared with placebo.[13]

Beta-blockers and Digoxin

In an individual patient data meta-analysis, beta-blockers reduced the risk of CV mortality in HFmrEF patients in sinus rhythm, but did not improve endpoints in HFmrEF patients with AF.[14] Digoxin, on the other hand, did not improve prognosis in a post-hoc analysis of the DIG trial for HFmrEF patients.[15] Clinical Trials that investigated the effect of drug therapies for HFmrEF are described in Table 1.

Current needs

Previous guidelines suggested HFmrEF patients should be treated as HFpEF. However, as previously mentioned, these patients benefit from multiple therapies that HFpEF patients do not. In addition, as seen, HFmrEF is similar to HFrEF. Future RCTs should randomize HFmrEF patients so guideline recommendations can be extended to this group. This could be accomplished through the inclusion of HFmrEF in HFrEF trials or by conducting trials specifically for this population, although this is a challenging alternative.

Conclusions

HFmrEF mostly resembles HFrEF and benefits from multiple therapies. The transition from its former name HF with mid-range ejection fraction to HFmrEF is appropriate and gives the sense that these patients benefit from HFrEF therapies. This may lead to an increase in the adoption of guideline-directed medical therapies, improving outcomes in this historically forgotten group of patients.

Author Contributions

Conception and design of the research: Correia ETO; Analysis and interpretation of the data, Writing of the manuscript and Critical revision of the manuscript for intellectual contente: Correia ETO, Mesquita ET.

Potential Conflict of Interest

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

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There were no external funding sources for this study.

Table 1 – Clinical trials describing the effect of drug therapies in Heart Failure with Mildly Reduced Ejection Fraction

Study	Drug	Methodology	LVEF range for the Effect	All-Cause Mortality	CV Mortality	CV Death or HF Hospitalization	HF Hospitalization
PEP-CHF[6]	Perindopril	Randomized Trial	> 45%	1.09 (0.75-1.58)	0.98 (0.63-1.53)	NR	0.86 (0.61-1.20)
CHARM[4]	Candesartan	Post-hoc analysis of a randomized trial	40-49%	0.79 (0.60-1.04)	0.81 (0.60-1.11)	0.76 (0.61-0.96)	0.72 (0.55-0.95)
I-PRESERVE[5]	Irbesartan	Randomized Trial	45-59%	NR	NR	0.98 (0.85-1.12)	NR
PARAGON-HF[7,8]	Sacubitril-Valsartan	Randomized Trial	45-50%	NR	NR	0.82 (0.63–1.06)	NR
TOPCAT[9,10]	Spironolactone	Post-hoc analysis of a randomized trial	44-50%	0.73 (0.49-1.10)	0.69 (0.43-1.12)	0.72 (0.50-1.05)	0.76 (0.46-1.27)
Xiang et al.[12]	Spironolactone	Meta-analysis of randomized trials	> 40%	NR	0.72 (0.31–1.69)	NR	0.84 (0.73–0.95)
Cleland et al.[14]	Beta-blockers	Meta-analysis of individual patient data	40-49%	SR: 0.59 (0.34-1.03); AF: 1.30 (0.63-2.67)	SR: 0.48 (0.24-0.97); AF: 0.86 (0.36-2.03)	SR: 0.83 (0.60-1.13); AF: 1.06 (0.58-1.94)	SR: 0.95 (0.68-1.32); AF: 1.15 (0.57-2.32)
EMPEROR-Preserved[13]	Empagliflozin	Randomized Trial	> 40%	1.00 (0.87-1.15)	0.91 (0.76-1.09)	0.79 (0.69-0.90)	0.73 (0.61-0.88)
DIG[15]	Digoxin	Post-hoc analysis of a randomized trial	40-49%	1.08 (0.85-1.37)	1.24 (0.94-1.64)	0.96 (0.79-1.17)	0.80 (0.63-1.03)

AF: atrial fibrillation; CV: cardiovascular; HF: heart failure; LVEF: left ventricular ejection fraction; SR: sinus rhythm.

Study Association

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

Ethics approval and consent to participate

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

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Reinnervation after Renal Denervation – A Myth?

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Introduction

Hypertension (HTN) is a leading risk factor influencing the global burden of cardiovascular disease.[1] In spite of the fact that measures such as lifestyle changes and pharmacological treatment reduce blood pressure (BP) and cardiovascular complications, worldwide, the treatment of HTN remains suboptimal with inadequately controlled BP in many patients.[2] In the ReHOT Randomized Study, the prevalence of resistant HTN was 11.7% among Brazilian hypertensive patients, which is in agreement with the prevalence reported in other international studies.[3,4] According to the current guidelines of the European Society of HTN, resistant HTN is defined when target BP values are not reached, despite prescription of triple therapy, including a diuretic at a maximum tolerated dose.[5] Sympathetic nervous system hyperactivity is thought to play a major role in resistant HTN. At the kidney level, the efferent sympathetic outflow to the kidneys leads to increased noradrenaline production, renal vasoconstriction and renin release, causing sodium retention. On the other side, afferent sympathetic fibers send signals to the brain to stimulate central sympathetic activity and contribute to neurogenic HTN.[6] Catheter-based renal denervation (RDN) has emerged as one of the most frequently used invasive methods for the treatment of resistant HTN.[7] It aims to ablate the afferent and efferent sympathetic nerves in the adventitia of the renal arteries using radiofrequency energy. It is performed through the insertion of the device catheter percutaneously into the femoral artery, which is then advanced into the main renal arteries under fluoroscopic guidance.[6] According to a meta-analysis, the rate of procedural complications is low and consists mainly in pseudoaneurysms at the vascular access site and renal artery dissection.[8] Nevertheless, its role in clinical practice is controversial and there is scarce information about the different responses to this procedure.[5] We report two cases of idiopathic resistant HTN treated with RDN. Both patients had a profound initial response to the procedure. Nevertheless, their BP was back to baseline values at the 24 and 18-month follow-up, respectively. An investigation to detect secondary causes of HTN was performed with no findings that justified the BP changes. Therefore, a new RDN was performed, with good results, lasting until the present day (6-month follow-up for patient 1 and more than 3-year follow-up for patient 2). This is a report about the heterogeneous response to RDN, the possible role of functional re-innervation and the potential development of supersensitivity to norepinephrine after RDN. These mechanisms could be responsible for increasing the BP back to baseline values after an optimal initial response.

Keywords

Resistant Hypertension/therapy; Renal Denervation; Renal - Re-Innervation; Blood Pressure, Monitoring Ambulatory/methods/ Diagnostic, Imaging/methods

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Case reports

Case 1

A 49-year-old man with a history of HTN, presented with episodes of dizziness and chest pain associated with hypertensive peaks. The patient was sedentary, overweight (height = 192cm, weight = 98kg, body mass index – BMI – = 26.6kg/m^2) and had a medical history of type 2 diabetes, dyslipidemia and gout. He was on five antihypertensive drugs: amlodipine 5mg/valsartan 80mg bid, spironolactone 100mg od, nebivolol 5mg od and chlortalidone 50mg od. He was an active smoker (5 pack-units-year) and had no history of alcohol or caffeine excess. On initial examination his office BP was 195/125mmHg, with no inter-arm disparity. His resting heart rate (HR) was 67 beats per minute (bpm) and the remaining physical examination was normal (normal cardiac sounds, absence of murmurs; palpable femoral pulses bilaterally; absence of abdominal bruits). There was evidence of HTN-mediated organ damage – HMOD – (left ventricular hypertrophy criteria on ECG – Sokolov-Lyon criteria 46mm; R wave in aVL 15mm – and moderate concentric hypertrophy of the left ventricle on echocardiography – interventricular septum, 16mm; posterior wall, 12mm; left ventricular mass index 134g/m^2). The patient had undergone a previous CT coronary angiogram that revealed no coronary disease. Secondary causes of HTN were excluded (screening with full biochemistry and hematology profile, imaging assessment and polysomnography) – see table 1 – and idiopathic resistant HTN was confirmed by ambulatory blood pressure monitoring (ABPM) – 24h average BP 159/106 mmHg. RDN was proposed and performed with the multielectrode Spyral catheter (Medtronic Inc., Santa Rosa, CA, USA), without complications. At the 6-month follow-up, the patient was asymptomatic, had lost 6kg by adopting better lifestyle habits (BMI = 24.7kg/m^2), was on four antihypertensive drugs (nebivolol was withdrawn due to sinus bradycardia – resting HR = 52bpm) and systolic and diastolic BP in ABPM had dropped to

Table 1 – Screening for secondary hypertension causes

	Patient 1	Patient 2	Reference Values
Plasma fractionated metanephrines:			
Metanephrine (pg/mL)	15.2	31.7	<60
Normetanephrine (pg/mL)	32.6	9.15	<120
Thyroid-stimulating hormone plasma concentration (uUI/mL)	2.3	1.1	0.4-4.0
Plasma renin activity (ng/mL/h)	1.76	1.29	1-4
Plasma aldosterone concentration (ng/dL)	32.1	3.42	5-30
Aldosterone-renin-ratio	18.21	2.65	<25
Serum creatinine concentration (mg/dL)	0.99	0.75	Females: 0.55-1.02 Males: 0.72-1.18
Urine analysis	Negative for protein, erythrocytes and leucocytes	Negative for protein, erythrocytes and leucocytes	NA
Polysomnography (AHI)	3.2	7.6	<5
Computed tomography angiography	No hemodynamically significant stenosis	No hemodynamically significant stenosis	NA
Serum parathyroid hormone concentartion (pg/mL)	26	18	9-72
Serum calcium concentration (mg/dL)	9.8	9.3	8.8-10.6
Salivary cortisol 23.00h (ug/dL)	0.087	0.127	<0.15

AHI: apnea hypopnea index; NA: not applicable.

15 and 10 mmHg, respectively (24h average BP 144/96 mmHg). Nevertheless, at the 24-month follow-up, despite maintenance of weight loss, the patient had a 24h average BP of 181/120 mmHg in ABPM. His resting HR was 70bpm and nebivolol was reintroduced (the patient was back on five hypertensive drugs).

Case 2

A 74-year-old woman presented with episodes of headache associated with hypertensive peaks and excessive daytime sleepiness. The patient was sedentary, overweight (height = 155cm, weight = 63kg, BMI = 26.2kg/m^2) and had a medical history of HTN and dyslipidemia. She was medicated with four antihypertensive drugs: nifedipine 60mg in the morning and 30mg at dinner, perindopril 5mg bid, carvedilol 12.5mg bid and chlortalidone 50mg od. The patient had no history of smoking, alcohol or caffeine excess. On physical examination, her office BP was 200/90 mmHg, with no inter-arm disparity. Her resting HR was 58 bpm and the remaining physical examination was normal (normal cardiac sounds, absence of murmurs; palpable femoral pulses bilaterally; absence of abdominal bruits). There was no evidence of hypertension-mediated organ damage (HMOD): interventricular septum, 9mm; posterior wall, 9mm; left ventricular mass index, 79g/m^2. A previous CT renal angiogram revealed atheromatous plaques in the ostium of both renal arteries, but without hemodynamically significant stenosis. Secondary causes of HTN were assessed (Table 1), revealing mild obstructive sleep apnea. Nevertheless, the ABPM values did not improve with continuous positive airway pressure, despite confirmed compliance – 24h average BP 158/79 mmHg. RDN was proposed and performed with the multielectrode Spyral catheter (Medtronic Inc., Santa Rosa, CA, USA), without complications. At the 6-month follow-up, the patient had no cardiovascular symptoms. She had the same BMI and was still on four antihypertensive drugs, but the ABPM showed a 24h average BP of 110/60 mmHg (systolic and diastolic reduction of 48 and 19 mmHg, respectively). Nevertheless, at the 18-month follow-up, the patient had a new hypertensive episode (BP of 190/85 mmHg). A new ABPM was performed and revealed a 24h average BP of 146/70 mmHg.

Investigations and treatment

The patients were reassessed for secondary causes of HTN, but none was found. A new RDN was proposed, which they accepted**.** Both procedures were performed through the femoral artery, using the multielectrode Spyral catheter (Medtronic Inc., Santa Rosa, CA, USA), without procedural-related complications (Figure 1).

Outcome and follow-up

Case 1

Six months after the second procedure, the average 24h BP registered by ABPM was 159/103mmHg (systolic and diastolic BP drop of 22 and 17 mmHg, respectively). The patient was asymptomatic with a stabilized weight and there was no recurrence of sinus bradycardia. Antihypertensive medication remained unchanged.

BP response before and after both RDN procedures is illustrated in figure 2.

Case 2

At the 6-month follow-up of the second procedure, the average 24h BP registered by ABPM was 127/68mmHg (systolic and diastolic BP drop of 19 and 2 mmHg, respectively). The BP remained stable at the 1-year, 2-year and 3-year follow-up. During this period the patient's antihypertensive medication was progressively reduced due to hypotensive episodes. Overall, the patient general condition has improved, with no record of hypertensive symptoms or signs up to the present day.

BP response before and after both RDN procedures is illustrated in figure 3.

Discussion

The limitations of available pharmacological strategies to control BP in some patients is thought to reflect the complexity and multitude of potential mechanisms responsible for the genesis and maintenance of elevated BP. This led to a renewed interest in invasive strategies.[9,10] Renal sympathetic nerves contribute to the development and perpetuation of HTN, and the sympathetic outflow to the kidneys is activated in patients with essential HTN.[11] The chronic activation of the sympathetic nervous system constitutes a central mechanism in resistant HTN and has been a target of percutaneous RDN.[10]

There is robust evidence derived from well-designed and rigorously conducted sham-controlled studies (SPYRAL HTN-OFF MED, SPYRAL HTN-ON MED, and RADIANCE-HTN SOLO) supporting the efficacy and safety of RDN.[12-14] Nevertheless, the available results are short-term only, and long-term efficacy information is still lacking.[15] There is little information regarding the extent of re-innervation following catheter-based RDN in humans, but studies in animal models show evidence of functional and anatomical renal nerve re-innervation, along with denervation-related supersensitivity to norepinephrine. A study conducted in sheep assessed the effectiveness of renal nerve denervation with the Symplicity Flex™ catheter and the functional and anatomical re-innervation at 5.5 and 11-months post-denervation. It was found that the procedure effectively denervated the afferent and efferent renal nerves, but by 11 months post-RDN, there was functional and anatomical evidence of afferent and efferent renal nerve re-innervation.[16] Similarly, a study conducted in rats indicates that following RDN, functional re-innervation of the renal vasculature begins to occur between 14 and 24-days after the procedure, and that complete return of function may occur by 8 weeks. The study also suggested that the response to renal nerve stimulation during re-innervation could be due to a combination of regeneration of the nerve fibers

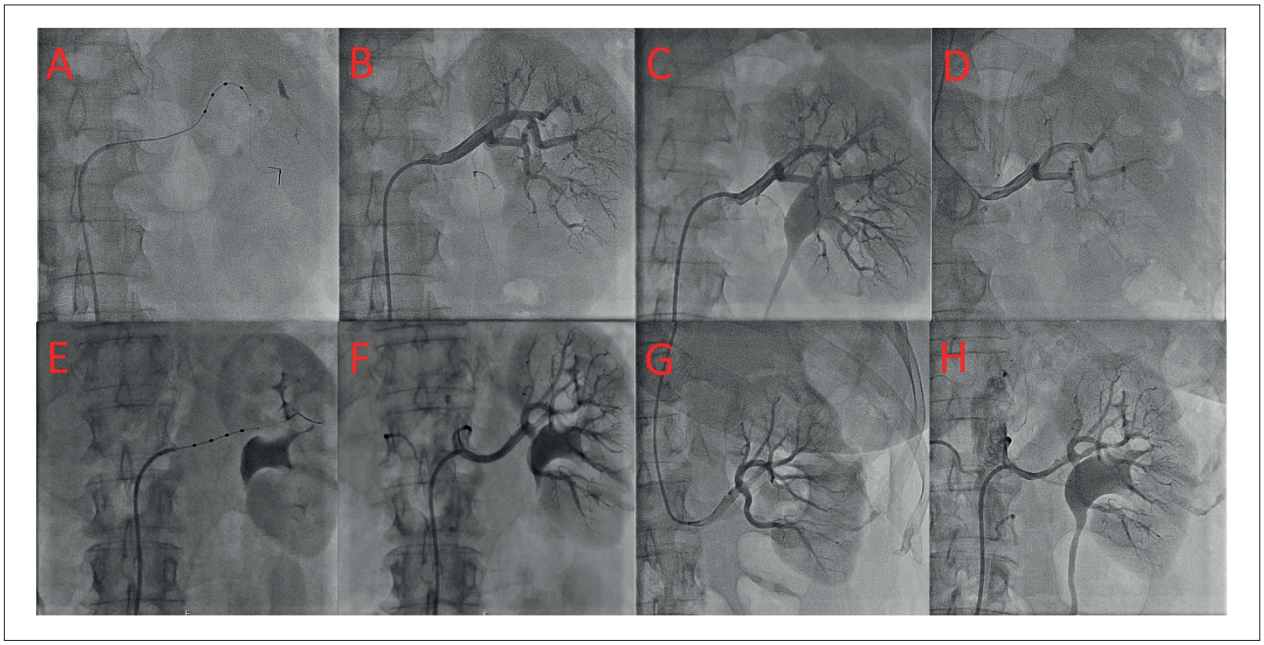

Figure 1 – *Assessment of the renal arteries. Panels A-D) case 1: left renal artery pre-1st RDN, immediately post-1st RDN, at the 6-month follow-up after the 1st RDN and immediately post-2nd RDN, respectively; Panels E-H) case 2: left renal artery pre-1st RDN, immediately post-1st RDN, at the 6-month follow-up after the 1st RDN and immediately post-2nd RDN, respectively. Only the left renal artery of each patient is shown. The contralateral renal artery was in similar conditions. RDN: renal denervation.*

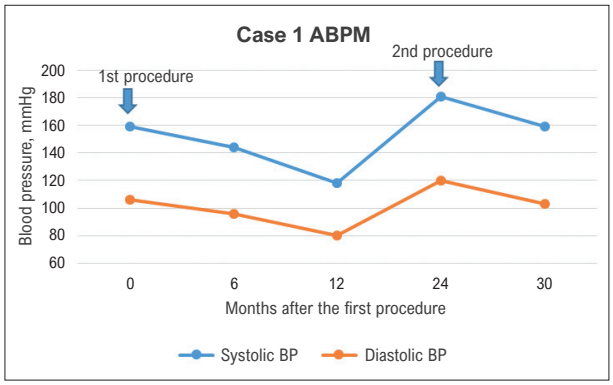

Figure 2 – *Case 1 blood pressure evolution recorded by ambulatory blood pressure monitoring, before and after both renal denervation procedures. ABPM: ambulatory blood pressure monitoring; BP: blood pressure.*

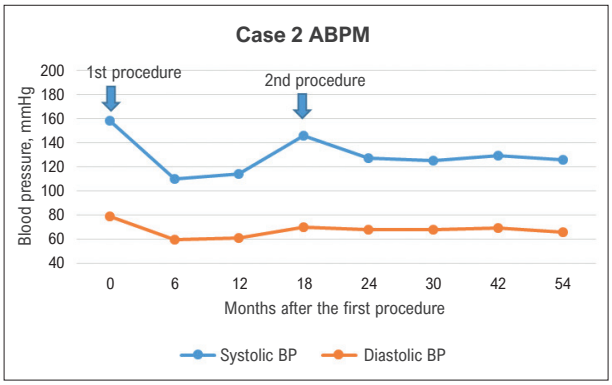

Figure 3 – *Case 2 blood pressure evolution recorded by ambulatory blood pressure monitoring, before and after both renal denervation procedures. ABPM: ambulatory blood pressure monitoring; BP: blood pressure.*

and denervation-related supersensivity to norepinephrine.[17] Although the final 3-year results of the Symplicity HTN-1 study[18] suggest that no re-innervation or any counter-regulatory mechanisms develop over time that could lessen the efficacy of the procedure, the two present cases, along with the evidence available on animal models, seem to indicate that this may not be universally true. The fact that both cases described herein showed marked BP response to the first RDN, followed by re-elevation of the BP to baseline values at follow up, could indicate that re-innervation plays a clinically significant role in the long-term efficacy of the procedure. Additionally, both patients responded to a repeat procedure, a fact that seems to further validate this hypothesis.

Taking these aspects together, the aim of this paper is to raise concerns about the possibility of re-innervation and the development of supersensitivity to norepinephrine after RDN. It is crucial to know whether re-innervation occurs, if it influences the long- term results of the intervention and in which subset of patients this phenomenon is more likely to occur.

Conclusions

Many patients are not able to reach target blood pressure values despite lifestyle changes and pharmacological treatment.

Catheter-based renal denervation is a safe and effective alternative for this subset of patients with resistant hypertension.

The two cases reported herein, along with the evidence available on animal models, could indicate that re-innervation may play a significant role in the long term efficacy of the procedure.

It is therefore crucial to know whether re-innervation occurs, if it influences the long- term results of the intervention and in which subset of patients this phenomenon is more likely to occur.

Author Contributions

Writing of the manuscript: Monteiro E, Costa G; Critical revision of the manuscript for intellectual content: Delgado-Silva J, Gonçalves L.

Potential Conflict of Interest

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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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Thoracic and Intramyocardial Pellets, an Incidental Finding in a Patient with Acute Myocardial Infarction

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Introduction

Penetrating cardiac trauma is fatal; approximately more than half of affected people die at the scene. Penetrating myocardial wounds are rare, and the retention of cardiac pellets is poorly documented in literature.[1] There are no standardized protocols for their diagnostic and therapeutic approach until now. Clinical presentation of a shotgun injury depends on the wound size, entry site, and the injury to the great vessels.[2] In penetrating chest trauma, both ventricles are injured with similar frequency, but the right ventricle is the most entry site because it forms most of the anterior surface of the heart.[3]

Case presentation

We present the case of a 59-years-old man with a family history of hyperlipidemia and acute myocardial infarction (AMI) and a personal history of chest trauma secondary to a shotgun injury in 2006, which did not deserve surgical treatment, no more event data, and type 2 diabetes mellitus diagnosed in 2016 under medical treatment with sitagliptin. The patient arrived at the emergency room in January 2018 with oppressive chest pain of 6 hours of evolution, intensity 8/10, radiated to the left arm, and diaphoresis. At admission, vital signs were within normal parameters, with blood pressure-120/70 mmHg, heart rate-75 bpm, oxygen saturation-92% and body mass index-26 kg/m^2.

Physical examination revealed an old keloid scar in the anterior thoracic region, a hyperdynamic apexian beat in the fifth left intercostal space, and no heart murmurs or abdominal lung sounds were detected. The electrocardiogram showed sinus rhythm, heart rate-73 bpm, Q wave in V1 to V4 leads with ST-segment elevation and inversion of the T wave in the same leads (Figure 1A). Laboratory tests showed leukocytosis (13.06 x10^9/L), elevated fibrinogen (638 g/L), hypokalemia (3.3 mEq/L), hyperglycemia (250 mg/dL), HbAC1-8.7%, positive markers of myocardial damage (CPK-411 IU/L, CPK-MB-53 ng/mL, and high-sensitive troponin-6.1 ng/dL), hypercholesterolemia (total cholesterol-256 mg/dL, c-HDL-35 mg/dL and c-LDL-186 mg/dL) and hypertriglyceridemia (278 mg/dL). A two-dimensional transthoracic echocardiogram (TTE) showed normal ventricular volume and left ventricular ejection fraction (LVEF) of 67%, type II diastolic dysfunction, and a hypoechoic image in the middle segment of the interventricular septum with posterior enhancement (Figure 1C-D). Cardiac catheterization showed a 95% obstruction in the middle segment of the left anterior descending artery, which required balloon angioplasty to obtain TIMI III flow; surprisingly, were observed countless spherical objects compatible with pellets in all cardiac regions (Figure 2). The posteroanterior chest X-ray revealed multiple radiopaque circular objects with a predominance in the anterior region of the thorax (Figure 1B). The 2D chest computed tomography (CT) showed multiple hyperintense spherical objects in the mediastinum, anterior thoracic wall, and the heart, apparently in the left atrium (LA) and the 3D-reconstruction CT confirmed the presence of intramyocardial pellets (Figure 3).

The patient was discharged 3 days later, hemodynamically stable, no surgical intervention was required, and conservative treatment was chosen due to the absence of cardiovascular symptoms or complications after 12 years of cardiac trauma. Follow-ups were scheduled every 3 months in the cardiology outpatient clinic, and changes in lifestyle and drug treatment with antiplatelet agents, statins and oral hypoglycemic agents were indicated. Currently, 42 months after follow-up, the patient is in NYHA functional class I.

Discussion

Gun violence is a serious public health problem, which causes the death of more than 250,000 people by year worldwide. Guenther and collaborators[4] identified up to 2020, 40 reported cases of cardiac injuries caused by a pellet gun. Of these, 90% were men, with an average age of 14 years old; 48% of the patients were reported hemodynamically unstable. Sternotomy was performed in 58% of the cases, a cardiopulmonary bypass in 18% and a pericardial window in 15%. The main affected sites were the right ventricle in 43%, the left ventricle in 33%, the right atrium in 15%, and the left atrium and great vessels were affected in 6%, respectively.[5] Complications include embolization caused by the shot (25%), death

Keywords

Myocardial Infarction/diagnostic, imaging; Wounds, Gunshot; Myocardial Contusion; Incidental Findings; Firearms; Lead

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Research Letter

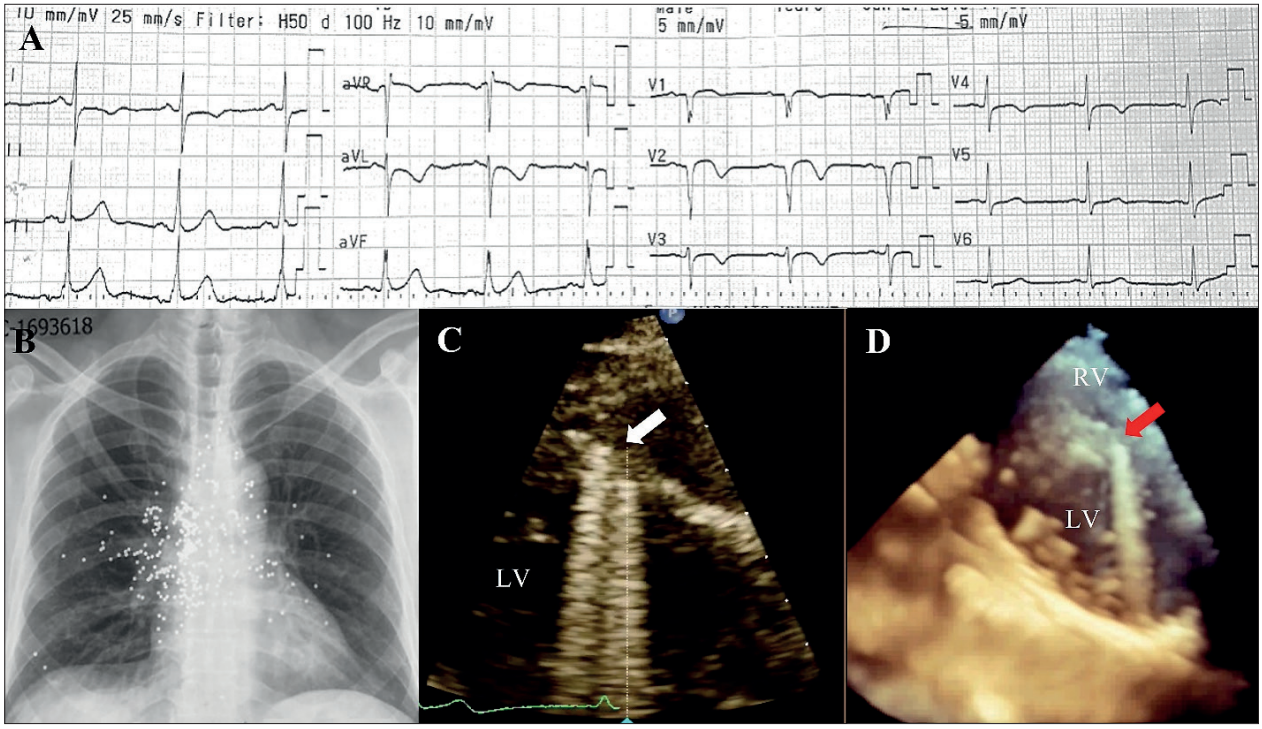

Figure 1 – *Multimodal imaging diagnosis. (A) 12-leads electrocardiogram with sinus rhythm, 73 bpm, Q wave in V1-V4 leads with ST-segment elevation and T wave inversion, suggesting anteroseptal wall ischemia. (B) Anteroposterior chest x-ray with uncountable radiopaque circular objects, metal density. (C) 2D-TTE with a hypoechoic image in the middle segment of the interventricular septum (arrow) with posterior enhancement. (D) 3D-TTE, similar to findings of figure 1C. LV: left ventricle; RV: right ventricle.*

(13%), massive hemorrhage, cardiac tamponade, direct damage to the free wall of ventricles or interventricular septum, dissection of coronary arteries and damage to the conduction system.[4-6] Cardiac trauma is one of the risk factors associated with the appearance of acute myocardial infarction; however, reported cases are isolated.[2-5]

CT and echocardiography are commonly the most used imaging studies to diagnose traumatic cardiac injuries. Two-dimensional TTE is the most accurate method for identifying cardiac lesions, whereas CT is the best for locating foreign bodies. The detection of intracavitary foreign bodies is an indication of their surgical removal due to the high risk of developing thrombotic events, while the presence of completely intramyocardial foreign bodies is more indicative of conservative management.[1,2,4]

Conclusion

Retention of intramyocardial pellets without symptoms is a rare condition in thoracic trauma, and cases associated with acute myocardial infarction are isolated. There are no standardized guidelines for this type of injury's diagnostic and management approach, probably due to the low number of reported cases. Also, we emphasize the use of multimodal imaging as an invaluable tool for the accurate diagnosis of this type of injury.

Author Contributions

Conception and design of the research: Fernandez-Badillo V, Espinola-Zavaleta N; Acquisition of data: Fernandez-Badillo V, Armendariz-Ferrari JC, Espinola-Zavaleta N; Analysis and interpretation of the data: Garcia-Cardenas M, Oliva-Cavero D; Statistical analysis: Oliva-Cavero D; Writing of the manuscript: Fernandez-Badillo V, Garcia-Cardenas M; Critical revision of the manuscript for intellectual content: Garcia-Cardenas M, Oliva-Cavero D, Armendariz-Ferrari JC, Alexanderson-Rosas E, Espinola-Zavaleta N.

Potential Conflict of Interest

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

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Ethics approval and consent to participate

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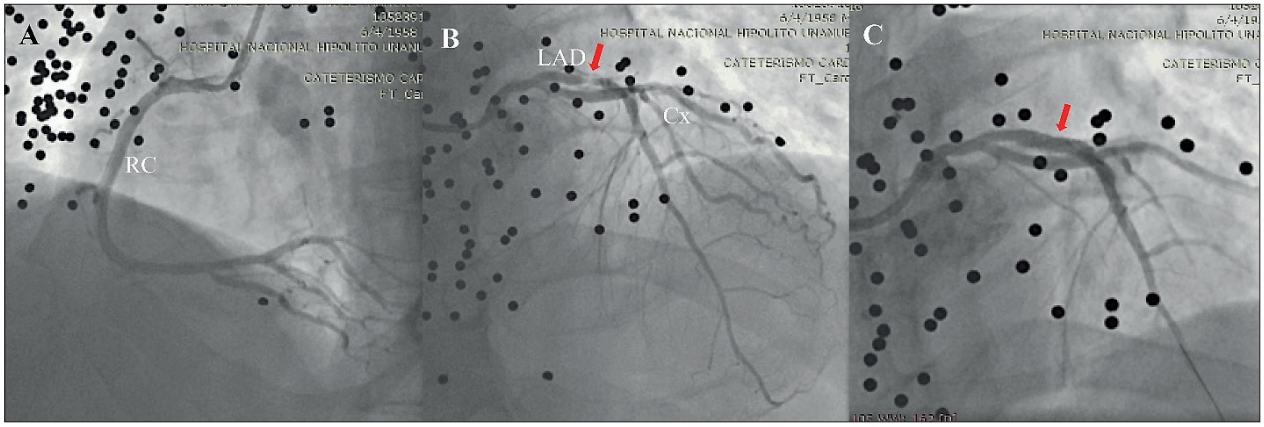

Figure 2 – *Cardiac catheterization. Presence of uncountable circular objects compatible with pellets. (A) Normal right coronary artery. (B) Left anterior descending artery with obstruction of 95% in the middle segment (arrow). (C) Successful left anterior descending coronary artery stenting (arrow), TIMI III flow. Cx: circumflex; LAD: Left anterior descending; RC: right coronary.*

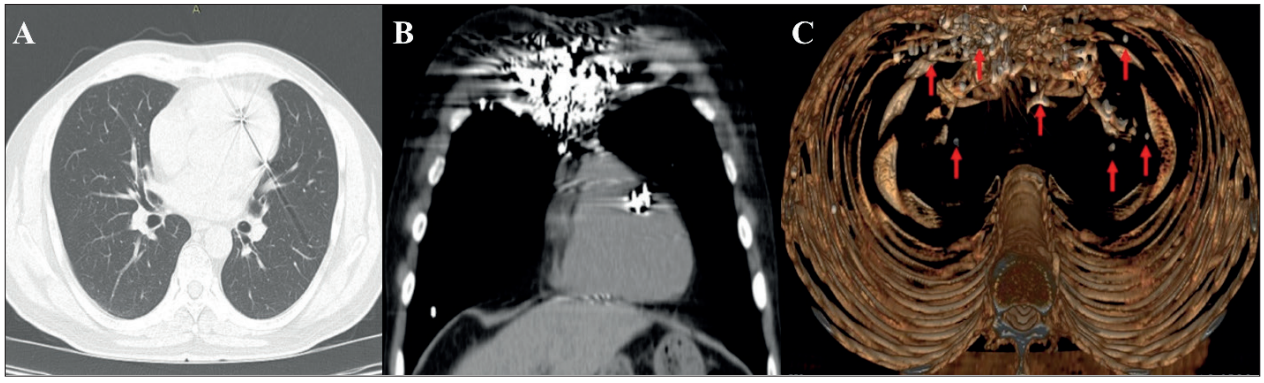

Figure 3 – *Chest computed tomography. (A, B). 2D-CT with hyperintense spherical objects in the mediastinum, anterior thoracic wall, and the heart, apparently in the left atrium. (C) 3D-reconstruction, pellets in mediastinum and intramyocardial (arrows).*

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Rare Presentation of Yolk Sac Tumor with Cardiac Involvement: Characteristics Detected by MRI

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Introduction

Primary cardiac tumors are extremely rare, with their incidence varying between 0.0017 and 0.28%, among which is the malignant germ cell yolk sac tumor (YST).[1]

Although transthoracic echocardiography (TTE) is often the first line in the evaluation of cardiac tumors, currently, due to its good spatial resolution and tissue characterization, cardiac magnetic resonance (CMR) imaging is the technique of choice for the evaluation of these tumors.[2,3] The intracardiac YST is a rare neoplasm, with few reported cases.[4-7]

Case report

A one-year-old female patient presented with episodes of cyanosis when crying. On physical examination, she had a heart rate of 132 bpm, a 2+/6+ systolic murmur, fixed splitting of the second heart sound, adequate perfusion, with wide pulses. Due to the signs of heart failure, a TTE was performed, which showed a heterogeneous and multilobulated mass in the right ventricle (RV), next to the interventricular septum, with an estimated area of 7.8 cm^2, some cystic areas and signs of calcification, with signs of obstruction in the right ventricle outflow tract (RVOT) (Figure 1).

