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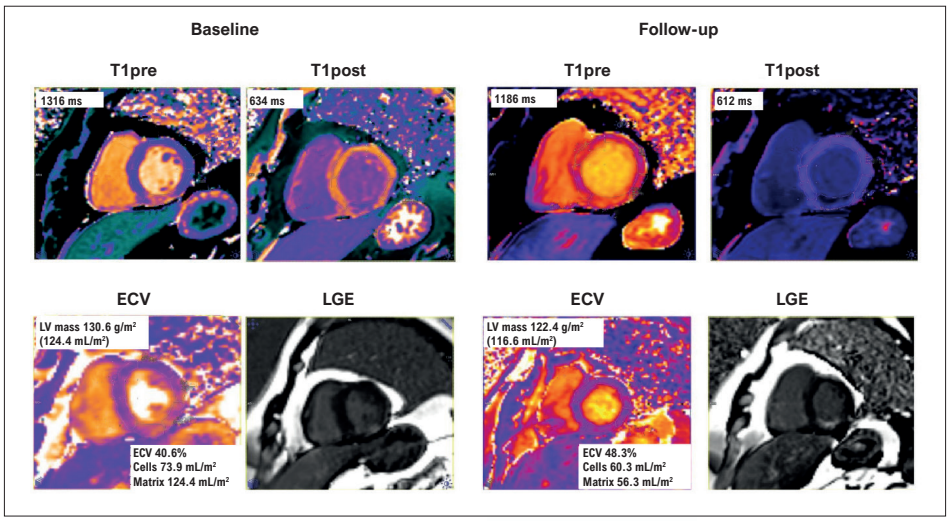

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REVISTA DA SOCIEDADE BRASILEIRA DE CARDIOLOGIA - Publicada desde 1948

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Coronary Tortuosity as a New Phenotype for Ischemia without Coronary Artery Disease

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Abstract

Background: **Coronary arteries tend to be more tortuous than other arteries and follow the repeated flexion and relaxation movements that occur during the cardiac cycle. Coronary tortuosity (CorT) leads to changes in coronary flow with a reduction in distal perfusion pressure, which could cause myocardial ischemia.**

Objective: **To assess the association between CorT and myocardial ischemia.**

Methods: **Between January 2015 and December 2017, 57 patients with angina and nonobstructive coronary artery disease detected by invasive coronary angiography (ICA) were retrospectively enrolled. Angiographic variables were analyzed to assess the presence and degree of tortuosity and correlated with their respective vascular territories on stress myocardial perfusion imaging (MPI). CorT was defined as coronary arteries with three or more bend angles ≤90°, measured during diastole. Statistical significance was determined at the 5% level.**

Results: **A total of 17 men and 40 women were enrolled (mean age 58.3 years). CorT was observed in 16 patients (28%) and in 24 of 171 arteries. There was a significant association between CorT and ischemia when analyzed per artery (p<0.0001). The angiographic factor most associated with ischemia was the number of bend angles in an epicardial artery measured at systole (p=0.021).**

Conclusion: **This study showed an association of CorT and myocardial ischemia in patients with unobstructed coronary arteries and angina. An increased number of coronary bend angles measured by angiography during systole was related to ischemia.**

Keywords: **Coronary Vessels; Ischemia; Myocardial Ischemia.**

Introduction

Ischemic heart disease is the leading cause of death in the developed world and limits patient quality of life in physical, social, financial and health aspects.[1] The recently published European Society of Cardiology Guidelines for the diagnosis and management of chronic coronary syndromes (CCSs) describe clinical scenarios in patients with a suspected or established CCS.[2] The clinical profile of angina with nonobstructive epicardial vessels has been increasingly recognized and associated with obesity, glucose intolerance and longer life expectancy.[3] Studies have suggested that up to 55% of patients referred for coronary angiography, even with typical symptoms, have no obstructions, and up to 40% of patients with normal or near-normal arteries (without obstructive lesions) on coronary angiography have ischemia, as demonstrated by stress tests.[4] Patients with angina pectoris who do not have significant coronary obstruction are still at increased risk for major cardiovascular events such as cardiovascular death, acute myocardial infarction, stroke, heart failure, and all-cause mortality.[5] These patients are also at a higher risk of heart failure with preserved ejection fraction.[6]

A possible mechanism related to ischemia in nonobstructive disease is coronary tortuosity (CorT). Reduction in distal perfusion pressure and coronary flow, leading to the appearance of myocardial ischemia can be observed in some cases of CorT. There are two causes for this pressure reduction: friction due to shear stress and the centrifugal effect within curves.[7] This association has been poorly addressed in the literature. The primary aim of this study was to assess the correlation between CorT and myocardial ischemia in patients without coronary obstruction, and the secondary aim was to verify the geometrical characteristics of each coronary vessel that could be correlated with ischemia.

Materials and methods

Patient selection

This was a retrospective study conducted at two medical centers. The study was approved by the institutional review

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board. All patients provided written informed consent before participating in the study.

A total of 57 subjects were included in the final analysis. We selected patients who underwent provocative tests with ischemic alterations and coronary angiography without obstructions. Of these patients, 28 patients had undergone a positive exercise test but had not undergone myocardial scintigraphy, which was then performed prospectively. The maximum interval between myocardial scintigraphy and coronary angiography was one year, regardless of the order in which they were performed.

Patients were enrolled if they were ≥18 years of age, had clinical complaints of angina pectoris, and had undergone invasive coronary angiography (ICA) that revealed no obstructive lesions (a nonobstructive lesion was defined as a lack of obstruction or an obstruction of less than 30%). Patients were excluded from the study if any of the following conditions were observed: heart failure, pulmonary hypertension, congenital disease, valvular heart disease, previous myocardial revascularization (surgical or percutaneous), hypertrophic cardiomyopathy, myocarditis, myocardial bridge, congenital anomalies of coronary origin (distribution and course), arteriovenous fistulas and coronary artery-left ventricular microfistulas, catheter-induced coronary spasm, anemia (hemoglobin <10 g/d/L), complete left bundle branch block or definitive pacemaker.

Clinical Data

Medical records were reviewed, and interviews were conducted with the patients. The functional class of the angina was verified according to the Canadian Cardiology Society[2] criteria, in addition to associated symptoms of dyspnea, history of comorbidities such as hypertension, diabetes mellitus, dyslipidemia, history of smoking and physical inactivity, and the available complementary exams.

Invasive coronary angiography

The ICA was used to rule out the presence of coronary obstructions and myocardial bridges and to assess the presence of CorT and its grading. Quantitative coronary angiographic analysis was performed using standard techniques. Severe CorT was defined as the presence of at least three consecutive curvatures with a curvature angle of less than 90 degrees of an epicardial coronary artery greater than 2 mm during diastole[7] (Figure 1).

For analysis of geometric parameters, the definition of severe CorT was considered. Thus, measurements were made of the bend angle (the angle formed by the intersection of the two lines at the exact point where the change in blood flow direction occurs- Figure 1) and of the most severe bend angle (the more acute the angle, the more tortuous the artery is). Note Figures 2 and 3 that show CorT in different angiographic projections.

Angiographic analysis was performed in diastole and in systole, in the left anterior descending (LAD), left circumflex (LCX), and right coronary (RCA) arteries (also of the left posterior descending artery in case of left dominance). The angiographic measurements of the LCX were made at the 30-degree left anterior oblique view with 30 degrees of caudal angulation, and at the 30-degree right anterior oblique view with 30 degrees of caudal angulation. Measurements of the LDA were made on the 30-degree right oblique anterior view with 60-degree cranial, and on the 30-degree anterior oblique left view with 60-degree cranial. Measurements of the right coronary artery were made on the 30-degree right anterior oblique view and on the 30-degree left anterior oblique view.

The analysis of the ICA images was performed by one observer blind with respect to the myocardial scintigraphy results.

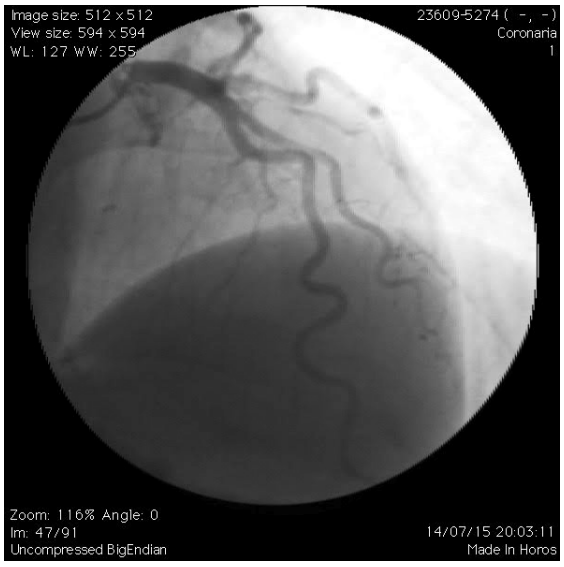

Figure 1 – *Coronary angiography demonstrating how the bend angle is measured.*

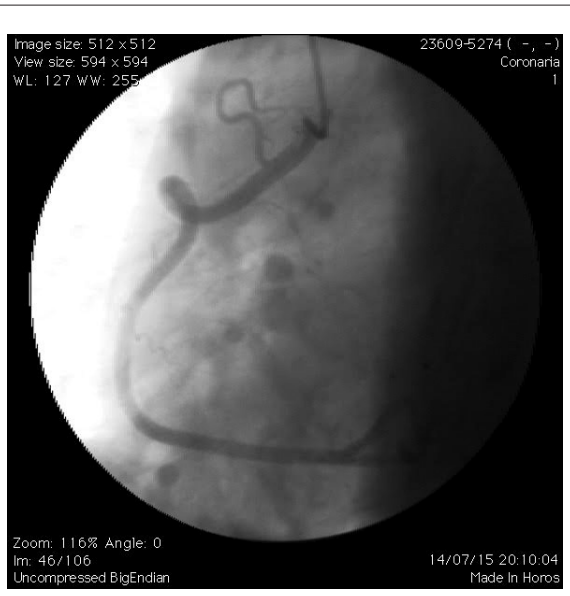

Figure 2 – *Coronary angiography showing severe curvature: coronary loop.*

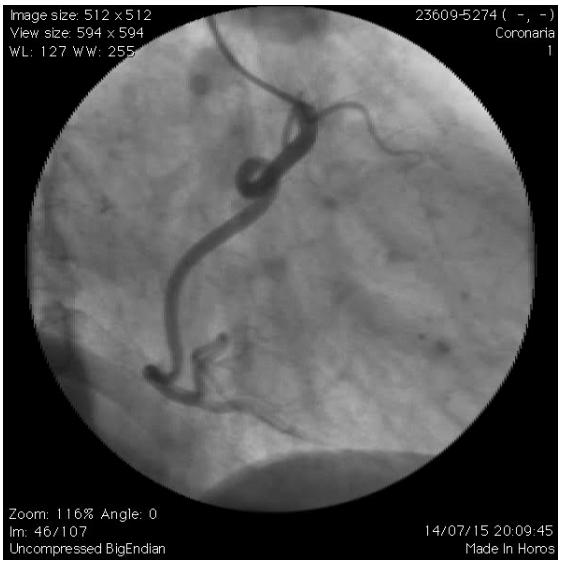

Figure 3 – *Coronary angiography showing coronary loop in an orthogonal view to that shown in Figure 2.*

Myocardial perfusion imaging

Myocardial perfusion imaging (MPI) was performed for the physiological evaluation of the presence and location of myocardial ischemia in all patients. Images were acquired on a Millenium MPR (General Electric, New York, United States) and an Infinia Hawk Eye (General Electric, New York, United States).

Images were interpreted by physicians of the Nuclear Medicine sectors of the respective hospitals and reviewed by an experienced examiner. Segments with deficits in the capture of radiotracer that normalized in the images acquired at rest were defined as ischemic. The 17-segment myocardial segmentation model was used, following the guidelines of the Cardiac Imaging Committee of the American Heart Association's Clinical Cardiology Board.[8]

The 28 patients who underwent myocardial scintigraphy after ICA were analyzed in a blinded manner.

Statistical analysis

Categorical variables were presented as absolute value and percentage. Continuous variables with normal distribution were expressed as mean and standard deviation and continuous variables with non-normal distribution as median and interquartile range. To evaluate the association between individual clinical variables and cardiological variables of CorT, binary logistic regression (bivariate analysis) was used. The clinical and cardiac explanatory variables were analyzed according to the presence or absence of CorT with the corresponding relative risk (RR), its respective confidence interval (95% CI) and the descriptive level (p value). Multivariable regression analysis was performed to identify independent predictors for the CorT outcome. The explanatory variables included in the multivariate regression were the same as those in the bivariate analysis, by logistic regression. The selection process of the variables was the stepwise forward method at the 5% level. The differences between the groups regarding numerical coronary angiography parameters and ischemia were analyzed by the Mann-Whitney U test and, for categorical parameters, by the chi-squared test ($\chi 2$) or Fisher's exact test. A prior analysis was performed to verify the normality of the variables. For this, the Shapiro-Wilk test was used together with a graphical analysis of the histograms. Statistical significance was determined at the 5% level. Statistical analysis was performed using SAS® System statistical software, version 6.11 (SAS Institute, Inc., Cary, North Carolina).

Results

Baseline characteristics

Clinical, myocardial perfusion (single-photon emission computer-assisted tomography, SPECT) and angiographic characteristics of the study participants are described in Table 1. The patients had a mean age of 58.3 ± 8.8 years and a mean body mass index of 29 ± 5.2 Kg/m^2 and was predominantly female (70.2%). Most patients had angina pectoris class II or III (71.9%) according to the Canadian Society of Cardiology classification. Patients were very symptomatic, with dyspnea being present in 56% of patients. Dipyridamole was the selected stress test in 39 patients (68%), exercise in 17 patients (29.8%) and dobutamine in one patient (1.7%). Myocardial scintigraphy was abnormal in 37 patients (64.9%) with a mean ischemic area of 5.9% ± 3.3%. Twenty patients had normal scintigraphy. The myocardial segments that showed the greatest transient perfusion deficit were those that were supplied by the LAD (43.9%), followed by the LCX (33.3%) and the right coronary artery (22.8%). ICA showed CorT in 28.1% of the patients, and the prevalence of tortuosity was higher in the LAD and LCX (17.5% each) and lower in the RCA (7%).

Age was the only significant independent predictor for CorT in our sample (p = 0.042; RR=1.08; CI=1.03-1.17) as we can see in Table 2.

Association between ischemia and the presence of CorT per vessel and in the sampled vessel territories

Evaluated per vessel (n = 171), the association between CorT and ischemia was highly significant. The frequency of ischemia in territories with CorT *versus* territories without CorT was 67% *versus* 28% (p<0.0001). The presence of CorT was associated with ischemia in the LCX (80% vs 21%; p=0.001) and the RCA (75% vs 19%; p=0.034) but not in the LAD (50% vs 42%; p=0.46).

Association between ischemia and angiographic parameters by vessel type

Table 3 provides the number of cases, median, minimum and maximum and corresponding descriptive level (p value)

Table 1 – Clinical, myocardial perfusion SPECT, and coronary angiographic characteristics of 57 patients included in the analysis

Characteristic	Value
Demographics	
Age (years), mean ± SD	58.3 ±8.8
Female sex	40 (70.2%)
Body mass index (Kg/m2), mean ± SD	29 ±5.2
*Creatinine Clearance (mL/min)**	93.6±29.4
Presenting symptoms	
Angina CCS I	14 (24.6%)
Angina CCS II	21 (36.8%)
Angina CCS III	20 (31.5%)
Angina CCS IV	2 (3.5%)
Dyspnea	32 (56.1%)
Cardiovascular risk factors	
Smoking	8 (14%)
Sedentarism	47 (82.5%)
Hyperlipidemia	27 (47.4%)
Diabetes	17 (29.8%)
Hypertension	51 (89.5%)
Left ventricular ejection fraction (%), mean ± SD	66.5 (10.2)
Medication	
Beta-blocker or calcium channel blockers	42 (73.7%)
Nitrates or trimetazidine	34 (59.6%)
Statins	30 (52.6%)
Aspirin	48 (84.2%)
Myocardial perfusion SPECT	
Abnormal SPECT	37 (64.9%)
If abnormal, myocardial impairment (%), mean ± SD	5.9 (3.3)
Abnormal SPECT in LAD territory	25 (43.9%)
Abnormal SPECT in LCX territory	19 (33.3%)
Abnormal SPECT in RCA territory	13 (22.8%)
Invasive Coronary Angiography	
Subjects with CorT	16 (28,1%)
LAD CorT	10 (17,5%)
LCX CorT	10 (17,5%)
RCA CorT	4 (7%)

**Cockcroft-Gault equation; SD: standard deviation. SPECT: single-photon emission computer-assisted tomography; CCS: Canadian Cardiovascular Society classification, LAD: left anterior descending artery; LCX: left circumflex artery; RCA: right coronary artery; CorT: coronary tortuosity.*

of the Mann-Whitney U test of the coronary angiography parameters, by occurrence of ischemia and artery type.

In this sample, no association was observed between ischemia and tortuosity parameters in the LAD or RCA, but this association was significant for the number of consecutive bend angles <90° (p = 0.025) and for the number of bend angles <90° measured at systole (p = 0.005) in the LCX.

Table 2 – Comparison of clinical characteristics by angiographic results (presence or absence of coronary tortuosity)

Characteristics	CorT (n = 16)	No CorT (n = 41)	p value
Age (years)	62.2 ± 7.5	56.8 ± 8.9	0.042
Female	13 (81.3%)	27 (65.9%)	0.26
BMI (kg/m^2)	29.2 ± 5.0	28.9 ± 5.3	0.84
Acetylsalicylic acid	14 (87.5%)	34 (82.9%)	0.67
Statin	8 (50.0%)	22 (53.7%)	0.80
Beta-blocker/ calcium channel blocker	13 (81.3%)	29 (70.7%)	0.42
Nitrate/ trimetazidine	8 (50.0%)	26 (63.4%)	0.36
Angina CCS I	2 (12.5%)	12 (29.3%)	
Angina CCS II	7 (43.8%)	14 (34.1%)	0.22
Angina CCS III/IV	7 (43.8%)	15 (36.6%)	0.25
Dyspnea	9 (56.3%)	23 (56.1%)	0.99
Hypertension	15 (93.8%)	36 (87.8%)	0.52
Diabetes	5 (31.3%)	12 (29.3%)	0.88
Dyslipidemia	6 (37.5%)	21 (51.2%)	0.35
Sedentarism	13 (81.3%)	34 (82.9%)	0.88
Smoker	2 (13%)	6 (14.6%)	0.84

BMI: body mass index; CorT: coronary tortuosity.

Association between ischemia and angiographic parameters in the sampled vessel territories

Table 4 provides the number of cases, median, minimum and maximum and the corresponding descriptive level (p value) of the Mann-Whitney U test of coronary angiography parameters by occurrence of ischemia and arterial territories (n = 171). There was a significant association between ischemia and the number of bend angles <90° measured at systole (p = 0.021) in the sampled vessel territories.

Discussion

Our study is dedicated to a phenomenon that has been increasingly recognized in clinical practice. There is considerable evidence that patients with ischemia without coronary obstruction do not have a benign prognosis, but so far, there are no guidelines to guide clinical practice.[6]

ICA lacks the sensitivity to diagnose functional coronary disorders, but can clearly detect some abnormalities, such as CorT. Until now, to our knowledge, there are no studies that assess whether CorT may represent another pathophysiological mechanism that leads to ischemia or be a marker of coronary microvascular dysfunction (CMD).

Table 3 – Ischemia according to angiographic parameters per vessel

	Ischemia			No Ischemia			p value
	N	Median	Range	N	Median	Range	
LAD							
most severe bend angle during diastole (degrees)	25	114	82-135	32	108	78.5-136	0.6
number of bend angles <90° during diastole	25	0	0-1	32	0.0	0-1	0.89
most severe bend angle during systole (degrees)	25	78	59.5-112	32	74.5	61.3-117	0.92
number of bend angles <90° during systole	25	1	0-2.5	32	1	0-3	0.9
LCX							
most severe bend angle during diastole (degrees)	19	79	58-109	38	102	74.3-120	0.083
number of bend angles <90° during diastole	19	1	0-3	38	0	0-1	0.025
most severe bend angle during systole (degrees)	19	55	46-96	38	97	52.5-121	0.077
systole number of bend angles <90° during systole	19	3.0	0-3	38	0	0-2	0.005
RCA							
most severe bend angle during diastole (degrees)	13	88	59.5-106.5	44	104	74.8-121	0.16
number of bend angles <90° during diastole	13	1	0-1.5	44	0	0-1	0.31
most severe bend angle during systole (degrees)	13	71	44-93	44	94	57.5-112	0.14
number of bend angles <90° during systole	13	1	0-2	44	0	0-1	0.24

LAD: left anterior descending artery; LCX: left circumflex artery; RCA: right coronary artery.

Table 4 – Angiographic parameters related to the presence of ischemia in all arteries

Angiographic parameters	Ischemia (n =57)		No Ischemia (n = 114)		p value
	median	Range	median	range	
most severe bend angle during diastole (degrees)	92	67-118	105	76-122	0.3
number of bend angles <90° during diastole	0	0-2.5	0	0-1	0.1
most severe bend angle during systole (degrees)	73	48.5-107	85.5	56.5-115	0.074
number of bend angles <90° during systole	1.5	0-3	1	0-2	0.021

Recognizing the presence of different mechanisms of ischemia in these patients may be important for performing stratified medicine, a new treatment approach for patients. In the CorMicA trial,[9,10] as in many other studies, women were predominant and presented with a different phenotype of CAD from men on coronary angiography because of a smaller number of coronary obstructions and decreased coronary flow reserve, findings that are associated with major cardiovascular events such as cardiovascular death and hospitalization for myocardial infarction and heart failure.[11] Li et al.[12] demonstrated that CorT is positively related to hypertension and female gender, but negatively linked with CAD.

El Tahlawi et al.[13] described that CorT is associated with subclinical atherosclerosis and increased coronary artery calcium score even in the absence of significant obstructive lesion. Another study was carried out showing the relationship between carotid intima-media thickness and the presence of CorT, and also in the presence of associated tortuosity in the retinal artery, thus suggesting an association with the subclinical form of atherosclerosis.[14]

Increased prevalence of females, advanced age, and hypertension is observed in patients with CorT and in patients with coronary microvascular dysfunction.[6,15-17] We can compare our findings with those reported in two other studies that used the same definition of CorT and demonstrated a correlation between CorT and ischemia. Gaibazzi et al.[16] found in a subgroup of 34 patients with the same characteristics (anginal pain on exertion and positive provocative test) the prevalence of 27.3% of CorT (n=9). Yang et al.[12] observed a 37.5% prevalence in a sample of 48 patients. Gaibazzi et al.[18] and Yang et al.[12] did not find any cardiovascular risk factors related to the presence of CorT, as in our study.