A CMR (Figures 2 and 3) was performed, which showed an expansive formation with a wide insertion base in the interventricular septum, showing no cleavage plane with the adjacent myocardium, with lobulated contours, extending into the RV cavity, measuring approximately 38 x 35 x 43 mm. This lesion had intermingled cystic areas, exhibiting low heterogeneous signal on T1 and a slightly high, equally heterogeneous signal on T2, in addition to heterogeneous gadolinium uptake in the late gadolinium enhancement (LGE) sequence, and contrast uptake in the perfusion sequence. The biopsy of a pulmonary lesion described as an epithelioid malignant neoplasm with extensive necrosis was performed, with a mitotic index of 10 mitoses x field and positive immunohistochemistry for SALL4, alpha-fetoprotein and PLAP in the cells of interest, being consistent with a germ cell neoplasm, compatible with a yolk sac tumor.

The patient was submitted to chemotherapy with cisplatin, but the control exams to assess disease evolution showed no significant changes in the TTE findings. Currently, a surgical approach is scheduled due to refractoriness to the chemotherapy.

Discussion

The characteristics of malignant cardiac tumors, which include the germ cell ones, have been studied in some reviews. CMR imaging is considered the method of choice for their evaluation, since it shows high accuracy in discriminating benign from malignant lesions, assesses the location, size and contours of the lesion. Moreover, the CMR has a significant diagnostic value for the signal characteristics of tissue components inside the tumors, including calcification, fat, fibrosis, hemorrhage, and cystic changes.[8] Of the germ cell tumors, the main characteristics visualized by CMR are the delayed heterogeneous gadolinium enhancement, and on cine-resonance and T1- and T2-weighted sequences, also a heterogeneous intensity.[8]

Among the main features that suggest malignancy are tumor size >5cm, irregular contours, multiple lesions, pleural or pericardial involvement, direct invasion of tissue planes, right heart location, and tissue characteristics such as signal heterogeneity on T1- and T2-weighted sequences and presence of contrast enhancement in the first pass, suggesting lesion vascularization.[9,10]

Therefore, we highlight the great usefulness of CMR, in this case, as an aid in the diagnosis and suspicion of a tumor of malignant etiology through some of the previously described characteristics, such as location in the RV, more irregular contours, heterogeneous signals in the T1 and T2 and LGE, in addition to contrast uptake in the perfusion sequence, which were described in our patient.

The standard treatment of primary nonseminomatous tumors, such as the YST, is a combination of neoadjuvant systemic chemotherapy with bleomycin or cisplatin, together with attempted surgical resection.[11]

This case report describes a very rare case of primary cardiac yolk sac tumor with malignant features confirmed

Keywords

Heart Neoplasms; Heart Failure; Neoplasms, Germ Cell and Embryonal; Diagnostic, Imaging; Echocardiography, Transthoracic/methods; Magnetic Resonance, Spectroscopy/methods; Drug Therapy

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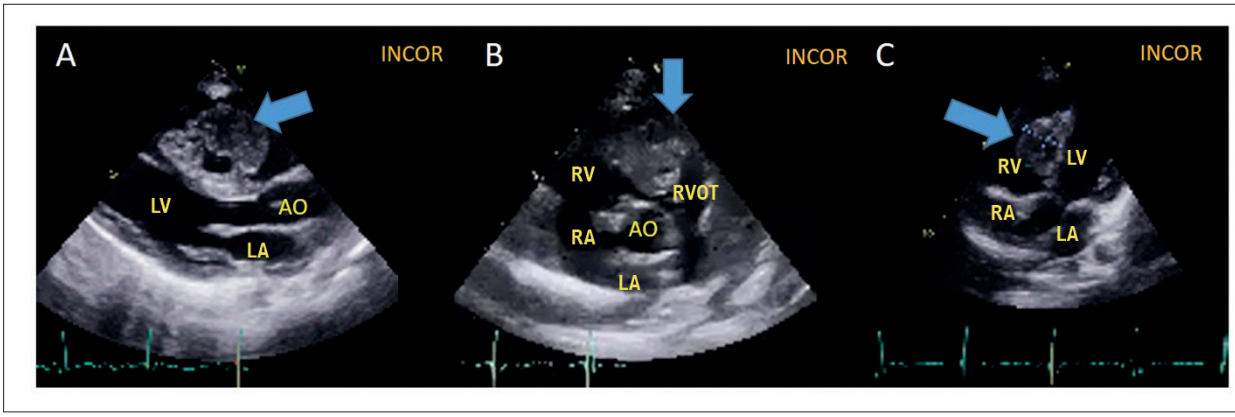

Figure 1 – *Transthoracic echocardiogram. (A) Longitudinal 3-chamber view in diastole showing heterogeneous mass in the RV (arrow). (B) Short axis with signs of RVOT obstruction (arrow). (C) Coronal 4-chamber lobulated image with projection to the RV (arrow). LV: left ventricle; RV: right ventricle; LA: left atrium; AO: aorta; RA: right atrium; RVOT: right ventricular outflow tract.*

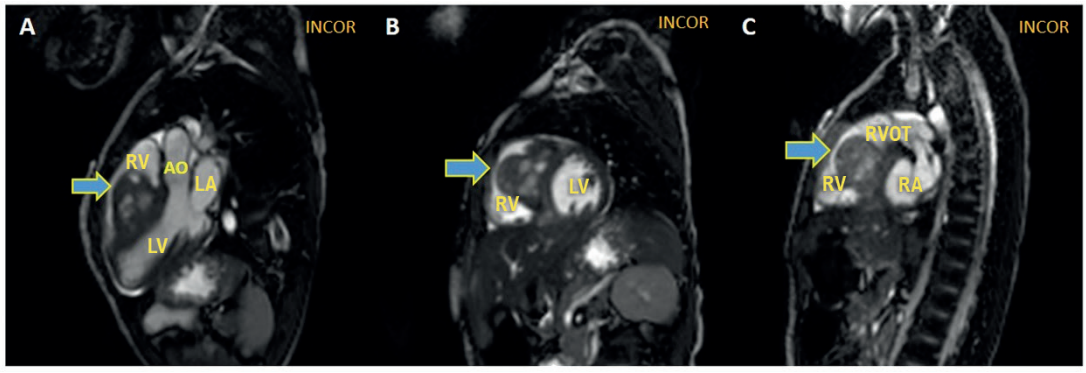

Figure 2 – *Cardiac magnetic resonance with steady-state free precession pulse sequence. (A) Longitudinal 3-chamber view in systole showing an expansive mass located in the intraventricular septum (arrow). (B) Short axis axial view showing mass with extension to the RV (arrow). (C) Short-axis axial view showing tumor obstruction in the RVOT (arrow). LV: left ventricle; RV: right ventricle; LA: left atrium; AO: aorta; RA: right atrium; RVOT: right ventricular outflow tract.*

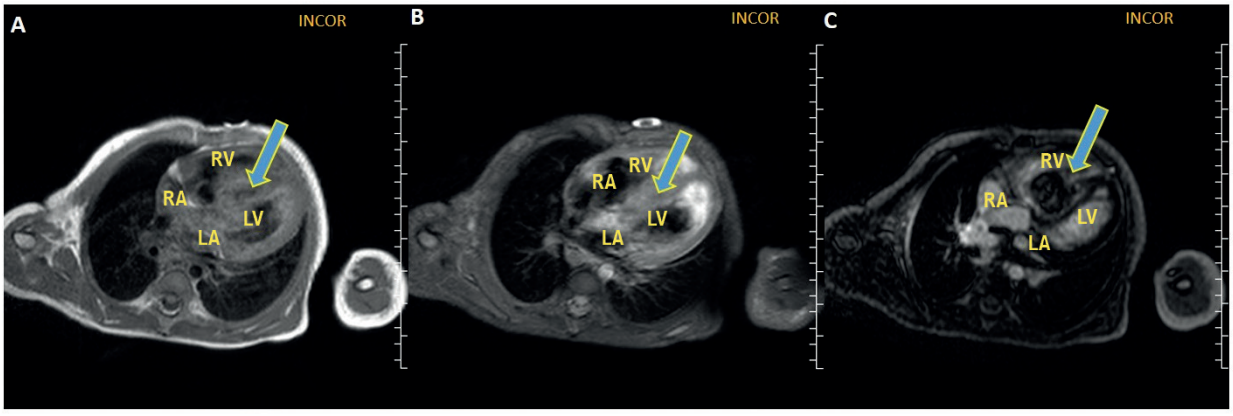

Figure 3 – *Cardiac magnetic resonance imaging. Tissue characteristics (A) FSE sequence without contrast, with fat saturation, 4-chamber coronal view, showing heterogeneous hyposignal in the septum (arrow). (B) T2-weighted FSE sequence without contrast, with triple inversion-recovery, 4-chamber axial view, showing a minimal increase in heterogeneous signal in the septum (arrow). (C) Late enhancement sequence, 4-chamber coronal view, presence of heterogeneous delayed enhancement in the septum (arrow). LV: left ventricle; RV: right ventricle; LA: left atrium; RA: right atrium.*

by biopsy, which did not show an adequate response to chemotherapy. The patient's CMR showed some of the characteristics that added to the possibility of malignancy, such as the size and heterogeneous LGE. Currently, imaging techniques such as CMR are very useful and, in some cases, they constitute the methods of choice to attain an adequate diagnosis.

Author Contributions

Conception and design of the research and Statistical analysis: de Paula KR; Acquisition of data: Espinoza C, Lata WR; Writing of the manuscript: Espinoza C, Jimenez RP, Fonseca EKUN; Critical revision of the manuscript for intellectual content: Jimenez RP, Fonseca EKUN.

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Letter to the Editor Regarding the Brazilian Guidelines of Hypertension – 2020

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Dear Editor

Initially, the Brazilian Society of Cerebrovascular Diseases (SBDCV) congratulates the Department of Arterial Hypertension of the Brazilian Societies of Cardiology, Hypertension, and Nephrology for the Brazilian Guidelines on Arterial Hypertension 2020 publication.[1] Our aim is to raise some issues related to stroke care and BP management in acute setting, an important topic of discussion and controversy. The guideline correctly attributes arterial hypertension as the main cause of ischemic stroke and intracranial hemorrhage. We would like to point out some issues regarding managing blood pressure (BP) in these patients.

Regarding BP control in patients with intracranial hemorrhage (ICH), the guidelines mentioned that "robust studies suggest that reducing BP (within 6h) to values <140/90 mmHg does not decrease important primary events, including mortality" (item 10.6.1), according to INTERACT-2 study.[2] The physiological response of increased BP levels in ICH is correlated with worse prognosis and hematoma expansion, as demonstrated in the INTERACT-1 study.[3] Subsequently, the INTERACT-2 trial compared intensive BP control [target systolic blood pressure (SBP) <140 mmHg] versus the guidelines-recommended levels (SBP <180 mmHg) in acute setting, and the primary outcome of death or functional dependence (modified Rankin Scale, mRS: 0-3 versus 4-6) were similar (55.6% in conventional treatment versus 52% with aggressive BP treatment, p=0.06).[2] Further, there was no significant difference in the shift distribution pattern in mRS. However, the ordinal analysis revealed a lower disability (mRS 0-2) with intensive BP treatment, with an odds ratio of 0.87 (95% confidence interval, 0.771.00; p=0.04), and additional better physical and mental quality, measured by EQ-5D scale.[2] Contrary to the 2020 Brazilian Arterial Hypertension Guidelines recommendation, and based on the results of this ordinal analysis, the current recommendation of the American Heart and American Stroke Association,[4] endorsed by the SBDCV, is to achieve an acute reduction of SBP in patients with ICH who present with high SBP (150-220 mmHg) without contraindications for intensive BP control. The SBP target is <140 mmHg, which can improve functional clinical outcomes. There is no sufficient data to systematically support the safety and effectiveness of the acute management of BP in patients with SBP >220 mmHg; however, a more aggressive reduction of BP in this profile of patients is reasonable, using intravenous drugs, dose titration and strict BP control in the acute phase.[4] Based on this trial and the recommendation of the societies mentioned above, we would like to suggest the correction of items 10.6.1 and 13.7 of the brazilian hypertension guideline, that states no benefit in reducing severe disability with intensive BP control.[1] We also emphasize that the proposed reduction in BP is safe.[2-4] The SBDCV does not recommend the proposed target of SBP <180 mmHg for acute ICH management.

Regarding the management of BP in acute ischemic stroke (IS), topic 10.6.2, we emphasize that BP reduction in patients who are candidates for thrombolysis should be performed when the values are >185/110 mm Hg in the first hour. After the end of thrombolysis, the recommended BP value is <180/105 mmHg in the first 24 h, as indicated in the hypertension guideline.[1]

Regarding topic 13.7.1, the recommended BP for the indication of thrombolytic treatment is <185/110 mmHg, and intravenous antihypertensive medication should be started immediately above this level. A contraindication to thrombolysis occurs only if refractory elevated BP occurs in three consecutive measurements, with an interval of 5 min, despite optimized treatment.

We are also unaware of the reference that suggests immediate BP reduction in patients with a transient ischemic attack (TIA), as suggested in Table 10.2.[1] In contrast, TIA is considered an equivalent to acute IS, and must be managed with the same parameters of a non-thrombolysed IS, or a IS not submitted to thrombectomy, that is, BP tolerability up to 220/120mmHg and suspension of oral antihypertensive drugs in the hyperacute phase of care, unless there are other impeding cardiovascular conditions to allow these blood pressure levels (e.g., acute myocardial infarction, aneurysm, or aortic dissection).[5] Thus, it is also worth reviewing the topic and table of recommendations

Keywords

Hypertension; Intracranial Hemorrhage; Isquemic Stroke; Risk Factors; Mortality; Acute Treatment; Blood Pressure.

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Letter to the Editor

for immediate BP reduction in TIA, as well as no reduction of BP in all types of IS (Table 10.2).

The denomination of stroke in our country is quite diverse, depending on the state or region of the country (use of terms "AVC - Acidente Vascular Cerebral" and AVE - Acidente Vascular Encefálico"), a fact that has been demonstrated in a Brazilian study.[6] For this reason, recently, the portuguese term "AVC" have been widely recommended by specialists in the field, patient organizations, together with the SBDCV and the Scientific Department of Cerebrovascular Diseases of the Brazilian Academy of Neurology, as well as in academic research, campaigns, educational activities, press releases and interviews, with the purpose of better educate the population regarding the disease, and to avoid using other terms that may confuse and hinder the rapid recognition, essential for immediate stroke treatment and better prognosis. Thus, for future hypertension guidelines, we suggest the use of this recommended standardized portuguese terminology: "AVC - Acidente Vascular Cerebral", instead of other terms, like "AVE".

Finally, we are grateful for the opportunity to present our observations. On behalf of the Brazilian Society of Cerebrovascular Diseases and the Scientific Department of Cerebrovascular Diseases of the Brazilian Academy of Neurology, our goal as a stroke society is to help and contribute with other partners in future discussions of topics involving managing patients with stroke.

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Reply

Response to the Brazilian Society for Cerebrovascular Diseases and the Scientific Department on Cerebrovascular Diseases of the Brazilian Academy of Neurology.

First, we would like to express our respect and gratitude to the reviewers for the careful reading of the 2020 Brazilian Guidelines on Arterial Hypertension (DBHA2020)[1] and for the comments on Chapter 10, more specifically on the topic 10.6 that addresses arterial hypertension (AH), and hemorrhagic and ischemic stroke.

It is worth pointing out that the DBHA2020[1] was developed by the collective effort of the Brazilian Society of Cardiology through the Department of Arterial Hypertension, the Brazilian Society of Hypertension, and the Brazilian Society of Nephrology, represented by 97 specialists chosen by scientific criteria. During the entire year of 2020, these experts worked together to construct this document, which was achieved by weekly meetings of the directive committee, two meetings with 18 chapter coordinators, and two plenary sessions of all members involved in the elaboration of the DBHA2020. The final text represents the opinion of the majority of this work group.

We will now discuss the questions raised by the authors of the Letter to the Editor, by first making the following considerations:

The question about the treatment target for HA, the time when treatment should be initiated, and the drugs of choice in cerebrovascular events is certainly a complex and challenging issue.

In January 2021, a narrative review summarized the main studies on ischemic and hemorrhagic stroke and pointed to a conservative approach in the acute phase, in addition to associated limitations that cannot be overcome even when strategies proposed by systematic reviews and meta-analyses are used.[2]

Regarding the item 10.6.1 of the DBHA2020,[1] which describes recommendations on the treatment of AH in the acute phase of hemorrhagic stroke: "In case of an increase in blood pressure, the odds of hematoma expansion, death and worse prognosis may increase. Robust studies have suggested that the reduction of blood pressure (within six hours) to levels < 140/90mmHg does not reduce important primary events, including mortality. Therefore, the immediate reduction of blood pressure in case of hemorrhagic stroke is not recommended, unless systolic blood pressure is > 220 mmHg". We reinforce that the text states that there is no evidence of reduction of primary events, which is in accordance with the Letter to the Editor submitted by the Brazilian Society of Cerebrovascular Diseases and by the Scientific Department of Cerebrovascular Diseases of the Brazilian Academy of Neurology, which affirms: "the phase 3 INTERACT-2 study evaluated the strict control of blood pressure in these patients, with a target systolic blood pressure below 140 mmHg *versus* the target recommended by guidelines (<180mmHg). Considering the primary outcome of death or functional dependence (modified Rankin Scale – mRS: 0-3), no statistically significance was found in this outcome by reducing blood pressure levels in the acute phase".

In our opinion, it is not appropriate to adopt guidelines' recommendations based on results obtained from secondary objectives, when the primary objective was not achieved. In Chart 10.2, the suggestion of reducing blood pressure (within six hours) in the acute phase after a hemorrhagic stroke was in line with the decision of the general coordination, chapter coordination and the plenary session, that this approach was in accordance with current scientific evidence.

As for the acute phase of ischemic stroke (item 10.6.2), the recommendation of the DBHA2020 is to reduce systolic blood pressure to values below 180 mmHg and diastolic blood pressure to values below 105 mmHg only for patients candidate for thrombolysis, with no evidence of clinical benefit for other patients. (Chart 10.2). Based on the close reading of the Letter to the Editor, we understand that there is a consensus on this recommendation, which coincidently is the same of the recently published European Stroke Organization (ESO), guidelines[3] and of the American Heart Association and American Stroke Association.[4]

In response to the comment on the management in the acute phase following a transient ischemic attack, we are in line with recommendations of other scientific societies, like the last European guidelines on arterial hypertension published in 2018 which recommends the same approach (see page 3086).[5]

In the ESO guidelines,[3] whose 11 authors work in the field of Neurology, the first sentence expresses the constructive possibility of divergence: "The optimal blood pressure (BP) management in acute ischemic stroke (AIS) and acute intracerebral hemorrhage (ICH) remains controversial". The document concludes that further randomized controlled studies are needed to support treatment targets, time and strategies to reduce blood pressure levels in the acute phase in different subgroups of patients with stroke.[6]

Finally, concerning the nomenclature used in the DBH2020[1] – stroke – it was considered by most specialists as the most appropriate to be used in the current document. We understand that this is a semantic rather than an anatomic issue, and that cerebrovascular disease may involve any encephalic structure. Curiously, the descriptor brain vascular accident has 28 alternative synonyms, including its abbreviation, BVA, recognized by the virtual health library.[6] However, this suggestion should be further discussed in a new update of the guideline, because of the arguments presented, and the familiarity with the term stroke by physicians in general.

Once again, we are grateful for the opportunity to have this technical and intellectual debate, and we hope that we have clarified the questions raised.

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Letter to the Editor

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Brazilian Society of Cardiology Guideline on Myocarditis – 2022

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Note: Guidelines are meant to inform and not to replace the clinical judgment of physicians, who must ultimately determine the appropriate treatment for patients.

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1. Epidemiology

The actual incidence of myocarditis is difficult to determine because the clinical presentations are highly heterogeneous and a large number of cases develop subclinically. Another contributing factor is the very low frequency of use of endomyocardial biopsy (EMB), the gold standard for diagnosis.[1]

A review of several postmortem studies addressing young victims of unexplained sudden death has showed that the incidence of myocarditis varies widely, accounting for up to 42% of cases.[2] The Global Burden of Disease Study 2013 has used the International Classification of Diseases coding in regional and global statistical analyses regarding 187 countries and estimated the annual incidence of myocarditis to be approximately 22 cases per 100,000 patients treated.[3] In cohorts of patients with dilated cardiomyopathy of undefined etiology, EMB-proven myocarditis has been detected in up to 16% of adult patients[4] and up to 46% of pediatric patients.[5]

Many studies have reported a higher prevalence of acute myocarditis in men compared to women.[6,7] Some studies have suggested that the most common clinical manifestation in adults is lymphocytic myocarditis; their median age is 42 years, while patients with giant cell myocarditis have a median age of 43 years.[8] However, newborns and children more typically exhibit fulminant myocarditis and are more susceptible to virus-induced pathogenicity compared to adults.[9,10]

Myocarditis has a wide prognostic spectrum depending on the severity of initial clinical symptoms and etiology. Patients with mild symptoms and no ventricular dysfunction often show spontaneous resolution and excellent prognosis.[11] However, approximately 30% of severe cases of EMB-proven myocarditis with associated ventricular dysfunction are expected to progress to dilated cardiomyopathy and heart failure (HF) with a poor prognosis. In pediatric patients, prognosis appears to be worse: 10-year heart transplant-free survival can be as low as 60%.[5]

2. Definition and etiology

Myocarditis is defined as an inflammatory disease of the myocardium that should be diagnosed by histological, immunological, and immunohistochemical criteria. Histological criteria include evidence of inflammatory infiltrates within the myocardium together with cardiomyocyte degeneration and necrosis of nonischemic origin. Quantitative immunohistochemical criteria to identify an abnormal inflammatory infiltrate, indicative of active myocarditis, are leukocyte count ≥14 cells/mm^2, including up to 4 monocytes/mm^2, with presence of CD3-positive T lymphocytes ≥7 cells/mm^2.[12]

Additionally, depending on cell type, the type of inflammatory infiltrate observed on histological diagnosis is used to classify myocarditis as lymphocytic, eosinophilic, polymorphic, giant cell myocarditis, or cardiac sarcoidosis.[13]

Myocarditis is caused by a wide variety of infectious agents, including viruses, protozoans, bacteria, chlamydiae, rickettsiae, fungi, and spirochetes (Table 1). It may also be triggered by

Table 1 – Etiology of acute myocarditis*

1 – Infectious myocarditis	
Viral	
RNA viruses	Coxsackieviruses A and B, echovirus, poliovirus, influenza A and B viruses, respiratory syncytial virus, mumps virus, measles virus, rubella virus, hepatitis C virus, dengue virus, yellow fever virus, Chikungunya virus, Junin virus, Lassa fever virus, rabies virus, human immunodeficiency virus-1
DNA viruses	Adenoviruses, parvovirus B19, cytomegalovirus, human herpesvirus 6, Epstein-Barr virus, varicella-zoster virus, herpes simplex virus, variola virus, vaccinia virus
Bacterial	*Staphylococcus, Streptococcus, Pneumococcus, Meningococcus, Gonococcus, Salmonella, Corynebacterium diphtheriae, Haemophilus influenzae, Mycobacterium (tuberculosis), Mycoplasma pneumoniae, Brucella*
Spirochetal	*Borrelia* (Lyme disease), *Leptospira* (Weil disease)
Fungal	*Aspergillus, Actinomyces, Blastomyces, Candida, Coccidioides, Cryptococcus, Histoplasma, Mucormycoses, Nocardia, Sporothrix*
Protozoal	*Trypanosoma cruzi, Toxoplasma gondii, Entamoeba, Leishmania*
Parasitic	*Trichinella spiralis, Echinococcus granulosus, Taenia solium*
Rickettsial	*Coxiella burnetii* (Q Fever), *R. Rickettsii* (Rocky Mountain spotted fever), *R. tsutsugamushi*
2 – Immune-mediated myocarditis	
Allergens	Tetanus toxoid, vaccines, serum sickness Drugs: penicillin, cefaclor, colchicine, furosemide, isoniazid, lidocaine, tetracycline, sulfonamides, phenytoin, phenylbutazone, methyldopa, thiazide diuretics, amitriptyline
Alloantigens	Heart transplant rejection
Autoantigens	Infection-negative lymphocytic myocarditis, infection-negative giant cell miocarditis associated with autoimmune disorders: systemic lupus erythematosus, rheumatoid arthritis, Churg-Strauss syndrome, Kawasaki disease, inflammatory bowel disease, scleroderma, polymyositis, myasthenia gravis, insulin-dependent diabetes mellitus, sarcoidosis, Wegener granulomatosis, rheumatic fever, immuno-oncology (immune checkpoint inhibitors)
3 – Toxic myocarditis	
Drugs	Amphetamines, anthracyclines, cocaine, cyclophosphamide, ethanol, fluorouracil, lithium, catecholamines, hemetine, trastuzumab, clozapine, interleukin-2, immune checkpoint inhibitors
Heavy metals	Copper, iron, lead
Miscellaneous	Scorpion sting, snake and spider bites, bee and wasp stings, carbon monoxide, inhalants, phosphorus, arsenic, sodium azide
Hormones	Pheochromocytoma
Physical agents	Radiation, electric shock

*Source: *Adapted from Caforio et al.[5]*

noninfectious mechanisms in toxic myocarditis (drugs, heavy metals, radiation) and by autoimmune and hypersensitivity mechanisms (eosinophilic myocarditis, collagenosis, virus-induced disease, heart transplant rejection).[14,15]

Viral infection is the most prevalent trigger of myocarditis, particularly in children. The most common cardiotropic viruses are enterovirus, parvovirus B19 (B19V), adenovirus, influenza A virus, human herpesvirus (HHV), Epstein-Barr virus, cytomegalovirus, hepatitis C virus, and human immunodeficiency virus (HIV). Some evidence suggests that there may be regional differences in the prevalence of viral agents, with a predominance of adenoviruses, parvoviruses, and herpesviruses in the European population[16] and enteroviruses in the American population.[17] However, these epidemiological differences may be partially explained by outbreaks of specific viral infections occurring over the years across different regions of the world as well as variations in viral detection techniques. Thus, the actual influence of geographic factors on cardiotropic viral infections remains controversial.[18]

In South America, especially some regions of Brazil, Chagasic myocarditis caused by *Trypanosoma cruzi* is one of the most prevalent causes of acute myocarditis, with particular importance after a recent report of outbreak of cases associated with oral transmission in the Brazilian Amazon.[19] Systemic autoimmune diseases such as Churg-Strauss syndrome and hypereosinophilic syndrome are associated with eosinophilic myocarditis. Giant cell myocarditis and sarcoidosis are rare but clinically significant because, if diagnosis is made early, there is specific treatment that may ensure an improved prognosis.[20,21]

Autoimmune myocarditis may develop with exclusive cardiac involvement or with systemic manifestations in the setting of autoimmune diseases. The most frequent diseases are sarcoidosis, hypereosinophilic syndrome, scleroderma, and systemic lupus erythematosus.

New immunotherapies for cancer treatment may be associated with risk of myocarditis. Cases linked to immune checkpoint inhibitors, such as nivolumab and ipilimumab, have been recently reported.[22-24]

2.1. Genetic factors in the etiopathogenesis of myocarditis

In classic descriptions of the etiopathogenesis of myocarditis, evidence of mechanisms involving viral action and autoimmune reaction is well documented. Little is said about genetic predisposition. Many authors believe that genetic phenomena are likely to contribute to the development of viral and/or autoimmune myocarditis.[12,25]

Laboratory data consistent with this hypothesis have been documented in a study of 342 family members of patients with dilated cardiomyopathy. The presence of cardiac antibodies was found to be higher in that group compared to the control group.[26]

The likelihood of a complex interaction between genetic (linked to individual predisposition) and nongenetic (linked to the offending agent) causes in the ultimate progression to dilated cardiomyopathy is also widely recognized. The problem is that the scientific evidence supporting such hypothesis is limited.[27]

There is evidence that, in susceptible mouse strains, infection and inflammation trigger autoimmune reactions in the heart, generally as a result of myocyte necrosis and subsequent release of autoantigens previously hidden in the immune system. The same strains of genetically predisposed animals develop lymphocytic or autoimmune giant cell myocarditis and then dilated cardiomyopathy after immunization with cardiac autoantigens (eg, cardiac myosin).[28]

Evidence also suggests that myocarditis may be present in specific cardiomyopathies (eg, arrhythmogenic cardiomyopathy) leading to changes in the phenotype and abrupt progression of the disease. In this context, some mutations may increase the susceptibility to myocarditis.[29]

Nonetheless, in general, myocarditis is still classified as a nonfamilial acquired disorder, with evidence from experimental studies indicating that genetic changes may provide greater susceptibility to this disease.

3. Pathophysiology

In simple terms, the pathophysiology of myocarditis can be divided into infectious and noninfectious. Infectious myocarditis is the most common form and includes a wide range of viruses, bacteria, protozoans, fungi, and other rare pathogens (see Table 1). Viruses are the most commonly involved and experimentally studied agents. In noninfectious myocarditis, autoimmunity is present through specific diseases, drugs, and autoantibodies; genetic predisposition plays an important role in both (see Table 1).

Murine models suggest that the development of viral myocarditis has three phases: acute (a few days), subacute (a few weeks to months), and chronic (development of dilated cardiomyopathy);[30] also, two pathogenic mechanisms are described: direct cytopathic effect of the virus and virus-induced anticardiac immune response.

Phase 1 corresponds to initial infection, which may heal without sequelae, or lead to HF or death, or progress to phases 2/3.[31] In most patients with viral myocarditis, the pathogen is eliminated and the immune system reduces activity with no further complications. However, in a minority of patients, the virus is not eliminated and causes persistent myocardial injury and inflammation secondary to antibody production.[17] Thus, viral myocarditis could be considered a precursor of dilated cardiomyopathy, with progression having been observed in 21% of patients within 3 years.[32]

Enteroviruses, especially coxsackievirus B3 (CVB3), initiate myocarditis by attaching to the coxsackievirus and adenovirus receptor (CAR) and decay accelerating factor (DAF), culminating in cell death by apoptosis[33] or necroptosis.[34] Infected cardiomyocytes are then lysed, which results in cytosolic release of proteins and viral products. After the acute phase, the course of the disease depends on genetic basis and includes two possibilities: progression to dilated cardiomyopathy or resolution.[35-39] Coxsackievirus infection activates innate and adaptive immune responses, initially including the production of interferon and activation of toll-like receptors.[40] In the adaptive response, T- and B-cell deficiency leads to viral persistence and clinical deterioration.[41,42]

Another important aspect is the production of specific autoantibodies to cardiomyocytes, which is based on the release of cardiac peptides with molecular mimicry between cardiac proteins and viral agents. In the presence of costimulatory cytokines such as tumor necrosis factor (TNF) and interleukin (IL)-1, these antibodies promote an effector T-cell response.[43]

Other viruses such as B19V and HHV-6 have been increasingly described in cardiac biopsies, while enteroviruses and adenoviruses have shown a downward trend.[44] However, these viruses have also been detected in hearts without myocarditis or cardiomyopathies of other etiologies, making the interpretation of the association between presence of infectious agents in cardiac tissue and development of myocarditis more complex. Another finding has been the persistent influence of these agents on clinical outcomes.[45]

Regarding noninfectious myocarditis, animal models of autoimmune myocarditis with genetically susceptible strains have demonstrated the presence of CD4+ T cells reactive to autoantigens, such as myosin heavy chain, in the absence of infectious agents.[46] In addition to lymphocyte autoimmune responses, macrophage responses have been observed in cases of granulomatous myocarditis and eosinophilic myocarditis in situations of hypersensitivity.

Giant cell myocarditis is an autoimmune form of myocardial damage characterized histologically by an infiltrate of multinucleated giant cells as well as an infiltrate of T cells, eosinophils, and histiocytes. The marked presence of (cytotoxic) CD8 cells together with the release of inflammatory cytokines and oxidative stress mediators leads to intense myocyte damage and replacement by fibrosis, culminating in rapid loss of ventricular function and unfavorable clinical outcomes. Twenty percent of patients exhibit an association with autoimmune diseases such as Hashimoto thyroiditis, rheumatoid arthritis, myasthenia gravis, Takayasu arteritis, and others.[47] Sarcoidosis affects multiple systems, including the lungs in 90% of cases, and is associated with the accumulation of T lymphocytes, mononuclear phagocytes, and noncaseating granulomas in involved tissues.[48,49]

In drug-induced myocarditis, the time to hypersensitivity response varies from hours to months. Hypersensitivity is partly explained by a response to chemically reactive components that bind to proteins promoting structural changes. These particles are phagocytosed by defense cells, sometimes macrophages, which present them on the surface of these cells to T cells. Cytokines such as IL-5, which stimulates eosinophils, are then released as a delayed hypersensitivity response. This accumulation of IL-5 promotes major eosinophilic infiltration with increased hypersensitivity response and severe myocardial injury. Genetic predisposition appears to favor this response pattern.[50]

Hypereosinophilic syndrome may be associated with several systemic diseases, such as Churg-Strauss syndrome, cancer, and parasitic and helminthic infections, or with vaccinations. These can produce an intense inflammatory response in the myocardium, leading to cell damage with dysfunction and HF.[51,52] Pathophysiologically, similar to what happens in other organs, there is intense eosinophilic infiltration in the myocardium promoting the release of potent mediators of myocyte damage, leading to necrosis and loss of myocardial structure. These mediators include eosinophil-derived neurotoxin, eosinophil cationic protein, and eosinophilic protease. Also, the production of inflammatory cytokines such as IL-1, TNF-alpha, IL-6, IL-8, IL-3, IL-5, and macrophage inflammatory proteins promotes myocyte injury and loss with progression to myocardial dysfunction.[53]

More recently, nivolumab, an antitumor drug that acts as a checkpoint inhibitor, has been considered a cause of lymphocytic myocarditis. A possible pathophysiological mechanism suggests that myocardial cells could share antigens with tumor cells, thus being targets for activated T cells, resulting in inflammatory infiltration and development of HF and conduction disorders.[54]

4. Diagnostic evaluation

4.1. Diagnostic criteria for suspected myocarditis

Clinical suspicion of myocarditis as proposed by the European Society of Cardiology (ESC) Working Group on Myocardial and Pericardial Diseases is based on the association of clinical presentation with abnormal test results suggestive of myocardial inflammatory injury.[12,55]

By analyzing the most frequent clinical presentations of myocarditis and the diagnostic accuracy of additional evaluations for prognosticating myocardial inflammation, we propose that clinically suspected myocarditis be stratified into three levels: low, intermediate, and high diagnostic suspicion (Figure 1).[32,56-63] These suspicion criteria have been established by expert consensus and require further validation by clinical registries or multicenter studies.

4.1.1. Diagnostic evaluation flowchart

Our flowchart for diagnostic evaluation of myocarditis is based on the degree of clinical and prognostic suspicion (see Figure 1). Patients with low clinical suspicion have a favorable prognosis and, during clinical follow-up, are evaluated regarding the need for noninvasive coronary artery disease (CAD) stratification. Patients with intermediate clinical suspicion and favorable course undergo the same line of clinical follow-up and diagnostic investigation as low-risk patients. Patients with maintained or deteriorated clinical status, ventricular dysfunction , arrhythmias, or atrioventricular (AV) block should undergo coronary angiography and EMB. Patients with high diagnostic suspicion generally have a poor prognosis and should undergo coronary angiography and EMB for establishing etiology and then defining a specific treatment to improve the prognosis.[32,56,64,65]

4.2. Clinical evaluation: suspected clinical situations

Myocarditis manifests through different forms, ranging from mild and oligosymptomatic to severe cases associated with ventricular arrhythmias, hemodynamic instability, and cardiogenic shock. Sudden death is rare (8.6% to 12%) and affects mostly children and young adults.[66,67]

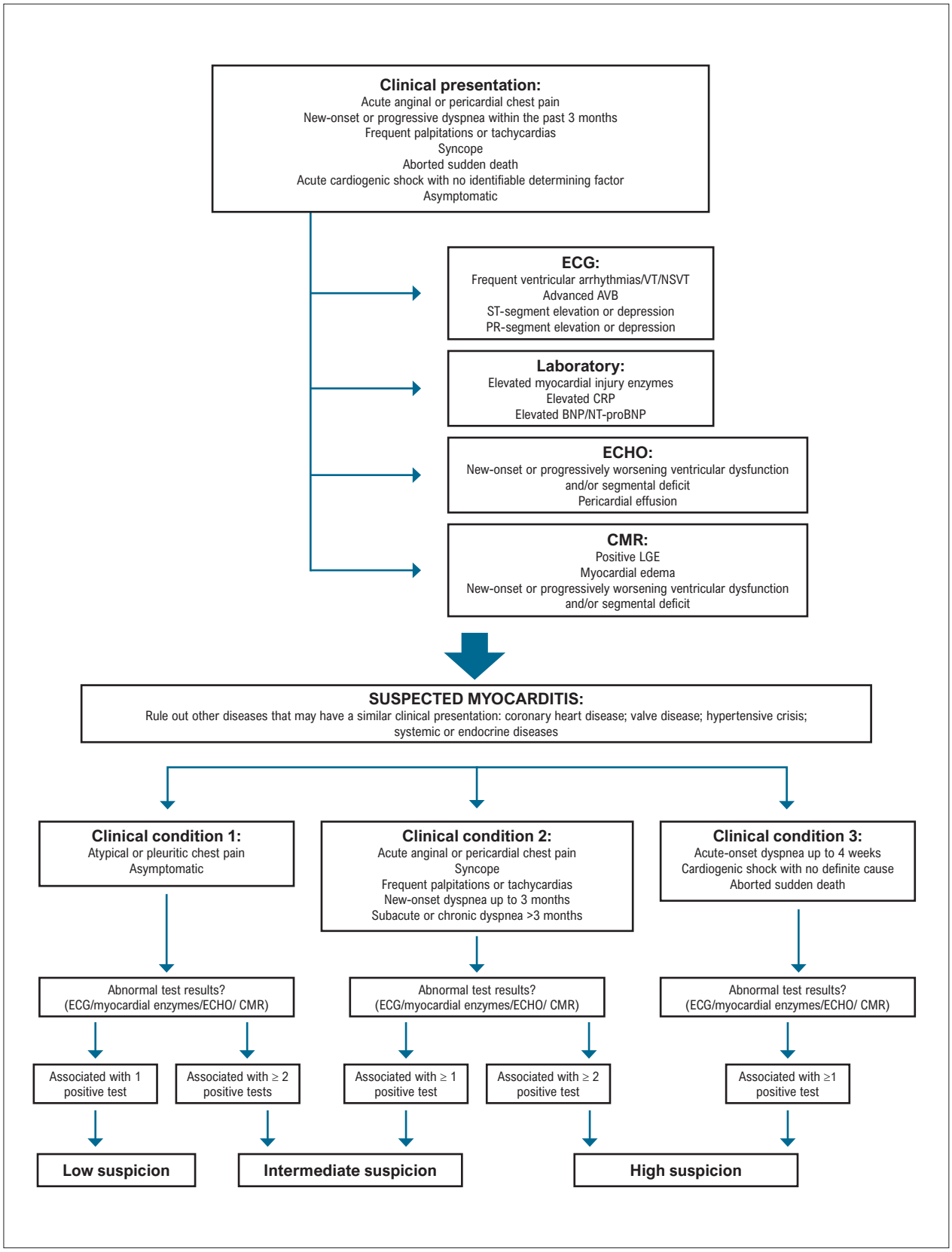

Figure 1 – *Algorithm for diagnostic stratification of clinically suspected myocarditis.*
AVB: atrioventricular block; BNP: brain natriuretic peptide; CMR: cardiac magnetic resonance; CRP: C-reactive protein; ECG: electrocardiogram; ECHO: echocardiogram; LGE: late gadolinium enhancement; NSVT: nonsustained ventricular tachycardia; PR: PR segment; ST: ST segment; VT: ventricular tachycardia.

The most common situation consists of young patients with chest pain suggestive of acute myocardial infarction (MI) with normal coronary arteries after respiratory or intestinal viral infection, although viral symptoms do not always precede myocarditis (10% to 80%).[68-70] Despite being predominant in young patients, the syndrome may appear at any age. Subclinical myocarditis, transient troponin elevation, or electrocardiographic changes may also occur after an acute viral infection consisting of nonspecific manifestations such as fever, myalgia, and respiratory or gastrointestinal symptoms.[68,71]

Myocarditis has different presentations, which are described below:[12,71,72]

a) Clinical condition similar to acute coronary syndrome (chest pain, electrocardiographic changes suggestive of ischemia; elevated myocardial necrosis markers with normal coronary arteries).
b) Acute new symptoms of HF (3 days to 3 months) in the absence of coronary heart disease or known cause of symptoms.
c) New-onset HF symptoms within the past months (>3 months) in the absence of coronary heart disease or known cause of symptoms.
d) Life-threatening conditions: unexplained ventricular arrhythmias, and/or syncope, and/or aborted sudden death; cardiogenic shock without associated coronary heart disease.

A) Manifesting as chest pain

Patients with chest pain may present with different electrocardiographic changes, such as ST-segment elevation or depression, T-wave inversion, or pathological Q waves. Segmental changes on Doppler echocardiography and elevated myocardial necrosis markers, especially troponin, in patients with normal coronary arteries are suggestive of myocarditis.[68,73] In most studies, these patients have a good short-term prognosis, and the degree of ventricular impairment is predictive of risk of death.[71,74] A minority develops persistent and recurrent myopericarditis with normal left ventricular function that may respond to colchicine.[75]

B) Manifesting as acute heart failure

Presentation may be acute, associated with the onset of HF symptoms within days, but also subacute/chronic, associated with new-onset cardiomyopathy in a patient with no apparent cause for abnormal myocardial function.

Myocarditis presenting as HF symptoms (dyspnea, fatigue, exercise intolerance) may be associated with mild impairment of ventricular function (left ventricular ejection fraction [LVEF]: 40% to 50%) that improves within weeks to months. However, a small number of patients may have significant ventricular dysfunction (LVEF <35%) and, of those, 50% develop chronic LV dysfunction; approximately 25% will need a heart transplant or ventricular assist device, while the remaining 25% will have improved ventricular function over the course of follow-up; a minority of cases may progress to cardiogenic shock and require mechanical circulatory support.[68,76-79] The risk of death or need for transplantation is strongly associated with the degree of hemodynamic compromise and left and right ventricular dysfunction, which may respond to standard drug treatment for HF.[80]

Fulminant presentation of the disease is characterized by sudden onset (days) of symptoms of advanced HF. These patients generally have severe ventricular dysfunction with minor changes in ventricular diameters. This is a dramatic presentation that requires early intervention.[68,81] When fulminant condition is associated with persistent ventricular tachycardia or no response to standard therapy, the prognosis is poor, and more severe forms of myocarditis, such as giant cell myocarditis, should be considered and investigated.[8]

C) Manifesting as chronic or progressive heart failure

Myocarditis confirmed by immunohistopathological criteria is found in up to 40% of patients with chronic cardiomyopathy who remain symptomatic despite drug treatment. The presence of inflammation shown by histology is associated with a poor prognosis.[71]

D) Manifesting as a life-threatening condition

- ***Arrhythmias or conduction disorders***

Patients with myocarditis may also present with conduction disorders, such as second- or third-degree or complete AV block, especially those with echocardiographic signs of hypertrophy due to interstitial edema.[82] The presence of heart block or symptomatic or sustained ventricular arrhythmias in patients with cardiomyopathy should raise suspicion for myocarditis with a definite cause (Lyme disease; sarcoidosis; arrhythmogenic right ventricular dysplasia, or Chagas disease in endemic areas).[71]

- ***Cardiogenic shock***

A small subgroup of patients presenting with sudden onset of HF within 2 weeks of viral infection may need inotropic and/or mechanical circulatory support. Ventricular function recovery generally occurs when they survive the initial condition, but adequate therapy should be initiated as early as possible.[71,81]

Table 2 summarizes the main clinical syndromes of suspected myocarditis and suggests possible agents responsible for each presentation of the disease.[83]

4.3. Biomarkers

4.3.1. Laboratory markers of inflammatory injury

No single biomarker is sufficient to diagnose myocarditis; however, some may be useful as prognostic markers. The most commonly used biomarkers are described below.

a) **Inflammatory markers.** Leukocyte count, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) may be high in patients with myocarditis. However, they are nonspecific and thus have no diagnostic value.
b) **Troponins.** Troponins are more specific than creatine phosphokinase (CPK) and creatine kinase MB (CKMB)

Table 2 – Description of clinical presentations and possible causes of the different clinical syndromes of myocarditis

Clinical syndrome	Clinical manifestations	Possible causes
Acute chest pain	Angina symptoms; CAD ruled out; ST/T-segment change; arrhythmias; intermittent troponin I/T and NT-proBNP elevations	Parvovirus B19 or other cardiotropic viruses associated or not with pericarditis
Acute HF	Dyspnea; edema; LV systolic and/or diastolic dysfunction; ECG change; intermittent troponin I/T and NT-proBNP elevations	Viral or nonviral myocarditis or inflammatory cardiomyopathy
Chronic HF	All HF symptoms for some time; CAD ruled out; ECG changes such as LBBB, RBBB, AVB; intermittent troponin I/T and NT-proBNP elevations	Viral or nonviral focal myocarditis or inflammatory cardiomyopathy
Life-threatening HF/arrhythmia	Cardiogenic shock; NYHA class III/IV HF; elevated troponin and NT-proBNP; severe arrhythmia; CAD ruled out	Giant cell myocarditis, eosinophilic myocarditis, toxic myocarditis

AVB: atrioventricular block; CAD: coronary artery disease; ECG: electrocardiogram
HF: heart failure. LBBB: left bundle branch block; LV: left ventricular; RBBB: right bundle branch block; ST/T: ST segment and T wave.

for myocardial damage and are often high in patients with myocarditis.[84] However, normal troponins do not exclude the diagnosis. Although they are not sufficient to establish the diagnosis, troponins may be suggestive of myocarditis, as long as obvious causes such as acute MI and acute HF have been excluded. In a small study investigating several biomarkers, troponins were predictive of the diagnosis of biopsy-proven myocarditis with an area under the curve of 0.87, a sensitivity of 83%, and a specificity of 80%.[85] Troponin is useful for diagnosing myocarditis in patients with acute-onset cardiomyopathy.[12,72]

c) **Natriuretic peptides.** Brain natriuretic peptide (BNP) and NT-proBNP might be high in myocarditis.[86] However, they are not useful for diagnostic confirmation, as different causes of HF may be responsible for their elevation. Nonetheless, they may be prognostic markers. In a study of biopsy-proven myocarditis, only NT-proBNP above the fourth quartile (>4,245 pg/mL) among several biomarkers was predictive of death or heart transplantation.[85]

4.3.2. Laboratory markers for etiopathogenic investigation

Viral serologies. Viral serologies are of limited value in diagnosing myocarditis, as IgG antibodies to cardiotropic viruses are highly prevalent in the general population in the absence of viral heart disease. A study has found no correlation between viral serology and biopsy findings.[87] In specific situations, serological screening for hepatitis C, HIV in high-risk individuals, and Lyme disease in endemic areas might be useful. Screening with serological markers should be dictated by high clinical suspicion for that disease (Table 3).

Immunohistochemical markers and viral genome analysis. These markers are superior to the Dallas criteria and, therefore, can be useful for an etiological diagnosis. The complication rate of EMB is low (Table 3).[88-90]

4.4. Electrocardiogram

An electrocardiogram (ECG) is commonly ordered to screen for myocarditis despite of its limited specificity, although patients frequently present with some ECG change.[12] Sinus tachycardia is possibly the most common form of presentation on ECG.[14] Some ECG changes are more suggestive of myocarditis than others. For example, ST-T segment elevation is typically concave in myocarditis (rather than convex in myocardial ischemia), diffuse without reciprocal changes, transient, and reversible during the course of the disease (Figure 2).[91]

An early repolarization electrocardiographic (ER-ECG) pattern in some patients with acute myocarditis may be the

Table 3 – Recommendations for initial laboratory evaluation of myocarditis

Indications	Class	Level of evidence
Use of inflammatory markers for the diagnosis of myocarditis	I	C
Myocardial injury biomarkers to aid in the diagnosis of myocarditis	I	B
BNP or NT-proBNP to aid in the diagnosis and prognostic stratification of myocarditis	I	B
Serological screening and/or antigen detection and/or PCR for the diagnosis of Covid-19 in suspected cases	I	B
Serological screening and/or antigen detection and/or RT-PCR for the initial evaluation of special cases of suspected myocarditis due to specific etiologies	IIa	C
Viral serologies in the routine evaluation of all cases of myocarditis	III	C

BNP: brain natriuretic peptide; RT-PCR: polymerase chain reaction.

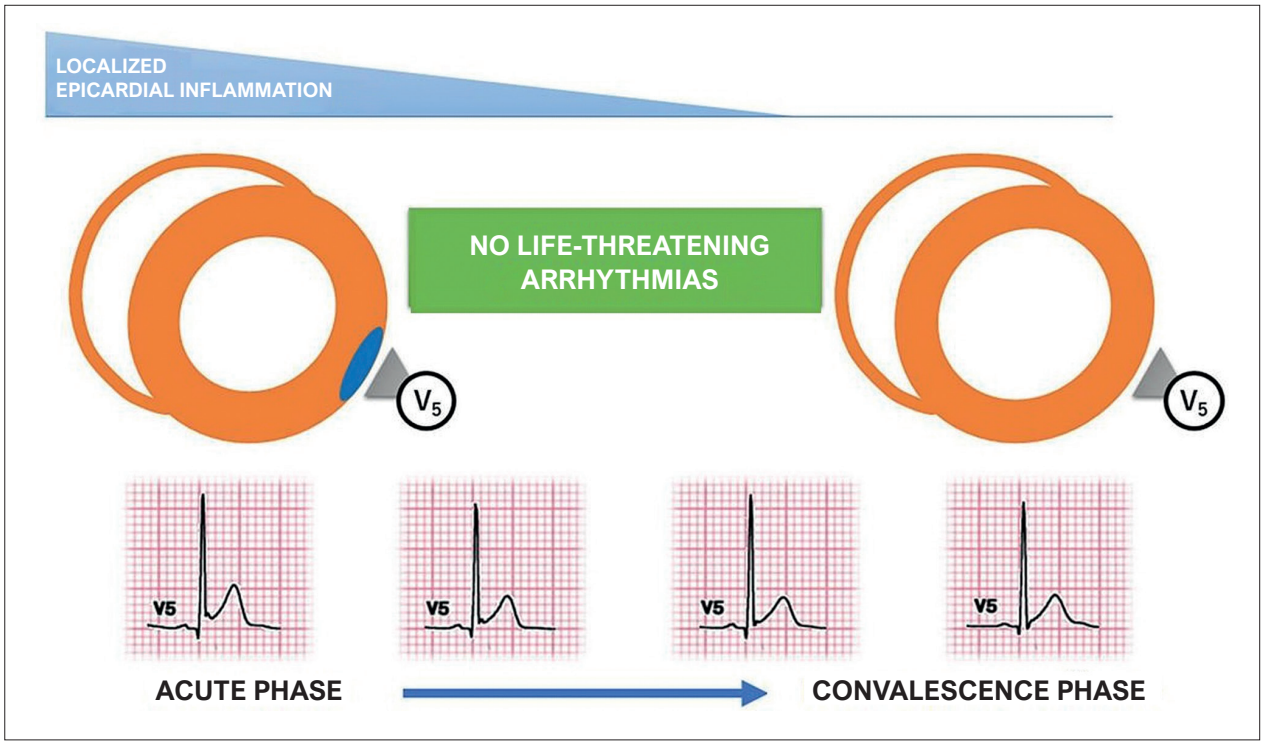

Figure 2 – *Course of early repolarization pattern in acute myocarditis. Adapted from Oka et al.*[91]

evidence of inflammation/edema in the LV epicardium. Oka et al.[91] showed that the ER-ECG pattern in acute myocarditis was transient and reversible, and was not associated with a poor prognosis.

AV block in the presence of mild LV dilatation may be due to a number of causes (including laminopathy) but may also be suggestive of Lyme disease, cardiac sarcoidosis, or giant cell myocarditis. Ogunbayo et al. reported that, among 31,760 patients with primary diagnosis of myocarditis, heart block was found in 540 (1.7%) – 21.6% were first-degree, 11.2% were second-degree, and 67.2% were high-degree. High-degree AV block was independently associated with increased morbidity and mortality.[92]

A recent meta-analysis showed that prolonged QRS duration was an early characteristic of fulminant myocarditis.[93] In a study of patients acutely admitted with myocarditis without previous HF who underwent EMB, prolonged QRS duration was an independent predictor of cardiac death or heart transplantation.[94]

A significant proportion of patients with acute myocarditis experience sudden cardiac death presumably due to cardiac arrhythmia. A recent study conducted by Adegbala et al. reported a total of 32,107 admissions for acute myocarditis between 2007 and 2014 in the United States. Of those, 10,844 (33.71%) patients had arrhythmias, with ventricular tachycardia (22.3%) and atrial fibrillation (26 .9%) being the most common types, and their presence had an impact on mortality.[95]

In sum, an ECG is a convenient tool for risk stratification and initial screening, but its diagnostic value is poor.[14]

4.4.1. Diagnostic criteria for electrocardiogram/Holter/stress testing[12]

The Twelve-lead ECG is a common practice in diagnostic investigation and prognostic evaluation of myocarditis (Table 4). The changes most often associated with myocarditis on Twelve-lead ECG and/or Holter and/or stress testing with any of the following: first- to third-degree AV block or bundle branch block, ST/T-wave change (ST elevation or non-ST elevation, T-wave inversion), sinus arrest, ventricular tachycardia or fibrillation and asystole, atrial fibrillation, reduced R-wave height, intraventricular conduction

Table 4 – Recommendations for performing an electrocardiogram in the evaluation of myocarditis

Indications	Class	Level of evidence
Electrocardiogram in suspected myocarditis	I	C
Electrocardiogram for prognostic evaluation in myocarditis	I	C

delay (widened QRS complex), abnormal Q waves, low voltage, frequent premature beats, and supraventricular tachycardia.

4.4.2. Prognosis

Prolonged QRS duration, high-degree AV block, ventricular tachycardia, and atrial fibrillation increase mortality.

4.5. Echocardiogram

An echocardiogram has a limited role in the diagnosis of myocarditis. It is a highly important tool for excluding other diseases and should always be performed in clinically suspected cases (Table 5).[96,97] There is no specific echocardiographic finding, and the changes will only reflect myocardial inflammation. Therefore, findings may range from segmental changes (differential diagnosis with ischemic heart diseases) to diffuse changes (global hypokinesia of one or both ventricles).[98,99] When involvement is acute and severe, the ventricular chambers are small (not dilated), and myocardial edema (increased wall thickness) and pericardial effusion, which are common findings in fulminant myocarditis, are present. Right ventricular (RV) involvement usually reflects a poor prognosis.[100]

Interestingly, echocardiography can be a useful adjunct to EMB not only for locating the ideal site for removing the specimens but also for guiding the interventionist and avoiding complications (Table 5).[101]

4.6. Cardiac magnetic resonance imaging

In the evaluation of patients with myocarditis, similar to the evaluation of other nonischemic cardiomyopathies, cardiac magnetic resonance (CMR) imaging is very useful for determining ventricular morphological and functional parameters. In fact, it has been extensively validated to quantify both LV and RV volume, mass, and function, and is currently considered the diagnostic gold standard for this evaluation. Because of its high spatial and temporal resolution as well as its three-dimensional nature making it independent of geometric assumptions, CMR has excellent accuracy and reproducibility, characteristics that are especially useful for longitudinal patient follow-up.[102]

However, the greatest value of CMR in the evaluation of patients with suspected or confirmed myocarditis lies in the ability to provide detailed tissue characterization. It thus allows the identification of inflammatory myocardial injury in the acute and subacute phases as well as scarring that is frequently present in the chronic phase of the disease. The CMR techniques classically used in the characterization of myocardial injury in patients with myocarditis are T2-weighted imaging and late gadolinium enhancement.[103-108]

On T2-weighted images, the greater the water content in a given tissue, the higher the signal intensity. Therefore, this technique assesses myocardial edema secondary to the inflammatory process in patients with acute myocarditis (known as edema imaging).[102-105] Late gadolinium enhancement, in turn, identifies regional necrosis in acute or subacute myocarditis as well as regional fibrosis in chronic myocarditis.[106,108-110] It is worth noting that the late enhancement pattern of myocarditis is very different from that of acute MI. The main difference is that late gadolinium enhancement in infarction always enhances the subendocardium. Transmural enhancement may also be present, but the subendocardial layer is always enhanced. In myocarditis, mesoepicardial enhancement is most often present, while the endocardium is usually spared. Furthermore, while enhanced regions in infarction tend to be unique, homogeneous, and distributed across the coronary territories, enhanced regions in myocarditis tend to be multifocal, heterogeneous, and sparse, not restricted to the coronary territories.

The original 2009 Lake Louise criteria (LLC)[105] were based on three CMR techniques. In addition to T2-weighted imaging (edema imaging) and late gadolinium enhancement, both mentioned above, it also included a technique called early gadolinium enhancement. The latter was eventually excluded from the updated diagnostic criteria after a study demonstrated that it did not add incremental diagnostic value to the other techniques. In fact, early gadolinium enhancement had not been clinically used in most CMR centers in the world.

Recently, new CMR techniques capable of measuring myocardial longitudinal (T1) and transverse (T2) relaxation times have been introduced as potentially sensitive and specific methods for the detection of myocardial inflammation.[111] T1 and T2 values are generally measured on a pixel-by-pixel basis and presented as parametric maps, the so-called myocardial T1 and T2 mapping. A T1 map can be acquired before contrast injection (native T1) and 15 to 20 minutes after contrast injection (when gadolinium concentration is relatively steady), thus allowing the calculation of myocardial extracellular volume (ECV). A T2 map is usually acquired only before contrast administration.

The introduction of T1 and T2 mapping was the key reason for a recent LLC update regarding the use of CMR in the diagnosis of myocarditis. According to

Table 5 – Recommendations for performing an echocardiogram in the initial evaluation of myocarditis

Indications	Class	Level of evidence
Echocardiogram for evaluation of cardiac structure and function	I	C
Echocardiogram for prognostic evaluation and stratification	I	C
Echocardiogram to guide endomyocardial biopsy	IIa	C

the new consensus recommendations,[104] this diagnosis is based on the presence of two main criteria that may or may not be associated with supportive criteria (Table 6). The first main diagnostic criterion aims to identify the presence of myocardial edema using T2-based techniques: (1) T2-weighted imaging (edema imaging) and/or (2) T2 mapping. The second main diagnostic criterion also allows the detection of myocardial edema, but its primary objective is to identify the presence of necrosis, fibrosis, and capillary leakage. This second main diagnostic criterion uses T1-based techniques: (1) late gadolinium enhancement and/or (2) T1 mapping (native T1 or ECV).

The new 2018 diagnostic criteria for myocarditis, myopericarditis, or perimyocarditis are listed in Table 6.[104]

The accuracy of CMR in patients with suspected myocarditis in the original LLC has been estimated at 78% (sensitivity, 67% and specificity, 91%).[105] These estimates have been subsequently confirmed in a meta-analysis that has demonstrated an accuracy of 83%, a sensitivity of 80%, and a specificity of 87%.[112] Similarly, a more recent meta-analysis has shown a sensitivity of 78% and a specificity of 88%, with an area under the curve (AUC) of 83%.[113] There are no consistent data on the accuracy of CMR using the new diagnostic LLC yet. However, a recent study including only 40 patients with acute myocarditis has demonstrated a sensitivity of 88% and a specificity of 96% for CMR using the new revised criteria (see Table 6).[114]

Recommendations for the use of CMR in the diagnostic and prognostic evaluation of patients with suspected acute myocarditis are summarized in Table 7.[57,104,109,114-116]

Based on the body of scientific evidence accumulated since the first version of this SBC guideline, we can now introduce CMR more accurately in the decision-making

Table 6 – Diagnostic criteria for myocarditis, myopericarditis, or perimyocarditis

Updated Lake Louise criterion 1 POSITIVE T2 CRITERION + 1 POSITIVE T1 CRITERION	Diagnostic target
MAIN CRITERIA	
Imagem baseada no T2	
Increased regional signal intensity in the LV (visual analysis) or	AND
Increased global signal intensity – ratio ≥2 or	
Regional or global increase in T2 times (T2 mapping)	EDEMA
T1-based imaging	
Regional or global increase in T1 times (T1 mapping) or ECV or	Increased T1 = edema (intra- or extracellular), hyperemia, capillary leakage, necrosis, fibrosis Increased ECV = edema (extracellular), hyperemia, capillary leakage, necrosis, fibrosis
Areas with increased signal intensity in a nonischemic distribution pattern on late enhancement imaging	Late gadolinium enhancement = necrosis, fibrosis
SUPPORTIVE CRITERIA	
Pericardial effusion on cine MRI or increased signal intensity of the pericardium on late enhancement imaging, T1 mapping, or T2 mapping	Pericardial inflammation
LV wall motion abnormality on cine MRI	LV dysfunction

LV: left ventricular; MRI: magnetic resonance imaging; ECV: extracellular volume.

Table 7 – Recommendations for the use of cardiac magnetic resonance imaging in the diagnostic evaluation of patients with suspected acute myocarditis

Indications	Class	Level of evidence
Evaluation of patients with elevated markers of myocardial necrosis and normal coronary arteries on angiography	I	B
Evaluation of patients with dilated cardiomyopathy and suspected myocarditis with a course >6 months, aiming to aid in the etiological investigation, exclude possible differential diagnoses, and provide prognostic information	I	B
Reassessment in 4 weeks for patients with intermediate or high prognostic risk after the acute episode, aiming to distinguish uncomplicated from complicated courses	IIa	B

framework for patients with suspected myocarditis according to the risk stratification approach proposed in Table 8.[109,115,117] This approach should be integrated into broad risk stratification criteria that include clinical presentation and additional testing.

4.7. Nuclear medicine

Nuclear medicine has played an increasing role in the evaluation of patients with myocarditis. New radiotracers and other technologies have allowed a whole new spectrum of contributions to the management of patients with suspected inflammatory myocardial diseases.

The pathophysiological changes of the different types of myocarditis will form the basis for the use of nuclear medicine techniques: the inflammatory process leading to myocardial injury is characterized by infiltration of lymphocytes and macrophages in the myocardium, by increased vascular permeability and increased glucose consumption at the inflammation site, and by cell necrosis with reduced tissue perfusion compared to intact myocardium. These characteristics will translate into increased uptake of gallium-67 citrate in the myocardium (especially useful in cases of sarcoidosis), increased accumulation of ^{18}F-fluorodeoxyglucose (^{18}F-FDG), and reduced myocardial perfusion seen with the tracers technetium (^{99m}Tc) sestamibi or thallium-201. Table 9 lists the most commonly used radiotracers for evaluating myocarditis.

4.7.1. Single-photon emission computed tomography (SPECT) radiotracers

Gallium-67 citrate is an established tracer for nuclear medicine imaging of infections that binds to inflammatory cells at sites of increased vascular permeability thanks to its characteristic binding to iron transport proteins such as lactoferin and leukocyte lysosomes. Gallium-67 has low sensitivity (36%) for detecting myocarditis in patients with new-onset dilated cardiomyopathy and thus should not be routinely indicated (Table 10).[118] The only type of myocarditis with a high positive yield for gallium-67 scintigraphy is sarcoidosis, in which giant cell granulomas are particularly avid for radiotracer retention. A positive gallium-67 scan is considered a major criterion for the diagnosis of cardiac sarcoidosis by the Heart Rhythm Society (HRS) expert consensus statement.[119] Another significant finding in patients with cardiac sarcoidosis is a perfusion defect caused by myocardial microvascular constriction in the vessels surrounding the granulomas. A perfusion defect seen at rest may disappear on stress imaging, a pattern called reverse distribution that may be associated with sarcoidosis.

Gallium-67 scintigraphy can be used as an alternative for patients without access to or with a contraindication

Table 8 – Risk stratification and likelihood of indication for endomyocardial biopsy based on cardiac magnetic resonance (CMR) parameters.

Prognostic risk	CMR parameter	Suggested approach	Indication for biopsy
Low	No changes in T1 and T2 No ventricular dysfunction	Clinical follow-up	No indication
Intermediate	Positive T1 or T2 Nonextensive late enhancement (<17 g and 13% of LV mass) Normal function or mild LV dysfunction	Clinical follow-up, repeat CMR at 1, 3, and 6 months	Stable: no indication Progressive dysfunction: possible indication
High	Positive T1 or T2 Extensive late gadolinium enhancement (>17 g or 13% of LV mass), or interventricular septal involvement, and/or moderate or severe LV dysfunction	Clinical follow-up, repeat CMR at 1, 3, and 6 months	Possible indication

LV: left ventricular.

Table 9 – Nuclear medicine tests frequently used in patients with suspected or confirmed myocarditis

Nuclear medicine test	Main indications	Advantages	Disadvantages
Gallium-67 scintigraphy	Myocarditis and sarcoidosis	Widely available	Less sensitive
^{18}F-FDG PET	Sarcoidosis, lupus myocarditis, unexplained cardiac arrhythmias	Highly sensitive, used for monitoring response to treatment	Less available, higher costs
^{123}I-mIBG scintigraphy	Assesses risk of ventricular arrhythmias	Identifies patients at risk of sudden death	Less available

^{18}F-FDG PET: ^{18}F-fluorodeoxyglucose positron emission tomography.

Table 10 – Recommendations for the use of nuclear medicine imaging in the diagnostic evaluation of patients with suspected acute myocarditis

Indications	Class	Level of evidence
^{18}F-FDG PET to aid in the diagnosis of myocarditis	IIa	B
Gallium-67 scintigraphy to aid in the diagnosis of myocarditis	IIb	B

^{18}F-FDG PET: ^{18}F-fluorodeoxyglucose positron emission tomography.

to gadolinium-enhanced magnetic resonance imaging (MRI) (claustrophobia, contrast allergy, renal failure) and may contribute to cases of suspected myocarditis based on clinical criteria (fever, recent history of respiratory or intestinal infection, elevated necrosis markers). It is also useful for the differential diagnosis between acute MI with normal coronary arteries and myocarditis, according to a study conducted by Hung et al.,[120] in which scans were positive when performed early after symptom onset.[120] Some patients with myocarditis may present with regional damage in the myocardium, which can be the etiology of arrhythmias. Consequently, gallium-67 scans may demonstrate focal accumulation in ventricular areas and even in the atria alone.[121]

4.7.2. Positron emission tomography (PET) radiotracers

^{18}F-FDG is taken up by inflammatory cells and actively transported independently of insulin action. Thus, when adequate suppression of myocardial glucose uptake is achieved, ^{18}F-FDG PET becomes a sensitive tool for the diagnosis of myocardial inflammation and monitoring of treatment response (Table 10).