We observed a significant relationship, already described in the literature, of CorT with advanced age[16,19,20] ($p = 0.042$). In this sense, CorT seems to be the end result

of structural and functional changes of the heart and perhaps represents an adaptation mechanism that allows the heart to dynamically modify its size and function.[21] It may be dependent on left ventricular hypertrophy and concomitant impaired relaxation, which have been found to be more common in elderly people. One probable explanation is that hypertrophy might affect the geodesic pattern of coronary arteries plausibly due to angiogenetic factors, which may be mediated by blood flow, wall stress, and growth factors.[21]

Unlike in other studies, we analyzed the relationship between CorT and ischemia by vessel and corresponding territory. In our sample, CorT was present in the LCX and LDA in 10 patients (17.5%) and in the RCA in four patients (7%). The relationship between CorT and ischemia in the LCX and RCA was significant, but this relationship was not found in the LAD territory. Abnormal angiographic findings of CorT were more evident in the LCX (number of bend angles measured in both systole and diastole and smaller bend angle measured in systole and diastole), which may explain the greatest frequency of ischemia in this territory.

Our study is the first to demonstrate that a specific parameter of vessel tortuosity is related to the presence of myocardial ischemia. The highest number of acute bend angles detected during systole in angiography was related to myocardial ischemia in patients without coronary obstructions. Studies investigating specific changes in coronary geometry and their correlation with myocardial ischemia are missing. Hassan et al.[22] created a tortuosity severity index and found that it was a strong predictor of anginal pain among patients with normal coronary arteries, despite a positive stress study, but they did not evaluate the presence of ischemia in the coronary territories, as we did.

The relation of ischemia with CorT was different among the coronary territories. The LAD did not demonstrate an association of CorT with ischemia. Yokota et al.[23] studied a group of patients with normal single-photon emission computer-assisted tomography (SPECT) and persistent symptoms using fractional flow reserve (FFR). In this study, they found that the FFR was significantly more abnormal in the LAD, demonstrating that the different amount of myocardium in the coronary territories may create heterogeneous interactions with coronary anatomy and ischemia.[23] Myocardial mass subtended by a lesion is an important factor predicting an FFR < 0.80, as demonstrated by Yoon et al.[24] New methods of estimating hemodynamic compromise in coronary flow, such as the contrast-flow quantitative flow ratio (cQFR), demonstrated the same type of discrepancies compared with myocardial SPECT measurements.[25] We can speculate that the differences in territories supplied by the coronary arteries may explain part of our results because the increased myocardial mass may recruit more collateral vessels in the microcirculation.

One important finding is the need for a more accurate and uniformly accepted definition of CorT to standardize new studies.[26] The adoption of more than one angiographic variable beyond the severity of bending angles and the number of bend angles, as well as dynamic measurements in both phases of the cardiac cycle (systole and diastole), is important. This becomes even more significant when we note that coronary angiography makes only two-dimensional measurements of a highly dynamic structure that exists in three dimensions.[27] Studies on computational fluid dynamics draw attention to the importance of measurements made by complex mathematical equations that would best explain how pressure distribution occurs along the coronary circulation and the flow within it.[28-34]

Limitations

Our study has some limitations. The first limitation is the small sample size of the study and its retrospective nature (Figure 4). We did not use angiographic information to establish a tortuosity index, which may be proposed in future studies. We did not perform coronary function testing, as it is not routinely used in clinical practice.

Conclusions

CorT is associated with myocardial ischemia in selected cases. The number of bend angles assessed by systole in coronary angiography is linked to an increased risk of myocardial ischemia. An individualized analysis of the coronary artery anatomy and its corresponding territory is needed before considering a false-positive myocardial scintigraphy finding in patients with CorT.

Author Contributions

Conception and design of the research: Estrada A, Sousa AS, Mesquita CT, Villacorta H; Acquisition of data: Estrada A; Analysis and interpretation of the data and Statistical analysis: Estrada A, Villacorta H; Writing of the manuscript: Estrada A, Mesquita CT, Villacorta H; Critical revision of the manuscript for important intellectual content: Sousa AS, Mesquita CT, Villacorta H.

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 article is part of the thesis of master submitted by André Estrada, from Universidade Federal Fluminense.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Universidade Federal Fluminense under the protocol number CAAE 55255916.2.0000.5243. 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.

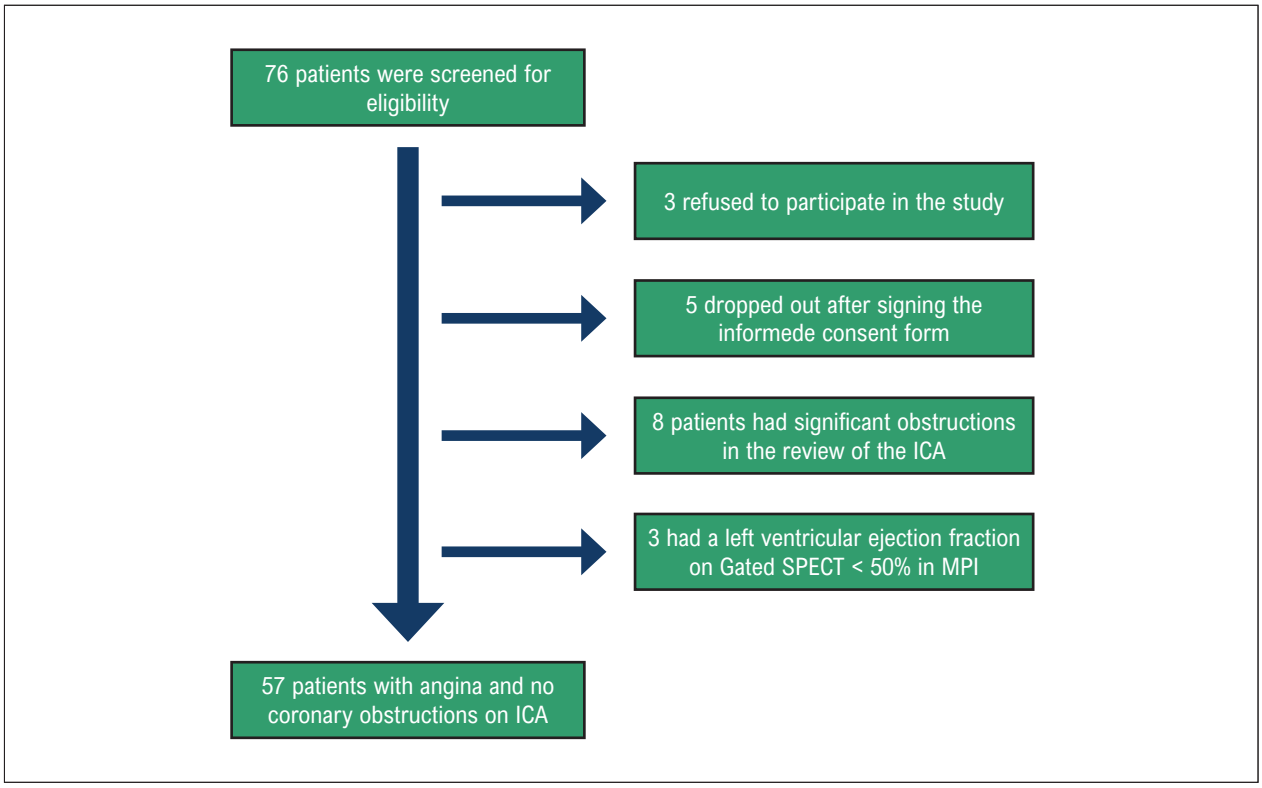

Figure 4 – *Research flowchart; GATED-SPECT: cardiac-gated single-photon emission computer-assisted tomography; MPI: myocardial perfusion imaging; ICA: invasive coronary angiography.*

Erratum

December 2022 Issue, vol. 119(6), pages 883-890

In the Original Article "Coronary Tortuosity as a New Phenotype for Ischemia without Coronary Artery Disease", with DOI: https://doi.org/10.36660/abc.20210787, published in the journal Arquivos Brasileiros de Cardiologia, 119(6): 883-890, in page 884, the correct figure is in the link: http://abccardiol.org/supplementary-material/2022/11906/2021_0787_fig-01 corrigida.jpg

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Coronary Tortuosity as a New Phenotype for Ischemia without Coronary Artery Disease

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Short Editorial related to the article: Coronary Tortuosity as a New Phenotype for Ischemia without Coronary Artery Disease

Coronary artery disease constitutes a great burden in many countries. In many cases, the detection of coronary ischemia by non-invasive imaging may not correlate with the presence of significant coronary stenosis. Therefore, the term "Ischemia with non-obstructive coronary artery (INOCA)" has emerged. Many theories have been proposed for such a phenomenon. Coronary tortuosity (CorT) is one of these etiologies that was found to be associated with subclinical atherosclerosis and increased coronary artery calcium score.[1] Besides, CorT is associated with the same risk factors of ischemia, such as smoking, old age, arterial hypertension and dyslipidemia.[2] CorT was thought to be a phenomenon; however, the association of this phenomenon with multiple cardiovascular disorders augments its clinical impact. Li et al.[3] found that Hypertensive patients with CorT have more incidence of lacunar infarct.[3] Turgut et al.[4] concluded that CorT might indicate impaired left ventricular relaxation.[4] Dogdus et al.[5] proved that CorT negatively affects left ventricular function evaluated by 3D strain parameters with considerable depression of longitudinal deformation of the myocardium.[5]

In this study by Estrada et al.,[6] the investigators found a highly significant association between CorT and ischemia. The presence of ischemia in territories with CorT was more frequent than those without CorT (67% versus 28% ($p<0.0001$)) detected by myocardial perfusion imaging (MPI). This study analyzed the specific features of tortuosity concerning the presence of myocardial ischemia. They found that the number of bend angles detected in systole during coronary angiography is associated with a high risk of myocardial ischemia ($p = 0.021$). Some previous studies considered the geometry of CorT and suggested indices for grading such tortuosity depending mainly on the degree of angulation or bending.[7-9]

Multiple theories were proposed to explain the mechanism that CorT might precipitate ischemia. CorT may cause microcirculatory dysfunction by reducing distal filling pressures and blood flow. This may be due to shearing forces in tortuous arteries that could disturb flow dynamics.[10] Others suggested that simple degeneration of the elastin layer of the atherosclerotic vessel may lead to CorT.[9] Furthermore, CorT is considered by some investigators as a common finding in elderly and hypertensive patients with left ventricular hypertrophy due to elongation and dilatation of coronaries in a limited space of coronary sulci leading to bending or folding of the arteries.[11]

In addition to the abovementioned mechanical and hemodynamic theories, some investigators settled an inflammatory theory as a mechanism of atherosclerosis in the case of CorT. Li et al.[3] proposed a role for inflammatory reaction evidenced by high CRP levels that were found to be associated with CorT. In the same context, Naguib et al.[12] studied the association between CorT in patients without coronary lesions and high monocyte count to low HDL-C ratio (MHR) as a marker of inflammation and oxidative stress. They found that CorT has a significant relationship with MHR, which is now considered a prognostic marker for many cardiovascular diseases. Furthermore, Cerit et al.[13] found that plateletcrit, which is important for inflammation and thrombosis, was independently associated with CorT.

This study by Estrada et al.[6] studied the relationship between CorT-induced ischemia and the affected coronary branch. They found a significant association between CorT and ischemia in the LCX and RCA, but this association was not significant in LAD. Furthermore, the degree of CorT (evidenced by consecutive bend angles and the number of bend angles) had a significant association with ischemia only in LCX. I think this is the first study to analyze the relationship between CorT and ischemia in individual coronary territories.

However, there is still controversy regarding the actual relationship between CorT and coronary ischemia. Despite the previous findings, there are some votes against the role of CorT in atherosclerosis. Li et al.[2] failed to find a significant correlation between CorT and calcium score or diameter stenosis on multivariable analysis. However, this association existed between CorT and moderate calcium score among women.[2] In the same direction, Khosravani-Rudpishi et al.[14] found that tortuous vessels had a lower probability of coronary artery significant stenosis and a lower Gensini score.[14] Furthermore, controversial data were found regarding the severity of CorT and its association with significant coronary artery disease. While Hassan et al.[8] found that severe tortuosity is associated with an increased risk of ischemia, on the contrary, Groves et al.[7] found that patients with severe coronary tortuosity had a significantly lower incidence of significant coronary artery stenosis in coronary angiography.[7]

These apparently controversial data could be justified by hypothesizing that the tortuous vessels may develop atherosclerotic and calcific changes; however, these changes are away from the bends themselves.

I think we need further studies to develop a more valid tortuosity index and to correlate different grades of CorT with functional modalities of assessment of ischemia such as FFR and iFR.

Keywords

Coronary Artery Disease/complications; Myocardial Ischemia/complications; Atherosclerosis; Dyslipidemias; Calcium Metabolism Disorders/complications; Risk Factors; Diagnostic Imaging/methods

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Prevalence of Cardiovascular Complications in Individuals with Sickle Cell Anemia and Other Hemoglobinopathies: A Systematic Review

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Abstract

Background: **Sickle cell anemia (SCA) is a hereditary disease whose cardiovascular complications are the main cause of death, the same being observed in other hemoglobinopathies. Early identification of these changes can favorably modify the course of the disease.**

Objective: **To compare the prevalence of cardiovascular complications between individuals with SCA and individuals with other hemoglobinopathies.**

Method: **Following the recommendations of the PRISMA protocol, a systematic literature review was carried out with searches in PubMed/Medline databases, associated with a manual search. Studies that analyzed the prevalence of cardiovascular alterations in hemoglobinopathies (SCA, sickle cell trait, SC hemoglobinopathy, alpha-thalassemia and beta-thalassemia) were included. The methodological quality of the articles was assessed using the Newcastle-Ottawa scale.**

Results: **Four studies were selected for analysis, resulting in a sample size of 582 participants: 289 with SCA, 133 with SC hemoglobinopathy, 40 with beta-thalassemia, 100 healthy individuals and none with alpha-thalassemia or sickle cell trait. Dilatation of the cardiac chambers, left and right ventricular hypertrophy, pulmonary hypertension, diastolic dysfunction, mitral regurgitation and tricuspid regurgitation are more prevalent in SCA than in the other hemoglobinopathies considered. Myocardial iron overload is more frequent in thalassemia major than in sickle cell anemia. Systolic function is similar between different hemoglobinopathies.**

Conclusion: **There is greater cardiovascular impairment in individuals with SCA than in those with other hemoglobinopathies, reinforcing the necessity for regular cardiovascular follow-up in sickle cell patients.**

Keywords: **Anemia, Sickle Cell; Pregnancy Complications, Cardiovascular; Hemoglobinopathies.**

Introduction

The reduction in morbidity and mortality of individuals with sickle cell disease resulting from advances in specific therapies has become evident. As the age of these patients increases, the chronic effects of hemolytic anemia and vaso-occlusive episodes lead to chronic lesions of target organs, especially cardiovascular complications,[1] which are the main cause of death.[2] Despite therapeutic advances, adult mortality remains high even in developed countries, with a mean age below 50 years.[3]

Although improvements in blood transfusion protocols and the use of iron chelating agents have increased the survival of patients with thalassemia, the main cause of morbidity and mortality in these patients is heart disease,[4] responsible for 75% of deaths.[5] In Brazil, 10 to 20% of transfusion-dependent individuals with thalassemia have severe iron overload, with an incidence of heart disease of 5%.[6]

Thus, there are several cardiovascular complications involved in the clinical course of sickle-cell anemia, as well as in that of other hemoglobinopathies. This study aimed to compare the prevalence of cardiovascular complications among individuals with sickle-cell anemia and other hemoglobinopathies.

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Methods

Study design

Systematic literature review with a search guided by the PRISMA guideline, registered in PROSPERO, under the number CRD42021225542.

Search strategy

The search for articles was performed in the PubMed/Medline databases, using the following descriptors consulted by the Medical Subject Headings (MeSH) and Health Sciences Descriptors (DeCS) websites: "Sickle cell

disease", "Sickle Cell Anemia", "Hemoglobinopathies", "Hemoglobin SC Disease", "Haemoglobin SC", "Sickle Cell Trait", "Beta-thalassemia", "Alpha-thalassemia", "Cardiac", "Cardiovascular". A manual search of the articles was also performed. The Boolean operator "AND" was used to aggregate the descriptors.

Eligibility criteria

Observational studies and randomized and non-randomized clinical trials that met the criteria of analyzing the prevalence of cardiovascular changes in the following hemoglobinopathies (sickle cell anemia, sickle cell trait, SC hemoglobinopathy, alpha-thalassemia and beta-thalassemia) were included. Articles in English and Portuguese published between February 2011 and February 2021 were included. Duplicate publications, systematic reviews and meta-analyses, case reports, series reports and animal studies were excluded.

Identification and selection of studies

Two authors separately analyzed the title and the abstract of each work, identifying which ones met the inclusion criteria. A third researcher evaluated the articles in which there was disagreement, completing the selection of articles eligible for full reading. Subsequently, a complete reading of each study was performed by one of the authors, in order to ensure the criteria of the systematic review, until reaching the final list of works included in the review.

Data extraction and analysis

The extracted data were: title, author, year of publication, design, period and place of study, sample size and objectives. The variables pulmonary hypertension, left ventricular diastolic and systolic dysfunction, right ventricular dysfunction, presence of mitral regurgitation and tricuspid regurgitation were analyzed.

Methodological quality

The methodological quality of the studies was evaluated using the Newcastle-Ottawa scale, a tool indicated for the analysis of cohort and case-control studies. The methodological quality score of the cohort studies was calculated in three components: group selection (0 - 4 points), quality of adjustment for confounding (0 - 2 points) and outcome assessment (0 - 3 points). In case-control studies, group selection (0 – 4 points), quality of adjustment for confounding (0 – 2 points) and exposure (0 – 4 points) were evaluated. The maximum score is 9 points, representing high methodological quality. Two independent researchers judged the quality/risk of bias of the papers.

Results

Identification and selection of studies

From the electronic database and manual search, 325 articles were identified. After removing duplicate articles and selecting by reading titles, abstracts and full texts, 4 articles were included in the qualitative synthesis of the work. The selection of studies is represented in the flowchart in Figure 1.

General characteristics of studies

Of the four articles selected, three are cohort studies and one is a case-control study. The years of publication ranged from 2016 to 2019. The sample size ranged from 110 to 180 participants, totaling 582 participants: 289 patients with sickle cell anemia, 133 with SC hemoglobinopathy, 40 with beta-thalassemia, 100 healthy individuals and none with alpha-thalassemia or sickle cell trait. Twenty individuals had other sickle cell disease genotypes that did not meet the inclusion criteria for this study. Table 1 presents the general characteristics of the studies.

Results

Adjagba et al. found that, although right ventricular dilatation was similar between HbSS and HbSC patients, left ventricular dilatation was more frequent in sickle cell anemia than in SC hemoglobinopathy, having been observed in 51.4% vs 24.2% of patients, respectively [OR = 2.1 (1.11-4.03)], the same occurring with dilatation of both ventricles, present in 38.9% x 12.5% of patients with each genotype, respectively [OR = 3 .4 (1.19-8.13)]. No significant differences were observed between genotypes in the frequency of left myocardial dysfunction measured by left ventricular shortening fraction and E/e´

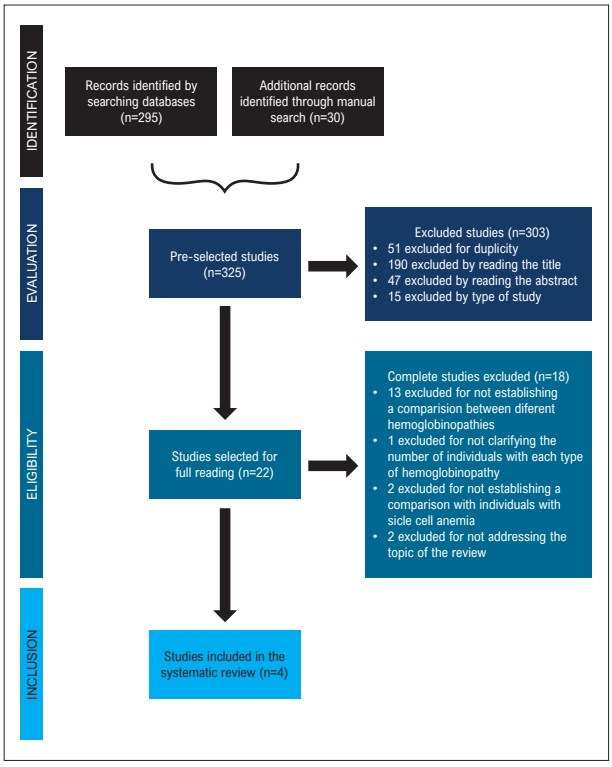

Figure 1 – *Study selection flowchart.*

Table 1 – General characteristics of the selected studies

Author	Year of publication	Title	Performance period	Place of performance	Study design	Sample size	Objective
Philippe M. Adjagba, Gaston Habib, Nancy Robitaille, et al	2016	Impact of sickle cell anaemia on cardiac chamber size in the paediatric population	Not mentioned	Canada	Retrospective cohort	n = 110	To describe the extent of myocardial abnormalities and determine hematologic indices that could primarily affect cardiac function in patients with sickle cell disease
Jamie K. Harrington, Usha Krishnan, Zhezhen Jin, et al	2017	Longitudinal Analysis of Echocardiographic Abnormalities in Children With Sickle Cell Disease	1994 - 2013	United States	Retrospective cohort	n = 172	To identify clinical and laboratory parameters associated with the development of cardiac abnormalities
Paul Guedeney, François Lionnet, Alexandre Ceccaldi, et al	2018	Cardiac manifestations in sickle cell disease varies with patient genotype	Maio 2008 Maio 2015	France	Retrospective cohort	n = 180	To describe cardiac remodeling and its correlations in patients with HbSC and to compare with patients with sickle cell anemia and with healthy individuals
Antoine Fakhry AbdelMassih, Khaled M. Salama, Carolyne Ghobrial, et al	2019	Discrepancy in patterns of myocardial involvement in beta-thalassaemia vs. sickle cell anaemia	April 2017 October 2018	Egypt	Case control	n = 120	To compare left ventricular mechanics in thalassemia and sickle cell patients using the latest 2D spot tracking analysis software

ratio. Left ventricular hypertrophy (LVH) was observed in 25% of patients with SCA, which was not observed in the sample with HbSC.

Harrington et al. evaluated 829 echocardiograms performed in 172 patients, and observed a cumulative incidence of echocardiographic abnormalities. The mean age at the first electrocardiogram was 8.74 ± 3.49 years of age (ranging from 5.12 to 19.7 years of age), with a mean of 4.82 ± 3.06 studies performed per patient over a period of 6.88 ± 5.16 years. The age distribution of the first echocardiogram was: 78 (45.4%) aged 5 to 7 years or younger, 72 (41.8%) aged 7 to 13 years or younger, and 22 (12.8%) above 13 years of age. LVH, increased left ventricular end-systolic diameter (LVESD) and left ventricular end-diastolic diameter (LVEDD) were found at an earlier age than abnormal tricuspid regurgitation velocity (TRV), this last one found mainly in late childhood and at the beginning of the adolescence. The prevalence of echocardiographic abnormalities was 25%, 41%, 58%, 7%, and 25% for LVH, increased LVSD and LVDD, decreased LV EF, and increased TRV, respectively. In addition, patients with HbSS and HbSβ0-thalassemia were 8.04% more likely to have LVH, 8.37% more likely to have LV dilatation at the end of systole, and 11.9% more likely to have LV dilatation at the end of diastole. The chance of developing increased tricuspid regurgitation velocity and decreased LV fractional shortening were similar between the genotypes involved in the study.