Most studies on the use of ^{18}F-FDG PET in myocarditis have focused on cardiac sarcoidosis, and a recent meta-analysis has demonstrated a sensitivity of 84% and a specificity of 83%.[122] For ^{18}F-FDG PET to be helpful in sarcoidosis or other inflammatory cardiac conditions such as myocarditis, infective endocarditis, or transplant rejection, adequate patient preparation is crucial to prevent circulating insulin from leading to noninflammatory ^{18}F-FDG accumulation in the myocardium. The most commonly indicated preparation protocols include prolonged fasting (12 to 18 hours) before radiotracer injection and a high-fat, protein-permitted diet, while the utility of heparin remains unclear.[123,124] Diagnostic evidence of inflammatory activity is focal ^{18}F-FDG uptake in the myocardium, while the presence of ^{18}F-FDG uptake in the RV and the presence of inflammatory uptake in hypoperfused areas, the so-called mismatches, have prognostic significance, as they reveal increased metabolism with reduced perfusion.[124] ^{18}F-FDG PET is also used to monitor treatment response in cardiac sarcoidosis and to assess the activity of extracardiac disease. A monitoring algorithm is proposed in Figure 3, adapted from Young et al.[125]

CMR is the standard diagnostic technique for myocarditis not associated with sarcoidosis. Increased signal intensity of T2-weighted images (edema), increased early gadolinium enhancement (hyperemia), and late myocardial gadolinium uptake (late enhancement for necrosis) have a combined sensitivity of 67% and specificity of 91% for the diagnosis of myocarditis. However, there are frequent limitations to proper use of the technique, such as poor signal quality on T2-weighted images, artifacts, and inability to use gadolinium contrast media. In such cases, ^{18}F-FDG PET is quite useful as a complement to the diagnostic investigation and is available in PET-CT systems or, more recently, in PET-MRI systems.[126] PET-MRI studies have shown that PET is superior to MRI in identifying areas of active cardiac inflammation.[127]

^{18}F-FDG PET-CT has been successfully used to identify active inflammation in conditions such as systemic lupus erythematosus,[128] giant cell myocarditis,[129] scleroderma,[130] and even rheumatic carditis.[131] Recently, ^{18}F-FDG PET has been increasingly used in the investigation of cardiac sarcoidosis and chronic myocarditis, including Chagas disease, as a cause of ventricular arrhythmias.[132] It is also useful for investigating conduction disorders, especially in individuals below 50 years of age with AV block; in these patients, PET has identified several cases of sarcoidosis and even cardiac tuberculosis as a cause of conduction disorder.[133] In a study conducted by Tung et al., 50% of patients with unexplained myocardiopathy and ventricular arrhythmias had a positive ^{18}F-FDG PET scan indicating the presence of myocarditis not suspected by other techniques.[134]

4.7.3. Additional perspectives

New radiotracers have been evaluated in patients with myocardial inflammation, such as gallium-68 DOTATATE, which has an affinity for somatostatin receptors that are expressed by inflammatory cells. Another radiotracer under analysis is ^{123}I-mIBG, which assesses cardiac presynaptic adrenergic innervation. Although this radiotracer does not directly identify an inflammatory state, it bears an important relationship to increased risk of ventricular arrhythmias, particularly in patients with chronic Chagasic myocarditis, demonstrating viable myocardial areas that are denervated and thus more vulnerable to sustained ventricular tachycardia.[135]

4.8. Coronary computed tomography angiography and coronary angiography

Acute myocarditis may mimic acute MI with typical chest pain, ECG abnormalities similar to ST- or non-ST-segment elevation MI, high cardiac enzymes, and hemodynamic instability.[136]

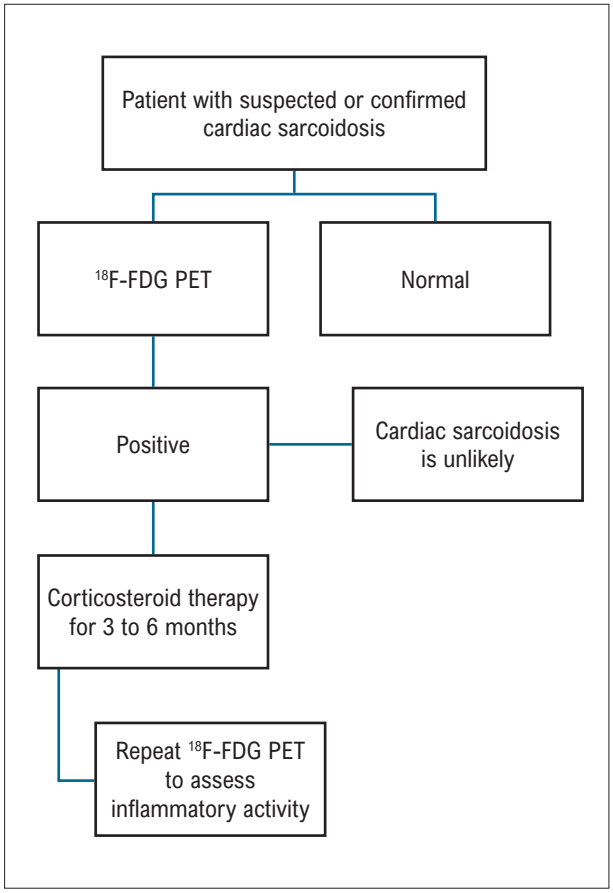

Figure 3 – *Proposed algorithm for diagnosis and monitoring of treatment response in cardiac sarcoidosis. ^{18}F-FDG PET: ^{18}F-fluorodeoxyglucose positron emission tomography. Adapted from Young et al.[125]*

In suspected myocarditis with infarct-like presentation, CAD must be excluded by percutaneous or tomographic coronary angiography. Routine coronary angiography should also be performed during the investigation of a new dilated cardiomyopathy.[137]

An analysis of 46 publications evaluating the underlying pathophysiology of myocardial infarction with nonobstructive coronary arteries (MINOCA) has revealed a typical infarct on CMR in only 24% of patients, myocarditis in 33%, and no significant abnormality in 26%.[138] Young age and high C-reactive protein (CRP) were associated with myocarditis, while male sex, treated hyperlipidemia, high troponin ratio, and low PCR were associated with true MI.[139]

Because patients with acute myocarditis mimicking ST-segment elevation MI have a favorable prognosis, correct diagnosis must be established to prevent unnecessary and potentially hazardous treatments.[139]

Cardiac computed tomography (CT) is a simple and rapid examination that provides a comprehensive assessment of the characteristics of coronary arteries and myocardial tissue. In practice, first-pass CT acquisition allows the evaluation of coronary anatomy and LV enhancement. Delayed CT acquisition is performed 3 to 5 minutes later without any reinjection of contrast medium, allowing iodine uptake to be seen on late contrast-enhanced images in a similar fashion as CMR.[140,141]

Computed tomography angiography and CMR have their own and unique ways to avoid invasive coronary angiography, exclude (significant) CAD, and detect other diseases such as acute aortic dissection, pulmonary embolism, myocarditis, and stress cardiomyopathy.[142]

The wide availability of CT combined with the possibility of ruling out acute coronary syndrome (ACS) with coronary CT angiography during the same examination makes it promising for refining acute myocarditis imaging (Table 11).[141]

In children with suspected myocarditis and Kawasaki disease, CT angiography can be used in the assessment of coronary artery abnormalities.[143]

The latest ESC guideline suggests that, in the absence of angiographically significant CAD (stenosis ≥50%) or preexisting conditions that could explain the clinical setting, patients who have at least one of the five clinical presentations (acute chest pain; acute or worsening HF with ≤3 months of dyspnea, fatigue, and/or signs of HF; chronic HF with >3 months of dyspnea, fatigue, and/or signs of HF; palpitations, symptoms of unexplained arrhythmias and/or syncope and/or aborted death; unexplained cardiogenic shock) and/or certain supportive diagnostic tests (ECG, Holter, troponin, ventricular function abnormalities and edema and/or late gadolinium enhancement with a classic myocardial pattern) should be considered as having "clinically suspected myocarditis" and should undergo an additional evaluation.[12,72]

4.9. Endomyocardial biopsy: indications, technique, and complications

Histopathological analysis of myocardial tissue is an important diagnostic and prognostic tool in patients with

Table 11 – Indication for coronary computed tomography angiography in the diagnostic evaluation of patients with suspected acute myocarditis

Indication	Class	Level of evidence
Coronary computed tomography angiography for exclusion of severe obstructive coronary heart disease in myocarditis investigation as an alternative to coronary angiography in patients with low or intermediate pretest probability of CAD	I	C

CAD: coronary artery disease.

myocarditis. EMB with standard histopathological (Dallas criteria)[144] and immunohistochemical criteria is the current gold standard for diagnosis of myocarditis.[137]

The Dallas criteria alone have limitations by virtue of a high degree of interobserver variability in pathological interpretation and an inability to detect noncellular inflammatory processes, and yields a diagnosis in approximately 10% to 20% of patients.[15] Therefore, according to the WHO definition, immunohistochemistry with a panel of monoclonal and polyclonal antibodies is mandatory to identify the different inflammatory components.[145,146]

Viral genome analysis of diseased myocardium, when coupled with immunohistochemical analysis, has improved the diagnostic accuracy and prognostic utility of EMB.[147] Viral screening for enteroviruses, influenza viruses, adenoviruses, cytomegalovirus, Epstein-Barr virus, B19V, and HHV is recommended.

However, as some viral genomes (eg, B19V) can be detected in normal hearts and ischemic and valvular heart diseases,[148] complementary use of virus-specific mRNAs may be required to define active infection.[149]

4.9.1. Considerations for indication

Early EMB in severe clinical presentations provides important information to the differential diagnosis of specific types of myocarditis (giant cell, allergic, eosinophilic, sarcoidosis) leading to different treatments (eg, immunosuppressants) and prognoses (Table 12).[150]

It is also used in the differential diagnosis of diseases that may mimic myocarditis (arrhythmogenic right ventricular cardiomyopathy, Takotsubo cardiomyopathy, peripartum cardiomyopathy, inflammatory/storage disorders).[150]

Currently, the main indication for EMB consists of patients with new-onset HF (less than 2 weeks) accompanied by a severe clinical presentation (hemodynamic instability, use of inotropic or mechanical circulatory support, being refractory to medical treatment) or high-risk arrhythmias (sustained or symptomatic ventricular arrhythmias or high-degree heart blocks) (Table 12).[151,152]

However, it is known that the previous recommendations were notably based on the Dallas criteria, whose diagnostic, prognostic, and therapeutic value is limited. With the use of immunohistochemical and viral genome analyses, there is a growing trend towards a more liberal application of EMB in clinically suspected myocarditis regardless of pattern and severity of presentation.[12]

However, the value of EMB is questionable in patients who have low-risk syndromes and respond to standard treatment with no prospect of therapeutic or prognostic implications. Finally, in intermediate-risk syndromes, EMB should be considered in case of maintenance or worsening of symptoms, ventricular dysfunction, arrhythmias, conduction disorders (Figure 4).[153]

4.9.2. Prognosis

While the Dallas criteria are not an accurate predictor of clinical outcomes, immunohistological evidence of myocardial inflammation is associated with an increased risk of cardiovascular death and need for heart transplantation.[153]

In giant cell myocarditis, the severity of necrosis and fibrosis is associated with an increased risk of death and transplantation.[154]

The absence or presence of residual enteroviral genomes in repeated samples has correlated with progression to end-stage cardiomyopathy, while spontaneous viral clearance has been associated with improved systolic function.[155]

4.9.3. Technique

The procedure should be performed in a catheterization laboratory by an experienced interventional cardiologist. Local anesthesia is used with conscious sedation if required, always under the supervision of an anesthesiologist.

EMB is safely performed under direct fluoroscopy guidance and should be supported by echocardiography,

Table 12 – Recommendations for the use of endomyocardial biopsy

Indications	Class	Level of evidence
New-onset HF (<2 weeks), undefined cause, unresponsive to standard treatment, with hemodynamic deterioration	I	B
New-onset HF (2 weeks to 3 months), undefined cause, associated with ventricular arrhythmia or second- or third-degree atrioventricular block	I	B
In the presence of clinically suspected severe lymphocytic myocarditis, giant cell myocarditis, necrotizing eosinophilic myocarditis	I	B
HF with onset >3 months and <12 months, undefined cause, unresponsive to optimized standard therapy	IIa	C
HF due to dilated cardiomyopathy of any duration with suspected allergic reaction and/or eosinophilia	IIa	C
Frequent ventricular arrhythmias with or without symptoms, undefined cause	IIb	C
Clinical suspicion supported by noninvasive diagnostic methods of myocarditis	IIb	C

HF: heart failure.

which will serve as a guide for correct positioning of the bioptome to avoid puncturing the RV free wall.

CMR is particularly useful for facilitating a guided approach, given its ability to distinguish normal from diseased myocardium, and has been assessed to increase predictive values.[155]

There are no comparative studies to recommend RV or LV biopsy; however, LV EMB should be carefully analyzed in cases of restricted or predominant LV disease.

Samples should be obtained from the RV, especially the distal portion of the interventricular septum and the apical trabecular component, avoiding the RV free wall. The number of samples will depend on the studies to be performed. In the investigation of viral myocarditis, 10 samples should be used (6 for viral screening, 2 for hematoxylin-eosin staining, and 2 for immunohistochemistry). In the investigation of infiltrative or deposition diseases, 6 specimens are required (2 for hematoxylin-eosin staining, 2 for immunohistochemistry, and 2 for electron microscopy). Hematoxylin-eosin staining and immunohistochemistry samples should be placed in a 10% buffered formalin vial and should not be refrigerated. Viral screening samples should be placed in Eppendorf® microtubes (without embedding medium), and these should be placed in containers with dry ice to be quickly transferred to -70-degree refrigerators for storage. Electron microscopy samples should be placed in Eppendorf® tubes with optimal cutting temperature compound.

EMB may be repeated if required to monitor response to etiology-directed therapy or if sampling error is suspected in patients with unexplained HF progression.[156]

4.9.4. Complications

Although conventional EMB is considered a safe procedure, different complications have been reported.

In experienced centers, the major complication rate for EMB is <1%, which is similar to that of coronary angiography.[97] The use of echocardiography combined with fluoroscopy significantly reduces the risk of inadvertent puncture that could cause myocardial perforation or coronary artery injury.[155]

Complications of vascular access and sheath insertion can be distinguished from complications of the biopsy procedure. Complications of vascular access are accidental arterial puncture, prolonged bleeding, hematoma, and vascular dissection.

Commonly described complications of the biopsy procedure include vasovagal reaction, AV block of varying degrees, RV free wall perforation, pneumothorax,

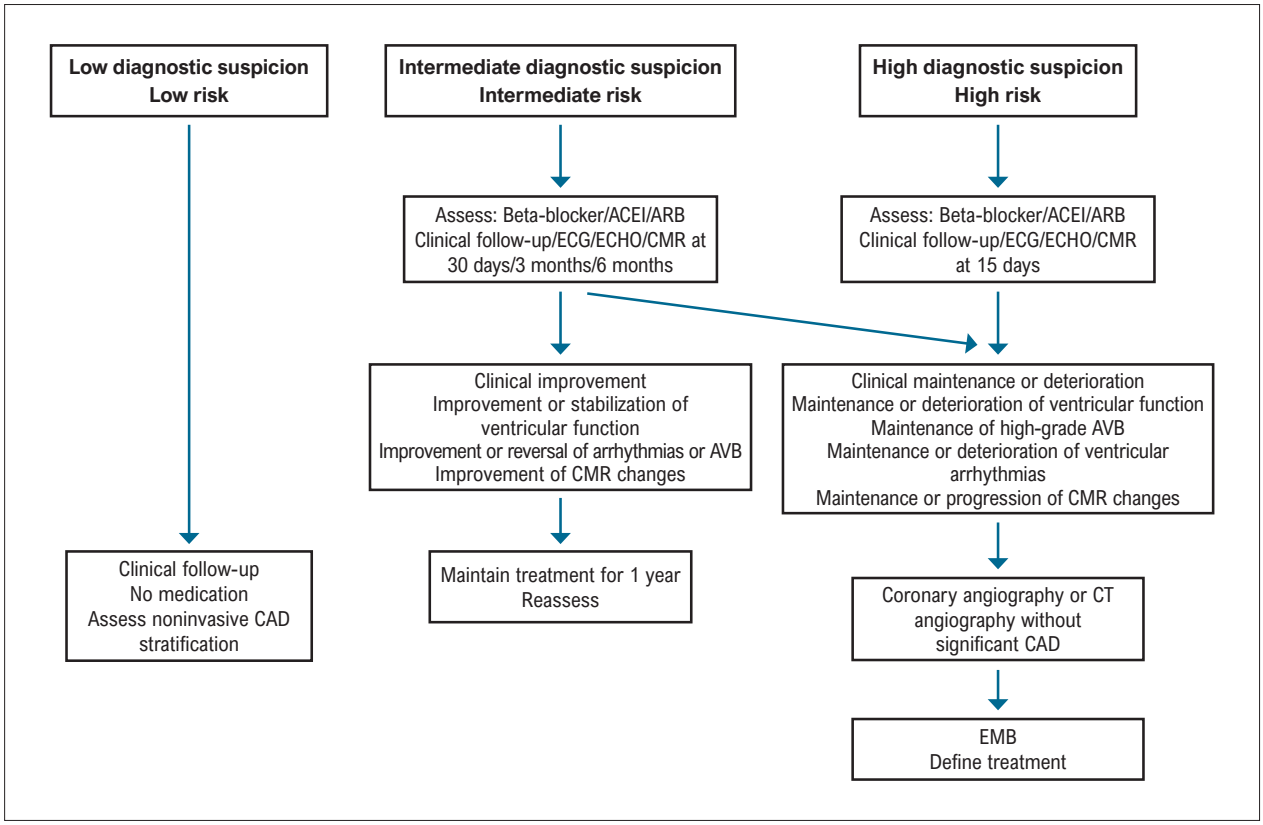

Figure 4 – *Therapeutic flowchart for myocarditis based on clinical suspicion and prognosis.*
ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; AVB: atrioventricular block; CAD: coronary artery disease; CMR: cardiac magnetic resonance; CT: computed tomography; ECG: electrocardiogram; ECHO: echocardiogram; EMB: endomyocardial biopsy.

interventricular septal perforation, access site hematoma, intracardiac fistulas, retroperitoneal hematoma (femoral access), pericardial effusion, thrombus displacement, cardiac tamponade, tricuspid valve chordal rupture, and ventricular arrhythmias.[157]

In sum, the risk of EMB depends on the patient's clinical status, the operator's experience, and all the technologies available to prevent, diagnose, and manage complications.

4.10. Histological analysis and viral screening – Molecular biology and genome

4.10.1. Histological analysis

Myocarditis is defined as an inflammatory disease of the myocardium that should be diagnosed by histological and immunohistological criteria. According to the Dallas criteria, active myocarditis is histologically defined as an inflammatory infiltrate of the myocardium with necrosis of adjacent myocytes, whereas borderline myocarditis is diagnosed when an inflammatory infiltrate is present but no injury/necrosis is demonstrated in the cardiac cells.[158]

However, the Dallas criteria are considered diagnostically inadequate in patients with clinically suspected myocarditis because of variability in interpretation, lack of prognostic value, and low sensitivity due to sampling error. These limitations can be overcome by immunohistological staining of infiltrating cells (leukocytes/T lymphocytes/macrophages) and surface antigens (intercellular cell adhesion molecule-1 [ICAM-1]/human leukocyte antigen [HLA-DR]).

In addition to the diagnosis of myocarditis, histopathological evaluation using histological criteria is key to classifying myocarditis as lymphocytic, eosinophilic, giant cell, granulomatous, and/or polymorphic, which generally reflect different etiopathogeneses of the inflammatory process.[12]

Furthermore, histological examination of paraffin sections by different staining protocols (hematoxylin-eosin, elastica-van Gieson [EvG], periodic acid-Schiff [PAS], Azan) is used to detect myocardial cell death, scarring, fibrosis, dysfunction, cardiomyocyte abnormalities, and pathological vascular conditions. Amyloidosis, iron and glycogen deposition, and other storage diseases can be excluded or specified by additional staining.

4.10.2. Immunohistochemical analysis

Immunohistochemistry has significantly increased the sensitivity of EMB and provides prognostic information. The diagnostic accuracy of immunohistology for detecting inflammation is greater than that of histological criteria. Immunohistochemical evaluation is based on specific antigen-antibody reaction analysis. A count ≥14 leukocytes/mm^2 with the presence of T lymphocytes ≥7 cells/mm^2 was considered a realistic cutoff point to achieve the diagnosis of myocarditis.[12]

Quantification of additional infiltrating cells, including macrophages (Mac-1/CD69), CD4+, CD8+ cells, and cytotoxic cells (perforin), and quantification of HLA-DR and ICAM-1 are mandatory to further characterize inflammatory cell populations. Thus, accurate characterization and quantification of myocardial inflammation is relevant for establishing a prognosis and identifying different markers of virus-negative, infectious, chronic/acute autoimmune myocarditis (see Figure 4).

Additional immunofluorescence staining methods should be used to define humoral rejection on heart transplant EMB, such as C3d and C4d staining, or to obtain amyloid subtyping.

4.10.3. Gene expression profile analysis

Idiopathic giant cell myocarditis and cardiac sarcoidosis are rare disorders causing acute HF with cardiogenic shock and/or life-threatening ventricular arrhythmias in the absence of other etiologies. Prognosis is extremely poor, with 4-year survival rates of less than 20%.[159]

A major barrier to correct diagnosis is sampling error by histological examination of EMB. Distinct differential gene expression profiles have been identified and allowed a clear discrimination between tissues harboring giant cells and those with active myocarditis or inflammation-free controls. Also, disease-specific gene expression profiles change during effective treatment and are suitable for therapy monitoring.[160]

4.10.4. Viral analysis

Microbial genomes are determined, quantified, and sequenced by polymerase chain reaction (PCR)-based methods, including nested RT-PCR and quantitative PCR assays, providing viral load analysis. Sequencing of the amplified viral gene product is mandatory.

Importantly, all viruses that may cause the disease should be analyzed. The most commonly reported cardiotropic viral genomes in the myocardium are B19V, enterovirus, adenovirus, influenza virus, HHV-6, Epstein-Barr virus, cytomegalovirus, hepatitis C virus, and HIV (Table 13).

B19V is the predominant cardiotropic virus in myocarditis. The clinical impact on the heart is still a matter of debate. Transcriptionally active cardiotropic B19V with positive replicative intermediates on EMB appears to be clinically relevant because patients with myocarditis characterized by such virus have abnormal gene expression compared to control patients with latent B19V. However, despite the causative agent being of viral origin, PCR results may be negative because of viral clearance.

Although viruses are thought to be the most common cause of myocarditis, viral titers are not useful for diagnosis and treatment.

5. Treatment

5.1. Therapeutic flowcharts

Most cases of myocarditis have a favorable prognosis with spontaneous regression of clinical symptoms and preserved ventricular function not requiring therapeutic intervention. The therapeutic flowchart for myocarditis in most patients

Table 13 – Common viruses on endomyocardial biopsy

Virus type	
Adenovirus	Parvovirus B19
Arbovirus	Poliomyelitis virus
Arenavirus	Rabies virus
Coronavirus	Respiratory syncytial virus
Coxsackievirus (A, B)	Rubella virus
Cytomegalovirus	Vaccinia virus
Dengue virus	Varicella-zoster virus
Echovirus	Variola virus
Encephalomyocarditis virus	Zika virus
Epstein-Barr virus	Human immunodeficiency virus
Hepatitis B virus	Influenza virus (A, B)
Hepatitis C virus	Metapneumovirus
Herpes simplex virus	Mumps virus
Human herpesvirus 6	

is guided by diagnostic suspicion, since only a minority of patients will undergo EMB (Figure 4).[65]

Patients with low diagnostic suspicion of myocarditis presenting with no signs of severity, preserved ventricular function, and no ventricular arrhythmias have a favorable prognosis and should be clinically monitored with no need for drug therapy. In patients with intermediate diagnostic suspicion of myocarditis presenting with preserved ventricular function or ventricular dysfunction with progressive improvement, cardioprotective therapy with beta-blockers, angiotensin-converting enzyme inhibitors (ACEIs), or angiotensin receptor blockers (ARBs) is used to preserve or improve ventricular function.[12,55]

Patients with high diagnostic suspicion presenting with any of the indicators of poor prognosis, such as clinical deterioration, hemodynamic instability, maintained or progressive ventricular dysfunction, frequent ventricular arrhythmias, and significant conduction disorders, should undergo EMB for investigation of inflammation and etiologic agent. This will allow establishing a specific therapy with immunosuppression,[161,162] immunomodulation,[163-166] and antiviral drugs,[167-170] which may be beneficial in terms of clinical improvement, functional class, ventricular function, and survival (Figure 5).[8,162,171-175]

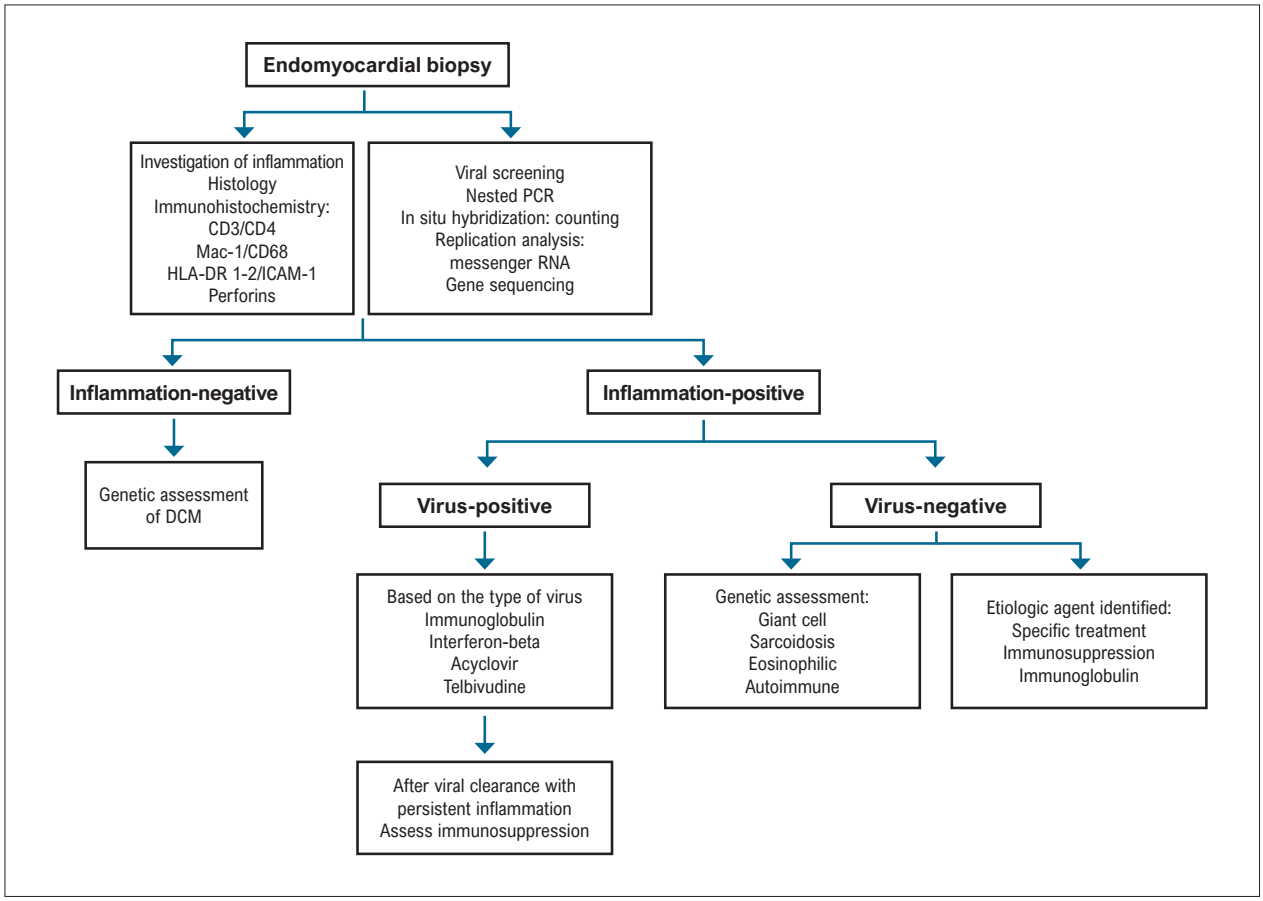

Figure 5 – *Therapeutic flowchart for myocarditis based on endomyocardial biopsy results. PCR: polymerase chain reaction; DCM: dilated cardiomyopathy*

5.2. Immunosuppression: indications and types

Immunosuppressive therapy in myocarditis is used to suppress the inflammatory response and autoimmune activity with the purpose of improving clinical status and ventricular function and thus reducing mortality.

In lymphocytic myocarditis, despite the pathophysiological rationale for using immunosuppression based on the presence of myocardial inflammation on EMB combined with absence of viral genome, the evidence supporting this hypothesis is limited. Factors such as spontaneous regression of inflammation, lack of uniform diagnostic criteria in the studies, reduced number of patients in most trials, heterogeneity of the clinical characteristics of study populations, and paucity of studies evaluating mortality reduction alone hamper an analysis of the clinical benefits of immunosuppressive therapy in lymphocytic myocarditis (Table 14).[55,161,162,172,176-179]

In the Myocarditis Treatment Trial (MTT),[178] which included patients with myocarditis meeting the Dallas criteria combined with the presence of ventricular dysfunction, immunosuppression for 6 months was not superior to conventional treatment in improving ventricular function and survival, although infectious agents were not investigated. The Tailored Immunosuppression in Inflammatory Cardiomyopathy (TIMIC) study, an Italian double-blind, randomized, placebo-controlled trial,[162] demonstrated improved ventricular function with immunosuppression in patients with myocarditis on biopsy (more than 7 lymphocytes per mm^2), HF for more than 6 months, and absence of viral genome on EMB. Thus, although the evaluated phase was different from the acute phase of myocarditis, the study demonstrated the benefit of immunosuppression in the absence of viral genome in the myocardium. However, the nonidentification of specific viruses only means that the investigated viruses are not present and does not rule out the possible presence of other microbes.[162] Also, qualitative findings of microbes on EMB do not establish an undoubted causal relationship with the development of myocarditis/myocardiopathy, since viral genomes can be found in cardiomyopathies of other specific etiologies and even in normal hearts.[45,180,181] Taking B19V as an example, as its presence in myocardial tissue on qualitative PCR assay is common, other techniques documenting a low amount of copies[167] or absence of RNA transcription[182] could infer a noncorrelation with the development of myocarditis/myocardiopathy, allowing immunosuppression to be considered, even when the genome of this virus is present.

Immunosuppression is well established in myocarditis due to autoimmune disorders, and different strategies should be considered for each entity. Most strategies consist of corticosteroids usually combined with additional immunosuppressive drugs (Table 15).[183-188]

Despite the low incidence, the diagnosis of giant cell myocarditis cannot be delayed because of the severity of clinical manifestations, and the treatment consists of intensive combined immunosuppression. A classic study conducted by Cooper et al.[8] showed that survival increased from 3 to 12 months with combined immunosuppression (corticosteroid and/or azathioprine and/or cyclosporine and/or antilymphocyte antibody) compared to no immunosuppression or only corticosteroids.[8] A more recent study demonstrated a 5-year survival of 58% with the combined use of corticosteroids, cyclosporine, and azathioprine.[189] In refractory cases, antilymphocyte antibodies,[190] mycophenolate mofetil,[191] and sirolimus[192] have been described.

Table 14 – Analysis of the clinical benefits of immunosuppressive therapy in lymphocytic myocarditis

Author	Design	Intervention	Placebo	N	Disease	Duration of symptoms	Inclusion	Virus-positive EMB	LVEF	Outcomes
Parrillo et al., 1989	Randomized, controlled	Prednisone	No	102	DCM	Mean: 8 months	Idiopathic	Yes No	>35%	Neutral
Latham et al., 1989	Randomized, controlled	Prednisone	No	52	DCM	<2 years, mean: 1.6 to 1.8 months	Idiopathic	Yes No	<40%	Neutral
Wojnicz et al., 2001	Randomized, controlled, open-label	Prednisone + azathioprine	Yes	84	DCM	>6 months	HLA	Yes No	<40%	Improved EF
Wojnicz et al., 2006	Randomized, controlled, open-label, 2-center	Atorvastatin	No	74	DCM	>6 months	HLA	Yes No	<40%	Improved EF/ NYHA functional class
Frustaci et al., 2009	Randomized, controlled, double-blind, multicenter	Prednisone + azathioprine	Yes	85	DCM	>6 months	CD3 >7, CD45 >14 virus-negative	Yes Yes	<45%	Improved EF
Merken et al., 2018	Case series	Prednisone + azathioprine	No	180	DCM	Mean: 8 to 11 months	CD3 >7, CD45 >14 Virus-negative	Yes Yes	<45%	Improved transplant-free survival/EF

DCM: dilated cardiomyopathy; EMB: endomyocardial biopsy; HLA: histocompatibility antigen; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association.

Eosinophilic myocarditis may be idiopathic or secondary to drug hypersensitivity reactions, autoimmune diseases (eosinophilic granulomatosis with polyangiitis or Churg-Strauss syndrome), hypereosinophilic syndrome, infections, and cancer. Immunosuppression is also considered in this setting, usually with corticosteroids. A recent literature review demonstrated peripheral eosinophilia in 75% of patients, immunosuppression in 80%, and combined therapy in 20% (especially Churg-Strauss and hypereosinophilic syndromes), with high 30-day mortality (13% hypereosinophilic syndrome, 17% idiopathic, 23% Churg-Strauss syndrome, and 40% hypersensitivity).[193]

The most commonly used immunosuppressive therapy in patients with confirmed myocarditis consists of corticosteroids alone or in combination with azathioprine (Table 16), with the diagnosis by EMB of inflammation with no viral infection as determinants for immunosuppression (Table 17). Patients undergoing immunosuppressive therapy should be continuously monitored for the development of side effects, as these may significantly increase both morbidity and mortality.[55]

5.3. Antiviral therapy: indications and types

The prognosis of inflammatory cardiomyopathy/myocarditis is negatively affected by viral persistence. In viral cardiomyopathy, certain viruses are closely associated with a spontaneous course of viral infection, since spontaneous viral elimination is accompanied by clinical improvement, but this does not apply to patients who develop viral persistence.[194-197]

Patients with enteroviral and adenoviral genomes on EMB should be treated with interferon-beta (IFN-ß) (4 million units subcutaneously every 48 hours in the first week, 8 million units subcutaneously every 48 hours from the second week on, for 6 months). A nonrandomized study demonstrated that administration of IFN-ß to patients positive for enteroviral and adenoviral infection induced viral elimination, reduced myocardial injury, and significantly improved long-term survival.[198,199] In a subsequent phase 2 study – Betaferon in Chronic Viral Cardiomyopathy (BICC) trial –, 143 patients with symptoms of HF and biopsy-proven enterovirus, adenovirus, and/or

Table 15 – Indications for immunosuppression in autoimmune myocarditis

Giant cell myocarditis	Rare but fulminant, improved prognosis with combined immunosuppression	Combined corticosteroid (cyclosporine + azathioprine)
Sarcoidosis	Systemic disease primarily affecting the lungs. Myocarditis in 10%, blocks, tachyarrhythmias, and ventricular dysfunction	Combined corticosteroids (cyclophosphamide, methotrexate), biologics in refractory cases
Systemic lupus erythematosus	Myocarditis in 50%, might be subclinical; rare with current immunosuppression; might accelerate atherosclerosis	Corticosteroid pulse therapy (followed by oral therapy for weaning), combined therapy (cyclophosphamide), plasmapheresis, IVIg
Systemic sclerosis	Myocarditis or secondary to pulmonary hypertension. Arrhythmias, conduction disorders, and ventricular dysfunction	Combined corticosteroids (cyclophosphamide, azathioprine)
Behçet disease	Myocarditis is rare (0.5%), poor prognosis	Combined corticosteroids (colchicine, anticoagulation)
EGPA (Churg-Strauss syndrome)	Myocarditis in up to 50%; history of asthma, presence of eosinophilia; chest pain, palpitations, and cardiogenic shock	Combined corticosteroids (cyclophosphamide)
Rheumatoid arthritis	Myocarditis in 30%, might be subclinical; rare with current immunosuppression; might accelerate atherosclerosis	Combined corticosteroids (methotrexate, biologics)

Table 16 – Immunosuppressive therapy with corticosteroids

Giant cell myocarditis Corticosteroid pulse therapy – methylprednisolone 500 to 1,000 mg for 3 to 5 days; prednisone – 1 mg/kg and then slow and gradual withdrawal Antilymphocyte antibody – Thymoglobulin – 1.5 mg/kg/day, according to the evolution of CD3 T lymphocytes – cyclosporine – 3 to 8 mg/kg Azathioprine – 2 mg/kg
Lymphocytic and eosinophilic myocarditis Up to week 4 – 1 mg/kg Weeks 5 to 12 – reduce dosage by 0.08 mg/kg/week Weeks 13 to 20 – maintain dosage at 0.3 mcg/kg/day Weeks 21 to 24 – reduce dosage by 0.08 mg/kg/week TIMIC study: prednisone – 1 mg/kg for 4 weeks and 0.33 mg/kg for 5 months; azathioprine – 2 g/kg for 6 months
Sarcoidosis Prednisone – 30 mg/day – remove 5 mg per month for 12 to 24 months Combination when corticosteroid withdrawal is difficult: methotrexate – 10 to 20 mg/week Azathioprine – 2 mg/kg; hydroxychloroquine – 200 to 400 mg/day Leflunomide – 10 to 20 mg/day

Table 17 – Indications for immunosuppressive therapy in myocarditis

Indications	Class	Level of evidence
In the presence of positive myocarditis – giant cell, autoimmune disorders, sarcoidosis, and eosinophilia – associated with ventricular dysfunction	I	B
In the presence of endomyocardial biopsy-proven positive myocarditis and negative viral screening in patients with chronic heart failure, with the purpose of improving clinical status and ventricular function	IIa	B
In acute heart failure unresponsive to standard therapy	III	C

B19V genomes were randomly assigned to double-blind treatment and received either placebo or IFN-ß for 24 weeks, in addition to standard HF treatment. Compared to placebo, viral elimination and/or viral load reduction were higher in the IFN-ß groups. IFN-ß treatment was associated with favorable effects on NYHA functional class, quality of life, and patient global assessment. In retrospective analyses, IFN-ß treatment was found to be significantly less effective in eliminating B19V infection.[171]

A high prevalence of HHV-6 has been detected in the myocardial tissue of patients presenting with symptoms of HF in a clinically suspected setting of myocarditis. Interestingly, HHV-6 is able to integrate its genome into telomeres of human chromosomes, which allows transmission of HHV-6 via the germline. Chromosomally integrated HHV-6 (ciHHV-6) appears to be associated with an increased risk of myocarditis and may lead to severe HF. HHV-6 is also not eliminated by IFN-ß, but symptoms of HHV-6 reactivation and HF have decreased after a 6-month treatment period with ganciclovir followed by valganciclovir (ganciclovir 1,000 mg/24h intravenously for 5 days, then valganciclovir 900 mg/24h or 1,800 mg/24h for 6 months) in symptomatic patients with reactivated ciHHV6 (positive messenger RNA).[200]

B19V infection of the heart muscle is still a matter of debate. Initial data have provided evidence that antiviral nucleoside analogue reverse transcriptase inhibitors such as telbivudine can improve the clinical outcomes of patients with positive B19V DNA and replicative intermediates.[201] However, a large randomized, placebo-controlled clinical trial is now required to evaluate the results.

5.4. Immunomodulation (immunoglobulin and immunoadsorption): indications and types of immunoglobulins

The rationale for the use of intravenous immunoglobulin (IVIg) in the treatment of myocarditis is based on their ability to interact widely with the immune system. They are able to stimulate the complement system and immune cells to release anti-inflammatory cytokines and inhibit the release of proinflammatory cytokines.[83]

Immunoglobulins have been assessed in different settings such as chronic HF,[202,203] dilated cardiomyopathy,[166,204] peripartum cardiomyopathy,[205] acute myocarditis,[164,165,206,207] fulminant myocarditis,[208] and viral myocarditis.[167,169]

Although some of these studies suggest a potential benefit of immunoglobulin, a randomized controlled trial evaluating adult patients with new-onset dilated cardiomyopathy (<6 months) or myocarditis did not demonstrate evidence of beneficial effect of immunoglobulin on ventricular function in the treatment group versus the control group. There was improvement in ventricular function and even normalization in 36% of cases during follow-up, regardless of the study group. It is worth noting that the biopsy did not include any viral screening, and only 16% of patients had myocarditis confirmed by the presence of inflammation on biopsy.[166]

In patients with acute myocarditis, early studies have suggested an improvement in ventricular function and a tendency to higher 1-year survival with high-dose IVIg.[164] However, a 2005 systematic review found 17 studies including only one randomized controlled trial (62 patients), and did not demonstrate any benefit of IVIg in patients with acute myocarditis. The authors concluded that there is insufficient evidence to recommend routine use of IVIg in this setting.[207] More recently, a small randomized, multicenter study (41 patients) evaluated the short-term prognosis of patients with acute myocarditis or new-onset cardiomyopathy undergoing IVIg therapy compared to patients who did not receive IVIg. The study revealed improved short-term survival among patients who received IVIg and no significant difference in ventricular function between groups. However, there was a significant reduction in inflammatory cytokines in the treated group. The study hypothesizes a potential benefit of immunoglobulins and suggests their mechanism of action; however, because of the small number of patients, the evidence is insufficient to recommend unrestricted use of IVIg in patients with acute myocarditis.[209]

In viral myocarditis, nonetheless, there are data demonstrating the benefits of immunoglobulin. In a pilot study evaluating patients with B19V myocarditis, IVIg significantly reduced viral load and improved cardiac function.[167] In an analysis of 152 patients with adenovirus- or B19V-positive myocarditis, immunoglobulin improved exercise capacity, LV ejection fraction, and NYHA functional class. There was a significant reduction in inflammation in both groups of patients and a significant reduction in viral load only among patients with adenovirus-positive myocarditis; approximately 40% of patients with B19V infection had viral persistence.[169] These findings suggest a potential benefit of immunoglobulin in patients with EMB-proven viral myocarditis.

Current data, although insufficient for routine recommendation of IVIg, are indicative of a potential

benefit of immunoglobulin in patients with biopsy-proven myocardial inflammation, especially viral myocarditis caused by adenoviruses and B19V.

5.4.1. Immunoadsorption

The pathogenesis of progression to ventricular dysfunction in dilated cardiomyopathy involves inflammatory processes that can be identified and quantified by immunohistochemical methods, which suggests a causal relationship between myocarditis and cardiomyopathy.[210] The presence of lymphocytes, mononuclear cells, and increased gene expression of HLA antigens is frequent, as well as that of antibodies against mitochondrial and contractile proteins; B1 receptors and muscarinic receptors have also been described in dilated cardiomyopathy.[211-214]

These cardiac antibodies are extractable by immunoadsorption, and some studies have tested the efficacy of this method in the treatment of patients with dilated cardiomyopathy/myocarditis.[215,216] In a small controlled study, 25 patients were randomized to either undergo immunoadsorption followed by IgG substitution or continue conventional therapy, and a significant reduction in myocardial inflammation (decreases in CD3 cells, CD4 and CD8 lymphocytes, and HLA class II antigen expression) was found in the treated group.[217] In other small randomized studies, improvement in hemodynamics and ventricular function was observed.[216]

Current data suggest that immunoadsorption may be a new and promising therapeutic approach for patients with dilated cardiomyopathy and the presence of cardiac antibodies. However, to date, evidence is based on small uncontrolled studies or open-label controlled studies compared to conventional therapy, and their results require confirmation by large randomized, prospective, multicenter studies.[218] An ongoing double-blind, placebo-controlled, multicenter study will evaluate the effects of immunoadsorption followed by IgG substitution in patients with dilated cardiomyopathy.[219] Only with the results of this large study will we be able to establish a grade of recommendation for this therapy in the setting of dilated cardiomyopathy/myocarditis.

5.5. Conventional cardioprotective therapy

5.5.1. No ventricular dysfunction

The therapeutic approach for patients with myocarditis with preserved ventricular function aims to prevent the development of ventricular dysfunction or malignant arrhythmias. In patients with suspected diagnosis and intermediate risk, beta-blockers and ACEIs or ARBs can be used for at least 12 months to reduce mortality and morbidity. The decision to extend therapy will be based on the assessment of ventricular function and arrhythmogenic potential. As no clinical trials have addressed patients with this myocarditis profile, management should follow the SBC chronic and acute heart failure guidelines.

5.5.2. Ventricular dysfunction and hemodynamic stability

Therapeutic management of ventricular dysfunction in myocarditis should be in line with current HF guidelines.[55,220,221] Medications recommended for all hemodynamically stable patients with symptomatic ventricular dysfunction, such as cardioprotective therapy, unless contraindicated, are known as triple therapy – ACEIs or ARBs, beta-blockers, and mineralocorticoid receptor antagonists. ACEIs/ARBs and beta-blockers can be initiated in all individuals with HF with reduced ejection fraction, even if they are asymptomatic, unless contraindicated, and should be maintained when ventricular function normalizes. Spironolactone, a mineralocorticoid receptor antagonist marketed in Brazil, should be initiated when the patient is already taking other medications and maintaining symptoms (NYHA II-IV functional class), and should be avoided in patients with creatinine >2.5 mg/dL or persistent hyperkalemia (Table 18).

5.5.3. Hemodynamically unstable patients with ventricular dysfunction: therapeutic approach

Patients with acute myocarditis and systolic ventricular dysfunction may fit into different clinical models. Likewise, clinical response to therapy is quite variable, and there may or may not be a clear manifestation of low cardiac output or evidence of systemic hypervolemia. The use of inotropes is warranted in at least three situations: a clear low-output state, cardiorenal syndrome refractory to optimization of diuretic therapy, and mixed venous oxygen saturation (SvO_2) below 60% with invasive hemodynamic criteria for low output. According to the line of care, invasive monitoring for patients with no clear response to this therapy should be considered (Table 19).[222-225]

5.6. General recommendations: physical activity and vaccination

Myocarditis is an important cause of sudden death in athletes, which may occur in both the acute and chronic phases. This is related not only to the degree of myocardial inflammation but also to the triggering of complex arrhythmias and the development of left ventricular dysfunction.[226-228]

Competitive or recreational athletes with active myocarditis should not participate in competitive sports or high-intensity exercise until the end of convalescence. There is no consensus on how long this period is. Until recently, the recommendation was to wait at least 6 months after the onset of clinical manifestations. Currently, some experts recommend shorter periods, such as 3 months, for resuming exercise training and competitive sports depending on the presence of symptoms, arrhythmias, ventricular dysfunction, inflammatory markers, and ECG changes[12,229] (Table 20).

The European Consensus Document for Cardiovascular Prevention and Rehabilitation recommends that, in patients with HF, including those with myocarditis, exercise training should be of moderate intensity (up to 50% of VO_2peak or 60% of predicted maximal heart rate), provided there is no laboratory evidence of inflammation or arrhythmias.[230]

Table 18 – Recommendations for general pharmacological measures in myocarditis

Indications	Class	Level of evidence
Treatment with prognostic-modifying drugs for symptomatic or asymptomatic patients with left ventricular systolic dysfunction, according to current heart failure guidelines	I	C
Maintenance of neurohormonal blockade therapy after normalization of ventricular function	I	C
Consider neurohormonal blockade drugs in patients with evidence of myocardial fibrosis without dysfunction	IIa	C

Table 19 – Inotropes used in hemodynamically unstable patients with myocarditis and ventricular dysfunction[222-225]

	Dobutamine	Milrinone	Levosimendan
Clinical practice in myocarditis	B1 selective agonist, which promotes inotropism by direct stimulation of beta-receptors.	Experimental murine models suggest protective effects of milrinone and levosimendan over dobutamine on vasodilation in myocarditis. It acts as a phosphodiesterase inhibitor at any dose, thus increasing calcium concentration in cardiomyocytes. Systemic vasodilation contributes to increased cardiac output.	There are experimental murine models demonstrating a reduction in cell apoptosis and inflammatory cytokines with levosimendan in acute myocarditis. However, there is no robust evidence to recommend it as a cardioprotective agent in patients with myocarditis or to prove its clinical benefit over other inotropes. It acts as a calcium sensitizer up to 0.2 mcg/kg/min; at higher doses, it works as a phosphodiesterase inhibitor, with no clinical use tested. There is no clinical evidence of continuous use for more than 48 hours.
Inotropism	Moderate	Important	Important
Vasodilation	Mild	Moderate to important	Moderate to important
Increased cardiac output	Low to moderate	Important, associated with vasodilation	Important
Risk of hypotension	Low	Important and dose-dependent, higher in patients with established renal dysfunction	Important, especially if bolus is used. Increases with increasing dose.
Risk of arrhythmias	Increases exponentially when higher than 10 mcg/kg/min	Increases in case of bolus dose (not recommended)	Increases in case of initial bolus, also dose-dependent, more commonly at 0.2 mcg/kg/min

Table 20 – Exercise recommendations for athletes and nonathletes with myocarditis[12,229]

Indications	Class	Level of evidence
Athletes may return to training and competitive sports, and nonathletes, to their usual physical activities, 3 to 6 months after myocarditis only if all of the following criteria are met: – LV systolic function within the normal range – Normal myocardial injury biomarkers – Absence of arrhythmias on 24-hour Holter and stress testing	IIa	C
With previous myocarditis, individuals should be reassessed periodically, especially during the first 2 years, owing to an increased risk of recurrence and silent progression of the disease	IIa	C
Return to competitive sports and physical activities in asymptomatic athletes and nonathletes with persistent late gadolinium enhancement on CMR is considered in the period of 3 to 6 months after myocarditis if normal LV function and absence of arrhythmias on 24-hour Holter and stress testing, and they should be followed-up periodically for the potential risk of tachyarrhythmias. In the presence of positive late gadolinium enhancement on CMR, they should be assessed annually	IIa	C

CMR: cardiac magnetic resonance; LV: left ventricular.

During the Covid-19 pandemic, professional athletes have needed to interrupt or postpone their activities because of the risk of contamination. With the relaxation of social distancing measures, the question now is how athletes can safely return to their activities. Athletes who have had Covid-19 may present with respiratory symptoms, muscle fatigue, and risk of thrombotic events. Because of such risks, a flowchart with recommendations for clinical assessment and return-to-play decisions has been developed to provide guidance for resuming physical activities (Figure 6).[231]

Vaccination follows the same recommendations as those for annual influenza and pneumococcal immunization of patients with HF in addition to other available vaccines (mumps, measles, rubella, poliomyelitis). There is no robust evidence that these predispose patients to exacerbation or development of acute myocarditis to outweigh the benefits of immunization.[231-235] The same rationale applies to Covid-19 vaccination. To be vaccinated, patients should not be in the acute phase of myocarditis, and the recommendation is to wait 3 months of the diagnosis (Table 21).

6. Special situations

6.1. Fulminant myocarditis

Fulminant myocarditis is currently defined by a pragmatic approach with predominantly clinical features, irrespective of histological findings, as follows: 1) clinical presentation of severe HF symptoms for less than 30 days; 2) hemodynamic instability with cardiogenic shock and life-threatening arrhythmias (including recovered or aborted cardiac arrest); and 3) need for hemodynamic support (inotropes or mechanical circulatory assist device).[236] In addition to the previously mentioned tests for evaluating patients with

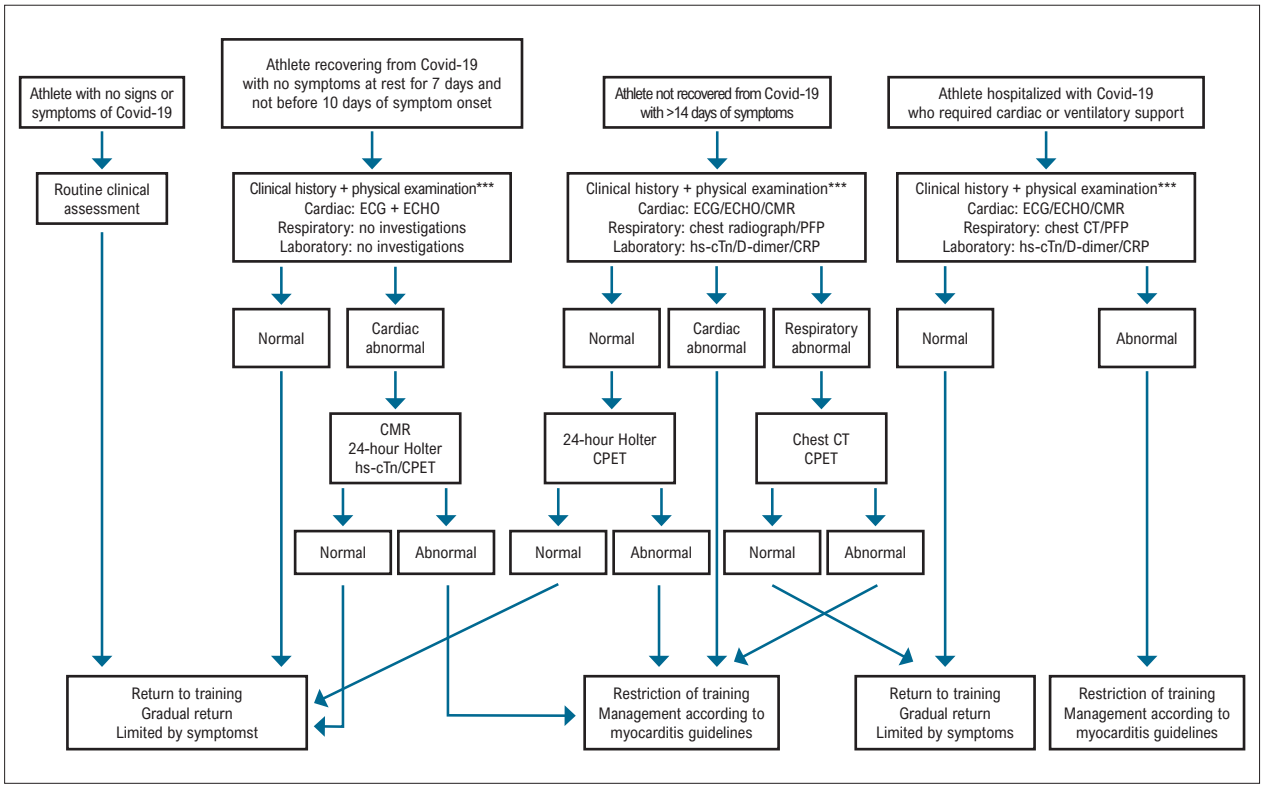

Figure 6 – *Flowchart for returning to exercise following Covid-19.*
**History and physical examination in the investigation of post-Covid-19 complications (neurological, gastrointestinal, and dermatological).*
CMR: cardiac magnetic resonance; CPET: cardiopulmonary exercise test; CRP: C-reactive protein; CT: computed tomography; ECG: electrocardiogram; ECHO: echocardiogram; hs-cTn: high-sensitivity cardiac troponin; PFP: pulmonary function test.

Table 21 – Vaccination recommendations in myocarditis

	Class	Level of evidence
Vaccines for influenza, pneumococcus, mumps, measles, rubella, poliomyelitis, and Covid-19. Patients should not be in the acute phase of the disease, and the recommendation is to wait 3 months of first diagnostic suspicion.	I	C

myocarditis, EMB is recommended in fulminant myocarditis. Results are usually positive and show multiple inflammatory foci, allowing histological characterization of the type of myocarditis.[237] The clinical course of fulminant myocarditis tends to be more dismal than those of nonfulminant types of myocarditis, with a lower likelihood of ventricular function recovery, higher mortality, and a higher chance of heart transplantation.[236,238]

6.1.1. Diagnostic evaluation

The diagnosis of fulminant myocarditis involves the diagnostic criteria of myocarditis per se, including clinical features of acute HF, elevated troponins and inflammatory markers, nonspecific ECG changes such as T-wave inversions and/or ST-segment abnormalities, and acute ventricular function changes. In the setting of cardiogenic shock, right heart catheterization and coronary angiography are essential for guiding management. Echocardiography is a key diagnostic tool, since patients with fulminant myocarditis are frequently unable to undergo MRI. Echocardiographic findings are highly dependent on the form and timing of presentation. Patients with fulminant myocarditis typically have normal diastolic dimensions but increased septal thickness at presentation, whereas patients with acute (nonfulminant) viral myocarditis may present with either normal or increased diastolic dimensions but normal septal thickness consistent with other forms of dilated cardiomyopathy.[15,64,72,98,239,240]

The decision to perform EMB at the time of cardiac catheterization is in line with those of the ESC 2013[15] task force. EMB can be considered the initial diagnostic procedure when MRI is not possible (eg, shock, presence of metal devices), if experienced operators and cardiac pathologists are available. According to the guidelines, therefore, the indications for EMB would be present for most patients with fulminant myocarditis (Figure 4) . Higher accuracy can be achieved by adding viral genome analysis, immunohistology, or transcriptomic biomarkers if there is diagnostic uncertainty despite histology.

In addition to confirming diagnosis, EMB in fulminant myocarditis can be decisive for defining therapy. Immunohistochemical analysis has been considered mandatory because of known diagnostic limitations of the Dallas criteria, especially interobserver variability, which possibly limits diagnostic confirmation to no more than 20% of cases.[15,64,72,239,240] According to the WHO definition for diagnosis of active myocarditis, immunohistochemical detection of mononuclear infiltrates (T lymphocytes or macrophages) using a cutoff point of 14 cells/mm^2 or over is required in addition to increased expression of HLA class II molecules.[146]

Viral genome detection in biopsy specimens is feasible (limited availability in Brazil) and, when coupled with immunohistochemical analysis, increases diagnostic accuracy and provides etiologic and prognostic information.

For fulminant myocarditis, a class I, level C indication has been considered even when only histological analysis is present (Dallas criteria). Conventional histological analysis is widely available and enables etiologic diagnosis that may lead to changes in therapeutic approach and specific treatment for presentations such as necrotizing eosinophilic myocarditis, giant cell myocarditis, sarcoidosis, amyloidosis, and myocarditis associated with known autoimmune diseases.

6.1.2. Therapeutic approach

The recognition of the causal factor through histological investigation by EMB allows the establishment of specific therapeutic strategies, such as immunoglobulin in viral myocarditis, immunosuppression in nonviral, autoimmune myocarditis, or corticosteroids in sarcoidosis, necrotizing eosinophilic myocarditis, or giant cell myocarditis. A randomized clinical trial of immunosuppression in 85 patients with myocarditis with proven absence of viral persistence (TIMIC study) demonstrated a clear beneficial effect on ejection fraction. However, these patients had more than 6 months of diagnosis and proven absence of virus.[162] Clinical trials of immunosuppression in patients with fulminant myocarditis do not exist. One option that has been tested is the use of high-dose of immunoglobulin, which has been shown to be beneficial over ventricular function and functional class, and has shown survival benefit;[208,209,217] although it has been demonstrated in a clinical trial with 62 patients, in which only 16% had biopsy-proven myocarditis the absence of benefit.[166]

Supportive treatment should include vasoactive drugs and possibly vasopressors, and should be used in situations allowing the introduction of vasodilators. Immediate failure of drug treatment and volume replacement should lead clinicians to consider indication for hemodynamic support with mechanical circulatory assist devices. The most common devices are intra-aortic balloon pump, percutaneous devices such as TandemHeart and Impella, extracorporeal membrane oxygenation (ECMO), and paracorporeal ventricular assist devices, which are all used as a bridge to recovery or to heart transplantation (Figure 7). Short-term support devices are indicated for 7 to 10 days.[241] After that and while stabilization is not achieved, ECMO or artificial ventricles are indicated to provide support for a longer period, allowing patients a greater chance of recovery from ventricular dysfunction[242] (see section on *Cardiogenic shock*).

6.2. Sarcoidosis

6.2.1. Diagnosis

Sarcoidosis is a granulomatous inflammatory disease of unknown etiology characterized by noncaseating granulomas. It may involve multiple organs, especially lungs (90%), skin, lymph nodes, central nervous system, eyes, liver, heart, and others.[243] Although clinically manifest cardiac sarcoidosis only affects 5% to 10% of patients with sarcoidosis, autopsy studies have revealed that cardiac involvement is present in 20% to 30% of patients on advanced cardiac imaging. With CMR or PET imaging, cardiac involvement has increased to 40%.[244-246] In addition to different definitions for the same

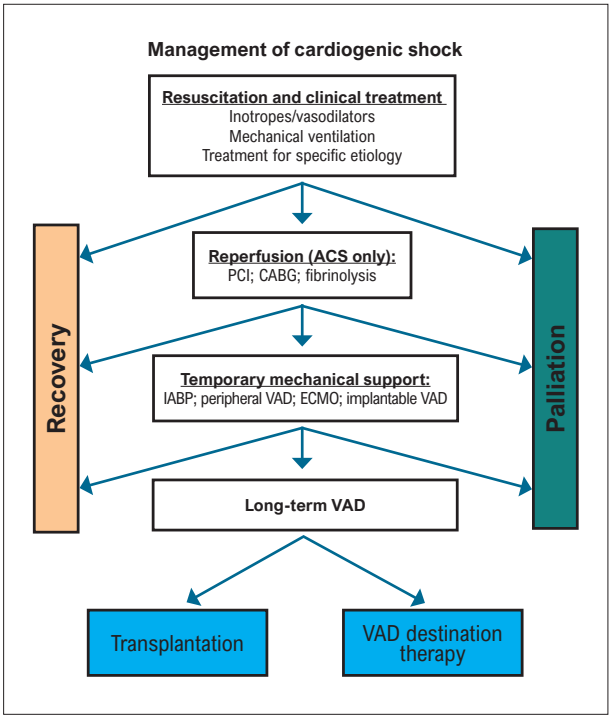

Figure 7 – *Approach for initial stabilization of patients with cardiogenic shock. ACS: acute coronary syndrome; CABG: coronary artery bypass grafting; ECMO: extracorporeal membrane oxygenation; IABP: intra-aortic balloon pump; PCI: percutaneous coronary intervention; VAD: ventricular assist device. Adapted from Kociol et al.[63]*

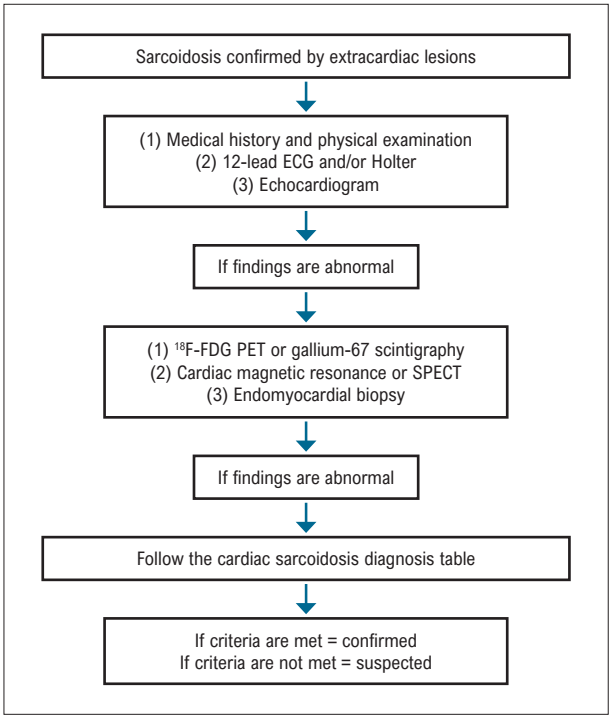

Figure 8 – *Diagnostic flowchart for cardiac sarcoidosis after the diagnosis of extracardiac lesions. ECG: electrocardiogram; PET: positron emission tomography; SPECT: single-photon emission computed tomography. Adapted from Terasaki et al.[247]*

entity, another factor that seems to have an impact on the increased prevalence of sarcoidosis is the refinement of imaging methods.

Currently, it is recommended the use of the guidelines of the Japanese Circulation Society (SJC) launched in 2019 (Table 22, Figures 8 and 9). Among the changes suggested in this document, we have that the abnormally high tracer accumulation in the heart with positron emission tomography by ^{18}F-FDG-PET/computed tomography, which was categorized in the "Guidelines for the diagnosis of cardiac involvement in patients with sarcoidosis", in 2006, was promoted to the higher criteria, as well as the late enhancement by gadolinium of the myocardium on CMR with gadolinium. In the current JCS guidelines, a clinical diagnosis of cardiac sarcoidosis is also made when the patient shows clinical findings strongly suggestive of cardiac involvement and pulmonary or ophthalmic sarcoidosis as well as at least two of the five characteristic laboratory findings of sarcoidosis. Finally, the definition of isolated cardiac sarcoidosis was proposed for the first time.

6.2.2. Treatment and prognosis

Immunosuppressive treatment of cardiac sarcoidosis is based on clinical experience and expert opinion given the lack of randomized trials. The goal of treatment is to reduce inflammatory activity and prevent fibrosis, and the approach should be guided by the magnitude of the inflammatory process and the degree of myocardial involvement.[248]

Immunosuppressive treatment is recommended in the following situations: left ventricular dysfunction, ventricular arrhythmias, hypermetabolic activity on ^{18}F-FDG PET, conduction disorders, late gadolinium enhancement on CMR, or right ventricular dysfunction in the absence of pulmonary hypertension.[248-250]

There are three lines of treatment for sarcoidosis – first line: corticosteroids; second line: methotrexate and azathioprine in cases of intolerance or chronic use of corticosteroids; and third line: anti-TNF antibodies (infliximab and andalimumab) in cases of failure of previous treatments.[251]

Corticosteroid is the drug of choice. In a systematic review of corticosteroid therapy for ventricular conduction disorders, 27 of 57 patients (47.4%) improved with treatment.[252] However, because responses are unpredictable, patients with conduction disorders and cardiac sarcoidosis should receive a pacemaker or implantable cardioverter-defibrillator.[119,253]

Older studies evaluating the effect of corticosteroids on ventricular function have suggested preservation of ventricular function in patients with normal function at diagnosis, improvement in ventricular ejection fraction in patients with mild-to-moderate dysfunction, and no improvement in patients with significant ventricular dysfunction.[119] However, a Finnish

Table 22 – Japanese Circulation Society recommendations for the diagnosis of cardiac sarcoidosis[247]

Critérios para envolvimento cardíaco
Cardiac findings should be assessed on the basis of major and minor criteria. Clinical findings satisfying the following 1) or 2) strongly suggest the presence of cardiac involvement.
1. Two or more of the five major criteria (a) to (e) are met.
2. One of the five major criteria (a) to (e) plus two or more of the three minor criteria (f) to (h) are met.
Major criteria
a. High-grade atrioventricular block (including complete atrioventricular block) or fatal ventricular arrhythmia (eg, sustained ventricular tachycardia and ventricular fibrillation)
b. Basal thinning of the ventricular septum or abnormal ventricular wall anatomy (ventricular aneurysm, thinning of the middle or upper ventricular septum, regional ventricular wall thickening)
c. Left ventricular contractile dysfunction (left ventricular ejection fraction less than 50%) or focal ventricular wall asynergy
d. ^{67}Ga citrate scintigraphy or ^{18}F-FDG PET reveals abnormally high tracer accumulation in the heart
e. Gadolinium-enhanced MRI reveals delayed contrast enhancement of the myocardium
Minor criteria
f. Abnormal ECG findings: ventricular arrhythmias (nonsustained ventricular tachycardia, multifocal or frequent premature ventricular contractions), axis deviation, or abnormal Q waves
g. Perfusion defects on myocardial perfusion scintigraphy
h. Endomyocardial biopsy: monocyte infiltration and moderate or severe myocardial interstitial fibrosis Diagnostic guidelines for cardiac sarcoidosis
Diagnostic guidelines for cardiac sarcoidosis
1. Histological diagnosis group (those with positive myocardial biopsy findings): cardiac sarcoidosis is diagnosed histologically when endomyocardial biopsy or surgical specimens demonstrate noncaseating epithelioid granulomas.
2. Clinical diagnosis group (those with negative myocardial biopsy findings or those not undergoing myocardial biopsy): the patient is clinically diagnosed as having cardiac sarcoidosis (1) when epithelioid granulomas are found in organs other than the heart, and clinical findings strongly suggestive of the previously mentioned cardiac involvement are present; or (2) when the patient shows clinical findings strongly suggestive of pulmonary or ophthalmic sarcoidosis; at least two of the five characteristic laboratory findings of sarcoidosis (bilateral hilar lymphadenopathy, high serum angiotensin-converting enzyme activity or elevated serum lysozyme levels, high serum soluble interleukin-2 receptor levels, significant tracer accumulation on 67Ga citrate scintigraphy or ^{18}F-FDG PET, a high percentage of lymphocytes with a CD4/CD8 ratio of >3.5 in bronchoalveolar lavage fluid). Clinical findings strongly suggest the previously mentioned cardiac involvement.
Diagnostic guidelines for isolated cardiac sarcoidosis
Prerequisites
1. No clinical characteristics of sarcoidosis are observed in any organs other than the heart (the patient should be examined in detail for respiratory, ophthalmic, and skin involvements of sarcoidosis. When the patient is symptomatic, other etiologies that can affect the corresponding organs must be ruled out.
2. ^{67}Ga scintigraphy or ^{18}F-FDG PET reveals no abnormal tracer accumulation in any organs other than the heart.
3. Chest CT reveals no shadow along the lymphatic tracts in the lungs or no hilar and mediastinal lymphadenopathy (minor axis >10 mm).
Histological diagnosis group
1. Isolated cardiac sarcoidosis is diagnosed histologically when endomyocardial biopsy or surgical specimens demonstrate noncaseating epithelioid granulomas.
Grupo de diagnóstico clínico
1. Isolated cardiac sarcoidosis is diagnosed clinically when the criterion (d) and at least three other criteria of the major criteria (a) to (e) are satisfied. When the patient meets at least four criteria for cardiac involvement other than the criterion (d), or when the patient meets the criteria (b) and (d) plus one of the remaining criteria, the patient should be suspected to have isolated cardiac sarcoidosis.

^{18}F-FDG PET: ^{18}F-fluorodeoxyglucose positron emission tomography; CT: computed tomography; ECG: electrocardiogram.
Adapted from Terasaki et al.[47]

study suggested an improvement in left ventricular function with immunosuppressive treatment in patients with severely compromised ventricular function (LVEF <35%), but no changes were observed in those with normal or moderately decreased function at the start of treatment. Perhaps such differences are associated with early diagnosis and treatment.[254]

Studies on ventricular arrhythmia are more limited; however, the cause of arrhythmia appears to be secondary to scarring, and perhaps the corticosteroid effect on these patients is of little benefit.[255] Catheter ablation in ventricular tachycardia may be considered after implantable cardioverter-defibrillator insertion or antiarrhythmic drug failure.[256]

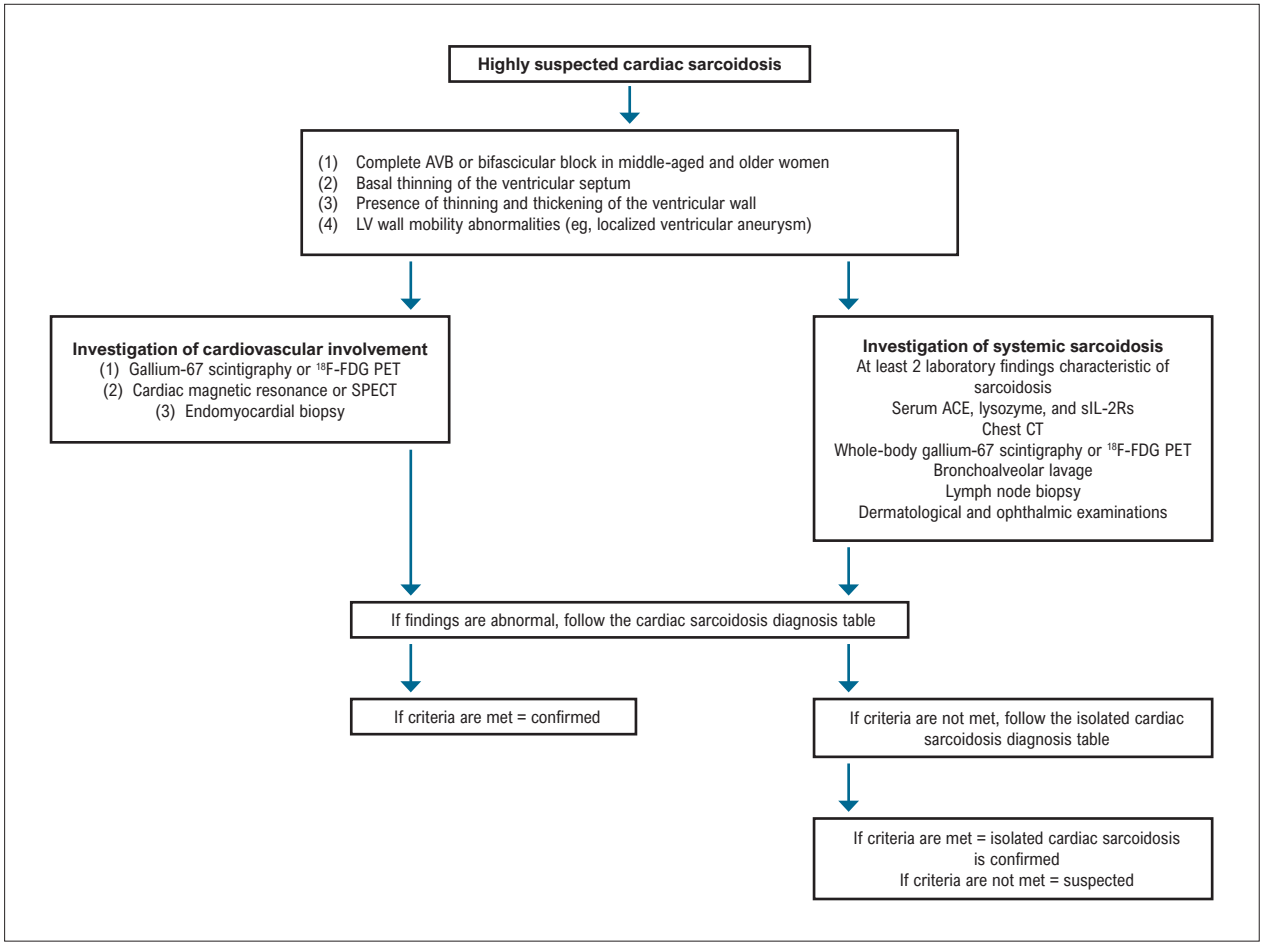

Figure 9 – *Diagnostic flowchart for cardiac sarcoidosis in patients who present with cardiac manifestations and are strongly suspected to have cardiac sarcoidosis.*
AVB: atrioventricular block; CT: computed tomography; LV: left ventricular; PET: positron emission tomography; SPECT: single-photon emission computed tomography; 18F-FDG PET: 18F-fluorodeoxyglucose positron emission tomography. Adapted from Terasaki et al.[247]

The suggested treatment algorithm (Figure 10) consists of an initial prednisone regimen (30 mg/day to 40 mg/day) followed by a repeat PET scan within 4 to 6 months to assess disease activity and guide subsequent pharmacological treatment.