Guedeney et al. compared cardiac remodeling between individuals with HbSS and HbSC hemoglobinopathies and healthy individuals, involving 180 patients. LV dilatation was greater in patients with HbSS than in subjects with HbSC [LVDD/BS = 32 mm/m^2 (IQR: 29-33) x 28 mm/m^2 (IQR: 26-30), respectively, $p < 0.0001$; LVEDV/BS = 91 mL/m^2 (IQR: 73-105) x 64 mL/m^2 (IQR: 54-72), respectively, $p < 0.001$], the same occurring with AE [LAV/SC = 49 mL/m^2 (IIQ: 42-60) x 33 ml/m^2 (IQ: 30-38), respectively, $p < 0.001$]. Likewise, LVH was more frequent in SCA than in HbSC [MVE/SC = 101 g/m2 (IQR: 84-115) x 76 g/m^2 (IQR: 65-87), $p < 0.001$; LVM/H = 39 g/m (IQR: 24-48) x 32 g/m (IQR: 28-36), $p < 0.001$], regardless of the indexing method (body surface or height), noting that the LVH was mostly eccentric. In patients with HbSS, an increase in pulmonary systolic blood pressure – assessed by TRV – was observed in 32 (53%) patients, similar between HbSC patients and controls. LV diastolic dysfunction was more prevalent in SCA than in HbSC and healthy subjects ($p = 0.04$). Left ventricular ejection fraction (LVEF) was similar in the three groups.

AbdelMassih et al. evaluated the pattern of myocardial involvement in 120 patients in a case-control study. Myocardial T2* was more indicative of myocardial iron overload in patients with beta-thalassemia major than in those with SCA (myocardial T2* = 16.6 ± 1.8 ms; 25.5 ± 2.2 ms, respectively). The global longitudinal strain (GLS) was similar between patients with beta-thalassemia major and those with SCA, but both groups had lower GLS values when compared to healthy individuals (GLS = -15 ± 1.6%; -21.5 ± 1.9%, individuals with beta-thalassemia major and healthy, respectively; GLS = -15 ± 1.2%; -21.5 ± 1.9%,

individuals with SCA and healthy, respectively). There was a difference between the groups of hemoglobinopathies when the epicardial and endocardial GLS were evaluated: the epicardial GLS was lower in patients with beta-thalassemia major (epicardial GLS = -10.9 ± 2%; -19.9 ± 1.7%, in the beta-thalassemia major and SCA, respectively), endocardial SGL was lower in sickle cell patients (endocardial GLS = -19.95 ± 1.7%; -10.65 ± 1.6%, in beta-thalassemia major and SCA, respectively). It was found that systolic function by LVEF assessed by M-mode and LV fractional shortening was normal and similar in the 3 groups of patients (LVEF = 73.2 ± 3.3 %; 71.2 ± 1.7; 72 .4 ± 2.9, in the beta-thalassemia major group, SCA and healthy individuals, respectively; LV shortening fraction = 35.5 ± 2%; 35.5 ± 0.98%; 37.5 ± 3.3% , in the beta-thalassemia major group, SCA and healthy individuals, respectively), the same being observed for LV diastolic function by the E/e´ ratio (E/e´ = 6.89 ± 2; 6.6 ± 1.9 ; 6.52 ± 1.49 in the beta-thalassemia major group, SCA and healthy subjects, respectively). LVEF assessed by the 3D mode was lower in patients with SCA than in controls (LVEF = 62% ± 11.2 x 66% ± 13.2, respectively) and also lower in patients with beta-thalassemia greater than in controls (LVEF = 61% ± 10.1 x 66% ± 13.2, respectively), being similar in both hemoglobinopathies. The main results are shown in Table 2.

Risk of bias of selected studies

The methodological quality of the studies included in this review was high. Of the cohort studies, one scored eight points on the Newcastle-Ottawa scale and two scored nine points on the same scale. The case-control study obtained 8 points on the scale used.

Discussion

Cardiovascular complications are the main cause of morbidity and mortality in patients with HbSS. The role of the echocardiogram for the early identification of cardiac alterations in these patients is highlighted, as evidenced by the findings of this study. Thus, a higher prevalence of ventricular hypertrophy, dilatation of cardiac chambers, diastolic dysfunction, mitral and tricuspid regurgitation and pulmonary hypertension was observed in individuals with sickle cell anemia compared to those with the other hemoglobinopathies considered in this study.

Dilatation of the cardiac chambers, especially the LV, results from compensatory myocardial remodeling in response to chronic anemia.[7-12] The analysis of associations between echocardiographic variables in patients with sickle cell disease showed that individuals with higher LVDD/BS had higher LAV/BS and TRV values, as well as lower LVEF, indicating left systolic dysfunction with repercussions in the right chambers.[2,10] LVH was independently associated with changes in the echocardiographic parameters of diastolic dysfunction, such as a decrease in the deceleration time of the early mitral inflow velocity, an increase in the E/e´ ratio and an increase in the velocity of tricuspid regurgitation, which can be explained by the reduction in left ventricular compliance in these patients.

Diastolic dysfunction is among the main cardiovascular alterations reported in sickle cell disease, and the frequency of this finding depends on the echocardiographic parameters used to assess diastolic function, the patient's age and associated comorbidities.[9] Vasconcelos et al.[9] explained the occurrence of normal diastolic function in individuals with sickle cell disease as a result of a young age (mean age of 26.5 years), absence of comorbidities and use of tissue Doppler, whose greater specificity derives from its ability to measure myocardial velocities, not suffering alterations with preload changes.[13]

The association verified by Whipple et al.[14] between decreased e´M and e´T and also decreased LVGLS and RVGLS, suggests that the increased prevalence of diastolic dysfunction in children with sickle cell disease reduces myocardial deformability, measured by the GLS. In patients with HbSC, while Adjagba et al.[7] observed a similar E/e´ ratio between these patients and individuals with HBSS, Guedeney et al.[15] found a higher frequency of left ventricular diastolic dysfunction in patients with SCA and systemic arterial hypertension, which corroborates the hypothesis suggested by Desai et al.[8] that the impairment of diastolic function in this group of patients results from increased afterload. These data suggest that diastolic dysfunction is frequent, early and likely to have a multifactorial etiology in individuals with SCA.

In patients with sickle cell disease, systolic function is normally preserved. However, a significant prevalence of low left ventricular systolic function has already been demonstrated in patients with HbSS and HbSC.[7] An early marker of systolic dysfunction, the GSL measures myocardial deformability, and the increase in its values indicates the existence of a baseline condition altering myocardial deformability as a compensatory mechanism. When evaluating the association of GLS with traditional measures of ventricular systolic function – LVEF and STTAP – in children with sickle cell disease, Whipple et al.[14] showed agreement between these variables: decreased LVGLS and RVGLS associated with decreased LVEF and STTAP. The decrease in STTAP reflects impaired RV systolic function. As LV systolic function is usually preserved in sickle cell disease, abnormal STTAP may indicate chronic elevation of pulmonary pressures. Furthermore, the RVGLS was impaired by high pulmonary pressure and RV diastolic dysfunction.[12]

In the comparison between SCA and beta-thalassemia major, the included case-control study[16] showed a predominance of subendocardial dysfunction in SCA and subepicardial dysfunction in beta-thalassemia major, explained by the high vascularity of the epicardium with consequent iron deposition. Myocardial T2* was strongly correlated with epicardial GLS but not with endocardial GLS. In turn, the decrease in subendocardial GLS seen in SCA is justified by the microvascular disease in these patients, characterized by possible subendocardial microvascular ischemia, through NO depletion and suggested by the increase in LDH.

Regarding the parameters to assess systolic function, it is worth mentioning that, in the same study, LVEF measurements differed according to the method used: when

Table 2 – Main results of the selected studies

Author/year of publication	Population	Analyzed cardiovascular parameter	Cardiovascular alteration found	Conclusion
Philippe M. Adjagba et al. (2016)	110 patients with sickle cell disease (72 HbSS; 32 HbSC; 6 HbSβ – thalassemia)	RVV LVV LVM FSLV E/e´ relation MPI	RVD LVD Diastolic dysfunction Systolic dysfunction Abnormality in LVM	LVD was higher in patients with SCA (HbSS) than in patients with SC hemoglobinopathy (HbSC); LVH was observed only in patients with SCA (HbSS) and the abnormality in LVM was more prevalent in this group of patients; RVD, FSLV and E/e´ relation were similar between the patients with SCA (HbSS) and the individuals with SC hemoglobinopathy (HbSC).
Jamie K. Harrington et al. (2017)	172 patients with sickle cell disease (117 HbSS; 41 HbSC; 5 HbSβ^{0} – thalassemia; 9 HbSβ^{+} – thalassemia)	LVM LVESD LVEDD FSLV TRV	LVH LVD at the end of the systole and at the end of the ao final da sístole e ao final da diastole ↓EF OF LV ↑TRV	Patients HbSS e HbSβ0-thalassemia were more likely to develop LVH, LVD at the end of the sistole and at the end of the diastole. The chance of developing increased TRV and decrease of FSLV were similar between all genotypes involved in this study.
Paul Guedeney et al. (2018)	120 patients with sickle cell disease (60 HbSS; 60 HbSC) and 60 healthy patients	LVEDD/BS LVM/BS LVM/H LVEDV/BS CI TRV EFLV EM wave A wave E/A relation DT e´ wave E/e´ relation LAV/BS	LVD at the end of diastole LAD LVH ↑CI ↑TRV ↑E/e´relation LVDD	LAD, LVD e CI were higer in HbSS patients than in HbSC patients and the controls; LVH, increase of TRV and diastolic dysfunction disfunção of LV were more frequent in HbSS patients than in HbSC patients and the controls (HbSS patients had higher: E wave, E/A relation, DT, e´wave, E/e´ relation); LAD, LVD, LVM/BS, LVM/H, E/e´ relation were higer in HbSC patients than in the control; e´ wave was smaller in HbSC patients than in controls; CI e TRV were similar between HbSC patients and the controls; EFLV was similar between the 3 groups.
Antoine Fakhry AbdelMassih et al. (2019)	40 patients with sickle cell anemia (HbSS), 40 patients with beta thalassemia major (β0/β0) and 40 healthy patients	EFLV FSLV E/e´ relation GLS GLS epicardial SGL endocardial T2* miocardyal	Myocardial iron overload ↓GLS Subendocardial dysfunction Subepicardial dysfunction	T2* myocardial was higher in patients with beta thalassemia major than in patients with SCA; GLS was similar between patients with beta thalassemia major and those with SCA, but both groups of patients had GLS reduced in comparision with healthy individuals; Epicardial GLS was lower in patients with beta thalassemia major than in patients with SCA; Endocardial GLS was lower in patients with SCA than in patients with beta thalassemia major; The systolic function and the diastolic function of left ventricle were normal and similar between the 3 groups.

A wave: Wave of atrial contraction in mitral flow; CI: Cardiac index; DT: Deceleration time; e´ wave: Tissue Doppler early diastolic velocity wave; E/e´ relation: Relation between E wave in the mitral flow and the e wave by tissue Doppler; E/A relation: Relationship between E and A waves in mitral flow; EF: Ejection fraction; EFLV: Ejection fraction of left ventricle; EM wave: Rapid filling wave in mitral annulus mitral flow; FSLV: Fraction of shortening of the left ventricle; GLS: Global longitudinal strain; LAD: Left atrial dilatation; LAV/BS: Left atrial volume indexed by body surface; LV: Left ventricle; LVD: Left ventricular dilatation; LVDD: Left ventricular diastolic dysfunction; LVEDD: Left ventricular end-diastolic diameter; LVEDV/BS: Left ventricular end-diastolic volume indexed by body surface; LVEF: Left ventricular ejection fraction ; LVH: Left ventricular hypertrophy; LVESD: Left ventricular end-systolic diameter; LVM: Left ventricular mass; LVM/BS: Left ventricular mass indexed by body surface; LVM/H: Left ventricular mass indexed by height; LVV: Left ventricular volume; MPI: myocardial performance index; RVD: Right ventricular dilatation; RVV: Right ventricular volume; TRV: Tricuspid regurgitation velocity; T2: Myocardial relaxometry of cardiac magnetic resonance.*

evaluated by the M-mode, LVEF was similar between the 3 groups, however, when analyzed by 3D echocardiography, LVEF was shown to be lower in individuals with SCA than in healthy individuals and similar in comparison with those with major beta-thalassemia.

Right ventricular function is commonly assessed through TRV and systolic excursion of the tricuspid annulus plane. TRV was included among the predictors of adverse events in the work by Vasconcelos et al.[9] Furthermore, TRV ≥ 2.5 m/s was a predictor of mortality within 3 years by Damy et al.[10] In this work, elevated TRV was associated with lower LVEF and higher LAV/BS, changes commonly associated with high filling pressures and the risk of postcapillary pulmonary hypertension.

It is noteworthy that most studies were carried out with relatively small samples. In addition, the cardiovascular variables analyzed differed in the included studies. Despite the limitations, the present review should be considered an update tool on a pathology of systemic involvement, allowing a better understanding of cardiovascular alterations in the different genotypes of hemoglobinopathies.

Conclusion

The prevalence of cardiovascular complications such as cardiac chamber dilatation, LVH and RVH, pulmonary hypertension, diastolic dysfunction, mitral regurgitation and tricuspid regurgitation are higher in patients with SCA than in individuals with the other hemoglobinopathies considered in this study. Overall, there were no differences between the systolic function of patients with SCA and those with other hemoglobinopathies.

Author Contributions

Conception and design of the research, Acquisition of data, Analysis and interpretation of the data and Writing of the manuscript: Lopes A; Critical revision of the manuscript for important intellectual content: Lopes A, Dantas MT, Ladeia AMT.

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.

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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Sickle Cell Anemia as the First in the Hierarchy for Cardiac Alterations, Drives Attention to the Whole Spectrum of Hemolytic Anemias

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Short Editorial related to the article: Prevalence of Cardiovascular Complications in Individuals with Sickle Cell Anemia and Other Hemoglobinopathies: A Systematic Review

The focus on the cardiac repercussions of Hemolytic Anemias has been greatly emphasized by publications issued by academic and official government documents that are easily accessed by all health professionals, mainly articles that aim at Sickle Cell Anemia[1,2] and Thalassemia.[3,4]

Sickle cell disease is the most frequent genetic hemoglobinopathy worldwide.[5] Thanks to the improvement of the medical management of these patients, their life expectancy has improved in recent years.[6] However, cardiopulmonary complications remain one of the main causes of death in adult patients with sickle cell disease.[7]

Current knowledge about cardiac involvement in sickle cell disease is mainly derived from studies of sickle cell anemia genotypes.[8,9] Pulmonary systolic hypertension, assessed by increased tricuspid regurgitation rate (TRV) and left ventricular diastolic dysfunction diagnosed by ultrasound, has been associated with increased mortality and is characteristic of sickle cell anemia characterized by hemoglobin S[8-10] homozygosis. On the other hand, hemoglobin SC disease (HbSC), resulting from compound heterozygosity for two different mutations of the beta-globin gene, has a different pathophysiology[11] and a more attenuated clinical profile of clinical presentation.[12] Patients with HbSC usually have a relatively low hemolysis rate and only mild anemia.[11] In addition, the prevalence of obesity is higher in patients with HbSC than in sickle cell anemia.[13] This non-hematological comorbidity may contribute to cardiac remodeling.[14] Currently, echocardiography is recommended for routine follow-up of all patients with sickle cell disease, regardless of genotype.

Despite advances in the management of thalassemia major, heart disease remains the main cause of mortality in patients with this disease.[15]

Cardiac involvement in thalassemia encompasses a spectrum of disorders, including myocardial dysfunction, arrhythmias, hypertension and peripheral vascular disease.[16] Although cardiac siderosis (accumulation of iron in cardiac myocytes) as a consequence of repeated blood transfusions is considered the main etiological factor for myocardial dysfunction in transfusion-dependent patients, other pathophysiological mechanisms are increasingly recognized, especially in patients not dependent on transfusion.[17] Managing cardiac complications in thalassemia major depends on treating the underlying pathophysiology, which is often iron overload.

Susceptibility to iron toxicity and its phenotypic manifestations vary widely among thalassemia patients. At present, the detection of myocardial iron deposition by cardiac magnetic resonance imaging remains the best marker of future cardiac dysfunction.[18]

Echocardiographic studies suggest that myocardial deposition can directly affect left ventricular contractility, while in others, it may cause myocardial restriction of the left ventricle with concomitant pulmonary hypertension and predominant right heart failure.[19]

The rarest forms of Hemolytic Anemias have also to be investigated because they present particular characteristics that involve their clinical follow-ups.[20]

Keywords

Cardiovascular Diseases; Anemia, Sickle Cell; Anemia, Hemolytic; Hemonoglobinopathies/complications: Hypertension, Pulmonary/complications; Diagnostic, Imaging/methods.

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Original Article

Right Ventricle Involvement by Glycogen Storage Cardiomyopathy (PRKAG2): Standard and Advanced Echocardiography Analyses

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Abstract

Background: PRKAG2 syndrome is a rare, early-onset autosomal dominant inherited disease. We aimed to describe the right ventricle (RV) echocardiographic findings using two and three-dimensional (2D and 3D) modalities including myocardial deformation indices in this cardiomyopathy. We also aimed to demonstrate whether this technique could identify changes in RV function that could distinguish any particular findings.

Methods: Thirty patients with genetically proven PRKAG2 (R302Q and H401Q), 16 (53.3%) males, mean age 39.1 ± 15.4 years, underwent complete echocardiography examination. RV-focused, 4-chamber view was acquired for 2D and 3D measurements. Student's t or Wilcoxon-Mann-Whitney tests were used to compare numerical variables between 2 groups, and $p < 0.05$ was considered significant.

Results: Twelve patients (40%) had a pacemaker implanted for 12.4 ± 9.9 years. RV free wall mean diastolic thickness was 7.9 ± 2.9 mm. RV 4-chamber longitudinal strain (RV4LS), including the free wall and interventricular septum, was –17.3% ± 6.7%, and RV free wall longitudinal strain (RVFWLS) was −19.1% ± 8.5%. The RVFWLS apical ratio measured 0.63 ± 0.15. Mean RV 3D ejection fraction (EF) was 42.6% ± 10.9% and below normal limits in 56.7% of patients. Positive correlation occurred between RV 3DEF, RV4LS, and RVFWLS, especially for patients without a pacemaker ($p = 0.006$).

Conclusion: RV involvement in PRKAG2 syndrome is frequent, occurring in different degrees. Echocardiography is a valuable tool in detecting RV myocardial abnormalities in this condition. The use of 2D RV4LS, RVFWLS, and 3DEF offers reliable indicators of RV systolic dysfunction in this rare, challenging cardiomyopathy.

Keywords: PRKAG2 Syndrome/genetics; Glycogen Storage Disease/complications; Hypertrophy, Right Ventricular; Cardiomyopathy, Hypertrophic Familial; Echocardiography/methods; Pacemaker, Artificial; Stroke Volume.

Introduction

The PRKAG2 gene was initially described in 2000 as an active part of metabolism in the transcription process of AMP-activated protein kinase AMPK).[1,2] In nearly half of the reported cases, genomic changes involving this gene are due to the Arg302Gln mutation, which replaces arginine with glutamine at codon 302, known as R302Q. The literature also describes 28 additional mutations.[3] The PRKAG2 mutation results in loss of function of the γ2 subunit of AMPK and features a metabolic defect responsible for glycogen metabolic disease. The main phenotype consists of ventricular hypertrophy associated with abnormalities in the cardiac conduction system, including ventricular pre-excitation syndrome.[4]

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PRKAG2 mutation is considered a rare disease, although it is probably underestimated, because many cases are improperly diagnosed, often being labeled as familial sarcomeric hypertrophic cardiomyopathy. The inheritance pattern is dominant, with complete penetrance and varying degrees of expression and prevalence still unmentioned in the literature.[5,6]

Two- and three-dimensional (2D and 3D) echocardiography and myocardial deformation indices (strain/strain rate) by speckle tracking (STE) are relatively recent techniques, yet they are already used for assessing left ventricle (LV) function. More recently, these techniques have also been validated for assessing right ventricle (RV) function.[7,8]

Our research group recently published a study of the LV echocardiography findings in this same series of patients.[9]

The recognized importance of the RV in cardiomyopathies is radically changing, and this significantly affects cardiac physiology, hemodynamics, and the development of symptoms.[10] Compared to systemic circulation, pulmonary circulation has a much lower vascular resistance and greater pulmonary artery distensibility.[11-14]

We aim to describe the RV echocardiographic findings using 2D and 3D echocardiography and STE. We also aim to identify if this technique could eventually detect any particular changes in RV function in glycogen storage cardiomyopathy when compared to LV. As little research exists associating RV echocardiographic findings with PRKAG2 syndrome, we seek to investigate the presence of echocardiographic parameters that could suggest RV hypertrophy associated with glycogen deposit cardiomyopathy.

Methods

Patients and study protocol

This is an observational, clinical, transversal study, based on a cohort of patients with genetically proven PRKAG2 syndrome. Patients with other hypertrophic cardiomyopathy etiologies were excluded. The target population consisted of 30 patients from 5 families with PRKAG2 gene mutation (28 Arg302Gln and 2 His401Gln), detected utilizing Sanger sequential genetic testing. All patients underwent clinical examination, with a standard 12-lead electrocardiogram and echocardiogram. The institutional review board approved the protocol and all patients signed a written informed consent form. Our study was performed following the guidelines of Good Clinical Practice and was approved by the local ethics committees.

Echocardiographic analysis

All patients underwent a complete transthoracic echocardiography examination, following the recommendations of the American Society of Echocardiography (ASE) and the European Association of Cardiovascular Imaging (EACVI).[15] All studies were performed using a commercially available echocardiographic system, Vivid E9 machine (GE Healthcare, Horten, Norway). The examination included M-mode, 2D measurements, 2D STE of longitudinal strain, and 3D measurements according to The Guidelines for the Echocardiographic Assessment of the Right Heart in Adults: a report from the ASE.[16] The RV-focused, 4-chamber view was acquired for 2D and 3D measurements, and care was taken to obtain the image demonstrating the maximum diameter. RV 2D linear dimensions were measured, including RV basal, mid-cavity, and longitudinal dimensions. The RV outflow tract was measured at end-diastole in the parasternal long-axis view. RV wall thickness was measured in diastole, from the subcostal view, using M-mode imaging.