Yokoyama et al.[257] compared 18F-FDG PET/CT scans before and after corticosteroid therapy in 18 patients with cardiac sarcoidosis and observed that maximum standardized uptake value decreased significantly from baseline. A recent study used 18F-FDG PET/CT for the diagnosis and treatment of cardiac sarcoidosis with low corticosteroid doses and good disease control within 1 year of diagnosis.[258]

Immunosuppressive drugs other than corticosteroids are needed because of the long duration of treatment. They are indicated for patients who require a maintenance prednisone dose >10 mg/day and who cannot tolerate corticosteroid side effects.[248,250]

The following drugs are suggested: methotrexate,[257] azathioprine,[258] cyclophosphamide,[259] and tumor necrosis factor inhibitors.[260,261] The choice of drug will be determined by the type of extracardiac involvement; methotrexate, for example, should be avoided in patients with liver involvement, and studies of pulmonary, cutaneous, ocular, neurological, and multisystem sarcoidosis have suggested good efficacy for infliximab (Table 23).[262]

6.2.3. Prognosis

Cardiac sarcoidosis has a worse prognosis compared to dilated cardiomyopathy. Once the heart is affected, the prognosis is unfavorable. Cardiac involvement accounts for 85% of deaths from the disease.[183,243]

Kandolin et al.[256] reported the long-term effects of immunosuppressive treatment in a Finnish cohort, and 1-year, 5-year, and 10-year transplant-free survival rates were 97%, 90%, and 83%, respectively, during the 6.6-year follow-up period. In that study, presence of HF and cardiac function before corticosteroid therapy were the most important factors for estimated prognosis, which shows that early treatment is key.

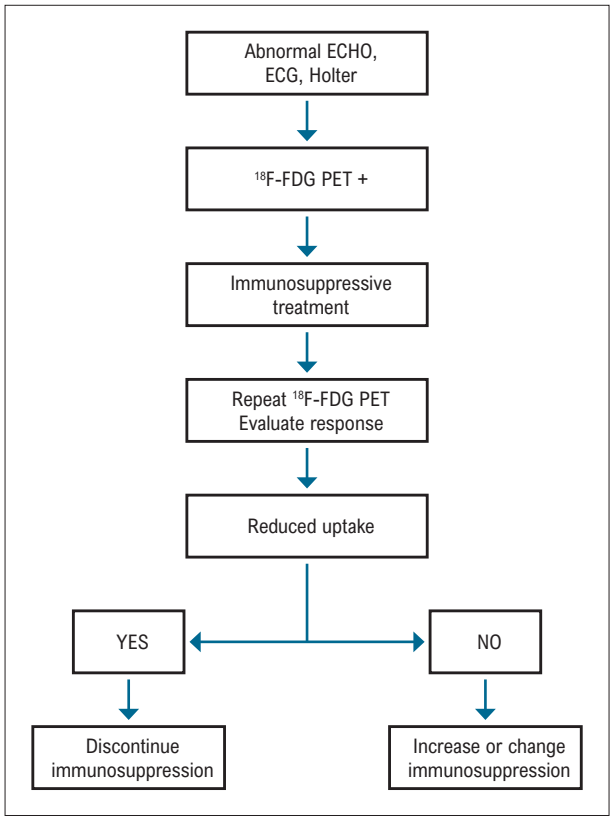

Figura 10 – *Sarcoidosis treatment algorithm*
ECG: electrocardiogram; ECHO: echocardiogram; ^{18}F-FDG PET: ^{18}F-fluorodeoxyglucose positron emission tomography. PET: positron emission tomography.

The presence of late gadolinium enhancement on CMR increased the risk of death, aborted sudden death, or cardioverter-defibrillator implantation by 30 times during a 2.6-year follow-up period,[262] and this finding was subsequently confirmed by meta-analyses. It has been suggested that the 20% fibrotic mass threshold is associated with risk of events.[263]

A study using PET imaging observed that 26% of reported adverse events, such as ventricular tachycardia and death, were cases of cardiac uptake on PET during a 1.5-year follow-up period. Conversely, extracardiac uptake was not associated with adverse events at follow-up.[264]

Another interesting finding is that patients with isolated cardiac sarcoidosis have a worse prognosis compared to patients with systemic sarcoidosis with cardiac involvement.[265] A Finnish study observed a high frequency of ventricular dysfunction and septal abnormalities on echocardiography and a high prevalence of late gadolinium enhancement on CMR, in addition to more significant associations with female sex and more severe left ventricular dysfunction. [266] In that study, HF at presentation, severe left ventricular dysfunction (<35%), and isolated cardiac sarcoidosis were also related to prognosis.[254]

Echocardiography with strain imaging (global longitudinal strain <17.3) was an independent predictor of mortality, HF, hospitalization, new arrhythmias, and development of cardiac sarcoidosis.[267]

Serum biomarkers such as BNP were related to the development of HF, whereas troponin was associated with the development of fatal arrhythmias,[268] lower ejection fraction, and poor prognosis.[269]

6.3. Giant cell myocarditis

6.3.1. Treatment

According to an international registry, giant cell myocarditis is the etiology of 12% cases of fulminant myocarditis and 3.6% of cases of nonfulminant myocarditis.[242] Treatment goals are limited because the mechanisms of giant cell myocarditis are not properly known, although an autoimmune mechanism involving myocardial inflammation mediated by T lymphocytes has been proposed.[270,271]

Giant cell myocarditis has a worse prognosis than eosinophilic and lymphocytic myocarditis, and is more frequently associated with HF, cardiac arrest, fibrillation and ventricular tachycardia, heart blocks, or simulated acute MI.[242,272] Without treatment, the course is usually fatal, with death within 5.5 months.[271] Even with treatment, giant cell myocarditis has a high mortality or requires early indication for mechanical circulatory support and/or heart transplantation.

Recently, a 5-year transplant-free survival of 42% has been reported. As important prognostic markers of early death or need for mechanical support or heart transplantation, troponin levels and moderate-to-severe necrosis or fibrosis on EMB have been described. Elevated BNP/NT-proBNP levels and significant LVEF reduction are additional prognostic markers.[191] Poor prognosis may be associated with myocardial injury or

Table 23 – Recommendations for immunosuppressive therapy in sarcoidosis

Indication	Class	Level of evidence
Prednisone 30 to 40 mg/day for 4 to 6 months	IIa	B
Additional immunosuppressants in case of corticosteroid therapy:		
Azathioprine 50 to 200 mg/day	IIb	C
Methotrexate 10 to 20 mg/week	IIb	C
Infliximab in pulmonary, cutaneous, ocular, neurological, and multisystem sarcoidosis	IIb	C
Leflunomide 10 to 20 mg/day	IIb	C

recurrent giant cell myocarditis.[273] After heart transplantation, recurrence has also been described.

Early diagnosis is critical and dependent on EMB results, or histological analysis of a heart explanted during heart transplantation, or myocardial specimens collected during ventricular assist device implantation.[270,274,275] Biopsy sensitivity might be limited by sampling error. Specimens are preferably collected from the apical portion of the RV septum because the risk of complications is lower. A negative biopsy does not necessarily exclude the diagnosis of giant cell myocarditis. EMB sensitivity has increased from 68% to 93% after repeating the procedure (Table 25).

The treatment of giant cell myocarditis is divided into the treatment of HF with reduced LVEF caused by myocardial injury or recurrent giant cell myocarditis, arrhythmias, and blocks, and the treatment of the probable mechanism with immunosuppressants.

The treatment of HF, hemodynamic disorders, blocks, and arrhythmias is consistent with the treatment of HF according to the SBC guidelines, including drugs and/or inotropes, pacemakers/defibrillators and/or mechanical circulatory support, and heart transplantation.[242] Heart transplantation might be indicated earlier because of the poor prognosis of giant cell myocarditis, even with immunosuppressants. Implantable cardioverter-defibrillator might be indicated for primary prevention of sudden or secondary death based on the high incidence of complex and severe arrhythmias.[276] It has been described that 59% of patients with giant cell myocarditis had sustained ventricular tachycardia or shocks for complex ventricular arrhythmias despite of being free from severe HF.

The indication for immunosuppressants is based on the results of case series or small randomized studies. Immunosuppressive drugs such as prednisone, cyclosporine, azathioprine, mycophenolate mofetil, everolimus, sirolimus or rabbit antithymocyte globulin, antithymocyte globulin or muromonab-CD3 have been used for cytolysis of T lymphocytes. After initial diagnosis, high-dose corticosteroids and/or rabbit antithymocyte globulin, antithymocyte globulin or muromonab-CD3 are generally used, and combination with long-term immunosuppressants is possible. Hemadsorption has also been reported (Table 26).[277]

Maintenance immunosuppression consists of a cyclosporine-based double or triple regimen.[270,278] However, there are important limitations to assessing the actual benefit. Combinations of prednisone, cyclosporine, azathioprine, and mycophenolate mofetil have been used, as well as use either alone or in combination with rabbit antithymocyte globulin or muromonab-CD3. Triple-drug immunosuppression has been shown to increase the chance of surviving and being transplant-free to 58% at 5 years.[191] However, immunosuppression must be maintained because of the possibility of recurrence. Combined immunosuppression (prednisone, cyclosporine, and azathioprine) appears to be more accepted, although other combinations have also been used, such as cyclosporine with rabbit antithymocyte globulin or rabbit antithymocyte globulin with high-dose corticosteroids. There are no comparative studies to confirm the best immunosuppression.[191,274] Cyclosporine combined with high-dose corticosteroids or muromonab-CD3 for 4 weeks decreases the degree of necrosis, cellular inflammation, and giant cells.[279]

Heart transplantation is indicated and has resulted in improved medium-term survival, but recurrence is 20% to 25%.[8,280] This is the treatment of choice despite a higher risk of rejection.[281]

6.3.2. Clinical manifestation and diagnosis

Giant cell myocarditis is recognized as a rapid and progressive disease, most often fatal unless heart transplantation is performed. Most cases are associated with an autoimmune process.

Table 24 – Indication for implantable cardioverter-defibrillator in sarcoidosis

Indications	Class	Level of evidence
Ventricular tachycardia/aborted cardiac death	I	C
LVEF <35% despite optimal treatment and period of immunosuppression and active inflammation	I	C
Unexplained syncope probably due to arrhythmia	IIa	C
Ejection fraction 35% to 49% and/or RVEF <40% despite optimal immunosuppressive treatment and MRI or PET evidence of extensive myocardial scarring	IIa	C
Ejection fraction 35% to 49% and/or RVEF <40% despite optimal immunosuppressive treatment	IIb	C

LVEF: left ventricular ejection fraction; MRI: magnetic resonance imaging; PET: positron emission tomography; RVEF: right ventricular ejection fraction.

Table 25 – Endomyocardial biopsy (EMB) recommendations in the diagnostic evaluation of giant cell myocarditis

Indications	Class	Level of evidence
EMB or analysis of a heart explanted during heart transplantation, or myocardial specimens collected during mechanical assist device implantation in patients with acute heart failure with severe or fulminant hemodynamic compromise	I	B
Suspected diagnosis of myocarditis associated with cardiac arrest, or ventricular fibrillation or tachycardia, or blocks, or simulated acute myocardial infarction	I	B

Giant Cell Myocarditis Study Group data showed that young, white adults were predominantly affected, with no sex difference. The most common manifestation was acute HF (75% of cases), but half of the patients developed complex ventricular arrhythmia in the course of the disease. Median heart transplant-free survival was 5.5 months.[8]

A more recent report on giant cell myocarditis showed a higher incidence in young adult women, and the main clinical manifestations were acute HF, AV block, and ventricular arrhythmias.[274]

Imaging studies do not show any specific changes in giant cell myocarditis. The diagnosis is based on characteristic findings on EMB, ie, a diffuse and mixed inflammatory infiltrate consisting predominantly of macrophages, followed in number by lymphocytes and typically dispersed multinucleated giant cells derived from macrophages, and, finally, by a lower proportion of eosinophils and plasma cells.[282]

6.4. Acute Chagasic myocarditis and reactivation

6.4.1. Clinical manifestations and modes of transmission, reactivation in immunosuppressed patients

In recent years, there has been an increasing number of cases of acute Chagas disease associated with both oral or vector-borne transmission and disease reactivation in Latin American countries. The main routes of acute Chagas disease transmission currently are oral (68.4%), vector-borne (5.9%), vertical (0.5%), transfusion (0.4%), accidental (0.1%), and unknown (24.7%), as described in a study of confirmed cases in the Brazilian Amazon.[19]

Vector-borne transmission occurs during or shortly after hematophagy, when triatomine bugs defecate and deposit their contaminated feces causing the infective forms of *Trypanosoma cruzi* to reach the skin, mucous membranes, and then the bloodstream. The incubation period ranges from 4 to 15 days. Oral transmission is associated with consumption of food or beverages contaminated with parasites. Currently, it is the most common cause of acute disease, causing outbreaks in endemic and nonendemic regions. The incubation period ranges from 3 to 22 days.[283]

Patients with acute Chagas disease may present with nonspecific signs and symptoms of infectious syndrome, such as fever, myalgias, facial edema, and arthralgias, in addition to signs related to the portal of entry such as a chagoma and Romaña sign in the vector-borne form and digestive bleeding in the oral form. [284]

Acute cases may or may not present with myocarditis and pericarditis. Autopsy reports have shown acute inflammation of the epicardium and myocardium with intense and diffuse inflammatory activity and extensive dissociation of cardiac fibers, with the amastigote forms of the parasite being observed.[285] Signs and symptoms compatible with HF have ranged from 26% to 58%. Severe cases with cardiac tamponade and cardiogenic shock from LV systolic dysfunction may occur. The lethality of oral transmission has ranged from 2% to 5% in the largest series. Abnormal findings on additional testing have ranged from 33% to 70% for ECG changes (right bundle branch block, first-degree AV block, acute atrial fibrillation, anterosuperior divisional block) and from 13% to 52% for echocardiographic changes. Pericardial effusion is the most frequent abnormality (10% to 82%), and segmental contraction changes, common in the chronic phase, are rarely found in the acute phase. Despite the occurrence of severe cardiac involvement, most patients show preserved systolic function with few cases of reduced EF. Most deaths are caused by significant pericardial effusion and cardiac tamponade.[286,287]

6.4.2. Diagnosis

Direct parasitology testing is the most indicated method for diagnosing acute myocarditis.[288] Indirect methods, such as blood culture and xenodiagnosis, have low sensitivity and thus are not suitable for the acute phase. Serology testing is not the best diagnostic method in the acute phase but may be performed when direct parasitology testing is persistently negative and clinical suspicion persists.

Wet mount examination to detect the parasite in the circulating blood is quick and simple, in addition to being more sensitive than stained smear examination. Ideal conditions for collection are the patient still being febrile and symptom onset having occurred within 1 month. Concentration methods (Strout, microhematocrit, buffy coat) are recommended when wet mount examination is negative, as they are more sensitive. They are also used when the acute course initiated over 1 month ago. Negative results in the first analysis should not be considered definitive, especially if symptoms persist, unless another etiology is proven.

PCR testing, being a molecular diagnostic technology, has become an important method to show recent infection,

Table 26 – Therapeutic recommendations in giant cell myocarditis

Indications	Class	Level of evidence
High-dose corticosteroid in combination with antilymphocyte antibodies and/or calcineurin inhibitors (cyclosporine or tacrolimus) and/or antiproliferative drugs (azathioprine or mycophenolate mofetil)	I	B
Maintenance immunosuppression with a corticosteroid and a calcineurin inhibitor (cyclosporine or tacrolimus) or a triple-drug regimen with addition of an antiproliferative drug (azathioprine or mycophenolate mofetil)	I	B
Heart transplantation	I	B
Indication for implantable cardioverter-defibrillator for primary or secondary prevention of complex ventricular arrhythmias	I	B

as it yields positive results days to weeks before circulating trypomastigotes are detected.[289-291] Peripheral blood and tissue collected on EMB can be used to detect early reactivation after heart transplantation, before the onset of clinical symptoms or graft dysfunction.[292]

Chagas disease reactivation in the post-heart transplant period ranges from 19.6% to 45%.[293] The condition may present as acute myocarditis with various degrees of HF, often accompanied by systemic manifestations. Erythema and subcutaneous nodules may appear on the skin and should be biopsied to identify amastigote nests. Monitoring should be routine, even if reactivation is not suspected. When there are no extracardiac clinical signs, biopsy should be performed.

6.4.3. Treatment

Trypanosomicidal drug treatment is indicated for patients with acute Chagas disease with or without manifestations of myocarditis and for those with chronic disease reactivation due to immunosuppression (transplanted patients) (Table 27).[294]

Benznidazole is the currently available drug for the treatment of *T. cruzi* infection.[295] Information, however, is based on nonrandomized studies with insufficient number of patients and follow-up duration. Although the definition of cure criteria remains controversial, there is a current consensus that benznidazole treatment should be performed in the acute phase and provides a likely long-term benefit.[296]

Benznidazole dose range in children is 5 to 10 mg/kg per day in two divided doses for 60 days. The adult dose is 5 mg/kg. Adverse reactions manifest in approximately 30% of patients, most frequently allergic dermatitis (30%) and peripheral sensory neuropathy (10%).

6.5. Myocarditis due to tropical diseases

Tropical diseases are infectious entities generally transmitted by vectors in tropical regions. Governments tend to ignore this issue and provide limited resources to control these diseases, which affects vulnerable populations in areas with inadequate sanitation and deficient health systems. The Brazilian Amazon is an endemic region for tropical diseases, although other regions of the country are also affected. Many tropical diseases may cause myocarditis and appear to contribute to the increased burden of heart disease in developing countries.[297] The tropical diseases that cause myocarditis and are prevalent in Brazil are malaria, dengue, chikungunya, Zika, and yellow fever (Table 28). These diseases should be considered in the investigation of myocarditis occurring in endemic areas.

Malaria is caused by the protozoans of the genus *Plasmodium* (in Brazil, the species *P. vivax* and *P. falciparum*), transmitted through the bites of *Anopheles* mosquitoes. Malaria is endemic in the Amazon region, where over 155,000 cases were diagnosed in 2019. *P. falciparum* causes the most severe forms of the disease and has been more significantly associated with the development of myocarditis.[298] Autopsy studies of severe cases of malaria show a large number of parasites in the myocardium and inflammation compatible with myocarditis. Most studies reporting on malarial myocarditis consist of inpatient case series assessed with ECG, myocardial injury markers, and echocardiogram.[299] These case series include severe cases and show changes in cardiac injury markers in up to 59% and echocardiographic changes such as reduced systolic function in up to 19% of patients. Many studies associating malaria with acute MI fail to properly define the evaluated outcome, with probable cases of myocarditis being described as infarctions. In acute malaria progressing to the severe form of the disease, myocardial dysfunction due to malarial myocarditis should be considered. Assessment with biomarkers of myocardial injury and ventricular function should be considered to optimize cardiovascular management.

Arboviruses cause infectious diseases such as dengue, Zika, chikungunya, and yellow fever. They are transmitted through the bites of *Aedes aegypti* mosquitoes. Cardiovascular involvement has been demonstrated especially in dengue, which is the most prevalent arboviral infection in Brazil. Dengue is also the disease with the highest rate of reported cardiovascular manifestations -- prospective studies have shown that 48% of patients with the severe form develop myocarditis. An autopsy study of four fatal cases of dengue revealed findings of myocarditis with edema, hemorrhage, mononuclear infiltrates, and presence of antigens and viral replication.[300]

Of all the previously mentioned arboviral diseases, chikungunya is the most symptomatic (80% of cases); however, it normally presents with mild symptoms and mostly affects joints and muscles. Still, the infection may manifest systemically and cause widespread damage or affect specific organs such as the heart. A case report of a patient with chikungunya who developed chest pain showed typical findings of myocarditis on MRI.[301] Several case series in epidemic settings have reported up to 37% of cardiovascular involvement, generally compatible with myocarditis.[302]

Of all the tropical infections discussed herein, Zika is the most recently discovered and has the highest percentage of asymptomatic cases; when there are clinical manifestations, these are predominantly congenital and involve the neurological system. Nonetheless, a few longitudinal studies have addressed nonneurological complications of this infection in adults and reported cardiovascular outcomes such as HF, arrhythmias, and acute MI, as well as Zika-associated myocarditis.[303,304] Also, prospective studies of congenital Zika have reported echocardiographic changes suggestive of cardiovascular damage. These findings, however, possibly do

Table 27 – Recommendations for the etiological treatment of acute Chagasic myocarditis

Indications	Class	Level of evidence
Acute infection, irrespective of mechanism of transmission	I	C
Reactivation of chronic *T. cruzi* infection	I	C

Table 28 – Characteristics of the main causes of tropical myocarditis

	Agent	Vector	Clinical manifestations
Malaria	*Plasmodium spp* (protozoan)	*Anopheles* mosquito	**Mild form:** fever, chills, headache, myalgias, and malaise **Severe form:** shock, seizures, mental confusion, renal failure, acute respiratory distress syndrome, coma, and death – There may be asymptomatic patients, especially in endemic regions
Dengue	Dengue virus	*Aedes aegypti* mosquito	**Mild form:** fever, headache, myalgia, arthralgia, retro-orbital pain and maculopapular rash, nausea, vomiting **Severe form (with warning signs):** severe abdominal pain, persistent vomiting (≥3 times/24 h), epistaxis, gingival bleeding, fatigue, restlessness or irritation, hematemesis or melena, altered mental status – Approximately 50% of patients have symptoms
Chikungunya	Chikungunya virus	*Aedes aegypti* mosquito	**Mild form:** fever, rash, arthralgia, myalgia, edema, and headache **Severe form:** severe neurological disease, myocarditis, and multiple organ failure **Chronic form:** persistent arthralgia and myalgia with associated edema, mostly in the wrists, hands, ankles, and feet. It might last for months or even years and result in disability – Approximately 80% of patients are symptomatic
Zika	Zika virus	*Aedes aegypti* mosquito	**Mild form:** fever (usually mild), rash, arthralgia, arthritis, myalgia, headache, conjunctivitis, and edema **Severe form:** need for hospitalization is uncommon and deaths are rare **Congenital form:** anomalies of the eye, heart, and brain such as microcephaly (most common) – Only about 20% of patients have symptoms
Yellow fever	Yellow fever virus	*Haemagogus* (wild) and *Aedes aegypti* (urban) mosquitoes	**Mild form:** sudden-onset fever, chills, headache, myalgia, weakness, fatigue, nausea, and eye redness **Severe form (toxic phase):** high fever, jaundice, epigastralgia, bleeding, hemorrhagic diathesis (hematemesis), shock, and organ failure – Approximately 50% of patients are symptomatic

not represent the actual impact of Zika on heart disease, as there is a lack of longitudinal studies.

Yellow fever is a neglected tropical arboviral disease that was restricted to the sylvatic cycle for a long time, with low incidence (underreporting) and limited geographic expansion, which contributed to few cases being studied and adequately reported, especially those involving the cardiovascular system. Still, with the increasing urbanization of this disease and the better understanding of its pathophysiological mechanisms, some studies have demonstrated a relationship with the heart. The PROVAR+ study, for example, reported, respectively, 48% and 52% of echocardiographic and electrocardiographic changes.[305] Also, postmortem studies have isolated the virus in cardiac tissue or demonstrated myocardial damage.

Therefore, although the association between tropical diseases and myocarditis is based on case series and few studies with a well-defined diagnosis of myocarditis, the diagnostic investigation of common regional diseases is warranted in cases of myocarditis in endemic areas. To this end, antigen screening or serology testing for arboviral infections and thick blood smear examination for malaria should be included. Once these diseases are diagnosed, an infectious disease specialist should be consulted to guide the specific treatment of malaria or supportive treatment of arboviral diseases. Another clinical situation consists of patients with confirmed arboviral infection or malaria which progresses to a severe form, especially shock; in these cases, cardiac injury should be evaluated with markers of myocardial necrosis and myocardial function, and echocardiography should be used for the diagnosis of myocardial involvement (myocarditis). Management should include optimization of myocardial function.

6.6. Covid-19-related myocarditis

Human coronaviruses have been linked to myocarditis.[306-308] During the Toronto severe acute respiratory syndrome (SARS) outbreak, SARS-CoV RNA was detected in 35% of autopsied hearts.[309] This increases the possibility of direct viral damage to cardiomyocytes[310-312] (Table 29).[313]

6.6.1. Possible pathophysiology of SARS-CoV-2-related myocarditis

The mechanisms of myocardial injury are not well established but probably involve the following: myocardial injury secondary to oxygen supply-demand mismatch; microvascular injury; systemic inflammatory response; stress cardiomyopathy; acute nonobstructive coronary syndrome; and direct viral myocardial injury[314] (Figure 11).[315]

6.6.2. Direct viral myocardial injury

Case reports of myocarditis in patients with Covid-19 provide evidence of cardiac inflammation but do not determine the mechanism. SARS-CoV-2 infection is caused by the binding of viral surface spike protein to the

Table 29 – Representative studies addressing the acute cardiovascular manifestations of coronavirus infection and their clinical implications[311-313]

Virus	Sample size	Cardiovascular manifestations	Outcomes
SARS	N=121	Hypotension, tachycardia, bradycardia, cardiomegaly, and arrhythmia	Mostly transient
	N=15	Cardiac arrest	Death
	N=46	Subclinical diastolic impairment without systolic involvement on echocardiography	Reversible on clinical recovery
MERS	N=1	Acute myocarditis and acute-onset heart failure	Recovered
Covid-19	N=14	Myocardial injury (manifesting with increased high-sensitivity cardiac troponin I) in five patients	Four patients required intensive care
	N=138	Acute cardiac injury (7.2%), shock (8.7%), and arrhythmia (16.7%)	Most patients required intensive care

Source: Adapted from Xiong et al.[313]

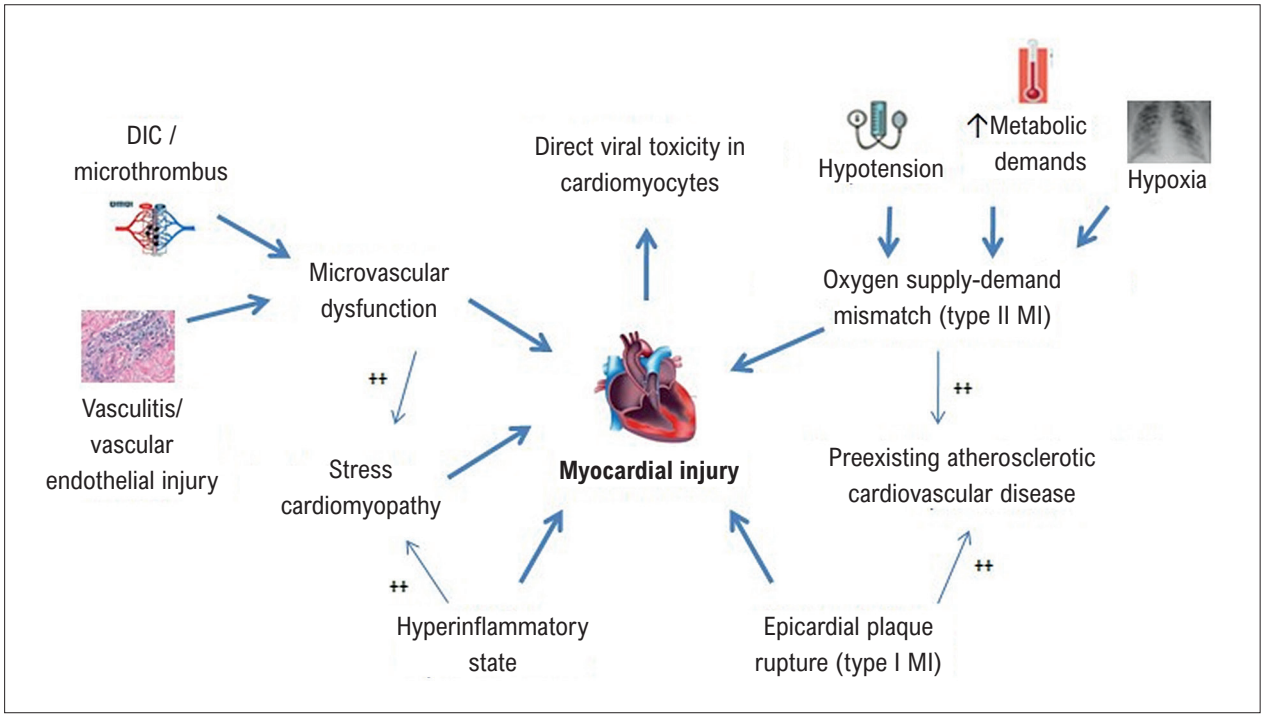

Figure 11 – *Potential mechanisms of myocardial injury in Covid-19.*
MI: myocardial infarction; DIC: disseminated intravascular coagulation. Source: Adapted from Atri D et al.[315]

human angiotensin-converting enzyme 2 (ACE2) receptor. However, the spike protein must first be cleaved at the S1/S2 sites and subsequently at the S2′ sites to enable binding to ACE2. Cleavage at the S1/S2 site appears to be mediated by transmembrane serine protease 2 (TMPRSS2)[316,317] (Figure 12).[318]

To date, there is only one report of biopsy-proven SARS-CoV-2 myocarditis with viral inclusions or viral DNA detected in myocardial tissue.[319] However, viral particles were not present in cardiomyocytes, only within macrophages in the cardiac interstitium. Another hypothetical mechanism of direct viral myocardial injury is through infection-mediated vasculitis. The ACE2 receptor is highly expressed in endothelial arteries and veins.[320]

ACE2 expression is limited in cardiomyocytes but high in pericytes. Covid-19 might attack pericytes, essential for endothelial stability, causing endothelial dysfunction, which leads to microcirculatory disturbances. This explains why, although ACE2 expression is limited in cardiomyocytes, Covid-19 might cause cardiac injury.[320] Autopsies have shown inflammatory infiltrates consisting of macrophages and, to a lesser extent, CD4+ T cells.[321-322] These mononuclear infiltrates are associated with regional necrosis of cardiomyocytes which, according to the Dallas criteria, defines myocarditis.[323]

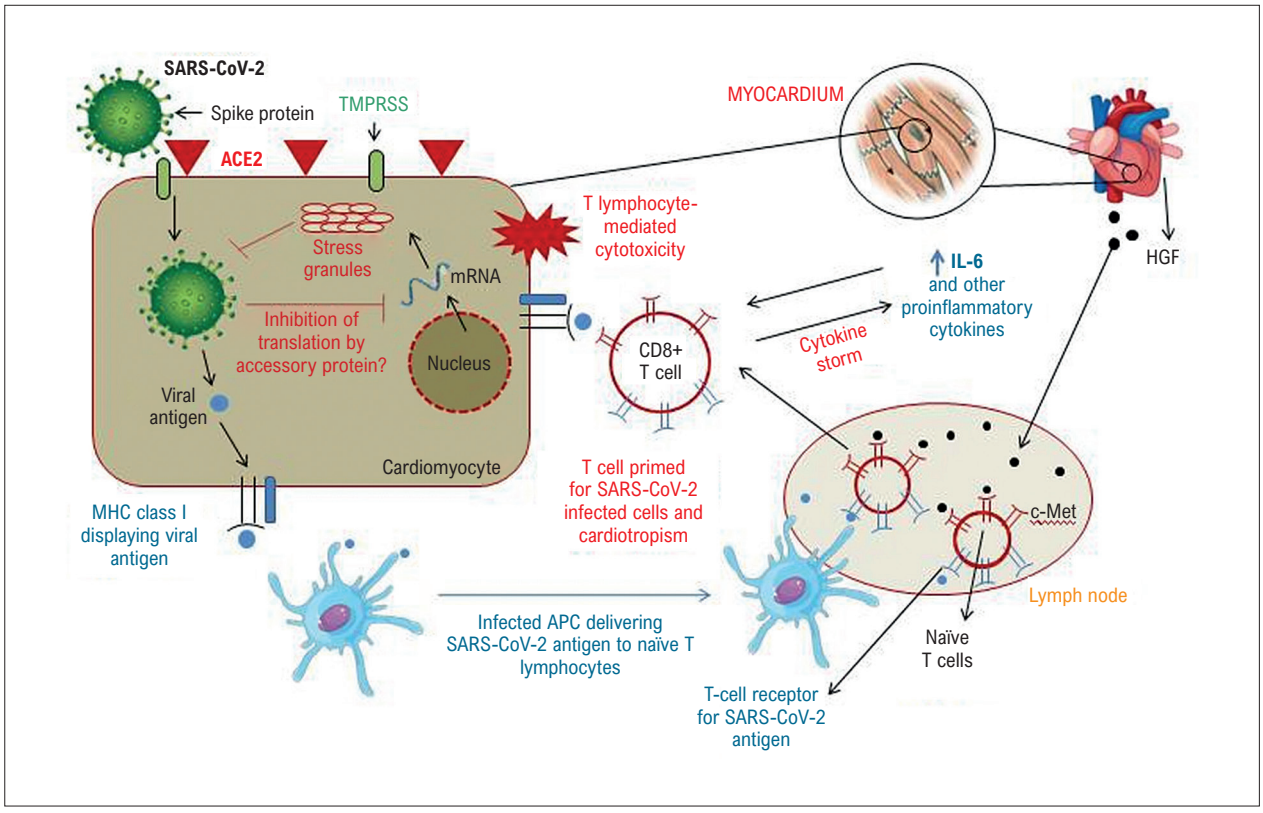

Figure 12 – *Proposed pathophysiology of SARS-CoV-2 myocarditis. SARS-CoV-2 uses the spike protein (primed by TMPRSS2) to bind ACE2 to allow cell entry. Intracellular SARS-CoV-2 might impair stress granule formation via its accessory protein. Without the stress granules, the virus is allowed to replicate and damage the cell. Naïve T lymphocytes can be primed for viral antigens via antigen-presenting cells and cardiotropism by the heart-produced HGF. The HGF binds c-Met, an HGF receptor on T lymphocytes. The primed CD8+ T lymphocytes migrate to the cardiomyocytes and cause myocardial inflammation through cell-mediated cytotoxicity. In the cytokine storm syndrome, in which proinflammatory cytokines are released into the circulation, T-lymphocyte activation is increased and releases more cytokines. This results in a positive feedback loop of immune activation and myocardial damage. ACE2: angiotensin-converting enzyme 2; APC: antigen-presenting cell; HGF: hepatocyte growth factor; IL-6: interleukin 6; MHC: major histocompatibility complex; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.*
Source: Adapted from Siripanthong B et al.[318]

6.6.3. Diagnosis of Covid-19-related myocarditis

The clinical presentation of SARS-CoV-2 myocarditis ranges from mild symptoms such as fatigue, dyspnea, and chest pain to severe cases of cardiogenic shock. Patients may present with signs of right HF, with increased jugular venous pressure, peripheral edema, and right upper quadrant pain. The most emerging presentation is fulminant myocarditis, defined as ventricular dysfunction and HF within 2 to 3 weeks of viral infection. Early signs of fulminant myocarditis frequently resemble those of sepsis.[14,324-329]

6.6.4. Laboratory

Troponin and NT-proBNP elevations have been observed in cases of Covid-19 myocarditis.[14,312,324-326]

Abnormal troponin levels are common in patients with Covid-19, especially when high-sensitivity cardiac troponin (hs-cTn) is used. Studies evaluating the clinical course of Covid-19 have reported detectable hs-cTnI in most patients, and hs-cTnI was significantly high in more than half of patients who died.[327,328]

Patients with Covid-19 generally demonstrate significantly elevated BNP or NT-proBNP. The significance of this finding is uncertain and should not necessarily trigger an evaluation or treatment for HF unless there is clear clinical evidence for diagnosis. In patients with Covid-19, increased BNP or NT-proBNP levels may also be secondary to myocardial stress as a possible effect of severe respiratory disease.