Tricuspid annular plane systolic excursion (TAPSE) was obtained by M-mode, measured from the tricuspid lateral annulus.

Inferior vena cava was measured proximal to the junction of the hepatic veins at end-expiration. RV 4-chamber longitudinal strain (RV4LS) was calculated by averaging values of all 6 RV segments. RV free wall longitudinal strain (RVFWLS) was obtained by averaging the 3 free wall RV segments: basal, mid, and apical. We also calculated the RVFW apical ratio using the equation: [apical peak systolic longitudinal strain (PSLS) / (basal PSLS + mid-PSLS)]. All data were reviewed offline. RV transthoracic 3D echocardiography was performed in all patients. Six electrocardiogram-gated consecutive beats were acquired to generate the full RV volume. Post-processing of real-time 3D images was performed using TomTec software 1.1, with the endocardial tracing of all planes. RV volumes were semi-automatically computed throughout the entire cardiac cycle, from which end-diastolic volume and end-systolic volume were obtained, and stroke volume and ejection fraction (EF) were calculated. Intra- and interobserver reproducibility were assessed on a subsample of 9 randomly selected patients.

Statistical analysis

The sample sized used was a convenience sample due to the rarity of this condition. Categorical variables were presented by absolute and relative frequencies and numerical variables as mean ± standard deviation if normally distributed and median ± interquartile range if abnormally distributed. The normality of the numerical variables was assessed using the Shapiro-Wilk test. Student's t or Wilcoxon-Mann-Whitney tests were used to compare numerical variables between 2 groups used for independent samples. The association between categorical variables was assessed using Fisher's exact test. Spearman's correlation coefficient was used to assess the association between 2 numerical variables.

The 30 cases were randomly assigned numbers from 1 to 30 using R software. To assess consistency and reproducibility, 2 independent observers randomly selected 9 numbers for remeasurement. The choice for the number of cases was arbitrary.

Mean differences and intraclass correlation coefficients (ICC) were obtained. Their intra- and interobserver confidence intervals (CI) were both 95%. Intra- and interobserver measurements were assessed using the Shapiro-Wilk test. Student t-tests for paired samples were used to compare mean differences.

The analyses were performed using R software version 3.5.2, and $p < 0.05$ was considered significant.

Results

Table 1 shows the clinical and demographic characteristics of the patients in the study. The majority were male, and more than half were asymptomatic. Palpitation was the most frequent clinical symptom. Pre-excitation syndrome, hypertension, and flutter were prevalent signs.

RV echocardiographic parameters are listed in Table 2. The 3D image quality was inadequate in 2 patients.

It is important to report that, during the echocardiogram, only 1 patient presented atrial fibrillation. Measured by the subcostal view using M-mode, RV lateral wall median diastolic thickness was 7.0 ± 3.0 mm (Figure 1). Only 3 patients presented normal values, and, in 1 patient, the measurement reached 20 mm. Only 3 patients showed TAPSE values below 17 mm.

Table 1 – Clinical and demographic characteristics of patients

Population, n = 30	
Male	16 (53.3%)
Age (years)*	39.1 ± 15.2
BMI (kg/m^2) *	26.9 ± 3.8
BSA (m^2)*	1.8 ± 0.2
Heart rate (bpm)**	60.0 (53.0 – 63.0)
Blood pressure	
Systolic (mmHg)**	120.0 (112.5 – 130.0)
Diastolic (mmHg)**	77.5 (70.0 – 80.0)
Signs and symptoms	
Pre-excitation	19 (63.3%)
Asymptomatic	16 (53.3%)
Pacemaker	12 (40%)
Hypertension	10 (33.3%)
Palpitations	7 (23.3%)
Flutter	6 (20%)
AF	4 (13.3%)
Shortness of breath	2 (6.7%)
Presyncope	2 (6.7%)

*AF: atrial fibrillation; BMI: body mass index; BSA: body surface area: bpm: beats per minute. Data showed as * mean ± standard deviation, ** median (1st – 3rd quartile).*

Table 2 – Echocardiographic RV parameters of 30 patients

Variable	
RVFW thickness (mm)**	7.0 (6.0 – 9.0)
TAPSE (mm)*	18.8 ± 3.7
RV basal cavity diameter (mm)*	37.6 ± 5.7
RV mid cavity diameter (mm)*	31.0 ± 6.1
RV longitudinal diameter (mm)**	49.0 (35.0 – 61.0)
RVOT PLAX diameter (mm)*	28.0 ± 4.0
IVC at end-expiration (mm)**	17.0 (16.0 – 19.0)
RV4LS (%) **	–18,8 (–14,0 – 20,9)
RVFWLS (%) **	–20.3 (–16.6 – 25.3)
RVFW basal LS (%) *	–18.0 ± 5.1
RVFW mid LS (%) *	–21.8 ± 5.8
RVFW apical LS (%) *	–24.3 ± 7.1
RV apical ratio*	0.63 ± 0.15
RV 3D EDV (mL) **	95.2 (76.2 – 129.9)
RV 3D ESV (mL) **	54.0 (44.8 – 69.6)
RV 3D SV (mL) **	44.6 (30.4 – 59.6)
RV 3D EF (%) *	42.6 ± 10.9

*EDV: end-diastolic volume; EF: ejection fraction; ESV: end-systolic volume; IVC: inferior vena cava; PLAX: parasternal long-axis; RV: right ventricle; RV4LS: right ventricle longitudinal strain; RVFW: right ventricle free wall; RVFWLS: right ventricle free wall longitudinal strain; RVOT: right ventricular outflow tract; SV: stroke volume; TAPSE: tricuspid annular plane systolic excursion; 3D: three-dimensional. Data showed as * mean ± standard deviation, ** median (1st – 3rd quartile).*

Parasternal long-axis anterior portion of RV outflow tract dimension at the proximal level presented higher values compared to normal in 23% of patients, as reported in the literature, except for the longitudinal dimension. This value suggests that the RV chamber increase occurred in the transverse section.

Tricuspid regurgitation was detected in half of patients, but only 4 presented pulmonary artery systolic pressure above normal limits, and the maximum estimated value reached 48 mmHg.

Inferior vena cava was dilated in only 2 patients.

In 3 patients, RV4LS was significantly reduced, relating to more thickened lateral wall (Figure 2).

Table 2 also shows the mean RVFWLS values of each segment. We can observe that the RVFWLS basal values are lower than medial ($p = 0.016$) and apical segments ($p < 0.001$).

RVEF was within normal limits in 13 patients and below 35% in 7 patients (Figure 3).

Patients with a pacemaker (PM) were significantly older ($p < 0.001$), and they had a higher proportion of atrial fibrillation compared to patients without PM ($p = 0.018$). The pacemaker was implanted at 38.1 ± 13 years, and the median time of use was 12.4 ± 9.9 years.

Patients with PM presented significantly lower values of 3D LVEF, fractional shortening, and 3D global circumferential strain.

We detected a statistically significant difference between measurements of RVFWLS basal and mid-segment between patients with and without PM, as shown in Table 3.

However, no other significant differences appeared among the RV echocardiographic findings between patients with and without PM.

The correlations between the strain variables and RVEF were assessed, as shown in Table 4. A positive correlation occurred between EF and RVFWLS ($r = 0.65$, $p = 0.006$), indicating that the higher the absolute value of RVFWLS, the higher the EF values. Considering RV4LS, correlation was lower in all patients and absent in patients with PM.

We also found a positive correlation between the reduction of LVEF and RVFWLS (less than 50% and −18%, respectively) ($r = 0.80$, $p = 0.05$).

The reproducibility of strain and 3D measurements, and the ICC and CI for inter- and intraobserver variability are summarized in Table 5.

Discussion

Mutations in the PRKAG2 gene alter AMPK homeostasis, and the echocardiographic assessment of patients with the mutation is an opportunity to assess the potential long-term systemic consequences of AMPK activation. By assessing these consequences, new lines of research could indicate metabolic pathways involved in the disease pathophysiology leading to partial or total phenotype recognition.[17] PRKAG2 syndrome has different cardiac phenotypes, ranging from an asymptomatic condition to sudden cardiac death, including biventricular hypertrophy, pre-excitation, atrioventricular conduction abnormalities, atrial flutter, and fibrillation.[18,19]

A large multicenter European cohort was recently published reporting data from 90 patients with PRKAG2 variants.[20] This study showed that patients with PRKAG2 genetic variants have a poor prognosis with a high rate of complications, including juvenile onset of conduction disease, advanced HF, and potentially lethal arrhythmias.

Evaluation of RV size and systolic performance is increasingly in demand due to its recognizable significance and prognosis, especially in hypertrophic cardiomyopathy, arrhythmogenic RV cardiomyopathy, and amyloidosis.[21] To the best of our knowledge, this research represents the largest RV echocardiographic study in a population with PRKAG2 mutation. We aimed to describe the RV findings in this rare genetic disorder and the occurrence of dysfunction, incidence, and degree of dysfunction.

The RV was affected in the great majority of patients. RV hypertrophy occurred in 90% of patients, presented a regular pattern, involved all portions of the chamber, and reached 20 mm in 1 case. This finding is similar to other infiltrative or genetic diseases.[22,23] Rosca et al.[23] related that patients with hypertrophic cardiomyopathy had increased RV wall thickness compared to controls with increased calculated sudden cardiac death risk.[23]

We evaluated these patients' myocardial deformation (RV4LS and RVFWLS), RV volumes, and EF. We found that the RVFWLS of basal segments showed lower values than mid and apical segments. However, the RVFW ratio showed that the RV strain analyses presented no apical

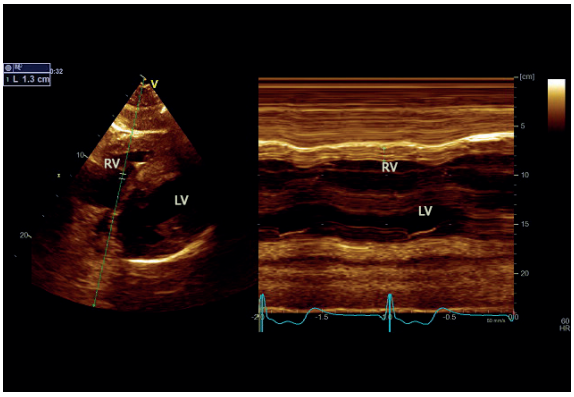

Figure 1 – *Measurement of end-diastolic right ventricle free wall thickness. Subcostal 2-dimensional image of the 4-chamber view. M-mode image indicating wall thickness at end-diastole (1.3 cm). LV: left ventricle; RV: right ventricle.*

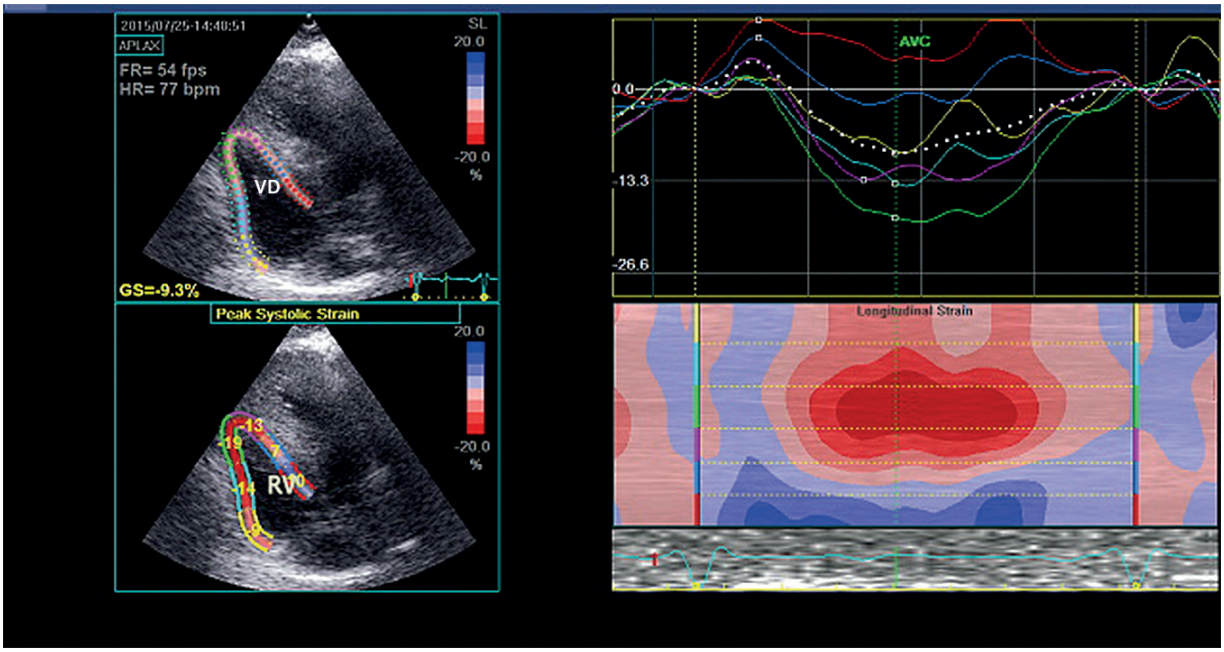

Figure 2 – *Two-dimensional speckle tracking analysis of the right ventricle from a focused apical 4-chamber view. The global average systolic strain values and time curves are obtained by tracking of a 6-segment region of interest. Right ventricle 4-chamber longitudinal strain measured 9.3%. GS: global strain; RV: right ventricle.*

sparing pattern, as described in systemic light-chain cardiac amyloidosis.[24] It is noteworthy that RVFWLS was feasible in all patients.

We found that RVEF was below normal limits in more than half of patients (56.7%), and, in 7 patients, RVEF was below 35%. These values were unaffected by PM, and they could indicate a differential signal of this disease when compared to other hypertrophic phenotypes. We considered normal RVEF ≥ 45%.[8] Some patients (17.2%) also presented reduced LVEF, especially patients with

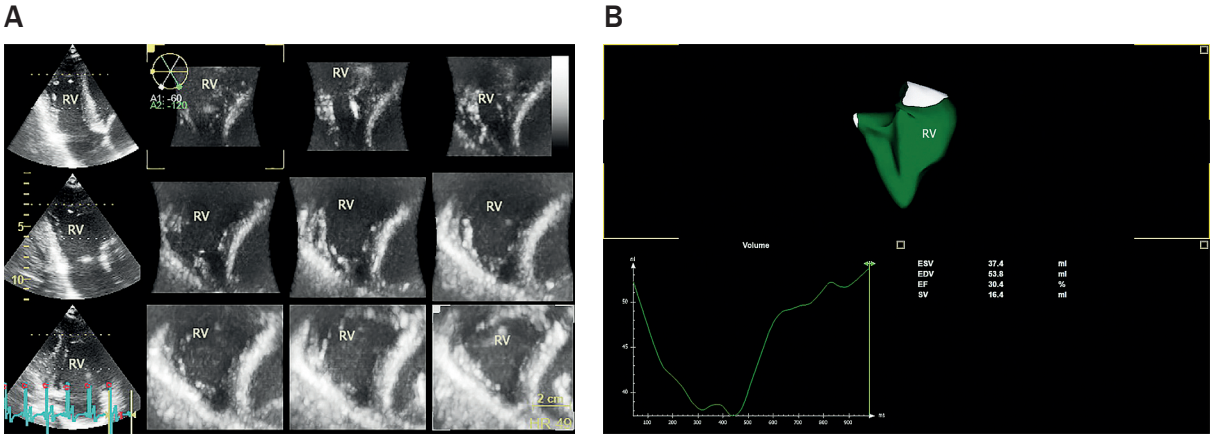

Figure 3 – *The 3-dimensional dataset was acquired from an RV-focused apical 4-chamber view. In A, there is a multiplanar short-axis view to verify the endocardial borders. In B, we can see the RV 3-dimensional model obtained with the volume curve. EDV: end diastolic volume; EF: ejection fraction; ESV: end systolic volume; RV: right ventricle; SV: stroke volume.*

Table 3 – Echocardiographic RV parameters of patients without and with pacemaker

Variable	Without PM (n=18)	With PM (n=12)	p-value
RVFW thickness (mm)**	7.0 (6.0 – 8.8)	8.0 (6.5 – 9.0)	0.233 W
TAPSE (mm)*	19.9 ± 2.9	17.0 ± 4.1	0.060 T
RV basal cavity diameter (mm)*	36.8 ± 4.7	39.0 ± 7.1	0.372 T
RV mid cavity diameter (mm)*	31.0 ± 5.4	31.1 ± 7.5	0.973 T
RV longitudinal diameter (mm)*	49.8 ± 13.4	49.0 ± 15.5	0.892 T
RVOT PLAX diameter (mm)*	27.0 ± 4.2	29.6 ± 3.3	0.088 T
IVC at end-expiration (mm)**	17.0 (16.0 – 18.8)	18.0 (16.5 – 19.5)	0.440 W
RV4LS (%) *	–18.5 ± 6.8	–13.0 ± 6.4	0.233 T
RVFWLS (%) **	–24.0 (–18.3 – –25.7)	–18.6 (–13.0 – 22.2)	0.187 W
RVFW basal LS (%) *	–19.7 ± 4.9	–15.6 ± 4.5	0.037T
RVFW mid LS (%) **	–26.0 (-18.5 – –26.5)	–19.0 (–14.5 – –23.5)	0.039 W
RVFW apical LS (%) *	–25.8 ± 7.3	–22.2 ± 6.6	0.200 T
RV apical ratio*	0.61 ± 0.18	0.65 ± 0.11	0.458 T
RV 3D EDV (mL)**	95.7 (84.9 – 119.0)	92.9 (69.2 – 149.5)	0.746 W
RV 3D ESV (mL)**	56.0 (45.7 – 68.4)	51.5 (43.4 – 79.8)	0.963 W
RV 3D SV (mL)**	45.1 (36.2 – 59.2)	30.6 (29.3 – 59.4)	0.742 W
RV 3D EF (%) **	48.5 (36.7 – 51.6)	37.5 (32.8 – 40.6)	0.259 W

*EDV: end-diastolic volume; EF: ejection fraction; ESV: end-systolic volume; IVC: inferior vena cava; PLAX: parasternal long-axis; PM: pacemaker; RV: right ventricle; RV4LS: right ventricle longitudinal strain; RVFW: right ventricle free wall; RVFWLS: right ventricle free wall longitudinal strain; RVOT: right ventricular outflow tract; SV: stroke volume; TAPSE: tricuspid annular plane systolic excursion; 3D: three-dimensional. Data showed as * mean ± standard deviation, ** median (1st – 3rd quartile). T Student's t and W Wilcoxon-Mann-Whitney test for independent samples.*

PM. As previously reported, patients with PM presented significantly lower values of 3D LVEF, fractional shortening, and 3D global circumferential strain.[25]

RVEF reduction occurred in a greater proportion of patients and will likely be a differential signal compared to other hypertrophic cardiomyopathies such as Fabry and Danon diseases.

Echocardiography is a practical, non-invasive technique to identify morphological and functional alterations in clinical practice.[15]

Even asymptomatic patients presented RV4LS and RVFWLS below normal reference limits. As the feasibility of 3D RV volume estimation has been proven in this syndrome, this method can be reliably applied in clinical diagnoses.[26,27]

Echocardiography presents no harmful effects in patients with PM, and it has lower cost, higher portability, and easier reapplication than cardiac magnetic resonance.[28]

We observed that conventional echocardiographic indices, like TAPSE, were unreliable indicators for RV dysfunction detection. In previous studies, with other infiltrative diseases, these indicators showed less sensitivity to detect functional myocardial alterations than RV 2D STE analyses.[27] Interestingly, by using Doppler, we detected no obstruction in the RV outflow tract at rest. A recently published case report detected a dynamic biventricular outflow tract obstruction in a patient with a syncopal episode. Genetic testing revealed that the patient was heterozygous for R302Q missense mutation in the PRKAG2 gene, as in the majority of our cases.[26]

We confirmed a positive correlation between RVFWLS and RVEF, with statistical significance. These findings indicate that the deformation indices are a fast and widely available method to detect dysfunction, comparable to 3D EF in patients with the PRKAG2 mutation. Additionally, a positive correlation occurred, associating reductions of both LVEF and RVFWLS.

We recognize limitations in the study, such as a relatively small number of patients. The software for obtaining RV4LS and RVFWLS was adapted from the software designed to measure the LV. Tricuspid regurgitation was detected in half of the study population, and increased systolic pulmonary pressure occurred in 4 patients, which was evaluated solely by this method.

Additional research using these criteria prospectively and the use of different imaging techniques for comparison are recommended to further validate our findings.

Table 4 – Correlations between 3D RV EF and RV4LS and RVFWLS in all patients and those without and with a pacemaker

Group	Variable	3D RV EF	p-value
All patients	RV4LS	r = 0.445	0.018
	RVFWLS	r = 0.594	0.001
Without PM	RV4LS	r = 0.475	0.054
	RVFWLS	r = 0.654	0.006
With PM	RV4LS	r = 0.355	0.286
	RVFWLS	r = 0.533	0.091

EF: ejection fraction; PM: pacemaker; r: Spearman's correlation coefficient; RV: right ventricle; RV4LS: right ventricle longitudinal strain; RVFWLS: right ventricle free wall longitudinal strain; 3D: three-dimensional.

Conclusion

RV involvement in PRKAG2 is frequent and occurs in different degrees. Echocardiography is a valuable tool in detecting RV myocardial abnormalities in PRKAG2 cardiomyopathy. Two-dimensional RV4LS, RVFWLS, and 3D EF are reliable indicators of RV systolic dysfunction in this rare disease. Additional longitudinal studies are warranted to further understand the natural history of RV involvement and determine its impact on patient outcomes.