Because of the low frequency and nonspecific nature of abnormal troponin or natriuretic peptide levels in patients with Covid-19, measurements should only be performed if the clinical diagnosis of acute MI or HF is under consideration. Abnormal troponin or natriuretic peptide results should not be considered evidence of acute MI or HF without additional diagnostic evidence.[329]

6.6.5. Electrocardiogram

ECG changes commonly associated with pericarditis, such as ST-segment elevation and PR-segment depression, are seen in myocarditis;[310] however, these findings are not sensitive enough to detect the disease, and their absence does not exclude the diagnosis.

For example, a patient with Covid-19-related myocarditis has shown neither ST-segment elevation nor PR-segment depression.[330] Other ECG abnormalities, including new bundle branch block, prolonged QT interval, pseudoinfarction pattern, ventricular extrasystoles, and bradyarrhythmia with advanced AV block, might be seen in myocarditis.[331]

Recently, a case series of patients with confirmed Covid-19 who presented with, at some point in the infection, ST-segment elevation on ECG was published.[332]

6.6.6. Imaging

A recent ESC document lists the conditions that must be considered in a situation requiring the use of any cardiovascular imaging method in patients with Covid-19: imaging studies should only be performed if the management is likely to be changed by the results or if saving a patient's life is at stake; the best imaging modality to meet the demand should be used considering the safety of the medical team regarding exposure; nonurgent, elective, or routine examinations should be postponed or even canceled.[333]

Thus, transthoracic echocardiography, despite playing a key role in the cardiovascular work-up of these patients, should not be routinely indicated in view of the current Covid-19 pandemic, and specific cases require careful consideration.[334]

Recent Society of Cardiovascular Computed Tomography (SCCT) recommendations for the use of coronary CT angiography in patients with Covid-19 include acute HF of unknown cause[335,336] (Table 30).[337]

The ESC document suggests that positive troponins and myocardial dysfunction or severe arrhythmia not explained by other methods may be an indication for CMR if the diagnosis is crucial for the treatment and the patient is stable enough to be safely transferred and undergo the procedure.[334]

In this context, current Society for Cardiovascular of Magnetic Resonance (SCMR) guidance suggests that CMR examinations should be considered judiciously and individually in cases of suspected acute myocarditis with immediate implications for patient management.[337] If CMR is performed, the results should be interpreted according to the LLC: (1) edema; (2) irreversible cell injury; and (3) hyperemia or capillary leakage[338] (Table 31).[337]

6.6.7. Endomyocardial biopsy

The AHA and the ESC recommend EMB for the definitive diagnosis of myocarditis, but both societies recognize its limitations.[339,340] In the SARS-CoV-2 era, the clinical utility and the role of EMB, currently the gold standard for the diagnosis of myocarditis, remain uncertain; also, performing noninvasive imaging, such as echocardiography and CMR, with adequate safety and isolation measures has been challenging.[341,342]

Another point to consider is that, in some cases, SARS-CoV-2 infection may not initially manifest through clear signs and symptoms of interstitial pneumonia but instead as myocarditis without respiratory symptoms, sometimes complicated by cardiogenic shock with a fulminating course.[14,316]

Additionally, there is limited evidence regarding the therapeutic treatment of SARSCoV-2-associated myocarditis. A case report showed that early therapy with glucocorticoids and immunoglobulins was beneficial to the patient.[316] Corticosteroids have been used in several viral respiratory infections (influenza, SARS-CoV, and MERS-CoV) with reports of limited benefit and, in some cases, delayed viral clearance and increased mortality.[333]

However, the ESC Working Group on Myocardial and Pericardial Diseases recommends the use of steroids in myocarditis due to proven autoimmune diseases and virus-negative myocarditis only after active infection is assessed on EMB.[340] Clearly, EMB is not always available in real-world practice, and its role in SARS-CoV-2-related myocarditis remains unknown. Furthermore, in the absence of randomized

Table 30 – Society of Cardiovascular Computed Tomography (SCCT) recommendations for the use of coronary computed tomography angiography in the context of Covid-19

Urgency category	Clinical conditions	Timing for examination
Elective	Asymptomatic or stable coronary artery disease Cardiomyopathy or stable structural heart disease (valvular, TAVI or AF ablation planning, congenital) Benign masses	> 8 weeks
Semiurgent	Chronic AF cardioversion Chronic or subacute prosthetic valve dysfunction	Within 4 to 8 weeks
Urgent	High-risk acute or stable chest pain Urgent structural interventions (TAVI, left atrial appendage occlusion, etc.) or acute AF cardioversion Acute heart failure of unknown cause Acute valve (or prosthetic valve) dysfunction Malignant mass biopsy planning	Within hours to <2 to 4 weeks (depending on severity)

Rule out thrombi when CMR is not feasible.
AF: atrial fibrillation; TAVI: transcatheter aortic valve replacement. Source: Adapted from Araujo-Filho et al.[337]

Table 31 – Society for Cardiovascular of Magnetic Resonance (SCMR) recommendations for the use of cardiac magnetic resonance (CMR) imaging in the context of Covid-19

Clinical conditions	Suggested timing for examination
• Investigation of ischemia and myocardial viability to guide urgent revascularization	Within 1 week depending on severity
• Suspected intracardiac mass or thrombus with contraindication to anticoagulation or in patients with suspected embolic events	
• Urgent ablation planning in unstable patients with severe arrhythmias	
• Pericardial constriction requiring potentially urgent surgery	
• Planning for percutaneous implantation of a prosthetic heart valve requiring urgent surgery	

Note 1: Choices based on expert consensus.
Note 2: Individual clinical status and contraindications to examination must be considered.
Source: Araujo-Filho et al.[337]

multicenter trials, routine use of immunoglobulin is also not recommended.

In conclusion, there are significant gaps in the assessment of MI in patients with SARS-CoV-2 infection that require a thorough diagnostic evaluation, prioritized treatments, and more aggressive strategies,[318,319] if necessary, especially in those who develop cardiogenic shock during fulminating myocarditis[332-342] (Figure 13).[318]

6.7. Acute cardiotoxicity of antineoplastic therapy

6.7.1. Antineoplastic agents inducing acute cardiotoxicity

The evolution of cancer treatment in recent decades has resulted in improved survival and quality of life for patients.[343] Simultaneously, however, increased longevity has led to longer exposure to cardiovascular risk factors, in addition to the potential risk of cardiovascular injury induced by

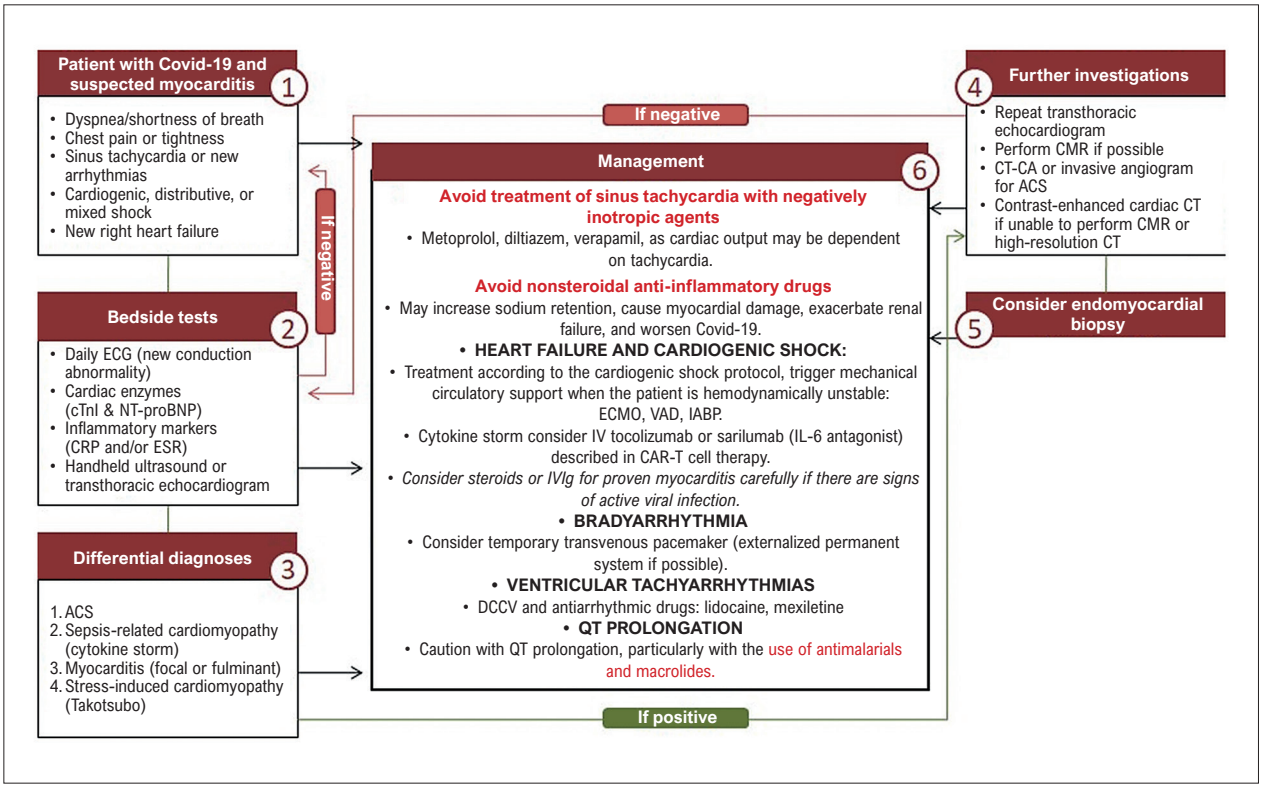

Figure 13 – *Suggested diagnostic and management protocol for SARS-CoV-2-related myocarditis.*
ACS: acute coronary syndrome; CMR: cardiovascular magnetic resonance; CRP: C-reactive protein; CT-CA: computed tomography-coronary angiogram; DCCV: direct current cardioversion; ECG: electrocardiogram; ECMO: extracorporeal membrane oxygenation; ESR: erythrocyte sedimentation rate; IABP: intra-aortic balloon pump; IVIg: intravenous immunoglobulin; QT: QT interval; VAD: ventricular assist device. Source: Adapted from Siripanthong et al.[318]

chemotherapy, radiotherapy, and immunotherapy.[344] Recent studies have demonstrated that there are two periods of increased occurrence of cardiovascular disease in patients with cancer: the first year after diagnosis and the years after cure, when patients are called survivors, a group that has shown significantly increased cardiovascular mortality.[345,346]

Myocarditis is an emerging toxicity of relevance. Recently, cancer treatment-related myocarditis has been noted as a result of the evolution of immunotherapy, more specifically immune checkpoint inhibitors (ICIs).[347,348] However, it is potentially associated with any therapy that modulates the immune system. Identifying myocarditis in oncology clinical trials is challenging given its relatively low incidence and high mortality rate.

Importantly, the following recommendations are based on expert consensus given the paucity of scientific data on this topic.

The classic model of cardiotoxicity consists of ventricular dysfunction caused by anthracyclines.[349] Anthracyclines are a class of chemotherapeutic drugs still widely used today. HF affects up to 30% of patients and usually appears months after treatment, being related to a cumulative dose above 300 mg/m^2. Most cases are subacute or chronic and manifest months and even years after treatment, with irreversibility being the predominant characteristic. Anthracycline-induced acute myocarditis is a rare manifestation that has no relationship with dose and is reversible in most cases.[350] The mechanism of toxic action is directly linked to the oxidative stress resulting from anthracycline metabolism, in addition to the inhibition of topoisomerase IIb, which ultimately leads to cardiomyocyte DNA damage through mitochondrial dysfunction and apoptosis.[351]

Cyclophosphamide is a nitrogen mustard that acts as an alkylating agent and is usually included in chemotherapy regimens involving the concomitant use of anthracyclines. It may result in acute toxic myocarditis with multifocal hemorrhage, characterized by endothelitis, hemorrhagic capillaritis, and thrombogenesis.[352]

ICIs currently are the most commonly studied model for inducing myocarditis, especially nivolumab, durvalimab, ipilimumab, pembrolizumab, and atezolizumab.[353] This therapy has revolutionized cancer treatment in recent years by improving the survival of patients with lung cancer, head and neck cancer, renal carcinoma, and melanoma, among others.[354] The mechanism of action consists of blocking the apoptosis of T lymphocytes (anti-CTLA4, anti-PD1, anti-PDL1), culminating in the activation of lymphocytes throughout the body. If this, on the one hand, reactivates the lymphocytes and antitumor immunity, on the other hand, activated T lymphocytes might trigger severe myocarditis, which is fatal in up to 50% of cases. Clinically, it affects 0.2% of patients and manifests, on average, 30 to 90 days after starting treatment.[355,356]

6.7.2. Diagnosis of acute cardiotoxicity

Myocarditis in patients with cancer should be diagnosed in situations of cardiac conditions without an alternative primary diagnosis (eg, acute coronary syndrome, trauma, etc.).[357] Clinical history should consider drug regimen, treatment duration, and other comorbidities. Laboratory diagnosis includes the measurement of biomarkers such as hs-cTn and NT-proBNP. In immunotherapy-related myocarditis, CPK measurement is also recommended because of an association with myositis in up to 20% of cases.[358]

An ECG may be useful for confirming suspected myocarditis. Possible findings are ventricular arrhythmias, ST-T wave abnormalities, PR-segment changes, bradycardias, and blocks.[357]

Echocardiography is the imaging test of choice for a diagnostic approach to myocarditis. It is performed at baseline and during follow-up to assess function over time. The most common findings include diffuse systolic dysfunction, segmental abnormalities, changes in ventricular sphericity, increased wall thickness, pericardial effusion, and strain changes.[357]

MRI is the most sensitive imaging modality for the diagnosis of myocarditis and can determine the prognosis. A combination of MRI findings has been termed the Lake Louise criteria (LLC) for the diagnosis of acute myocarditis. Many advances have occurred in the diagnosis of myocarditis via MRI, including improved tissue characterization using T1 and T2 mapping and extracellular calcium.[359]

EMB may be considered for investigation of chemotherapy- and immunotherapy-related myocarditis. Experts recommend performing a biopsy whenever possible because in many cases, before significant clinical manifestations, pathologic findings already show the severity of the pathogenic changes of cancer myocarditis.[360]

We describe below the main antineoplastic agents that potentially induce myocarditis and their manifestations (Table 32).

Table 32 – Characteristics of cancer treatment-induced myocarditis

	Anthracyclines	Cyclophosphamide	Immune checkpoint inhibitors
Incidence	10%	10%	0.2%
Mortality	20%	20%	50%
Clinical manifestation	Acute HF	Acute HF	Acute HF
Diagnosis	Clinical, laboratory, imaging, and biopsy	Clinical, laboratory, imaging, and biopsy	Clinical, laboratory, imaging, and biopsy
Reversibility	Usually reversible	Usually reversible	Usually irreversible
Reexposure	Possible	Possible	Not recommended

HF: heart failure.

6.7.3. Treatment of acute cardiotoxicity

When a diagnosis is suspected, treatment should be started immediately, as timing is an important factor to determine the course of the disease. Although there are no large prospective studies to guide treatment in ICI-associated myocarditis, immunosuppression is the cornerstone of treatment.

Intravenous steroids are widely used in immune-related adverse events (irAEs) and may be effective in ICI-associated myocarditis.[347] High-dose corticosteroids (eg, methylprednisone 1000 mg daily for 3 days followed by prednisone 1 mg/kg) are commonly used and may be associated with better outcomes.[22] Mahmood et al.[22] reported that 31% of 35 patients received corticosteroids, and that high-dose steroids were associated with lower peak troponin levels and lower rates of major adverse cardiac events (MACEs) compared to lower doses of corticosteroid. The American Society of Clinical Oncology (ASCO) recommends an initial corticosteroid dose of 1 mg/kg.[361] Therapy duration is unclear, but ASCO recommends tapering over 4 to 6 weeks in patients with irAEs. Serum cardiac biomarkers (eg, troponins, BNP) may be useful for defining the need for longer therapy duration after weaning.

Additional immunosuppression may also be used. Anecdotal evidence suggests that other immunosuppressants such as IVIg,[362] infliximab,[363] mycophenolate mofetil,[364] tacrolimus,[362] antithymocyte globulin,[365,366] plasmapheresis,[362] abatacept,[367] and alemtuzumab[368] may be effective. In a study conducted by Mahmood et al.,[22] a small number of patients received other nonsteroidal immunosuppressants; given the lack of robust data on their efficacy in ICI-associated myocarditis, such agents are generally reserved for refractory or very severe cases.

We suggest considering the addition of nonsteroidal immunosuppression in patients who do not show symptomatic, functional, or biomarker improvement within 24 to 48 hours of corticosteroid initiation. The choice of the second agent is not defined but may be motivated by availability and contraindications. Several sequential immunosuppressants may be required to achieve remission.[22]

We recommend initiating high-dose intravenous steroids at the time of diagnosis of ICI-associated myocarditis (methylprednisone 1 mg/kg/day). Cardiac biomarkers (troponin and BNP) should be measured sequentially. If cardiac biomarkers continue to increase despite the use of high-dose steroids, plasmapheresis should be initiated. An additional immunosuppressant may be required if cardiac biomarkers continue to increase or if the patient presents with new or more severe arrhythmias or HF (Figure 14). The choice of immunosuppressant depends on local experience and coexisting comorbidities (Table 33).

We recommend administering a single dose of infliximab (5 mg/kg) in the absence of contraindications (eg, tuberculosis, hepatitis). Alternatively, antithymocyte globulin (10 to 30 mg/kg), alemtuzumab (30 mg once), or abatacept (500 mg) may be used. Within 3 to 5 days of corticosteroid initiation, ventricular function should be examined by echocardiography or CMR. Patients showing significantly improved LV function (improvement in LVEF of at least 5%) can be converted to oral corticosteroids (prednisone 40 to 60 mg daily) for a long period (4 to 8 weeks). If biomarkers decline and the patient shows a clinical response, mycophenolate mofetil or tacrolimus can be used to shorten steroid chronicity. Given the high mortality and morbidity of immune-related myocarditis, ICIs should be discontinued even in patients with mild cardiotoxicity (Table 33).

Because of the potential reversibility of ICI-associated myocarditis, supportive therapies may be instituted after careful multidisciplinary consideration of the underlying malignancy status and recovery potential. Supportive strategies may include inotropic support, temporary or permanent pacemaker, and temporary mechanical circulatory support (eg, intra-aortic balloon pump,[6] percutaneous ventricular assist devices,[369] or ECMO).[362,364] A careful RV assessment should be performed prior to insertion of LV assist devices, as ICI-associated myocarditis is highly likely to affect the RV,[362,364,369] which may require biventricular support.[363,369] Furthermore, owing to the prothrombotic environment induced by the underlying neoplasm and irAEs, excluding LV thrombi with CMR or contrast-enhanced echocardiography before insertion of percutaneous LV assist devices is essential.[363]

Table 33 – Immunosuppressants used in the treatment of immune checkpoint inhibitor-associated myocarditis

Immunosuppressant	Class	Dose	Start	Duration
Methylprednisolone	Corticosteroids	1 mg/kg/day	At diagnosis	2 to 3 days
Prednisone	Corticosteroids	40 to 60 mg/day	Day 2-3	Slowly wean over 4 to 8 weeks
Infliximab	TNF-alpha inhibitor	5 mg/kg	Day 4-5	Single dose (may be repeated within a few months)
Antimonocyte globulin	?	10 to 30 mg/kg	Day 2-3	7 to 14 days
Tacrolimus	Calcineurin inhibitor	0.10 to 0.15 mg/kg/day	?	?
Mycophenolate mofetil	IMPDH inhibitor	1g 2×/day	?	?
Abatacept	CTLA-4 agonist	500 mg every 2 weeks	Day 7-14	Total of 5 doses
Alemtuzumab	Anti-CD52	30 mg	?	Single dose

IMPDH: inosine monophosphate dehydrogenase.

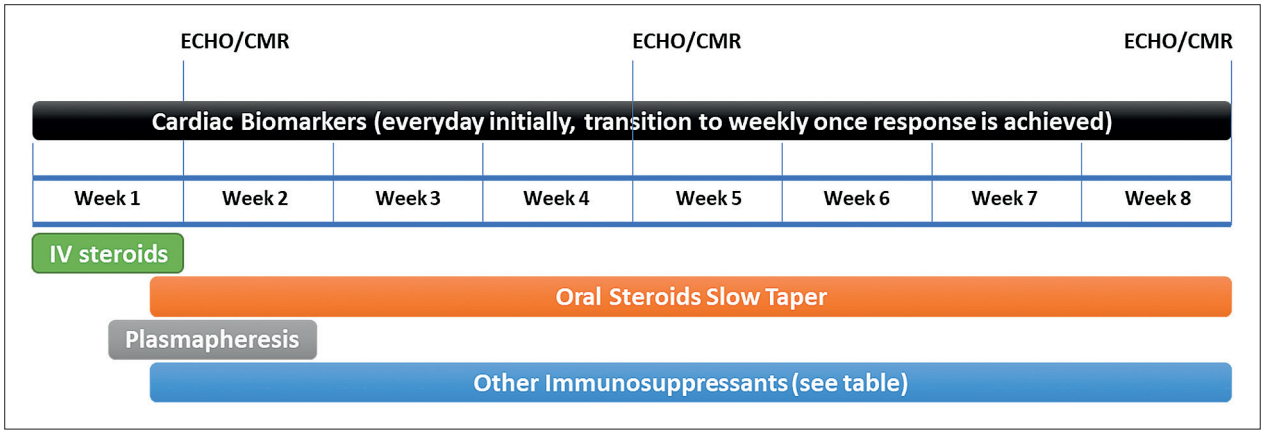

Figure 14 – *Proposed therapeutic course with immunosuppression, biomarkers, and ventricular function assessment. CMR: cardiac magnetic resonance; ECHO: echocardiogram; IV: intravenous.*

Drug therapy for HF should be initiated as tolerated. This includes angiotensin blockers (ACEI, ARB, angiotensin receptor-neprilysin inhibitor [ARNi]), beta-blockers, and mineralocorticoid antagonists (eg, spironolactone).

The safety of restarting ICI therapy after myocarditis has resolved is unknown. In a study of 40 patients who developed irAEs (1 ICI-associated myocarditis) and had ICIs reintroduced (43% used the same agent), 22 (55%) developed recurrent irAEs during a 14-month follow-up period. Extrapolating these data to ICI-associated myocarditis and considering the high probability of recurrent irAEs with reintroduction, ASCO recommends permanent discontinuation of ICIs in all cases of immune-related myocarditis.[370] There is a report of successful reintroduction in one case of mild myocarditis.[371] Also, reintroduction of ICI might be attempted in select cases of mild, asymptomatic (grade I) ICI-associated myocarditis,[361] especially with low-risk ICIs such as pembrolizumab. However, this recommendation remains controversial.

6.7.4 Prognosis

The prognosis of ICI-associated myocarditis is challenging because of the rare nature of this condition. In a multicenter registry of 35 patients with ICI-associated myocarditis, nearly half (n = 16) developed MACEs over 102 days (6 cardiovascular deaths, 3 cardiogenic shocks, 4 cardiac arrests, and 3 complete heart blocks).[22,347] In a French registry of 30 patients with ICI-associated myocarditis at two centers, eight patients died from cardiovascular complications. A recent study that followed-up 101 patients with ICI-associated myocarditis showed a MACE rate of 51% during a 162-day follow-up period.[347] The mortality rate among 250 patients with ICI-associated myocarditis reported to the US Food and Drug Administration Adverse Event Reporting System (FAERS) was 50%.[361] There was no difference in mortality rate by age, sex, year of reporting, or ICI type (antiprogrammed cell death protein-1/ligand-1 vs. anticytotoxic T-lymphocyte protein-4).[362] Mahmood et al.[22] found that patients with ICI-associated myocarditis and elevated troponin level at the time of discharge had significantly higher rates of MACEs (discharge troponin T ≥1.5 ng/mL: HR: 4.0; 95% CI: 1.5-10.9; p = 0.003). Escudier et al.[348] reported that 80% of patients with ICI-associated myocarditis and conduction disorder had cardiovascular death. A recent study of patients with ICI-associated myocarditis reported that global longitudinal strain obtained at diagnosis was strongly associated with MACEs over a 162-day follow-up period.[363] Given the small number of patients in those studies, it is difficult to identify risk factors contributing to a poor prognosis in patients with ICI-associated myocarditis.[364-368]

Overall, recovery rates with appropriate therapy have been substantial. A total of 67% of patients receiving steroids showed recovered LV function in a French registry on ICI-associated myocarditis.[347] Recovery has also been described in patients with fulminant ICI-associated myocarditis requiring mechanical circulatory support.[369-374]

6.7.5. Prevention

Most published studies on the prevention of chemotherapy-induced cardiotoxicity have focused on anthracyclines and anti-HER2 agents.

Prevention of cardiotoxicity should start before cancer treatment with an evaluation of cardiovascular risk and a conversation between the cardiologist and the oncologist in order to plan the best approach during cancer treatment.

Patients at higher risk of developing cardiotoxicity are those with classic risk factors for cardiovascular disease (hypertension, diabetes mellitus, dyslipidemia, smoking, obesity, and sedentary behavior, among others) or those with higher exposure to cardiotoxic drugs (high cumulative doses of anthracyclines, cardiotoxic drug combinations, and a history of chemotherapy or radiotherapy).[375,376]

The main recommendations for preventing cardiotoxicity are described in Table 34.

Dexrazoxane, an iron chelator, is the only cardioprotective drug that has been approved for prevention of cardiotoxicity. Its protective effect against anthracycline cardiotoxicity has been proven in several studies addressing both the adult and

Table 34 – Measures to prevent cardiotoxicity

Chemotherapeutic drug	Cardioprotective measure
	Identify cardiovascular risk factors
	Treat comorbidities (hypertension, diabetes mellitus, dyslipidemia, smoking, sedentary behavior, obesity)
	Moderate-intensity aerobic exercise
	Arrhythmias: avoid QT prolonging drugs, manage electrolyte abnormalities
	Minimize cardiac radiation
Anthracyclines	Limit cumulative dose (mg/m2):
	Daunorubicin <800
	Doxorubicin <360
	Epirubicin <720
	Mitoxantrone <160
	Idarubicin <150
	Use liposomal formulations
	Perform continuous infusions
	Use less cardiotoxic analogues (epirubicin, idarubicin)
	Assess use of cardioprotective drugs (dexrazoxane, ACEIs, beta-blockers, statins)
Trastuzumab	Assess use of cardioprotective drugs (ACEIs, beta-blockers)

ACEIs: angiotensin-converting enzyme inhibitors; QT: QT interval. Source: Adapted from Zamorano et al.[377]

pediatric populations.[376-383] The limitations of dexrazoxane are the high cost and some potential adverse effects, such as interference in the efficacy of anthracyclines, risk of secondary tumor development (controversial evidence),[384,385] and bone marrow toxicity. Dexrazoxane is indicated for adults with advanced or metastatic breast cancer who have previously received a cumulative dose of 300 mg/m^2 of doxorubicin, 540 mg/m^2 of epirubicin, when continuing treatment with anthracyclines is required.

The use of cardiovascular drugs such as beta-blockers, ACEIs, and ARBs in the prevention of cardiotoxicity secondary to anthracyclines is controversial and has been based on few clinical trials.[386-391] Some evidence has shown benefits of beta-blockers and ACEIs in patients who have used high cumulative doses of anthracyclines or in high-risk patients with positive troponin during chemotherapy.[386,390] At lower cumulative doses of anthracycline, this benefit has not been shown with beta-blockers,[389,392] but there has been a slight preventive effect with ARBs.[389]

The CECCY trial,[392] a Brazilian study which tested the use of beta-blockers for primary prevention of anthracycline-induced cardiotoxicity, did not demonstrate a preventive benefit of carvedilol. However, carvedilol was associated with reduced troponin levels and a lower percentage of patients with onset of diastolic dysfunction.

Regarding the use of trastuzumab, some studies suggest a benefit in the prevention of cardiotoxicity[393,394] as well as after the onset of cardiotoxicity by helping in the recovery of ventricular dysfunction.[395] The decision to discontinue or restart chemotherapy must be made jointly by weighing the risks and benefits of maintaining cancer treatment.

6,8. Myocarditis in children and adolescents

6.8.1. Causal factors

Myocarditis in children and adolescents has a particular etiology, and underdiagnosis may occur because its initial presentation is similar to those of a number of common viruses in childhood. Over 83% of patients are estimated to attend the emergency department at least twice before diagnosis.[396] In retrospective analyses, chest pain has been predominantly reported in children over 10 years of age, and the most commonly observed signs in younger patients have been tachypnea, fever, and respiratory distress[397] (Table 35). The application of diagnostic algorithms in emergency rooms has shown promising results, including the possibility of increasing the number of suspected patients (Figure 15).[239,398] Regarding etiology, studies evaluating the collection of a viral panel in the acute phase and biopsy confirmation have found a predominance of B19V, followed by enteroviruses, coxsackievirus B, and HHV.[398] Cases of arboviral diseases – dengue, Zika, and chikungunya – have been described in endemic regions across the world.[399] More recently, new presentations have emerged with the SARS-CoV-2 pandemic, including myocardial injury associated or not with multisystem inflammatory syndrome whose pathophysiology remains unclear.[400] Survivors of childhood cancer treatment, especially those undergoing treatment with anthracyclines and ICIs, are at high risk for the onset of an inflammatory process leading to HF in adulthood.[401]

6.8.2. Prognosis

Estimating the incidence and prevalence of pediatric myocarditis is challenging because of the wide spectrum of

Table 35 – Most common clinical findings at initial presentation of myocarditis in children and adolescents

Signs and symptoms	Below 2 years of age	Preschoolers	School-age children and adolescents
Specific	Signs of HF	Signs of HF	Signs of HF
	History of viral disease in the past 3 to 6 weeks	History of viral disease in the past 3 to 6 weeks	Chest pain
	Chest pain (uncommon)	Chest pain (unlikely)	History of viral disease may not be so clear
Nonspecific	Fever	Dyspnea on exertion	Dyspnea on exertion
	Lethargy	Tachycardia at rest	Tachycardia at rest
	Irritability	Muscle fatigue	Muscle fatigue
	Perfusion change	Arrhythmia	Arrhythmia
	Decreased intake	Shock	Shock
	Tachycardia at rest		
	Arrhythmia		
	Shock		

HF: heart failure.

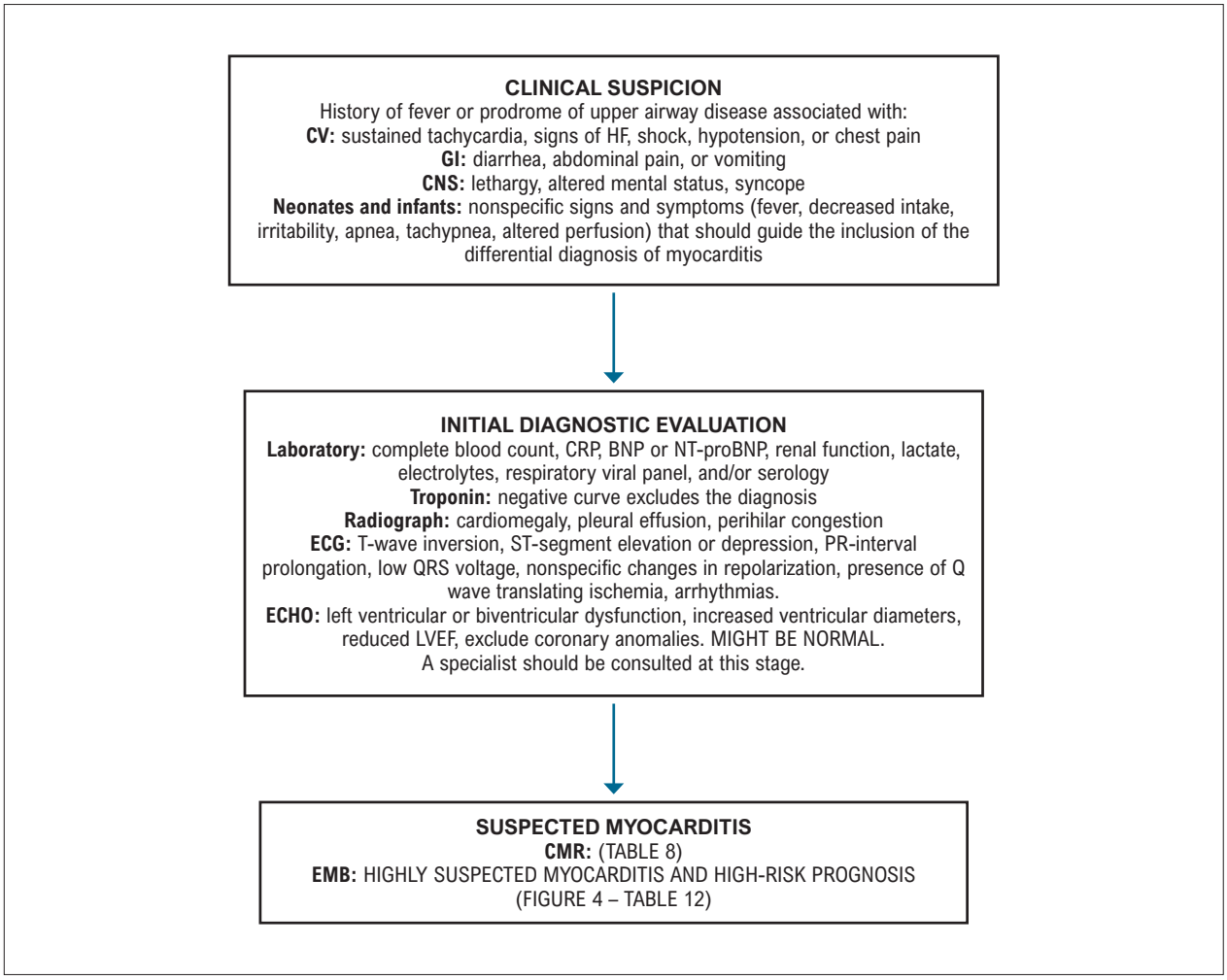

Figure 15 – *Flowchart for investigation of suspected myocarditis in children and adolescents.*
BNP: brain natriuretic peptide; CMR: cardiac magnetic resonance; CNS: central nervous system; CRP: C-reactive protein; CV: cardiovascular; EMB: endomyocardial biopsy; GI: gastrointestinal; HF: heart failure; LVEF: left ventricular ejection fraction.

symptoms, which may range from a mild viral infection without hemodynamic compromise to congestive HF with ventricular dysfunction, arrhythmias, and sudden death.[164,402-405] As the symptoms are often nonspecific, a significant number of cases are not diagnosed, which makes the actual incidence and prognosis difficult to characterize. However, this is the most common etiology of dilated cardiomyopathy in children.