Author Contributions

Conception and design of the research: Pena JLB, Melo FJ, Santos WC, Moura I, Nakashima GP, Freitas NC, Sternick EB; Acquisition of data: Pena JLB, Santos WC, Moura ICG, Nakashima GP, Freitas NC, Sternick EB; Analysis and interpretation of the dat and Writing of the manuscript: Pena JLB, Melo FJ, Santos WC, Moura ICG, Nakashima GP, Freitas NC, Sternick EB; Statistical analysis: Pena JLB,

Table 5 – Intra- and interobserver data variability

	Intraobserver		Interobserver	
	Mean* (95% CI)	ICC (95% CI)	Mean* (95% CI)	ICC (95% CI)
RV4LS	0.4 (0.6; 1.5) ^{NS}	0.99 (0.93; 1.00) †	1.0 (2.0; 0.7) ^{NS}	0.98 (0.74; 1.00)†
RVFWLS	0.1 (2.4; 2.6) ^{NS}	0.94 (0.65; 0.99)†	0.4 (1.9; 2.7) ^{NS}	0.96 (0.75; 0.99)†
3D EF	1.3 (1.2; 3.9) ^{NS}	0.94 (0.66; 0.99)†	0.3 (2.5; 3.2) ^{NS}	0.93 (0.61; 0.99)†

**Mean of differences between intraobserver measurements (first and second measurements) and interobserver (observer 1 and observer 2 [collected study data]). CI: confidence interval; EF: ejection fraction; ICC: intraclass correlation coefficient; RV4LS: right ventricle longitudinal strain; RVFWLS: right ventricle free wall longitudinal strain; 3D: three-dimensional. †P-value < 0.05; NS P-value ≥ 0.05. All intra- and interobserver differences showed normal distribution, as assessed by the Shapiro-Wilk test.*

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Potential Conflict of Interest

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

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Study Association

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Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Faculdade Ciências Médicas -MG under the protocol number 98623018.9.0000.5134. 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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Focusing on the Right Ventricle in PRKAG2 Syndrome

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Short editorial related to the article: Right Ventricle Involvement by Glycogen Storage Cardiomyopathy (PRKAG2): Standard and Advanced Echocardiography Analyses

The *PRKAG2* gene encodes the adenosine monophosphate-activated protein kinase (AMPK) gamma 2 regulatory subunit. AMPK has a central role in cellular energy homeostasis. Pathogenic variation in *PRKAG2* causes an autosomal dominant syndrome comprising ventricular hypertrophy, supraventricular arrhythmias, electrocardiographic pre-excitation and conduction system abnormalities.[1-3] The genetic background of this syndromic presentation was discovered in 2001.[4]. Histologically there is myocyte glycogen accumulation, and the typical pattern of hypertrophy is usually described as biventricular and concentric, similar to other metabolic phenocopies of hypertrophic cardiomyopathy (HCM),[5] with systolic dysfunction as another possible "red-flag" feature. The more frequent pathogenic variants are p.Arg302Gln and p.Asn488Ile.[1] Due to the condition's rarity, most publications consist of small case series or case reports, with few exceptions.[3]. None of the previous publications specifically report right ventricular imaging findings in this condition.

Expanding on their previous work, where 3D echocardiography and strain imaging findings of the left ventricle were described in a cohort of 30 patients with PRKAG2 syndrome,[6] Pena et al.[7] provide a short report focusing on the right ventricle (RV), using the same cohort, in the current edition of this Journal.

Relevant findings include a high prevalence of RV hypertrophy (present in 27 out of 30 patients), a more significant basal right ventricular stain reduction compared to mid and apical segments, and an abnormally low RV ejection fraction in 17 patients (which is below 35% in 7). Importantly, only 4 patients had increased pulmonary artery systolic pressures, so it does not seem that the RV abnormalities are secondary to increased filling pressures from the left. Expected findings included patients with pacemakers having worse RV ejection fraction and poorer myocardial deformation and a correlation between right ventricular strain and ejection fraction.

These findings confirm the impression of biventricular hypertrophy as a characteristic feature of this condition, in common with other metabolic diseases.[5] The study also showed a high prevalence of RV systolic dysfunction, with potentially significant clinical and prognostic consequences. Previous investigations have shown that RV hypertrophy in HCM was correlated with an increased calculated sudden cardiac death risk score and independently related to the presence of ventricular arrhythmias.[8] The relevant next step will be an investigation of the clinical impact of this RV involvement in terms of outcomes in the PRKAG2 syndrome.

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Keywords

PRKAG2 Syndrome; Echocardiography/methods; Hypertrophy, Right Ventricle; Myocardial Deformability; Stroke Volume.

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Epicardial Fat Volume Is Associated with Endothelial Dysfunction, but not with Coronary Calcification: From the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil)

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Abstract

Background: **The increase in epicardial fat volume (EFV) is related to coronary artery disease (CAD), independent of visceral or subcutaneous fat. The mechanism underlying this association is unclear. Coronary artery calcium (CAC) score and endothelial dysfunction are related to coronary events, but whether EFV is related to these markers needs further clarification.**

Objectives: **To evaluate the association between automatically measured EFV, cardiovascular risk factors, CAC, and endothelial function.**

Methods: **In 470 participants from the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil) with measures of EFV, CAC score and endothelial function, we performed multivariable models to evaluate the relation between cardiovascular risk factors and EFV (response variable), and between EFV (explanatory variable) and endothelial function variables or CAC score. Two-sided p <0.05 was considered statistically significant.**

Results: **Mean age was 55 ± 8 years, 52.3% of patients were men. Mean EFV was 111mL (IQ 86-144), and the prevalence of CAC score=0 was 55%. In the multivariable analyses, increased EFV was related to female sex, older age, waist circumference, and triglycerides (p<0.001 for all). Higher EFV was associated with worse endothelial function: as compared with the first quartile, the odds ratio for basal pulse amplitude were (q2=1.22, 95%CI 1.07-1.40; q3=1.50, 95%CI 1.30-1.74; q4=1.50, 95%CI 1.28-1.79) and for peripheral arterial tonometry ratio were (q2=0.87, 95%CI 0.81-0.95; q3=0.86, 95%CI 0.79-0.94; q4=0.80, 95%CI 0.73-0.89), but not with CAC score>0.**

Conclusion: **Higher EFV was associated with impaired endothelial function, but not with CAC. The results suggest that EFV is related to the development of CAD through a pathway different from the CAC pathway, possibly through aggravation of endothelial dysfunction and microvascular disease.**

Keywords: **Atherosclerosis; Intra-Abdominal Fat; Obesidade Abdominal.**

Introduction

Visceral fat is the most studied ectopic fat deposit, and increased visceral adiposity is related to glucose intolerance, insulin resistance and cardiovascular diseases, independent of body mass index (BMI).[1] Epicardial fat shares many of the pathophysiological properties of other visceral fat deposits, but with additional potential effects on the coronary inflammatory and atherosclerotic process.[2] Researchers from "The Framingham Heart Study[3,4] and the "Multi-Ethnic Study of Atherosclerosis (MESA)[5,6] studied the association of epicardial fat volume (EFV) with cardiovascular risk factors and identified that EFV not only correlates with obesity and metabolic disorders, but also with the presence of hypertension and coronary artery disease (CAD). In a systematic review published in 2015, the authors described nine studies that evaluated the capacity of EFV to predict major cardiovascular events. Although the findings are not consistent for all studies, the majority suggest that EFV quantification is significantly associated with clinical outcomes.[7]

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Recent studies have shown that epicardial fat deposits are associated with CAD but not with coronary artery calcium (CAC) score, which evaluates the calcification in coronary arteries and has been shown in large prospective studies to be associated with the risk of future cardiovascular events.[8] These studies suggested that EFV could be related to other mechanisms of plaque formation different from calcified plaques.[9,10] Nerlekar et al.[11] demonstrated, in a meta-analysis published in 2017, the progressive association between the presence of epicardial fat and high-risk atherosclerotic plaques, which are those with high lipid content, little calcification and a thin fibrotic cap.[11] Another study demonstrated that higher EFV was associated with vulnerability of plaques in the coronary arteries.[12]

Our objective was to evaluate the association between EFV with cardiovascular risk factors and subclinical markers of atherosclerosis – CAC and microvascular endothelial function, both predictors of cardiovascular events.[13,14]

Methods

Participants

Our sample included participants from the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil), which aims to study the determinants of cardiovascular disease and diabetes in 15,105 Brazilian adults. The eligibility criteria included active or retired employees of five universities and one research institute, aged 35 to 74 years, who volunteered to participate. Further details of the study design were published elsewhere.[15] In the Investigation Center of ELSA-Brasil in Minas Gerais (3,115 participants), endothelial function assessment through peripheral arterial tonometry (PAT), and computed tomography (CT) for CAC evaluation were performed. The PAT exam was introduced partway through the baseline, resulting in 1,535 valid examinations.[16] Of these, 550 participants were randomly selected for reassessment of PAT on the same day of the CT, and 546 attended. EFV measurements were done in 501 randomly selected participants with valid CT scans and PAT using R Development Core Team software (2020) R. Thirty patients were excluded due to technical problems in the EFV analyses (n=4) and in PAT analyses (n=26) and one patient who had an EFV measurement considered outlier was excluded, leaving a final sample of 470 participants (Figure 1).[16] ELSA-Brasil was approved by the Research Ethics Committees of the participating institutions and the National Research Ethics Committee (CONEP 976/2006). All participants signed an informed consent form.

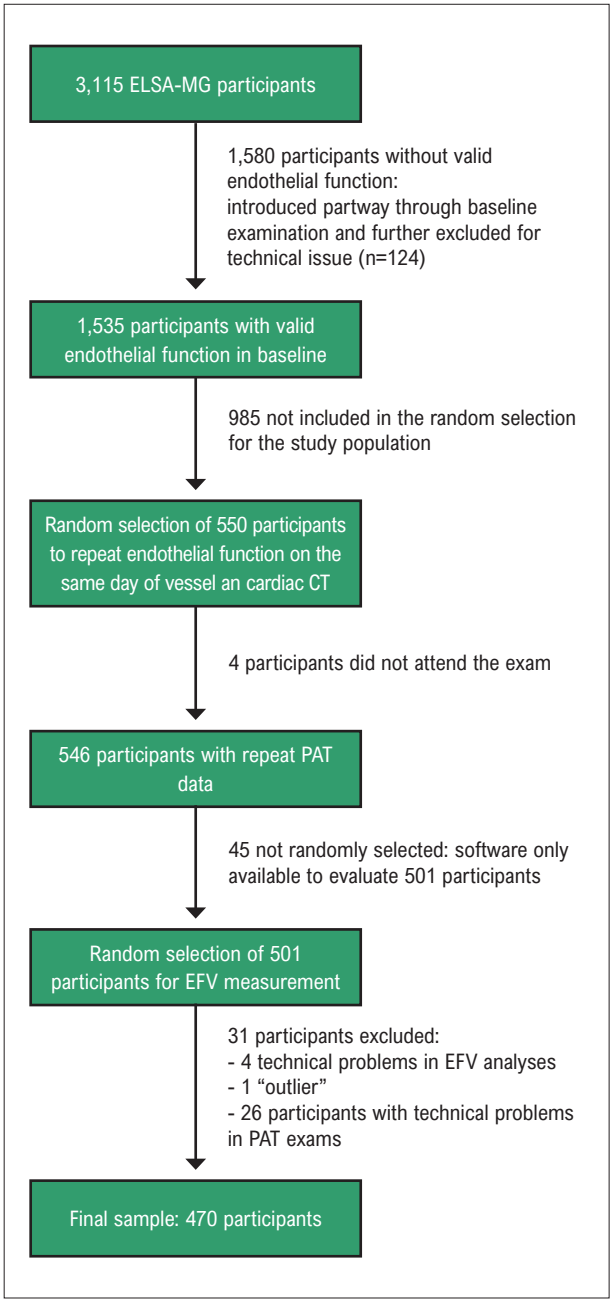

Figure 1 – *Flowchart of Participants. CT: computed tomography; PAT: peripheral arterial tonometry; EFV: epicardial fat volume.*

Study protocol

Demographic variables were collected during the study baseline and clinical characteristics in the second visit. Age, sex, self-reported race, schooling, physical activity, obesity, central obesity, smoking, alcohol use, hypertension, diabetes mellitus (DM), dyslipidemia, hypertriglyceridemia, and the *Framingham risk score for CAD,*[17] which estimates the probability of developing a coronary event in 10 years, were used in the analyses. Data collection followed the ELSA-Brasil protocol, whose details can be found elsewhere.[18-20] Physical activity was evaluated using the International Physical Activity Questionnaire-short form (IPAQ-SF),[21] in which each type of activity is weighed by its energy requirements defined in MET (metabolic equivalent of task). The physical activity time per week is then converted to MET minutes (MET-min/week). The participant is considered sedentary if the sum of MET-min/week is <600; moderately active if 600-3000 MET-min/week and active if > 3000 MET-min/week. Participants were classified as current smokers or non-smokers and, regarding alcohol use, they were classified as non-users, non-heavy

drinkers or heavy (men with consumption ≥210g alcohol/week and women with consumption ≥140g alcohol/week) drinkers. Hypertension was determined by patient report, systolic blood pressure (SBP) ≥ 140 mmHg, diastolic blood pressure (DBP) ≥90 mmHg or use of antihypertensive medications. DM was determined by participant report, use of antidiabetic medication, or fasting glycemia ≥ 126 mg/dL, or glucose level ≥ 200 mg/dL after two hour of oral glucose overload, or glycated hemoglobin ≥ 6.5%. The Framingham risk score for CAD was used as a categorical variable, stratified into low (<10%), intermediate (10-20%) and high (>20%) cardiovascular risk.

Assessment of EFV

We performed non-contrast enhanced, ECG-triggered cardiac CT scans to assess CAC and EFV, using a 64-slice CT scanner (Lightspeed, General Electric). Images were acquired during respiratory apnea for 8-12 seconds. EFV was quantified using a standardized, validated and fully automated method described by Shahzad et al.[22] In brief, this method included two phases: (1) heart segmentation, (2) quantification of EFV in mL. The segmentation of the heart was performed using multi-atlas segmentation and registration using the Elastix software described by Klein et al.[23] For the EFV quantification a window width range of -30 to -200 Hounsfield units was used. A manual calibration was carried out for the present study, using MeVisLab software for manual delimitation of the pericardial sac of 15 participants, as shown in (Figure 2). The results were compared to those obtained by Elastix software and calibrated.

CAC score measures

The images were transferred to a GE ADW 4.5 workstation and to the Imaging Server of the ELSA-Brasil, where CAC score was calculated by the Agatston method by a *radiologist* with 10 *years* of *experience*, blinded for clinical information.

Endothelial function measures

PAT exam was performed by two certified examiners using the Endo-PAT2000 (Itamar Medical Ltd., Caesarea, Israel) on the same day of the CT.[16,24] Briefly, the cuff was placed in the participant's nondominant arm, 2 cm above the cubital fossa, and PAT probes on each index finger. Baseline pulse amplitude (BPA) was measured for five minutes. Arterial flow was interrupted on one side for five minutes by inflating the cuff at suprasystolic pressure. After five minutes, the cuff was deflated to induce reactive hyperemia, and the PAT signal was recorded for another five minutes. The contralateral finger was used to control for systemic changes. Two variables from PAT were used: mean BPA, which reflects the basal vascular tone and is calculated by logarithmically transforming the mean BPA values of both arms, and the PAT ratio, which reflects the response to reactive hyperemia. PAT ratio is the ratio of pulse amplitude 90 to 120 seconds after cuff release to the mean BPA. This result is divided by the corresponding ratio from the control finger and transformed to its natural logarithm.

Statistical analysis

Categorical variables were expressed as frequencies and percentages, continuous variables as mean ± standard deviation or median and interquartile range, according to the result of the Kolmogorov-Smirnov test. Due to the right-skewed distribution of EFV, the natural logarithm of EFV was used in the analyses in which EFV was the dependent variable (association with cardiovascular risk factors). In analyses in which EFV was the independent variable, quartiles of EFV were constructed (association with subclinical measures of atherosclerosis: CAC score and endothelial function). CAC score was dichotomized at 0 or >0, and endothelial function measurements were analyzed as continuous variables.

Statistical analyses were performed in three steps and through models adapted to the distribution of the response variables: 1- evaluation of the univariable and multivariable association between cardiovascular risk factors and EFV through linear regression; 2- evaluation of the univariable and multivariable association between EFV and CAC score through logistic regression; and 3- evaluation of the

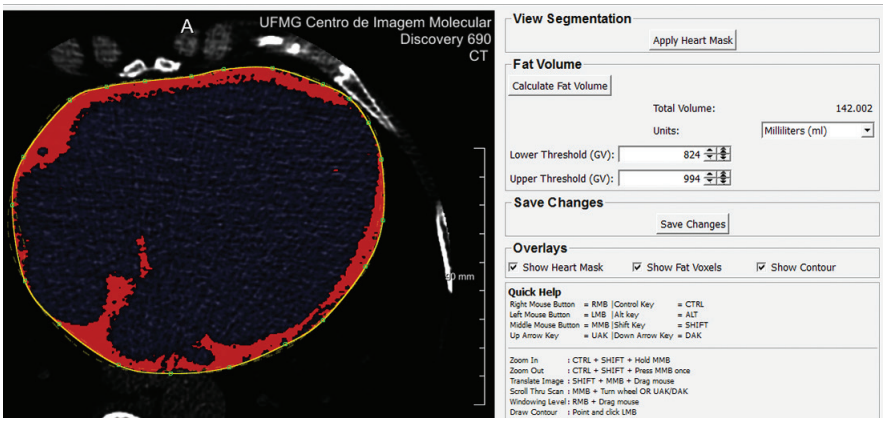

Figure 2 – *Manual calibration to assess epicardial fat volume in 15 participants of the ELSA-Brasil.*

univariable and multivariable association between EFV and measures of endothelial function through linear regression.

The variables were considered in four multivariable models determined *a priori* and retained if they showed association in the univariable analyses with p <0.10, as follows: Model 1, adjusted for sex and age; Model 2: Model 1, plus race, and schooling; Model 3: Model 2 plus physical activity, BMI, waist circumference, and smoking; Model 4: Model 3 plus SBP, antihypertensive use, DM, total cholesterol/HDL, and triglycerides.

BMI and waist circumference were not included simultaneously in models 3 or 4, due to a collinearity with a variance inflation factor (VIF) close to 8. If both were statistically significant, waist circumference was included, because it is a measure of ectopic fat, like EFV. The *Framingham risk score for CAD* was analyzed separately because it already represents an assessment of CAD risk, incorporating the combined effect of several cardiovascular risk factors.

Two-sided p <0.05 was considered statistically significant. Due to the numbers of variables in the model, Bonferroni correction was performed and a p<0.0038 was considered statistically significant. All analyzes were performed using R Development Core Team software (2020).

Results

Table 1 shows the characteristics of participants. Mean age was 55 ± 8 years, with 52.3% men. For race, 50.9% were white, 33.0% were mixed and 12.3% were black. A high proportion of sedentary (59.2%) and highly educated participants were observed, the latter reflecting the work of participants (university employees). Mean BMI was 26.9 ± 4.6 kg/m² and median waist circumference was 92 (84-101) cm. Median EFV was 111 (86-144) mL. A CAC=0 was detected in 261 (55.5%) participants. Mean BPA was 6.57 ± 0.62 and mean PAT ratio was 0.42 ± 0.34.

Table 1 – Characteristics of study participants (n = 470)

Characteristcs	
Age, y	55 ± 8
Sex, men %	246 (52.3)
Race*, %	
Black	58 (12.3)
Brown	239 (50.9)
White	155 (33)
Educational level, %	
Incomplete elementary school	10 (2.1)
Complete elementary school	17 (3.6)
High school	87 (18.5)
University degree	356 (75.7)
Physical activity status, %	
Sedentary	278 (59.1)
Moderately active	172 (36.6)
Active	20 (4.6)
Smoking, %	34 (7.2)
Excessive drinker, %	48 (10.2)
BMI, kg/m²	26.9 ± 4.7
Waist circunference, cm	91.8 (84.4 – 100.7)
Diabetes mellitus, %	81 (17.2)
Hypertension, %	183 (38.9)
SBP, mmHg	121 ± 16
Hypertension treatment, %	159 (33.8)
Total/HDL cholesterol	3.84 ± 0.96
Tryglicerides, mg/dL	108 (79 – 155)
CAC = 0†, %	261 (55.5)
EFV, mL	111 (86 -144)
BPA	657 ± 0.62
PAT ratio	0.42 + 0.34

** We excluded 13 participants (yellow and indigenous), as they represented a small sample; five participants did not provide the data, and †1 participant did not have data. BMI: body mass index; BPA: baseline pulse; CAC: coronary calcium score; HDL: high density lipoproteins; EFV: epicardial fat volume; BPA: baseline pulse amplitude; PAT: peripheral arterial tonometry; SBP: systolic blood pressure.*

Association between cardiovascular risk factors and EFV

The univariable association between cardiovascular risk factors and EFV is shown in Supplementary Table 1. As the variable EFV was transformed to its natural logarithm, the increase of 0.1 in the coefficient of each explanatory variable indicates a 10.5% increase in EFV. Only smoking, physical activity and schooling were not statistically associated with EFV. Regarding race/skin color, black and mixed individuals showed significantly lower EFV than white individuals. An increase in EFV was observed with the progression of cardiovascular risk assessed by the Framingham Risk Score for CAD (Supplementary Figure 1).

In the multivariable analysis (Table 2), the following covariates remained associated with a higher EFV: male sex, olderfat volume age, waist circumference, and triglycerides. In the final model, black race remained associated with lower EFV.

Association between EFV and CAC

Regarding the association between EFV and CAC, the crude logistic analysis revealed increased chances of CAC>0 among people in the third and fourth quartiles of EFV. However, these associations lost statistical significance in the multivariable analysis (Table 3) in all the models considered. The univariable analysis of CAC with cardiovascular risk factors is shown in Supplementary Table 2.

Association between EFV and endothelial function

In the univariable association (Supplementary Table 3), we observed a statistically significant association of all quartiles of EFV with endothelial function measures. We also noticed a dose response gradient for EFV quartiles

Table 2 – Linear regression models of the association between cardiovascular risk factors and epicardial fat volume

Variable	Model 1		Model 2		Model 3		Model 4	
	β	IC 95%	β	IC 95%	β	IC 95%	β	IC 95%
Age	1.01	(1.01 – 1.02) †	1.01	(1.01 – 1.02) †	1.01	(1.007 – 1.013) †	1.01	(1.01 – 1.02) †
Sex (reference men)	0.76	(0.71 – 0.82) †	0.77	(0.72 – 0.82) †	0.87	(0.82 – 0.93) †	0.87	(0.81 – 0.93) †
Race (reference white)								
Black	...	...	0,85	(0.77 – 0.95)*	0.83	(0.76 – 0.91) †	0.85	(0.77 – 0.93) †
Brown	...	...	0.92	(0.86 -0.99)*	0.93	(0.88 – 1.00)*	0.94	(0.88 -1.00)
Waist circuference	...	...	...	...	1.02	(1.01 – 1.02) †	1.02	(1.01 – 1.02) †
Excessive drinker					1.06	(0.97 – 1.17)	1.05	(0.95 – 1.15)
Diabetes Mellitus	...	...	...	...	...	...	0.96	(0.88 – 1.04)
SBP	...	...	...	...	...	...	1.00	(0.996 – 1.001)
Hypertension treatment	...	...	...	...	...	...	0.99	(0.92 – 1.06)
Total/HDL Cholesterol	...	...	...	...	...	...	0.98	(0.95 – 1.02)
Tryglicerides	...	...	...	...	...	...	1.00	(1.000 - 1.001)*

** p<0.05, †p< 0.001. β exponential regression coefficient. CI: confidence interval; SBP: systolic blood pressure; HDL: high density lipoproteins.*

Table 3 – Logistic regression models of the association between quartiles of epicardial fat volume and presence of coronary calcium

Variable	OR	CI 95%	p-value
Model 1 (reference first quartile)			
Second quartile	1.07	(0.60 – 1.91)	0.823
Third quartile	1.19	(0.66 – 2.14)	0.565
Fourth quartile	1.72	(0.93 – 3.19)	0.082
Model 2 (reference first quartile)			
Second quartile	0.99	(0.54 – 1.80)	0.966
Third quartile	1.03	(0.56 – 1.90)	0.921
Fourth quartile	1.48	(0.79 -2.79)	0.221
Model 3 (reference first quartile)			
Second quartile	0.91	(0.50 – 1.68)	0.776
Third quartile	0.78	(0.41 – 1.49)	0.455
Fourth quartile	0.87	(0.41 – 1 .52)	0.709
Model 4 (reference first quartile)			
Second quartile	0.94	(0.50 – 1.74)	0.838
Third quartile	0.81	(0.42 – 1.59)	0.547
Fourth quartile	0.88	(0.41 – 1.87)	0.734

OR Odds Ratio CI confidence interval. First quartile (22.8-86.2), Second quartile (86.2-112), Third quartile (112-144), Fourth quartile (144-331). Model 1: sex, age. Model 2: Model 1, plus race and schooling. Model 3: Model 2, plus physical activity level, BMI, waist circumference and smoking. Model 4: Model 3, plus SBP, antihypertensive use, DM, total cholesterol / HDL and triglycerides.

and measures of endothelial function: the mean BPA was progressively higher and PAT ratio lower – reflecting more impaired endothelial function – in the higher EFV quartiles (Figure 3). In the multivariable analysis, the association remained statistically significant in all models (Table 4).

Discussion

The present study evaluated EFV by an automated method its association with cardiovascular risk factors and subclinical markers of atherosclerosis – CAC score and endothelial function in 470 participants of the ELSA-Brasil. The main findings of the present study were: 1) Association of EFV with most cardiovascular risk factors. In the multivariable analysis, higher EFV was seen for: male sex, older age, white race, and higher triglycerides and waist circumference; 2) EFV was not associated with the presence of CAC in multivariable models; 3) Increased EFV was associated with endothelial dysfunction in multivariable models, in a dose-response manner. Our findings generate the hypothesis that epicardial fat deposits may be linked to CAD through a distinct pathway from calcified plaques, but rather potentially related to endothelial dysfunction, microvascular disease and possibly predominantly lipidic non-calcified plaques.

First, median EFV was 111 (IQ 86-144) mL, which is comparable to the results observed by Bos et al. (101 mL, IQ 80-130),[25] and in the Framingham Heart Study (108 ± 40) mL,[10] suggesting that, although nutritional transition is in a slightly delayed stage in Brazil, comparing to European countries and the US, ectopic fat deposits appear to be present in a similar manner. Bos et al.,[25] using the same fully automated method described by Shahzad et al.,[22] evaluated the association between EFV, the presence of calcification in vessel beds and cardiovascular risk factors, in a cross-sectional analysis. The authors observed that an increase in EFV was associated with an increase in the volume of coronary and external carotid artery calcification, but only in men (difference in calcification volume with increase of one standard deviation of EFV: 0.12 [95% CI: 0.04, 0.19] and 0.14 [95% CI: 0.06, 0.22], respectively).[25] We did not find an association between EFV and CAC score after adjustment for cardiovascular risk factors. The

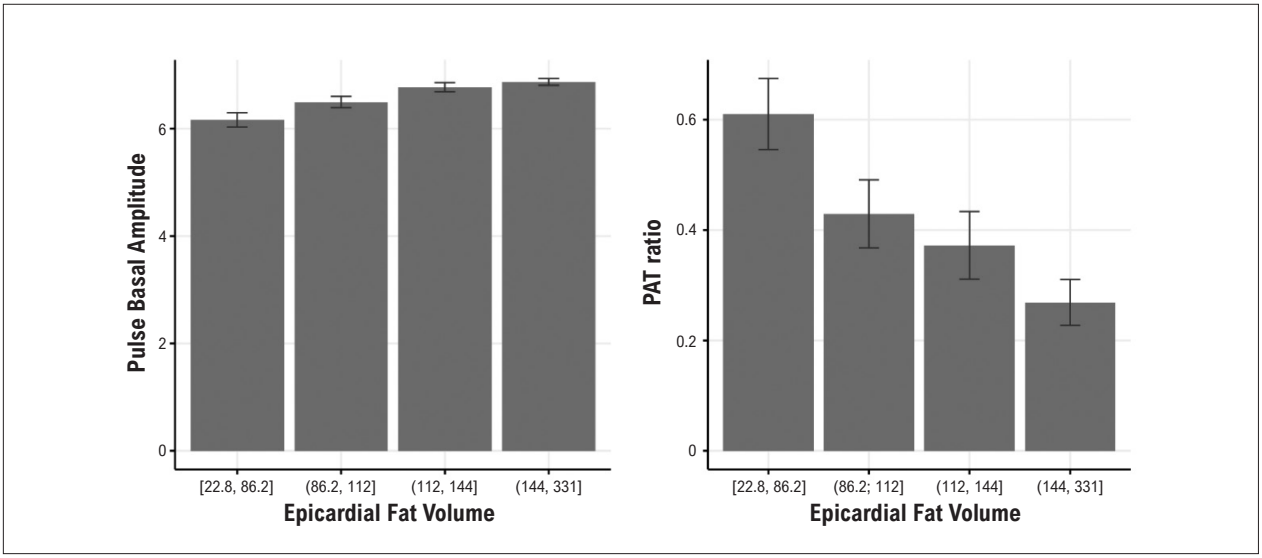

Figure 3 – *Endothelial function measures (mean) according to the epicardial fat volume stratified in quartiles. PAT: peripheral arterial tonometry.*

Table 4 – Logistic regression models of the association between epicardial fat volume and endothelial function

Variable	Basal Pulse Amplitude		PAT ratio	p-value
	OR (CI 95%)	p-value	OR (CI95%)	
Model 1 (reference first quartile)				
Second quartile	1.31 (1.14 – 1.49)	0.001	0.86 (0.79 – 0.93)	<0.001
Third quartile	1.63 (1.42 – 1.87)	< 0.001	0.83 (0.76 – 0.89)	<0.001
Fourth quartile	1.62 (1.40 – 1.88)	< 0.001	0.77 (0.71 – 0.84)	<0.001
Model 2 (reference first quartile)				
Second quartile	1.22 (1.07 – 1.40)	0.003	0.87 (0.81 – 0.94)	<0.001
Third quartile	1.54 (1.35 – 1.77)	< 0.001	0.84 (0.77 – 0.91)	<0.001
Fourth quartile	1.54 (1.33 – 1.78)	< 0.001	0.79 (0.73 – 0.86)	<0.001
Model 3 (reference first quartile)				
Second quartile	1.22 (1.06 – 1.39)	0.004	0.88 (0.81 – 0.95)	0.001
Third quartile	1.52 (1.32 – 1.75)	< 0.001	0.85 (0.78 – 0.92)	<0.001
Fourth quartile	1.49 (1.26 – 1.77)	< 0.001	0.80 (0.73 – 0.89)	<0.001
Model 4 (reference first quartile)				
Second quartile	1.22 (1.07 – 1.40)	0.004	0.87 (0.81 – 0.95)	0.001
Third quartile	1.50 (1.30 – 1.74)	< 0.001	0.86 (0.79 – 0.94)	<0.001
Fourth quartile	1.50 (1.28 – 1.79)	< 0.001	0.80 (0.73 – 0.89)	<0.001

OR Odds Ratio CI confidence interval. First quartile (22.8-86.2), Second quartile (86.2-112), Third quartile (112-144), Fourth quartile (144-331). Model 1: sex, age. Model 2: Model 1, plus race and schooling. Model 3: Model 2, plus degree of physical activity, BMI, waist circumference and smoking. Model 4: Model 3, plus SBP, antihypertensive use, DM, total cholesterol / HDL and triglyceride.

distinct profile of the populations studied may explain the differences, since older and more women were evaluated by Bos et al. Regarding the results, we did not perform an analysis stratified by sex due to our smaller sample size.

In a more recent publication by Lee et al.[10] from the Framingham Heart Study, the association between EFV and CAC was assessed longitudinally[10] in 1,732 participants of the Offspring and Third Generation Cohorts (49.6% men, mean age 49.9 years), who were followed for 6.1 years. The study evaluated 1,024 participants with baseline CAC score =0 and 708 participants with baseline CAC score > 0. No association was observed between the increase in EFV and the progression of CAC score after adjustment for BMI, waist circumference and visceral adipose tissue, nor between

incident CAC and EFV, what corroborates our findings of no association between higher EFV and CAC after adjusting for clinical variables.[10] The absence of association reported here was also described in a recent meta-analysis published by Mancio et al.,[9] which demonstrated that the association between EFV and CAC was not maintained in multivariable models, but higher EFV remained associated with obstructive or significant coronary stenosis, and major adverse cardiovascular events.[9] The authors hypothesize that EFV is associated with CAD through other mechanisms and forms of presentation that differ from the burden of calcified plaques. Another possible hypothesis is that the mechanism of association between EFV and CAD may express different moments in the natural history of the disease, being earlier as compared to CAC expression.[26]

In order to better understand the mechanism by which epicardial fat and CAD may be related, we further investigated the association of EFV with microvascular endothelial function.[27] We found that higher EFV was strongly associated with impaired microvascular function, even in multivariable models. The association between impaired endothelial function and higher EFV has been demonstrated in other studies. However, while all these studies have used flow-mediated dilation (FMD),[28-32] the method used to evaluate endothelial function in ELSA-MG was PAT. FMD differs from PAT in the vessels in which endothelial function is evaluated: while FMD evaluates it in the brachial artery - a conduit vessel - PAT assesses the microvasculature.[14,33,34] Considering that endothelial dysfunction is a predictor of cardiovascular events,[33,35] our results support the hypothesis that higher EFV is related to CAD by different pathways from the formation of calcified atherosclerotic plaques, including endothelial dysfunction, microvascular disease, and lipid-rich non calcified plaques. Due to the proximity of epicardial fat to the coronary arteries, the epicardial fat tissues may exert vasocrine effects on the vessels, when inflammatory mediators produced by epicardial fat act on the vessels, leading to endothelial dysfunction.[11] Given the possibility of our results represent an epiphenomenon, we performed models that tried to minimize this effect by adjusting for confounding variables.

Our study has some limitations. It is a cross-sectional study that precludes inferences about causality. However, this study is included in a cohort study, and the follow-up of participants for major adverse cardiovascular events will be possible in further publications. The sample size did not permit analysis of subgroups stratified by sex or obesity status as it represents a subsample of the large ELSA cohort. Furthermore, only microvascular endothelial function was studied and its evaluation in other arterial beds could complement our findings. However, microvascular endothelial function more strongly correlates with metabolic cardiovascular risk factors[14,34] – which, in turn, are more closely related to obesity phenotypes – as compared with endothelial function evaluated at conduit vessels.[34] In addition, we did not use the gold standard method to evaluate endothelial function because it is an invasive method. These limitations are counterbalanced by the strengths of our study: we used an automated method to evaluate EFV, which may facilitate its use on a large scale, and we had a comprehensive cardiovascular profile of the individuals, assessed by standardized methods. In addition, we will be able to longitudinally follow these individuals, which may bring further perspectives of the relation of EFV with CAD. Lastly, we evaluated the relationship between EFV, CAC and endothelial function, in attempt to better understand the association of EFV with the different mechanisms involved in CAD.

Conclusion

In the present study, higher EFV was associated with cardiovascular risk factors and worse measures of endothelial function. In addition, EFV was not associated with CAC in multivariable models. Taken together, our results generate the hypothesis that higher EFV may be associated with CAD through a different pathway from CAC, potentially related to endothelial dysfunction, microvascular disease and predominance of non-calcified plaques.

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Author Contributions

Conception and design of the research: Martins KPMP, Barreto SM, Ribeiro ALP, Brant LCC; Acquisition of data: Martins KPMP, Barreto SM, Bos D, Pedrosa J, Araújo LF, Foppa M, Duncan BB; Analysis and interpretation of the data: Martins KPMP, Barreto SM, Bos D, Pedrosa J, Ribeiro ALP, Brant LCC; Statistical analysis: Azevedo DRM; Obtaining financing: Barreto SM, Duncan BB, Ribeiro ALP; Writing of the manuscript: Martins KPMP, Brant LCC; Critical revision of the manuscript for important intellectual content: Barreto SM, Bos D, Pedrosa J, Azevedo DRM, Araújo LF, Foppa M, Duncan BB, Ribeiro ALP, Brant LCC.

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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*Supplemental Materials

For additional information, please click here.

Refining Cardiovascular Risk: Looking Beneath the Calcium Surface

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Short Editorial related to the article: Epicardial Fat Volume Is Associated with Endothelial Dysfunction, but not with Coronary Calcification: From the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil)

Atherosclerotic cardiovascular disease (ASCVD) is a systemic disease initiated by an endothelial influx of lipid particles, including low-density lipoproteins (LDL), with subsequent endothelial activation via local recruitment of inflammatory cells.[1] This local process – elicited by age-determined exposure to genetic, environmental, and lifestyle ASCVD risk factors – is the first step of a process that will lead to a chronic, low-grade systemic inflammatory state.[2] Prolonged exposure of the endothelium to ASCVD risk factors and this inflammatory state will increase the number of vulnerable plaques and may eventually lead to plaque rupture resulting in ASCVD events.

Multiple efforts have focused on measuring systemic and endothelial inflammation. Ridker et al. showed that C-reactive protein (CRP) levels were positively associated with future ASCVD events.[3] Subsequent trials, including the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER), proved the existence of a targetable, important residual inflammation component (later denoted as the NLRP3 inflammasome) through treatment with rosuvastatin.[4] On the imaging side, investigators from the Framingham Heart Study, were the first to show that pericardial and visceral fat volumes from non-contrast CT scans were associated with increased levels of inflammatory markers such as CRP and IL-6 as independent risk factors for ASCVD.[5] Using coronary CT angiography (CCTA), it was discovered that measurement of pericoronary adipose tissue (PCAT) density – resembling perivascular fat inflammation – provided additional discriminatory value for predicting ASCVD events, independent from inflammatory high-risk plaque features.[6]

In this issue of *Arquivos de Brasileiros de Cardiologia*, Martins and colleagues tested the relation between epicardial fat volume, endothelial function and coronary artery calcium (CAC) among 470 participants from the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil) who underwent non-contrast CT imaging.[7] Epicardial fat volume was assessed using a fully automatic, validated method before manual calibration using MeVisLab,[8] while the endothelial function was assessed using peripheral artery tonometry. In a relatively young cohort with a mean age of 55, the authors found that epicardial fat volume was associated with multiple risk factors, including older age, male sex, waist circumference and triglycerides. The main finding of this study was that epicardial fat volume was not associated with CAC but with endothelial dysfunction in multivariable analyses.

These findings, unique to the studied Brazilian cohort, add incrementally to an understanding that extravascular (pericardial) adipose tissue deposits and inflammation are associated with intravascular endothelial dysfunction and inflammation. In particular, the absence of a profound relationship with CAC, which was also observed in several other studies,[9] suggests distinct pathways of atherosclerotic risk and underlies the need to look beyond the patient's coronary artery calcium score alone, which represents a marker of stable plaque. CAC scoring provides a rough estimate of the amount of total plaque present; unlike CCTA, it cannot detect non-calcified plaque burden nor distinguish vulnerable plaque from the highest density, lower risk calcified lesions, which may represent plaque stability from treatment.[10,11]

Identifying endothelial dysfunction and microvascular disease through non-contrast imaging is an attractive strategy, particularly in regions where newer non-invasive methods are unavailable. Such methods to measure intravascular endothelial dysfunction include stress positron emission tomography (PET) to quantitatively measure myocardial blood flow and gadolinium-enhanced cardiovascular magnetic resonance (CMR) imaging to measure the myocardial perfusion reserve index.[12] in the absence of these techniques as well as the CCTA-derived PCAT, measurement of epicardial fat volume from non-contrast CT imaging could provide important additive risk-stratifying information on endothelial inflammation, dysfunction, and presence of vulnerable plaque beyond solely analyzing CAC.[13]

The authors are to be congratulated on the performed study. It is important to recognize, however, the evident limitations of the work. First, given the relatively young study population, 56% of patients in this study had no coronary artery calcium present, questioning the power of the analysis to exclude a relationship between epicardial fat volume and coronary artery calcium. In contrast to the multivariate analysis adjusted for several ASCVD risk factors, the univariate analysis of the current study showed that patients with above-median epicardial fat volume did have more CAC. Although the available evidence is conflicting, there seems to be at least a modest association between epicardial fat volume and coronary artery calcium score in larger

Keywords

Coronary Computed Tomography Angiography; Epicardial Fat; Coronary Artery Calcium; Plaque; Atherosclerosis.

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studies.[14] Still, when added to a risk score comprising CAC, epicardial fat volume significantly improved the prediction of obstructive coronary artery disease; in a study by Zhou et al. in 5743 patients, confirming the potential of epicardial fat volume beyond CAC scoring.[13] Second, the peripheral arterial tonometry method used in this study is a surrogate measure of endothelial (dys)function – as opposed to the gold standard of coronary vasoreactivity after intracoronary acetylcholine – and is also affected by external factors such as autonomic nervous system activation.[15] Therefore, it remains unknown whether the observed changes in peripheral artery tonometry ratio reflect endothelial dysfunction or merely increased sympathetic tonus in high-risk patients. Finally, the study does not correlate epicardial fat volume to clinical outcomes. Collectively, given the limitations and small cohort, the study should be interpreted as promising, intriguing, but hypothesis-generating.

In summary, atherosclerosis is a systemic, multifactorial, complex disease whose characteristics cannot be captured in a single metric. Whether using contrast or non-contrast imaging, one must look beneath the calcium surface - identifying endothelial inflammation and dysfunction resulting in non-calcified high-risk plaque components - to enhance precision in ASCVD risk stratification.

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Defibrillation Threshold Testing and Long-term Follow-up in Chagas Disease

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Abstract

Background: **Sudden cardiac death is the most common cause of death in chronic Chagas cardiomyopathy (CCC). Because most CCC patients who are candidates for implantable cardioverter-defibrillators (ICD) meet criteria for high defibrillation threshold values, a defibrillator threshold test (DTT) is suggested.**

Objectives: **We investigated the use of DTT in CCC patients, focusing on deaths related to ICD and arrhythmic events, as well as treatment during long-term follow-up.**

Methods: **We retrospectively evaluated 133 CCC patients who received an ICD mainly for secondary prevention. Demographic, clinical, laboratory data, Rassi score, and DTT data were collected, with $p < 0.05$ considered significant.**

Results: **The mean patient age was 61 (SD, 13) years and 72% were men. The baseline left ventricular ejection fraction was 40 (SD, 15%) and the mean Rassi score was 10 (SD, 4). No deaths occurred during DTT and no ICD failures were documented. There was a relationship between higher baseline Rassi scores and higher DTT scores (ANOVA = 0.007). The mean time to first shock was 474 (SD, 628) days, although shock was only necessary for 28 (35%) patients with ventricular tachycardia, since most cases resolved spontaneously or through antitachycardia pacing. After a mean clinical follow-up of 1728 (SD, 1189) days, 43 deaths occurred, mainly related to progressive heart failure and sepsis.**

Conclusions: **A routine DTT may not be necessary for CCC patients who receive an ICD for secondary prevention. High DTT values seem to be unusual and may be related to high Rassi scores.**

Keywords: **Chagas Disease; Chagas Cardiomyopathy; Tachycardia, Ventricular; Defibrillators, Implantable; Electric Countershock.**

Introduction

Sudden cardiac death (SCD) due to ventricular tachycardia (VT) or ventricular fibrillation is the most common cause of death in patients with chronic Chagas cardiomyopathy (CCC).[1]

Implantable cardioverter-defibrillators (ICD) have been extensively used and validated in ischemic and dilated cardiomyopathies, both for primary and secondary prevention. ICDs are recommended for secondary prevention in CCC after recovery from SCD or an unstable VT event. Definitive guidelines have not yet been produced[2,3] since no specific randomized trials for ICD in CCC are available, although some are ongoing.[4] Clinical guidelines for dilated cardiomyopathies have been inferred, although CCC usually involves peculiarities that lead to more severe clinical and pathological presentations. The occurrence of SCD in young and asymptomatic patients[5] has been known since Carlos Chagas' original observations of the disease. In addition, inappropriate shocks, electrical storms, and other device-related complications seem more prevalent in CCC patients, since they are usually younger, have a more active lifestyle, and have a higher propensity to arrhythmic events.[2] Hence, CCC presents a unique challenge regarding defibrillation threshold testing (DTT) before ICD implantation. No systematic evaluation of DTT has been published and most studies do not report whether it was performed or not.[6,7] Because most CCC patients who are ICD candidates have severe arrhythmic manifestations, low left and/or right ventricular ejection fraction, and extensive fibrotic replacement of working myocardium, CCC patients would be considered at risk of high defibrillation threshold values and would thus require DTT.[8] However, in low-income countries, where the need for general anesthesia would imply higher costs and longer procedures, avoiding DTT could be advantageous.

Due to a lack of data on shock failures, DTT was considered essential for earlier ICD models. This procedure was not completely predictable due to monophasic waveforms and lead design and placement, with some deaths and shock failures directly attributable to the test.[9] Refinements in lead design and shock waveforms led to safer DTT. Over the years, there have also been concerns that the shocks delivered during DTT accelerate ventricular dysfunction and cause more hospitalizations, so until recently, there was controversy about the need to perform DTTs.[10,11]

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Two recently published trials clarified the appropriateness of DTT for diseases other than CCC. SIMPLE (Shockless IMPLant Evaluation) was a randomized multicenter trial to evaluate the efficacy and safety of DTT when implanting an ICD.[12] With a sample of nearly 2500 patients, the trial concluded that DTT neither would affect mortality nor predict shock failures. The NORDIC ICD (NO Regular Defibrillation testing In Cardioverter defibrillator implantation) trial, with a similar design, evaluated 1077 patients and reached the same conclusions.[13]

A study that evaluated DTT in CCC showed a high prevalence of high threshold values.[14] However, in clinical practice, those patients also respond well to antitachycardia pacing, having less need for shocks.[15] Hence, we investigated the use of DTT in CCC patients, focusing on ICD-related deaths and arrhythmic events and treatment during long-term follow-up.

Methods

We conducted a retrospective evaluation of CCC patients who received an ICD at the Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo–Ribeirão Preto, Brazil, between 2001 and 2019. All patients had two positive serological tests for Chagas disease. Demographic (age, sex), clinical (ICD indication, functional class, echocardiographic data, electrocardiogram characteristics, medications in use at ICD implantation), and Rassi score[16] data were collected. The study was approved by our institution's ethics committee (CAAE:52530116.8.0000.5440).

DTT was performed for all patients per protocol and the data were collected. During the data collection period, the DTT routine changed due to greater team experience and new literature about its consequences. In general, ventricular arrhythmia was obtained with a timed shock during T-wave recording. Using St. Jude Medical devices, arrhythmia was induced with a continuous current. If arrhythmia could not be induced after two attempts, 50-Hertz burst pacing was applied. Finally, if 2 further attempts failed, DTT was finalized and the device was programmed for maximum energy.