With improvements in intensive care services, including mechanical circulatory support, the prognosis of children of all age groups has improved, and complete recovery has been possible even in cases of fulminant disease.[402]

Key outcomes in pediatric patients include complete recovery, progression to dilated cardiomyopathy, and death or heart transplantation.[405]

Children with viral myocarditis are believed to have a better prognosis than those with dilated cardiomyopathy. Survival in pediatric patients with myocarditis is up to 93%. However, a multicenter study addressing all age groups demonstrated a significant mortality in neonates and infants. Survival in this group ranged from 33% to 45%, and clinical improvement ranged from 23% to 32%. In children aged 1 to 18 years, survival was higher, approximately 78% to 80%, and clinical improvement ranged from 46% to 67%.[406] In a recent Pediatric Cardiomyopathy Registry (PCMR) study, children with biopsy-proven myocarditis had a 3-year survival of 75%; also, 54% had normalized ventricular dimensions and function, and only 20% showed persistent echocardiographic abnormalities.[404]

A study of 28 patients with confirmed myocarditis reported that only 17 survived and were discharged showing varying degrees of improved cardiac function. The remaining 11 patients progressed to refractory HF; seven required heart transplantation, and four died. Predictors of poor prognosis were ejection fraction below 30%, fractional shortening below 15%, left ventricular dilatation, and moderate-to-severe mitral regurgitation.[406]

Several case series of children requiring mechanical circulatory support for myocarditis have reported a survival rate between 67% and 83%. Of 21 patients mechanically supported with the Berlin Heart EXCOR device for myocarditis or dilated cardiomyopathy, 90% survived and were discharged.[407]

Prognosis in EMB-proven myocarditis depends on the severity of symptoms, histological classification, and biomarkers. Acute fulminant myocarditis is associated with higher survival. Giant cell myocarditis, although rare, is associated with a poor prognosis; median survival is 5.5 months, and mortality or transplantation rate is 89%.[406]

Myocarditis accounts for at least 50% of all dilated cardiomyopathies in childhood. The outcome of patients with viral myocarditis is better than that of patients with dilated cardiomyopathy. For this reason, myocarditis should always be suspected, and supportive measures should be initiated as early as possible to prevent a patient with myocarditis from being placed on a transplant waiting list without having a chance of recovery. The indication for transplantation in myocarditis should only be considered when recovery is unfavorable despite adequate therapeutic management (Table 36).

IVIg therapy has been included in immunomodulatory treatment of children with acute myocarditis at many centers, being used at a standard dose of 2 g/kg over 24 hours. This practice has been established since the classic 1994 study conducted by Drucker et al.[164] A tendency towards ventricular function recovery has been demonstrated in those who received immunoglobulin. In a cohort of 94 patients with new-onset cardiomyopathy, IVIg was administered to 22% of patients, and 5-year follow-up data have demonstrated a higher rate of recovery compared to patients who did not receive immunoglobulin.[408]

A Taiwanese study of 94 patients evaluated receiver-operating characteristic (ROC) curves and found that ejection fraction <42% (sensitivity, 86.7% and specificity, 82.8%) and troponin I >45 ng/mL (sensitivity, 62.6% and specificity, 91%) were most significantly associated with mortality.[403]

Several studies have shown that patients who survive the initial acute phase have a more favorable long-term outcome, unlike those with more insidious disease.

Histological evidence of myocarditis as a cause of dilated cardiomyopathy has been considered a positive prognostic indicator for recovery, with chances of cure ranging from 50% to 80% within 2 years.[402] Likewise, a delayed progression to chronic HF requiring heart transplantation may occur even after an initial clinical improvement.

Table 36 – Key information about myocarditis in children and adolescents

Myocarditis in children and adolescents
Key outcomes include complete recovery, progression to dilated cardiomyopathy, and death or heart transplantation
Intravenous immunoglobulin has become a standard practice in the treatment of myocarditis, but its effect on cardiac function is still not fully understood
The spectrum of clinical manifestations of myocarditis is very wide, ranging from a mild viral infection to congestive heart failure with cardiogenic shock requiring inotropic or mechanical circulatory support
Although endomyocardial biopsy is considered the gold standard for diagnosis of myocarditis, the risk of adverse events in children ranges from 1% to 5% (tachyarrhythmias, hypotension after anesthesia, ischemic changes, ventricular perforation). Therefore, this technique has not been routinely adopted[5]
Ejection fraction <42% and elevated troponin at diagnosis are most significantly associated with mortality
Patients who survive the acute phase have better long-term outcomes than those who have a more insidious condition
Myocarditis is the most common etiology of dilated cardiomyopathy in childhood

6.9. Myocarditis with pericardial involvement

6.9.1. Diagnosis and treatment

Myocarditis and pericarditis are often associated in clinical practice, representing different spectra within the group of inflammatory myopericardial syndromes (Table 37).[409,410] This is explained by both conditions sharing common etiological agents, mainly viruses.[411] However, myocardial and pericardial involvement are rarely of equivalent intensity (there is either predominance of myocarditis [perimyocarditis] or pericarditis [myopericarditis][412]), and differentiating between the two conditions is important for prognosis and treatment. Myopericarditis usually has a good prognosis, without progression to HF or constrictive pericarditis.[413-416] In the setting of acute myocarditis, pericardial involvement (perimyocarditis) has prognostic significance. Di Bella et al.[417] evaluated a cohort of 467 patients with idiopathic/viral acute myocarditis diagnosed by CMR and identified that approximately 24% of patients showed pericardial involvement. In addition, pericarditis caused a 2.5-fold increase in the risk of cardiac events (composite endpoint of death, cardiac transplantation, implantable cardioverter-defibrillator, and hospitalization due to decompensated HF).[416]

Myocarditis associated with acute pericarditis should be suspected in patients with a diagnosis of myocarditis and at least two of the following criteria: pleuritic chest pain (may be difficult to identify because of pain due to myocardium involvement), pericardial friction rub; ECG changes suggestive of pericarditis (widespread ST-segment elevation, PR-segment depression); and new or worsening pericardial effusion. Laboratory tests usually reveal leukocytosis with a predominance of lymphocytes (in viral cases) and elevated CRP and ESR. CMR is the most accurate noninvasive test for evaluating pericardial involvement in patients with myocarditis.[409,417] It detects inflammation, thickening, effusion, and masses in the pericardium and is indicated for cases whose diagnosis is unclear (grade of recommendation: I, level of evidence: C).[409,418]

In patients with myocarditis and pericardial involvement, treatment essentially depends on the underlying cause and should follow the recommendations for the treatment of myocarditis. In viral/idiopathic cases without ventricular dysfunction, the use of nonsteroidal anti-inflammatory drugs (NSAIDs) to control pericardial injury should be considered with caution using reduced doses, given that experimental studies have shown increased mortality and enhanced myocardial inflammation with NSAIDs.[411,419,420]

6.10. Acute myocarditis mimicking MI

Previous studies have indicated that 2.6% to 25% of patients with suspected MI actually have MINOCA. Several etiologies may be attributed to patients with suspected acute MI with culprit-free angiograms, among which acute myocarditis has been recognized as a particularly important factor.[421]

Typical clinical presentations of acute MI, such as chest pain, ST-segment elevation, and incremental serum markers, are commonly observed in patients diagnosed with myocarditis.[422,423] In addition, in the clinical setting of acute disease with elevated troponins, it may be clinically challenging to differentiate type 2 MI from nonischemic causes of myocardial injury, especially myocarditis. Type 2 MI is secondary to ischemia due to increased oxygen demand or decreased supply; it may be caused by coronary artery spasm, coronary embolism, anemia, arrhythmias, hypertension, or hypotension.[424]

"Myocardial ischemia" is used when there is evidence of elevated troponin values with at least one value above the 99th percentile upper reference limit. "Myocardial lesion", in turn, is used when there is an increase or decrease in troponin values. The diagnosis of acute MI is specified when there is acute myocardial injury with clinical evidence of acute myocardial ischemia, requiring both the detection of an increase and/or decrease in troponin values and the presence of at least one of the following conditions: symptoms of myocardial ischemia, new ischemic ECG changes, development of pathological Q waves, imaging evidence of new loss of viable myocardium, new wall motion abnormalities in a pattern consistent with an ischemic event, and/or identification of a coronary thrombus on angiography or autopsy.[424]

The clinical entities that may mimic ST-segment elevation MI include myocarditis/pericarditis, Takotsubo cardiomyopathy, J-wave syndromes (used to describe both Brugada syndrome and early repolarization syndrome), secondary repolarization abnormalities (eg, left bundle branch block, ventricular pacing, and ventricular hypertrophy), electrolyte disorders (hyperkalemia and hypercalcemia), and other nonischemic causes (eg, Wolff Parkinson-White syndrome, pulmonary embolism, intracranial bleeding, hypothermia, and postcardioversion). However, the course of ECG changes and differences in clinical history may help distinguish these conditions from acute MI.[425]

In vivo tissue characterization with CMR enables the identification of edema/inflammation in ACS/myocarditis and the diagnosis of chronic diseases and fibrotic conditions (eg, in hypertrophic and dilated cardiomyopathies, aortic stenosis, and amyloidosis).[425] In nonischemic diseases, the pattern and

Table 37 – Recommendations for the evaluation of myocarditis with suspected pericardial involvement

Indication	Class	Level of evidence
In patients with acute myocarditis and suspected pericardial involvement, cardiac magnetic resonance is recommended to support the diagnosis in doubtful cases.	I	C

distribution of late gadolinium enhancement may offer clues regarding etiology and prognostic significance.[425] Myocarditis usually causes subepicardial/midmyocardial scarring, typically (though not always) showing a noncoronary distribution with subendocardial sparing.[426,427]

In myocarditis, T2-weighted imaging may also identify regional inflammation, characteristically showing a noncoronary distribution. Conversely, parametric T1-mapping is also available and provides a quantitative and objective assessment of edema/inflammation (eg, in acute MI/myocarditis).[426,427] There is a dynamic interaction between inflammation and fibrosis in different precursors of HF, such as acute MI and myocarditis. Early diagnosis of HF with biomarkers and imaging tests is imperative; whereas CMR is useful for evaluating the extent of the injury, serial biomarker measurements indicate if inflammation and fibrosis are progressive.[427]

Clinically, myocarditis mimicking acute MI is an extremely complex case for physicians to accurately diagnose. The coronary anatomy must be investigated either with coronary angiography or coronary CT angiography. Furthermore, a correct diagnosis of myocarditis per se is a challenge due to nonspecific patterns of clinical presentation and the lack of a reliable and accurate diagnostic method. Although EMB is recommended in guidelines as the ideal diagnostic method, the diagnosis of myocarditis in routine practice is usually based on comprehensive consideration of medical history, clinical manifestations, and additional tests, among which CMR has significant advantage for detecting myocardial abnormalities and accurately discriminating patients with myocarditis from those with true MI.[421-423,425-427] Figure 16 shows a flowchart for evaluating patients with acute MI versus myocarditis.

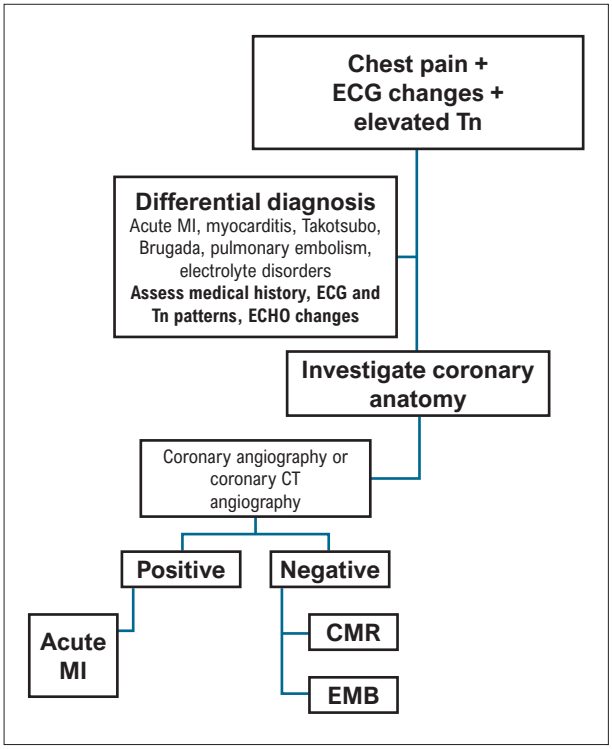

Figure 16 – *Differential diagnosis of chest pain: acute MI versus myocarditis. CMR: cardiac magnetic resonance; ECG: electrocardiogram; ECHO: echocardiogram; EMB: endomyocardial biopsy; MI: myocardial infarction; Tn: troponin.*

7. Rheumatic carditis

In 2018, the World Health Organization (WHO) acknowledged that rheumatic fever is endemic in low-income countries and developed a global action plan focused on prevention, diagnosis, and secondary prophylaxis.[428] Rheumatic fever is a biphasic disease whose acute outbreak manifests as variable combinations of arthritis, chorea, subcutaneous and cutaneous injuries, and myocarditis, which affects more than 50% of patients.[429] Approximately 5% of patients with acute rheumatic myocarditis have significant clinical manifestations that require medical attention, and up to 50% of patients with acute carditis progress to chronic rheumatic heart disease (late stage), specifically mitral and/or aortic valve disease.[430,431] The prevalence of rheumatic carditis is unknown, but data suggest that this is a common and underdiagnosed condition. In 2013, the Brazilian Unified Health System (SUS) reported 5,169 hospitalizations due to acute rheumatic fever.[432] Approximately 40 million people worldwide are estimated to currently live with chronic rheumatic heart disease, and this condition is believed to account for approximately 300,000 deaths annually.[433] A Brazilian study included 5,996 students from 21 schools in the state of Minas Gerais and identified a prevalence of chronic rheumatic heart disease of 0,42%, which is 2- to 10-fold higher than the mean rate documented in developed countries.[434]

Rheumatic carditis should be suspected upon an acute outbreak of rheumatic fever, initially by applying the Jones criteria, which were updated in 2015.[435] Patients should be stratified according to epidemiological considerations regarding the risk of rheumatic disease. Patients from regions where the incidence of rheumatic fever is higher than 2/100,000 school-aged children (5 to 14 years) per year or the prevalence of rheumatic valve disease is higher than 1/1,000 person-years are considered at high risk. A large portion of the Brazilian population is believed to live in regions with such characteristics. The 2015 update of the Jones criteria also included echocardiographic criteria and the possibility of using the criteria to diagnose recurrent rheumatic fever[436] (Table 38). Therefore, a rheumatic etiology should be considered for patients with carditis, especially young people in low-income regions and/or with a history of rheumatic valve disease.

In case of a documented acute outbreak of rheumatic fever or clinical manifestations of HF, an active investigation for rheumatic carditis is warranted. Rheumatic carditis is a pancarditis that affects the pericardium, myocardium, and endocardium in varying degrees. It mainly manifests through acute valvulitis, which affects 90% of cases as mitral and/or aortic acute regurgitant valvular disease.[437] In the presence of symptoms, the main mechanism is acute valvular disease (preferably mitral) and, less frequently and less intensely, myocarditis and pericarditis.[438] Therefore, the initial focus of investigation is the detection of valvular heart

Table 38 – 2015 update of the Jones criteria

First outbreak of rheumatic fever	Rheumatic fever recurrence
2 major criteria; or 1 major criterion and at least 2 minor criteria	2 major criteria; or 1 major criterion and at least 2 minor criteria; or 3 minor criteria
Low-risk population (<2/100,000 cases of acute rheumatic fever per year and <1/1,000 cases of rheumatic valve disease per year)	Moderate- or high-risk population (<2/100,000 cases of acute rheumatic fever per year and <1/1,000 cases of rheumatic valve disease per year)
Major criteria	**Major criteria**
– Carditis (clinical or subclinical)	– Carditis (clinical or subclinical)
– Arthritis (polyarthritis only)	– Arthritis (polyarthritis only, polyarthralgia, and/or monoarthritis)
– Chorea	– Chorea
– *Erythema marginatum*	– *Erythema marginatum*
– Subcutaneous nodule	– Subcutaneous nodule
Minor criteria	**Minor criteria**
– Polyarthralgia	– Monoarthralgia
– Fever (≥38.5°C)	– Fever (≥38°C)
– Elevated ESR (>60 mm in the first hour) and/or CRP > upper reference limit)	– Elevated ESR (>60 mm in the first hour) and/or CRP > upper reference limit)
– Prolonged PR interval corrected for age (in the absence of carditis)	– Prolonged PR interval corrected for age (in the absence of carditis)
Evidence of a preceding group A β-hemolytic streptococcal infection (positive throat culture; positive rapid test; scarlet fever; increased titers of anti-streptococcal antibodies)	Evidence of preceding group A β-hemolytic streptococcal infection (positive throat culture; positive rapid test; scarlet fever; increased titers of anti-streptococcal antibodies)

CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate.

disease, which can be achieved by physical examination; however, transthoracic echocardiography is required, and transesophageal evaluation is recommended for uncommon situations with an inadequate window.[439] A 12-lead ECG, besides detecting a prolonged PR interval, may also detect a long QT and changes consistent with pericarditis and left chamber overload.[440] Troponin and CKMB levels are usually low, which indicates minimal myocardial damage.[431,441] Chest radiography may be helpful in identifying cardiomegaly and congestion.[442] After the initial evaluation, there are four possible diagnostic hypotheses:[443,444]

a) Subclinical carditis: clinical examination without alarming changes, prolonged PR interval on ECG, and/or mild mitral and/or aortic regurgitation on Doppler echocardiography.
b) Mild carditis: tachycardia disproportionate to fever, detectable regurgitant murmur, prolonged PR interval on ECG, chest radiograph without alarming changes, and mild to moderate mitral and/or aortic regurgitation on Doppler echocardiography.
c) Moderate carditis: mild carditis criteria associated with mild symptoms of HF and/or prolonged QT and/or cardiomegaly and congestion on radiograph and/or mild-to-moderate left-chamber dilatation.
d) Severe carditis: limiting HF symptoms with significant valve regurgitation and/or significant cardiomegaly and/or systolic ventricular dysfunction.

Thus, rheumatic myocarditis per se is not very exuberant and should be suspected in the presence of criteria for rheumatic carditis, manifest HF, and no anatomically significant acute valvular disease. In this situation, a thorough evaluation of possible differential diagnoses of myocarditis is also essential.

Mild, moderate, and severe cases should be investigated with additional imaging testing. Gallium-67 scintigraphy is the most widely studied test, is highly specific and sensitive, and should be the first to be conducted.[445,446] Antimyosin scintigraphy and PET scanning are less sensitive but may be conducted if gallium-67 is unavailable or if there is evidence of other differential diagnoses.[447,448] Studies focusing on the use of MRI for rheumatic fever are lacking, especially because valvular involvement is predominant; thus, MRI is more useful for differential diagnoses.[449] EMB has low sensitivity but extremely high specificity, and the presence of Aschoff nodules is pathognomonic of rheumatic myocarditis. It is indicated for refractory or severe cases[450] (Table 39).

For all patients with rheumatic carditis, despite being a late immune response, streptococcal eradication is recommended.[451] The treatment of subclinical and mild presentations includes controlling the symptoms associated with acute outbreaks and monitoring disease progression. Moderate and severe cases should be treated with corticosteroids (initially via oral route) and pulse therapy if refractory disease.[452-455] Medications such as ACEIs, furosemide, spironolactone, and digoxin should be used if manifest HF.[450] Refractory disease means that valve surgery should be considered in the acute phase (Table 40).[456-457]

Table 39 – Diagnostic tests for rheumatic carditis

Indications	Class	Level of evidence
12-lead ECG	I	B[440]
Chest radiograph	I	C[442]
Transthoracic Doppler echocardiography	I	B[436,439]
Transesophageal Doppler echocardiography if difficult transthoracic visualization	I	C[436,439]
ESR and CRP (see the Jones criteria)	I	B[436]
Antistreptolysin O (see the Jones criteria)	I	C[436]
Antidesoxyribonuclease B as an alternative to anti-streptolysin O	IIa	C[435]
Alpha-1 acid glycoprotein for inflammatory activity monitoring	IIa	C[444]
Protein electrophoresis (alpha-2 globulin) for inflammatory activity monitoring	IIa	C[444]
Troponin as a diagnostic criterion	IIb	B[431,441]
Gallium-67 scintigraphy	IIa	B[445,446]
^{18}F-FDG PET/CT	IIb	B[448]
Cardiac magnetic resonance	IIb	C[449]
Endomyocardial biopsy	IIb	C[444,450]

CRP: C-reactive protein; ECG: electrocardiogram; ESR: Erythrocyte sedimentation rate.

Table 40 – Treatments for rheumatic carditis

Indications	Class	Level of evidence
Eradication of group A β-hemolytic *Streptococcus*: – Penicillin G benzathine 1,200,000 IU, deep IM, single dose for those >20kg – Penicillin G benzathine 600,000 IU, deep IM, single dose for those <20kg – Amoxicillin 50 mg/kg/day (maximum 1,500 mg) in 3 divided doses for 10 days – For those with penicillin allergy – erythromycin 40 mg/kg/days (maximum 1,000 mg) in 4 divided doses for 10 days	I	C[444, 451]
Rest if moderate or severe case	IIa	C[444]
Hospitalization for symptom control in moderate-to-severe carditis	IIa	C[444]
Prednisone 0.5 to 1 mg/kg/day (maximum 50 mg) orally; may be divided into 2 to 3 daily doses for 15 days, with subsequent 20% weekly dose reductions in subclinical or mild cases. Total duration: 4 to 8 weeks.	IIb	B[444,452,453]
Acetylsalicylic acid 100 mg/kg (maximum 3 to 4 g) in 4 divided doses or naproxen 20 mg/kg (maximum 1,000 mg) in 2 divided doses for subclinical cases with associated arthritis and/or pericarditis. Total duration: 2 weeks.	I	B[444,453]
Prednisone 1 to 2 mg/kg/day (maximum 60 mg) orally; may be divided into 2 to 3 daily doses for 15 days, with subsequent 20% weekly dose reductions in moderate-to-severe cases. Total duration: 12 weeks.	I	B[444,452,453]
Methylprednisolone 30 mg/kg/day in weekly cycles in severe cases or refractory to initial treatment.	IIb	B[454,455]
In the presence of signs/symptoms of ventricular dysfunction, treat HF with diuretics and neurohormonal blockers.	I	C[450]
Cardiac valve surgery in mild and refractory cases: – Mitral repair with a technique that allows annular growth – Preferred mechanical prosthesis for aortic replacement	I	B[456,457]

HF: heart failure.

8. Myocarditis due to autoimmune diseases

Cardiac involvement in autoimmune diseases may include the pericardium, myocardium, endocardium, valves, and coronary arteries. Regarding myocarditis, a few entities warrant special attention: sarcoidosis, giant cell myocarditis, Behcet disease, eosinophilic granulomatosis with polyangiitis, systemic lupus erythematosus, scleroderma, and rheumatoid arthritis. There are obvious limitations regarding the diagnosis of myocarditis and its prevalence in autoimmune diseases, but it should be considered when there are signs and symptoms suggestive of cardiac involvement, including arrhythmias, syncope, HF, chest pain, or elevated markers of myocardial necrosis, especially in patients with a history of autoimmune disease or when there is cardiac involvement associated with symptoms of inflammation affecting other systems.

Nonspecific inflammatory markers, including CRP/ESR and myocardial injury markers such as troponin and BNP, are usually elevated. ECG and echocardiography should be performed in all patients with autoimmune diseases when cardiac involvement is suspected.[12,188] MRI is a sensitive and specific method for the evaluation of myocarditis, in addition to providing further information for differential diagnosis.[458,459] PET is another noninvasive method of choice, especially for suspected sarcoidosis.[243] Autoimmunity markers such as antinuclear antibodies, rheumatoid factors, and antineutrophil cytoplasmic antibodies should be considered, and testing should be guided by clinical suspicion.[460] EMB is the gold standard for the diagnosis of myocarditis due to autoimmune diseases or other causes. EMB uses other techniques in addition to histology to differentiate infectious from noninfectious myocarditis as well as to identify vasculitis and other noninflammatory myocardial diseases.[151] The treatment of myocarditis due to autoimmune diseases was discussed elsewhere in this Guideline.

9. Management of cardiac arrhythmias in myocarditis

9.1. Noninvasive and invasive assessments of arrhythmias in the acute and chronic phases of the several causes of myocarditis

Cardiac arrhythmias are relatively common manifestations in patients with myocarditis and may appear at any phase of the disease. Arrhythmogenic mechanisms are directly and indirectly associated with the degree of myocardial inflammation.[55]

In the acute phase by viral aggression and inflammatory response, we have myocytolysis associated with fibrosis, which promote hyperactivity of the sympathetic system and ion channel dysfunction, especially in calcium regulation, creating the electrophysiological substrate for genesis of arrhythmias.[461] The higher the cell damage and the degree of inflammatory involvement, the higher the likelihood of ventricular arrhythmia, with reentry being the main arrhythmogenic mechanism.

A broad spectrum of bradyarrhythmias and tachyarrhythmias occur in the setting of myocarditis. AV block, changes in ventricular repolarization, and prolonged QT interval are common findings in the acute phase of the disease. Atrial fibrillation and atrial tachycardias may also occur in acute or chronic myocarditis.

Ventricular arrhythmias may manifest as extrasystoles and/or ventricular tachycardias. These conditions may be monomorphic or polymorphic and manifest as nonsustained or sustained (duration ≥30 seconds).

Symptoms vary according to the presentation of arrhythmia, hemodynamic status, and degree of left ventricular dysfunction, and may include palpitations, tachycardia, syncope, or sudden death.

Direct diagnostic methods for noninvasive assessment of arrhythmias include 12-lead baseline ECG, continuous 24- or 48-hour ambulatory ECG (Holter system), and event monitoring (Looper system).

ECG findings are usually abnormal in patients with myocarditis, although they lack specificity and sensitivity.[462] Ukena et al.[94] reported that prolonged QRS duration is an independent predictor of cardiac death or heart transplantation in patients with suspected myocarditis. QTc prolongation ≥440 ms, deviation of the QRS axis, and premature ventricular ectopic beats, which are part of the course of myocarditis, do not seem to be independent predictors of poor prognosis. An ECG is a very useful tool in the detection of sustained bradyarrhythmias and tachyarrhythmias.

Ambulatory ECG monitoring may be useful for recording paroxysmal arrhythmias. Symptom frequency dictates the duration of the recording: the more infrequent the symptoms, the more difficult monitoring is.

Twenty-four-hour ambulatory ECG (Holter) allows documentation of arrhythmias and AV conduction abnormalities. It also contributes to the assessment of the nychthemeral distribution of arrhythmias, the autonomic nervous system, and the probable electrophysiological mechanism.[463] We recommend performing 24-hour Holter during hospitalization to evaluate possible asymptomatic arrhythmias and intermittent AV conduction abnormalities (Table 41). Holter may also be indicated as a supportive method for risk stratification of sudden death in the acute phase of myocarditis.

In patients with myocarditis, the actual role of invasive electrophysiology in risk stratification of sudden death is still under investigation. Importantly, the reproducibility of significant arrhythmic events should vary according to

Table 41 – Recommendations for arrhythmia evaluation in acute myocarditis

Indication	Class	Level of evidence
Holter in patients with intermediate-to-high prognostic risk	I	C

the cause and type of myocardial involvement.[464] Cardiac sarcoidosis, for example, has a high degree of reproducibility of significant clinical events with programmed electrical stimulation, which is useful in decision-making. In patients who had nonsustained or sustained monomorphic ventricular tachycardia at some point during the course of the disease, the presence of significant late gadolinium enhancement or low-voltage areas on electrophysiology studies with electroanatomic mapping seems to indicate poor prognosis, and these findings may help to stratify the risk of sudden death.[465] In the absence of specific data, this method of risk stratification for sudden death should be used with caution, especially in asymptomatic patients.[259]

9.2. Arrhythmia treatment and sudden death prevention in the acute and subacute phases

Arrhythmias are mostly associated with myocarditis during the acute phase but may also appear during the chronic phase, depending on the degree of tissue damage (especially inflammation and residual fibrosis), showing a wide physiological basis (Table 42).[466,467] Arrhythmias may occur in 33.7% of hospitalizations due to myocarditis, manifesting as both tachycardia and bradyarrhythmia, and are associated with morbidities such as hyperthyroidism, age, obesity, HF, electrolyte imbalance, and valvular disease.[95] Preexisting cardiomyopathies such as arrhythmogenic RV dysplasia and preexisting channelopathies are also associated with the occurrence of arrhythmias in myocardial inflammation.[468,469]

Although rare, bradyarrhythmias are usually associated with AV blocks of varying degrees and mostly occur in the acute phase. Obongayo et al.[92] identified a 1.7% prevalence of AV block among hospitalized patients with myocarditis taken from the Nationwide Inpatient Survey, of which only 1.1% were high-degree AV blocks. Third-degree advanced AV block was associated with increased morbidity and mortality.

Atrial fibrillation may occur in up to 9% of hospitalized patients with acute myocarditis and is associated with increased hospital mortality (OR: 1.7; 95% CI: 1.1 to 2.7; p = 0.02), cardiogenic shock (OR: 1.9; 95% CI 1.3 to 2.8; p = 0.001), and cardiac tamponade (OR: 5.6; 95% CI: 1.2 to 25.3; p = 0.002).[470]

Ventricular arrhythmias have the highest probability of sudden death and may account for approximately one fourth of all arrhythmias reported in hospitalized patients with myocarditis. Ventricular tachycardia is the most frequent type.[95]

Arrhythmia management in the acute phase should be consistent with the transient nature of the process, and recurrent ectopia or nonsustained tachycardia should not be treated with specific antiarrhythmics, except beta-blockers when indicated. During this phase, a temporary pacemaker may be used for advanced AV block, and the indication for a definitive pacemaker or implantable cardioverter-defibrillator should follow conventional indications (Table 43).

Table 42 – Potentially triggering mechanisms of arrhythmia in patients with myocarditis

Direct viral injury generating myocardial cell lysis and innate immune response Viral persistence
Cell apoptosis
Fibrosis favoring reentry mechanisms Proarrhythmic effect of cytokines
Changes in cell gap junctions Infarction due to microvascular injury

Table 43 – Treatment and prevention of myocarditis-associated arrhythmia and sudden death

Indications	Class	Level of evidence
Treatment with beta-blockers, spironolactone, and sacubitril/valsartan for patients with LV systolic dysfunction	I	C
Temporary pacemaker for symptomatic bradyarrhythmias and/or advanced AV block in the acute phase of myocarditis	I	C
Antiarrhythmic therapy with amiodarone in symptomatic NSVT or sustained VT in the acute phase of myocarditis	I	C
ICD implantation for primary prevention of sudden death in patients with dilated cardiomyopathy in the chronic phase (>6 months) of myocarditis with optimized clinical treatment for classes II and III, LVEF ≤35%, and life expectancy of at least 1 year	IIa	C
Indication for ICD in the acute and subacute phases of myocarditis (<6 months)	III	C
Indication for antiarrhythmic agents for primary prevention of cardiac arrhythmias in patients with myocarditis	III	C

AV: atrioventricular; ICD: implantable cardioverter-defibrillator; LV: left ventricular; LVEF: left ventricular ejection fraction; NSVT: nonsustained ventricular tachycardia; VT: ventricular tachycardia.

10. Prognostic evaluation and follow-up

10.1. Prognosis and evolution markers

Myocarditis has a wide phenotypic diversity. Most individuals with acute myocarditis who also develop acute dilated cardiomyopathy improve within a few days.[14] Case series report rates between 10% and 20% of serious cardiovascular events in the long term and a risk of recurrence of 10%.[109]

Several clinical and laboratory factors are involved in prognosis. Maintenance of preserved ventricular function during the acute phase has been repeatedly associated with spontaneous improvement and no sequelae.[15] Other studies have reported that reduced levels of blood pressure and heart rate, syncope, RV systolic dysfunction, elevated pulmonary arterial pressure, and advanced NYHA functional class play an important role.[94] Etiology has also been shown to be valuable in the prognostic spectrum. Patients with acute lymphocytic myocarditis and preserved ventricular function showed spontaneous improvement and no sequelae. In contrast, the MTT study reported that patients with HF and LVEF <45% had a 4-year mortality rate of 56%. The course of giant cell and eosinophilic myocarditis is more dismal.[14] Patients with fulminant myocarditis have a dramatic short-term prognosis; however, when they survive, the prognosis is better compared to other causes.[17,98]

ECG was shown to have prognostic value in a recent study.[471] MRI, whose value for the diagnosis of myocarditis is outstanding, has been shown to be useful with late gadolinium enhancement;[109] however, a more recent study could not confirm the predictive value of MRI for long-term improvement or remodeling of ventricular function.[472] Despite advances in diagnosis, prognosis remains a challenge, probably due to numerous known and unknown factors as well as the different causes of myocarditis, which vary widely in terms of characteristics, clinical presentation, and genetic and immunological involvement, among others.[137]

10.2 Outpatient follow-up with additional evaluations

Clinical follow-up with ECG should be continuous in patients who have already been diagnosed. Given the undeniable value of ventricular function, imaging tests should also be performed. Echocardiography emerges as a useful and easily accessible alternative, providing the most relevant information in this setting (Table 44).

Table 44 – General follow-up recommendations in myocarditis[473,474]

Indications	Class	Level of evidence
Clinical follow-up of low-risk patients with ECG at 1, 3, 6, and 12 months, then annually	I	C
Clinical follow-up of low-risk patients with echocardiogram at 1, 6, and 12 months, then annually	I	C
For intermediate-risk patients, clinical and laboratory evaluation with Holter monitoring and imaging tests should be performed at 1, 3, and 6 months (echocardiogram and/or MRI according to availability), then annually	I	C
For high-risk patients with myocarditis, clinical and laboratory follow-up with Holter monitoring and imaging tests should be performed at 15 days, 1, 3, and 6 months (echocardiogram or MRI according to availability), then annually	I	C

CG: electrocardiogram; MRI: magnetic resonance imaging.

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