In the initial years of the study, the first internal defibrillation shock was programmed for 15 Joules, followed by 20 Joules. If defibrillation was unsuccessful, internal defibrillation at maximum energy was attempted, and if the arrhythmia persisted after 2 attempts, an external shock was delivered and the electrode was repositioned. In this initial protocol, if the 15-Joule attempt was successful, a 10-Joule shock was attempted.

Over the years, the maximum energy delivered by ICDs was increased and a 10-Joule safety margin was determined for the first successful shock during DTT. It was also determined that the first DTT shock was programmed for 20 Joules and, if successful, the DTT test was terminated. If unsuccessful, a 25-Joule shock was attempted, followed by repositioning of the electrode. A high DTT value was defined as < 10 Joules from the safety limit.

ICD parameters were collected at the time of implantation, and patients were followed up every 3 to 6 months regarding the time and type of arrhythmic events, as well as the therapy received and its efficacy.

Statistical analysis

Continuous variables were expressed as mean (standard deviation) if normally distributed. Data normality was assessed using histograms and the Shapiro-Wilk test. Qualitative variables were expressed as absolute values and percentages and were compared using chi-square for trend or Fisher's exact test. Analysis of variance (One-way ANOVA) with Bonferroni adjustment was used as a post-test to compare the relationship between Rassi score and DTT values. We used IBM SPSS Statistics version 25 (IBM Corp., Armonk, NY, USA) and a significance level of $p < 0.05$.

Results

We included a total of 133 CCC patients who received an ICD. The mean age was 61 (SD, 13) years and 72% were men. The mean left ventricular ejection fraction was 40 (SD, 15%) and the mean left ventricle diastolic diameter was 61 (SD, 10 mm) before implantation. The mean Rassi score was 10 (SD, 4). The vast majority of patients (120, 90.2%) received the device for secondary prevention. Documented VT was the reason for implantation in nearly half of the sample, followed by aborted sudden cardiac death. Table 1 presents the main clinical indications for an ICD in our sample and a summary of the demographic, clinical, and laboratory data. Table 2 summarizes the demographic and laboratory data according to Rassi tertiles, showing a trend toward earlier shocks with higher Rassi tertiles.

No deaths occurred during the implantation procedure or DTT.

At follow-up, the mean time to the first shock was 474 (SD, 628) days. A total of 100 patients received some ICD treatment (79 for VT and 21 for ventricular fibrillation). The first shock, set at 20 Joules, was effective in 88 patients. A lower value was obtained in 25% of the cases and a higher value was necessary for 12 (9%) patients. High DTT values ($\geq$ 30 Joules) were identified in 4 (3%) patients. Programming ranged from 10 (1 patient) to 35 Joules (1 patient). Figure 1 depicts the relationship between Rassi score and baseline DTT scores, showing the association between higher Rassi scores and a higher DTT scores (ANOVA = 0.007). All patients with high DTT scores had a Rassi score $\geq$ 13 points (Figure 2).

Only 2 (35%) VT patients required a shock, with most cases resolving spontaneously or through antitachycardia pacing programmed before the shock; multiple shocks were required in only 4 (14%) VT events. Only 4 (19%) ventricular fibrillation patients received more than 1 shock. After a mean clinical follow-up of 1728 (SD, 1189) days, 43 deaths occurred, which were mainly related to progressive heart failure and sepsis. No deaths could be attributed to ICD failure.

Table 1 – Baseline demographic, clinical, and laboratory data before implantable cardioverter-defibrillator implantation in 133 chronic Chagas cardiomyopathy patients

Age (years)	61±13
Male – N(%)	96 (72.2)
Rassi score	10.2±4.2
Systemic Hypertension –N(%)	46(34.6)
Diabetes Mellitus – N(%)	11(8.3)
Chronic Renal Failure – N(%)	22(16.5)
NYHA Class – N(%)	
I	48(36.1)
II	52(39.1)
III	28(21.1)
IV	03(2.3)
N/D	02(1.5)
Medications – N(%)	
ACEI	84(63.2)
Beta-blockers	100(75.2)
Diuretics	75(56.4)
ARB	23(17.3)
Amiodarone	93(69.9)
Oral anticoagulants	33(24.8)
Electrocardiogram Rhythm – N(%)	
Sinus	104(78.2)
Atrial fibrillation	8(6.0)
Pacemaker	21(15.8)
Echocardiographic data	
LVEF(%)	40±15
Left Ventricle End Diastolic Diameter (mm)	61±10
Left Atrium dimension (mm)	47±9
ICD indication – N(%)	
Primary	13 (9.8)
Documented Ventricular Tachycardia	66 (49.6)
Aborted sudden cardiac death	28 (21.1)
Syncope	21 (15.8)
Documented Ventricular Fibrillation	2 (1.5)
Near Syncope	2 (1.5)
Palpitations	1 (0.8)

NYHA: New York Heart Association; N/A: not available; ACEI: Angiotensin-Converting Enzyme Inhibitors; ARB: Angiotensin Receptor Blockers; ICD: implantable cardioverter-defibrillator; LVEF: Left ventricle ejection fraction.

Discussion

Our study presents data on the systematic use of DTT in patients with dilated cardiomyopathy, which is commonly associated with SCD and occurs mostly (but not exclusively) in a clinical setting of low left ventricular ejection fraction due to widespread fibrotic remodeling of the heart. Various high DTT score markers were present, but it should be pointed out that nearly half of the sample was < 60 years of age most were men with low left ventricular ejection fraction (< 40%). Hence, our population may be defined as at risk of in-hospital complications and high DTT scores.[8,17] It is also relevant that secondary prevention was the main reason for ICD implantation, since no guidelines have yet been established for primary prevention in CCC, and prospective randomized studies are needed in patients with high Rassi scores.

Our DTT protocol has evolved over two decades, reflecting the advancing technology of ICDs, as previously reported.[18] Only 3% of our sample had high DTT scores, close to the lowest values found in the literature (2.2 to 12%).[10] This original finding indicates that although having an extensively fibrotic myocardium, CCC patients may not demand many adjustments during an ICD procedure.

Another relevant finding in our cohort is that no deaths could be attributed to the procedure, corroborating the low incidence of procedure-related complications found in different countries,[9] as well as the results of a recent systematic review that "implant-related deaths are not consistently reported.[19]

Our results also demonstrate that VT was the most predominant potentially lethal arrhythmia in CCC patients and that antitachycardia pacing successfully restored rhythm in most cases, which agrees with previous reports in populations with CCC.[6,20] This reinforces the view that a well-established antitachycardia pacing protocol is essential for restoring rhythm without unnecessary shocks, especially since most CCC patients have a high prevalence of electrical storms.[21]

We identified a significant relationship between Rassi scores for overall mortality and DTT scores, which suggests that patients with high Rassi scores may actually need DTT; however, a larger trial is required to clarify this point.

It is reassuring that our follow-up showed no device failures, which is in line with previous independent reports. Finally, since the clinical course of CCC patients who survive SCD frequently involves progressive severe heart failure or death due to other clinical complications, it seems reasonable to assume that even with increased LV fibrosis and dysfunction, ICDs may continue to prevent SCD.

Our study has some limitations. First, although it is one of the largest available, our sample is from a single center. In addition, our DTT protocol changed due to improved knowledge and technical advances, which certainly influenced our results but could not be controlled due to ethical concerns. Finally, our results cannot be translated

Table 2 – Distribution of demographic, laboratory, and follow-up parameters according to Rassi tertile

Variable	Rassi tertile 1 (n=32)	Rassi tertile 2 (n=53)	Rassi tertile 3 (n=46)	Anova p-value
Age (years)	60 ± 11	62 ± 12	60 ± 14	0.788
Male (%)	75	62	83	0.062 *
Rassi score	4.97 ± 1.26	9.20 ± 1.19	14.93 ± 2.27	<0.001
LVEF (%)	44 ± 11	40 ± 15	36 ± 16	0.065
LVDD (mm)	57 ± 7	60 ± 10	65 ± 11	0.002
Shock Test (J)	18.2 ± 3.1	18.8 ± 2.6	20.5 ± 4.2	0.007
Time to first shock (days)	807 ± 964	410 ± 609	395 ± 412	0.071

** = chi-square test for trend. LVEF: left ventricular ejection fraction; LVDD: left ventricular end diastolic dimension.*

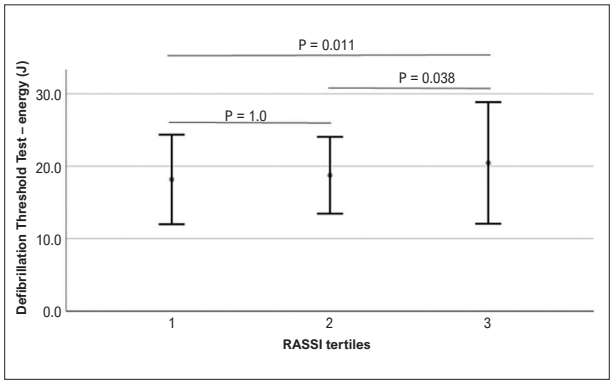

Figure 1 – *Defibrillation threshold test scores expressed as mean and standard deviation according to Rassi score tertiles, showing a progressive increase with higher Rassi scores (one-way ANOVA= 0.007) and Bonferroni post-tests, in which the main difference was between the third tertile, with the other two being statistically similar.*

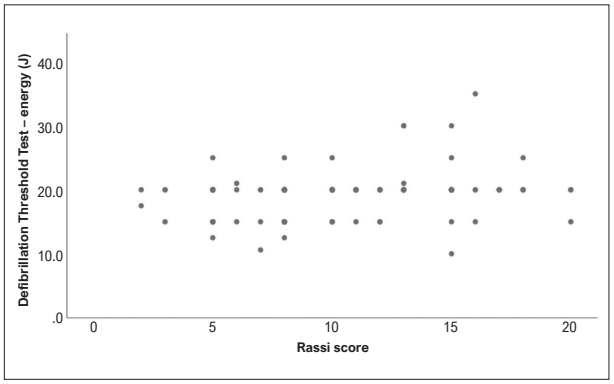

Figure 2 – *Defibrillation threshold test score distribution according to Rassi score. As can be seen, patients with high scores had a Rassi score ≥ 13. Note: Each point may represent more than one patient.*

to patients with CCC who receive an ICD for primary prevention.

Conclusions

Our data indicate that routine DTT may not be necessary for chronic Chagas cardiomyopathy patients who receive an ICD for secondary prevention. High DTT scores seem to be unusual and may be related to high Rassi scores. VT responsive to antitachycardia pacing is the most common form of ventricular arrhythmia and most ventricular fibrillation events are adequately treated with 1 shock. In addition, considering the limited resource in countries where CCC is endemic, it is probably cost-effective to skip DTT.

Author Contributions

Conception and design of the research: Rassi Jr A, Marin-Neto JA, Schmidt A; Acquisition of data: Campos MPC, Bernardes LFG, Melo JPC, Santos LC, Teixeira CHR, Scorzoni Filho A; Analysis and interpretation of the data: Pavão MLRC, Arfelli E, Scorzoni Filho A, Marin-Neto JA, Schmidt A; Statistical analysis: Marin-Neto JA, Schmidt A; Writing of the manuscript: Campos MPC, Marin-Neto JA, Schmidt A; Critical revision of the manuscript for important intellectual content: Pavão MLRC, Arfelli E, Scorzoni Filho A, Rassi Jr A, Marin-Neto JA, Schmidt 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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Defibrillation Threshold in Patients with Chronic Chagas' Heart Disease: Are There Benefits or not Worth the Risk?

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Short Editorial related to the article: Defibrillation Threshold Testing and Long-term Follow-up in Chagas Disease

The implantable cardioverter-defibrillator (ICD) is the best therapeutic option to prevent sudden cardiac death for several high-risk groups of patients. Basically, the ICD can recognize and stop ventricular tachycardia (VT) and ventricular fibrillation (VF) by triggering anti-tachycardia pacing (ATP) or shock therapy. The defibrillation threshold (DT) is the minimum shock energy required to terminate VF.

Historically, testing the ICD function via induction and termination of VF was considered mandatory to ensure that the ICD could properly detect and stop the arrhythmic event.[1]

Multiple series have identified clinical risk factors for elevated defibrillation energy requirements that could affect ICD performance: low left ventricle ejection fraction (LVEF), septal lead placement, cathodal shock polarity, older age, presence of congestive heart failure, higher NYHA functional class and usage of amiodarone and other antiarrhythmic drugs.[2-4] Because of that, DT was included as part of the implant protocol in the classic ICD trials and has also been widely incorporated into clinical practice.

However, the induction of a potentially fatal arrhythmia to determine the DT may not be risk-free, affecting morbidity and mortality. Complications can be related to the VF induction itself and its duration, to effects from deep sedation needed to perform the test and to adverse effects of additional necessary shocks. Furthermore, some clinical situations are either absolute or relative contraindications to DT, such as severe aortic stenosis, critical coronary artery disease, cardiogenic shock, and intracardiac thrombus.[5]

In this historical context and considering the technology improvement [the detection capability proved to be reliable, and the energy requirements to terminate VF is generally low (< 15 J)], the relationship between the performance and the success of DT to short- and long-term morbidity and mortality was questioned.[6]

Data from SCD-HeFT showed no correlation between DT and long-term mortality.[7] In two separate series of patients undergoing initial cardiac resynchronization therapy ICD implantation, DT was also not associated with an increase in mortality.[8,9] The impact of DT on subsequent mortality in patients undergoing ICD generator replacement or upgrade was evaluated in the REPLACE Registry, and there was no association between DT and subsequent mortality at 6 months.[10] The MODALITY trial demonstrated no difference in ventricular arrhythmia termination between single- and dual-coil leads (increased risk of shock failure was associated with right ventricular coil cathodal polarity).[2] In the SIMPLE trial, investigators randomized 2500 patients undergoing an initial implant of a left-sided ICD for either primary or secondary prevention indication to DT or no DT. There was no statistically significant difference in the secondary endpoint of total mortality between the groups (3.0 vs. 2.2%, p = 0.17).[11] The NORDIC ICD trial was designed to determine if no DT was non-inferior to DT for the primary endpoint of first shock efficacy in terminating all true episodes of VT or VF during follow-up, and as in the SIMPLE trial, total mortality was a pre-defined secondary endpoint. In this trial, 1077 patients were randomized to left-sided ICD implants with or without DT. Total mortality did not differ between the two groups.[12] Two subsequent meta-analyses demonstrated similar mortality findings.[13,14] Thus, the performance of DT at the time of ICD implant does not affect subsequent total mortality.

There are specific situations where DT remains a reasonable clinical consideration. These include right-sided implants, lead advisories and malfunction, inherited and congenital cardiovascular disease, and subcutaneous ICD. It is also important to note that those studies evaluating the impact of DT did not include chronic Chagas cardiomyopathy (CCC) patients.

Campos et al.[15] investigated the use of DT in CCC patients, focusing on deaths related to ICD and arrhythmic events and treatment during long-term follow-up. The authors retrospectively evaluated 133 patients who received an ICD mainly for secondary prevention. The mean patient age was 61 (SD, 13), and 72% were men. The baseline LVEF was 40 (SD, 15%), and the mean Rassi score was 10 (SD, 4). No deaths occurred during DT, and no ICD failures were documented. There was a relationship between higher baseline Rassi scores and higher DT scores (ANOVA = 0.007). The mean time to first shock was 474 (SD, 628) days, although shock was only necessary for 28 (35%) patients with VT since most cases resolved spontaneously or through ATP. After a mean clinical follow-up of 1728 (SD, 1189) days, 43 deaths occurred, mainly related to progressive heart failure and sepsis. Based on that results, the authors concluded that a routine DT might not be necessary for CCC patients who receive an ICD for secondary prevention.

Chagas disease is often neglected in countries where the disease is endemic due to the numerous limitations for developing robust research that can change the standard of treatment for the better. All new information must be valued and disseminated since countries like Brazil must deal with these patients for a long time.

Keywords

Chagas Disease; Chagas Cardiomyopathy; Ventricular Tachycardia; Defibrillators; Electroshock

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Inflammatory Phenotype by OCT Coronary Imaging: Specific Features Among *De Novo* Lesions, In-Stent Neointima, and In-Stent Neo-Atherosclerosis

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Abstract

Background: **Coronary stenosis can be caused de novo atherosclerosis, in-stent restenosis, and in-stent neoatherosclerosis, three entities that develop from a diverse pathophysiological milieu.**

Objective: **This study aims to investigate, using optical coherence tomography (OCT), whether or not coronary lesions related to these processes differ in their local inflammatory profile.**

Methods: **Retrospective analysis of patients with diagnosed or suspected coronary lesions who had undergone OCT imaging for clinical reasons. Macrophage and intra-plaque neovascularization were assessed by OCT and used as surrogates of local inflammation. A significance level of < 0.05 was adopted as statistically significant.**

Results: **From the 121 lesions, 74 were de novo, 29 were restenosis, and 18 were neoatherosclerosis. Neovascularization was found in 65.8% of de novo, 10.3% in restenosis, and 94.4% in neoatherosclerosis ($p<0.01$ for all). The volume of neovascularization was different among lesion types (950 vs. 0 vs. 6220, respectively [median values in 1000 x μm^3/mm]; $p<0.01$ for all), which were significantly higher in neoatherosclerosis and lower in restenosis. The presence of macrophages differed among the lesions (95.9% in de novo vs. 6.9% in restenosis vs. 100% in neoatherosclerosis [$p<0.01$ for all]). Moreover, the intensity of macrophagic infiltration was different among lesion types (2.5 vs. 0.0 vs. 4.5, respectively [median values of macrophage score]; $p<0.01$ for all), significantly higher in neoatheroscleosis and lower in restenosis.**

Conclusion: **When compared using coronary OCT, de novo atherosclerosis, in-stent restenosis, and neoatherosclerosis presented markedly different inflammatory phenotypes.**

Keywords: **Coronary Restenosis; Atherosclerosis; Stents.**

Introduction

Coronary atherosclerotic disease is a ubiquitous cause of morbimortality worldwide, frequently treated with stent implantation. However, it is well known that re-narrowing of the lumen of the stent may occur within the first months following percutaneous intervention, a phenomenon referred to as restenosis.[1] Both entities (i.e. *de novo* atherosclerosis and in-stent restenosis) originate from markedly distinct pathogenetic mechanisms. Atherosclerotic plaque formation is a complex, multifactorial, long-lasting condition modulated by multiple systemic and local risk factors.[2] On the other hand, in-stent restenosis is secondary to neointimal tissue growth, a vascular healing response triggered by vessel injury following device implantation.[3,4] More recently, neoatherosclerosis has been described as another distinct cause of in-stent lumen narrowing. It is largely believed to be an accelerated form of atherosclerotic plaque formation probably induced by a sustained local tissular response to the stent metallic scaffold itself.[5] The accumulation of inflammatory cells has been described as a central event for the development of *de novo* atherosclerosis[2,6,7] and in-stent restenosis,[8] as well as for neo-atherosclerosis.[9] Local inflammation is believed to be an integral part of those conditions, functioning as the decisive step through which the vessel wall is dynamically modified as the pathologic process progresses. To date, however, it has been poorly described whether inflammatory profiles do vary according to the underlying type of condition, and if the potential differences can be assessed by clinical tools. Intravascular optical coherence tomography (OCT) provides *in vivo* near histology-level imaging,[10] which has been largely used to investigate patients with coronary artery disease.[11-13] In addition to quantitatively measuring dimensional parameters, OCT has

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been validated as a tool to assess qualitative characteristics of the vessel wall, such as tissue type components, plaque accidents, and thrombus formation.[11,12] Also importantly, OCT has been shown to accurately detect macrophage infiltration[10,14] and intra-wall neovessel formation,[15] two features associated with subjacent local inflammation. The present study aims at investigating whether atherosclerosis, in-stent restenosis, and neo-atherosclerosis differ in their inflammatory phenotype (i.e., macrophage and neovessel presence and quantity) as assessed by OCT imaging.

Methods

Patient selection

We conducted a search in our institution's database for patients who had undergone coronary OCT in native coronary arteries for clinical indications, between January of 2012 and December of 2019. All OCT runs from every patient were revised, and selected for final analysis if presenting: i) one or more *de novo* atherosclerotic lesions (defined as a plaque arc ≥ 180°), or ii) one or more lesions in a previously implanted stent (defined as at least 300 μm of in-stent tissue thickness). Lesions in the same vessel were considered discrete, and counted as such, if separated by a normal segment longer than 10 mm. Lesions at the stent edges (5-mm proximal or distal) were not included for analysis. Also, the present report only included lesions which OCT examination was performed prior to any intervention. This study was approved by the local ethics committee and is in accordance with the Declaration of Helsinki.

Image acquisition and analysis

Image acquisition was performed using standard techniques, during injection of contrast media as described elsewhere,[16] using a frequency-domain OCT system (C7 or Ilumien OPTIS system, C7 DragonFly or DragonFly II imaging catheters, St. Jude Medical, St. Paul, MN).

Two independent reviewers blinded to any clinical information performed the evaluations of all OCT images. Any disagreement between the reviewers was resolved by consensus. Lesions were classified as *de novo*, in-stent restenosis, or in-stent neoatherosclerosis. The latter in-stent lesion was differentiated from the former by the presence of calcific or lipidic deposits in neoatherosclerotic lesions, as opposed to the homogenous appearance of the neointimal restenotic tissue (Figure 1).[17,18]

Lesions were analyzed using standard definitions, as suggested elsewhere.[18-21] Lipid tissue was defined as signal-poor regions with poorly defined, diffuse borders. Fibrous tissue was defined as a region with high backscattering and a relatively homogeneous signal. Calcific deposits were identified as signal-poor or heterogeneous structures with sharply delineated borders. The arc of calcium was measured at the frame with the largest extension of calcific deposit. Macrophages were identified by the presence of signal-rich, distinct, or confluent punctate images exceeding the intensity of background speckle noise (Figure 2A); macrophage accumulation was graded using a score from 0 to 4 in each frame and then summed the gradings for the whole lesion.[20] Neovascularization was defined as no-signal, intra-plaque structures without connection

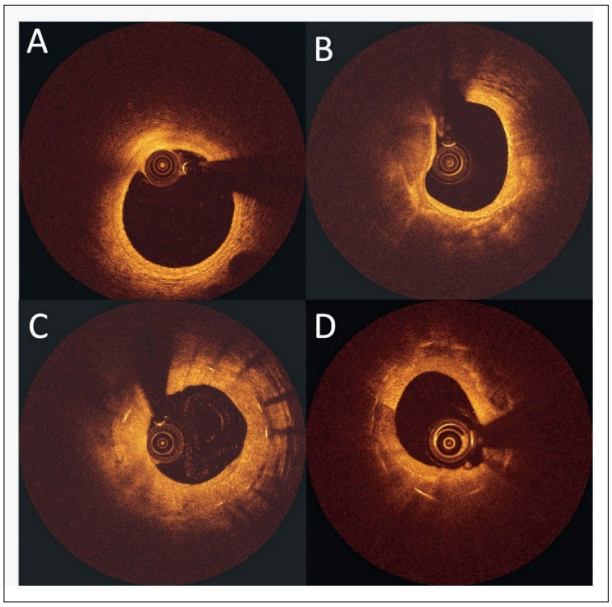

Figure 1 – *OCT images of a normal coronary artery (A), de novo atherosclerosis (B), in-stent restenosis (C) and neoatherosclerosis (D). In-stent restenosis is characterized by the homogenous appearance of the neointimal restenotic tissue, while neoatherosclerosis presents in-stent lipidic and calcific deposits.*

to the vessel lumen measuring between 50-300 μm and recognized in ≥ 3 consecutive frames (Figure 2B).[18,21] The volume of neovascularization was calculated by summing the area of neovascularization in each frame and then applying Simpson's rule. Both macrophage accumulation and volume of neovascularization were indexed by plaque length, to allow for comparison among lesions. Thrombus was defined as a mass protruding into the vessel lumen, typically with irregular contours, discontinuous from the surface of the vessel wall (Figure 3A). Thin-cap fibroatheromas (TCFA) were defined as a region with maximal lipid arc more than 90°and cap thickness <65 μm. Ruptured plaque was defined by the presence of intimal tearing, disruption, or dissection of the cap (Figure 3B).

Off-line quantitative OCT analyses utilized a dedicated software package (QIvus 3.0, Medis Medical, The Netherlands). Quantitative parameters included plaque length, minimal luminal cross-sectional area (CSA), and maximal luminal stenosis (minimal CSA ÷ mean [distal and proximal] reference lumen CSA). For *in-stent* lesions, neointimal area (stent CSA minus lumen CSA) and neointimal thickness (measured perpendicularly from stent strut to lumen) were also calculated.

Statistical analysis

Statistical analyses were performed using SPSS 26.0 (IBM Corp. Armonk, NY, USA). Categorical variables are presented as counts and frequencies and were analyzed using Chi-square or Fisher's exact test when appropriate. To test the normality of distribution, we performed a Shapiro-Wilks test. Continuous variables did not present normal distribution; therefore, their results are presented as median and interquartile range (IQR). We used the non-parametric Kruskall-Wallis test for multiple comparisons. When needed, pairwise comparisons

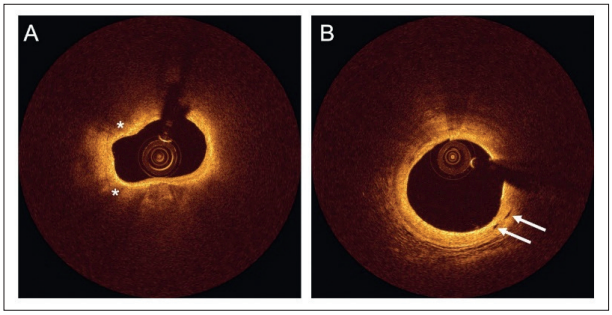

Figure 2 – *OCT images of macrophage infiltration and neovascularization. The white asterisks in A indicate signal-rich, punctate images compatible with macrophage infiltration in OCT images. The white arrows in B indicate no-signal, intra-plaque images compatible with neovascularization.*

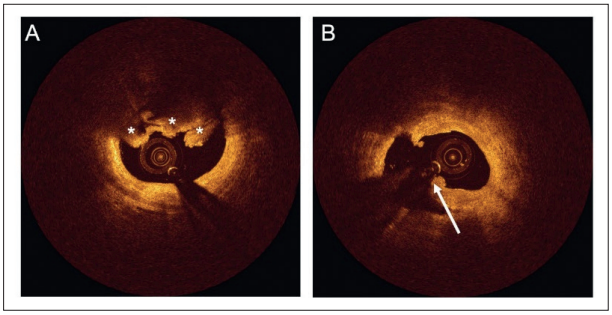

Figure 3 – *OCT images of thrombus and ruptured plaque. The white asterisks indicate thrombus (A) and the white arrow indicates plaque rupture (B).*

were performed using the Dunn-Bonferroni approach. A significance level of < 0.05 was adopted as statistically significant.

Results

Out of a total of 499 patients found in our database, 110 patients had at least one good-quality OCT run that imaged an entire lesion prior to any interventional manipulation, and comprised the present study population. Most patients were males, over 60 years of age, with multiple risk factors for coronary artery disease and presenting with acute coronary syndrome (ACS) upon hospital admission (Table 1).

In Table 2, we present the characteristics among the different types of plaque. Most characteristics were different

Table 1 – Demographic and clinical characteristics (n=110 patients)

Males	88 (80.0)
Age, years	63 (56 – 71)
Hypertension	75 (68.2)
Diabetes	33 (30.0)
Hyperlipidemia	90 (81.8)
Smoking (current or former)	61 (55.5)
Family history of CAD	60 (54.5)
Acute coronary syndrome	69 (62.7)

Numbers are counts (percentage) or median (interquartile range). CAD: coronary artery disease.

Table 2 – OCT characteristics of de novo, neointimal, and neoatherosclerotic lesions (n=121)

	De novo (n=74)	In-stent restenosis (n=29)	In-stent neoatherosclerosis (n=18)	p*
Calcification	56 (75.7)	-	10 (55.6)	< 0.01
TCFA	17 (23.3)	-	7 (38.9)	< 0.01
Plaque rupture	10 (13.9)	0	7 (38.9)	< 0.01
Thrombus	9 (12.5)	0	4 (22.2)	0.03
Neovascularization	48 (65.8)	3 (10.3)	17 (94.4)	< 0.01
Macrophage	71 (95.9)	2 (6.9)	18 (100)	< 0.01
Plaque length, in mm	24.1 (17.2-36.8)	25.8 (18.0-33.0)	23.5 (17.8-29.0)	0.9
Minimal luminal CSA, mm²	2.42 (1.64-3.51)	2.72 (1.77-4.52)	1.85 (1.35-3.18)	0.07
Max. luminal stenosis, %	65.5 (54.8-74.6)	45.7 (33.1-63.0)	66.2 (53.9-76.2)	<0.01
Max. IS tissue thickness, mm	-	0.74 (0.59-0.98)	1.13 (0.95-1.34)	< 0.01
Max. IS tissue CSA, mm²	-	3.54 (2.87-4.69)	4.96 (4.22-6.21)	<0.01
Neovasc. vol., 1000 x µm³/mm	950 (0-3400)	0 (0-0)	6220 (1250-13430)	< 0.01
Macrophage score	2.5 (0.9-4.9)	0.0 (0.0-0.0)	4.5 (3.1-7.3)	< 0.01

*Numbers are counts (percentage) or median (interquartile range). CSA: cross sectional area; IS: in-stent; LAD: left anterior descending artery; LCx: left circumflex artery; Max: maximal; Neovasc: neovascularization; RCA: right coronary artery; TCFA: Thin-cap fibroatheroma; Vol: volume. *P-value for the overall comparison among the groups.*

among the groups. Neovascularization was found in 65.8% of *de novo*, 10.3% in restenosis, and 94.4% in neoatherosclerosis (p<0.01 for all) (Table 2). Accordingly, the volume of neovascularization was different among lesion types (950 vs. 0 vs. 6220, respectively [median values in 1000 x μm^3/mm]; p<0.01 for all), being significantly higher in neoatherosclerosis and lower in restenosis (Figure 4).

The presence of macrophages differed among the lesions (95.9% in *de novo* vs. 6.9% in restenosis vs. 100% in neoatherosclerosis [p<0.01 for all]). Also, the intensity of macrophagic infiltration was different among lesion types (2.5 vs. 0.0 vs. 4.5, respectively [median values of macrophage score]; p<0.01 for all) (Figure 5), significantly higher in neoatheroscleosis and lower in restenosis (Figure 5).

When compared to stable patients, acute patients had more thrombus (16.2% versus 2.4%, p = 0.029) and lower intensity of macrophage infiltration (3.8 [1.2 – 5.9] versus 1.2 [0 – 3.6], p = 0.008). All other OCT features (plaque type; presence of neovascularization, macrophage, TCFA and plaque rupture; and volume of neovascularization) were not significantly different between the groups (p > 0.05 for all).

Discussion

Our study compared three different causes of coronary narrowing, namely de novo, restenotic and neoatherosclerotic lesions, and demonstrated marked differences among them in relation to their inflammatory phenotype by OCT, assessed by the presence and degree of macrophage accumulation and intra-lesion neovessels.

Inflammation is the cornerstone for understanding these three different processes that cause coronary stenosis. Pathogenesis of native coronary atherosclerosis has been extensively investigated in the last decades[2] and involves multiple inflammatory pathways. However, since coronary stenting is a somewhat recent technique, in-stent restenosis is a pathological entity that did not exist previously and is not entirely understood yet. Following percutaneous intervention, blood flow disturbances, migration and proliferation of smooth muscle cells and fibroblasts into the intima ensues, causing deposition of extracellular matrix, collagen, lymphocytes and macrophages.[4,8,22] Continuous inflammatory stimulus caused by the enduring metallic structures of the stent also leads to intra-plaque foreign-body reaction, accelerating atherosclerotic changes[23] and increasing the presence of neovascularization.[21] Also, incomplete maturation of endothelial cells due to the anti-proliferative drugs eluted by the stents impairs the barrier function usually carried out by the normal endothelium.[24] Both increased neo-vessel presence and immature endothelium are likely responsible for allowing a steep inflow of inflammatory cells into the neointimal tissue. Unlike native vessel atherosclerosis, that develops over decades,[2] neoatherosclerosis is an accelerated atherosclerotic process set in an abnormally healed vessel wall that can occur in a few years or even months following stent implantation, particularly with drug-eluting stents.[5] These differences are observed *in vivo* in our study, with neoatherosclerosis presenting significantly larger neovascularization volumes and macrophage density when compared to both *de novo* and restenotic lesions.

In-stent restenosis due to neointimal hyperplasia is believed to be limited to a certain timeframe following stent implantation[25] and was generally considered to be a somewhat benign, stable event, not frequently related to acute coronary events.[26] More recently, however, it has been observed that in-stent restenosis may present as acute coronary syndrome in more than 50% of the cases.[27] Neoatherosclerosis probably develops itself upon neointimal hyperplasia,[21] following plaque modifications that infiltrate lipids and macrophages, which are associated with plaque rupture and acute coronary events. Our study population

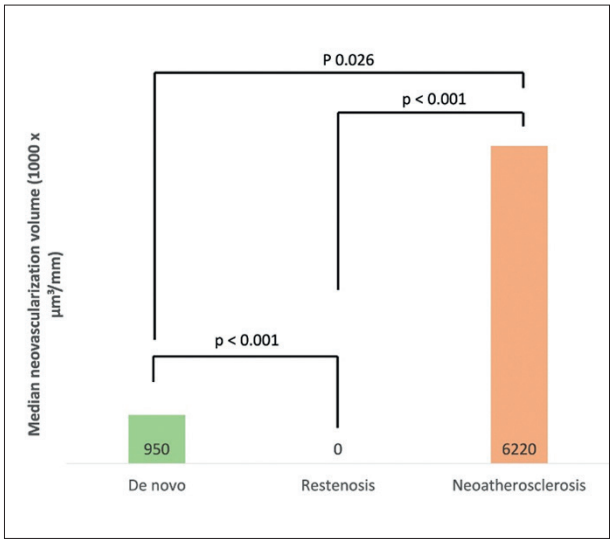

Figure 4 – *Neovascularization volume by lesion type.*

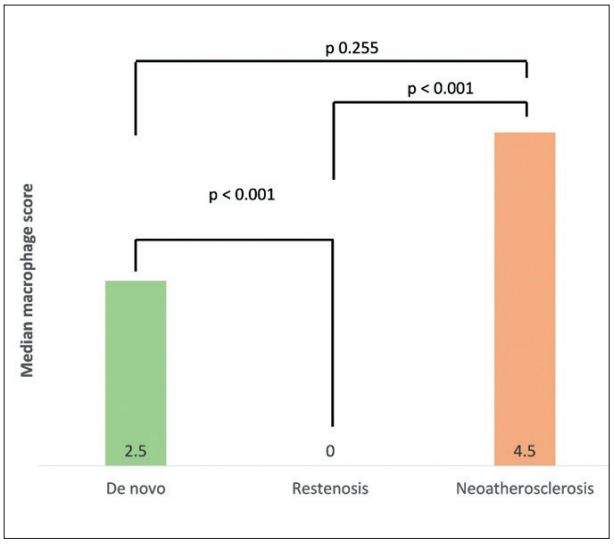

Figure 5 – *Macrophage score by plaque type.*

reflected such characteristics, with neoatherosclerotic plaques being significantly more prone to rupture than *de novo* and restenotic plaques, as well as presenting larger neointimal thickness and lumen sizes, which can be the result of such plaque modifications.

Our study has several limitations. It is an exploratory, observational, retrospective study, with a highly selected population of individuals with a high burden of cardiovascular risk factors and coronary artery disease, and most of our population (62.7%) was comprised of patients admitted to the hospital with acute coronary syndromes. Accordingly, it is not possible to extrapolate these findings to other clinical settings. Also, patients with acute coronary syndromes presented lower levels of macrophage infiltration in our sample. This finding may be explained by the fact that acute patients had significantly more thrombus when compared to stable patients, thus hindering the assessment of macrophage infiltration in these regions impossible in most cases. Although we had no information regarding the age or type of the stents implanted, in our opinion this was not detrimental to the interpretation of our findings, considering we were solely analyzing plaque characteristics.

Notwithstanding, this is supposed to be a hypothesis-generating study. Neoatherosclerosis is an important cause of late stent failure not reduced with the use of drug eluting stents and has a direct impact on the outcomes of coronary percutaneous interventions.[28] Risk factors such as hyperlipidemia, smoking and impaired renal function, all of which up-regulate systemic inflammation, have been associated with higher rates of neoatherosclerosis.[29,30] Additionally, inflammation by itself has been linked with increased cardiovascular risk.[2] New evidence has emerged proving *in vivo* that modulation of the inflammatory response and risk factors control can reduce the rates of major cardiovascular events[7] and reduce atherosclerotic plaque volume.[31] Nonetheless, these effects are yet to be proven to reduce neointimal hyperplasia and neoatherosclerosis rates. In a recent article,[32] Hashikata et al. demonstrated that the use of empaglifozin reduced neointimal hyperplasia at 12 months in diabetic patients when compared to standard glucose-lowering therapy. Mean neointimal thickness, volume and percentage were significantly lower in the empaglifozin group. Interestingly, this reduction was independent of lower glucose levels, suggesting a possible multi-factorial underlying mechanism. The current HUYGENS trial[33] included patients with non-ST segment elevation myocardial infarction who were treated with evolocumab or placebo in addition to intensive statin therapy for 52 weeks and underwent serial OCT and intravascular ultrasound imaging. The evolocumab group achieved lower LDL-C levels and imaging features that included a greater increase in minimum fibrous cap thickness, decrease in maximum lipid arc and plaque regression. More intensive lipid lowering with early addition of a PCSK9 inhibitor to statins after a NSTEMI produces stabilization and regression of coronary atherosclerosis. The improved clinical outcomes achieved with very low LDL-C levels associated with changes in plaque phenotype pave the way for these new lipid-lowering options become a perspective to prevent intra-stent neoatherosclerosis. Also, efforts are being made to produce stents with novel absorbable scaffolds[34] and better drug delivery to modulate tissular response,[35] thus allowing a more physiologic endothelial regeneration and reducing the substrate that originates neoatherosclerosis.

To the best of our knowledge, this is the first study directly comparing plaque inflammation of native vessel atherosclerosis with neointimal hyperplasia and neoatherosclerosis using OCT. In our understanding, these findings stress the importance of inflammation in the pathogenesis of stent failure, suggesting that the future of PCI probably lies in fine-tuning tissular response and not leaving a metallic footprint behind.

Further prospective studies with aggressive lipid-lowering therapy, blood pressure and glucose control, smoking cessation, and control of inflammation may modify the evolution of neoatherosclerosis.

Conclusions

In summary, when compared using OCT, *de novo* atherosclerosis, in-stent restenosis and in-stent neoatherosclerosis presented markedly different inflammatory phenotypes (i.e., neovessel volume and macrophage quantification).

Author Contributions

Conception and design of the research: Pinheiro LF, Garzon S, Mariani J, Caixeta AM, Lemos PA; Acquisition of data and Analysis and interpretation of the data: Pinheiro LF, Garzon S, Mariani J, Prado GA, Caixeta AM, Almeida BO, Lemos PA; Statistical analysis: Pinheiro LF, Garzon S, Prado GA, Caixeta AM, Lemos PA; Writing of the manuscript and Critical revision of the manuscript for important intellectual contente: Pinheiro LF, Garzon S, Lemos PA.

Potential Conflict of Interest

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

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Study Association

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Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Hospital Israelita Albert Einstein under the protocol number 3.722.061. 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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Macrophages and Neovascularization in In-Stent Neoatherosclerosis: An Accelerated Inflammatory Phenotype by OCT with Therapeutic Implications

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Short Editorial related to the article: Inflammatory Phenotype by OCT Coronary Imaging: Specific Features Among De Novo Lesions, In-Stent Neointima, and In-Stent Neo-Atherosclerosis

In this edition of *Arquivos Brasileiros de Cardiologia*, Pinheiro et al.[1] show optical coherence tomography (OCT) data with clear differences in inflammation and neovascularization among de novo atherosclerosis, in-stent restenosis due to intimal hyperplasia, and in-stent neoatherosclerosis.

Patients undergoing percutaneous coronary intervention with stent implantation may have recurrent symptoms of coronary heart disease due to in-stent restenosis due to vascular injury that triggers an intimal proliferative response,[2] minimized by current techniques and stents of new generation.[3] However, the neointimal lesion secondary to a delay in neoendothelialization can lead to symptom recurrence, usually during the first year of coronary intervention.[4]

In patients with acute coronary syndromes, pronounced inflammatory responses can be detected for weeks,[5] contributing to plaque instability[6] and infarcted mass and ventricular remodeling after myocardial infarction.[7] In addition, stent implantation also promotes systemic and local inflammation.[8]

Russel Ross[9] defined atherosclerosis as an inflammatory disease.[9] Pinheiro et al.[1] reported increased inflammatory activity and neovascularization among de novo lesions and intra-stent neoatherosclerosis. These two forms of atherosclerosis may have important differences in pathophysiology. Atherosclerosis in native arteries is related to cardiovascular risk factors, and it takes a long time to develop, but after acute coronary syndromes and/or stent implantation, systemic inflammation may accelerate its progression.[6] Intra-stent neoatherosclerosis is a new and fast form of atherosclerosis-related to vascular injury and inflammation.[4]

Complications such as atherosclerotic plaque rupture seem to be associated not only with plaque expansion[10] but also with characteristics of greater vulnerability (inflammatory content, thin fibrous cap, and higher lipid content).[11] OCT has properly addressed all these aspects. The article's findings have important implications:

The need for appropriate therapy (including highly-effective lipid-lowering therapies) to prevent the development of atherosclerosis in native coronary arteries and possibly in the intra-stent atherosclerosis.[12,13]

The study raises the debate about the relevance of residual inflammatory risk and the opportunity to use anti-inflammatory drugs.[14,15]

More studies are necessary to understand better intra-stent neoatherosclerosis and the need for more comprehensive strategies, to prevent this form of stent failure.

Keywords

Coronary Restenosis; Phenotype/inflammation; Percutaneous Coronary Intervention; Atherosclerosis; Diagnostic, Imaging/methods.

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Original Article

Wolff-Parkinson-White Presenting as QRS Alternans and Other Differential Diagnoses in a Large Pre-Participation ECG Screening Cohort

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Abstract

Background: **Wolff-Parkinson-White (WPW) syndrome is a proarrhythmic condition that may require restriction from strenuous activities and is characterized by ECG signs, including delta waves. We observed cases of intermittent WPW patterns presenting as QRS alternans ('WPW alternans') in a large pre-participation ECG screening cohort of young men reporting for military conscription.**

Objectives: **We aimed to determine the WPW alternans pattern, case characteristics, and the prevalence of other relevant differential diagnoses presenting as QRS alternans in a pre-participation setting.**

Methods: **One hundred twenty-five thousand one hundred fifty-eight prospective male military recruits were reviewed from January 2016 to December 2019. A review of electronic medical records identified cases of WPW alternans and WPW patterns or syndrome. Reviewing electronic medical records identified cases of relevant differential diagnoses that might cause QRS alternans.**

Results: **Four individuals (2.2%) had WPW alternans out of 184 individuals with a final diagnosis of WPW pattern or syndrome. Two of these individuals manifested symptoms or ECG findings consistent with supraventricular tachycardia. The overall prevalence of WPW alternans was 0.003%, and the prevalence of WPW was 0.147%. WPW alternans represented 8.7% of individuals presenting with QRS alternans, and QRS alternans had a prevalence of 0.037% in the entire population.**

Conclusions: **WPW alternans is a variant of intermittent WPW, which comprised 2.2% of WPW cases in our pre-participation screening cohort. It does not necessarily indicate a low risk for supraventricular tachycardia. It must be recognized at ECG screening and distinguished from other pathologies that also present with QRS alternans.**

Keywords: **Wolff-Parkinson-White Syndrome; Lown – Ganong – Levine Syndrome; Pre-Excitation, Mahaim-Type; Electrocardiography/methods; Electrocardiography/diagnosis.**

Introduction

Preparticipation physical evaluation prior to strenuous activities such as sports may allow for the detection of potentially disqualifying medical conditions, such as serious cardiac abnormalities. Electrocardiographic (ECG) screening is one of the modalities used in such evaluations to detect proarrhythmic conditions. It is recommended by multiple professional societies and guidelines,[1-3] with interpretation criteria including the European Society of Cardiology (ESC) 2010 criteria,[4] Seattle Criteria,[5] Refined Criteria (2014)[6] and most recently, the International Criteria for ECG interpretation in Athletes (2017).[7]

Wolff-Parkinson-White (WPW) is a potentially proarrhythmic condition that can be detected on ECG screening. The underlying abnormality is an accessory pathway that allows conduction from the atria to the ventricles, bypassing the atrioventricular node. This pre-excitation manifests as delta waves, short PR interval, prolonged QRS interval, and repolarization abnormalities on ECG. The WPW pattern on ECG in combination with symptomatic tachyarrhythmia constitutes WPW syndrome. Individuals with WPW require review and risk stratification before participating in strenuous activities. The conventional WPW pattern is readily recognizable by pre-excitation on every beat but can rarely present intermittent pre-excitation on alternate beats (i.e., with QRS alternans, defined by alternating amplitude, morphology, or duration of the QRS complex). This phenomenon may

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make recognition challenging, and only isolated case reports exist of the 'WPW alternans' phenomenon in the literature.[8-10] These cases were sporadically identified rather than systematically collected.

WPW alternans must also be distinguished from other etiologies of QRS alternans. In emergency settings, a key differential diagnosis that is classically described is pericardial tamponade (where there are QRS alternans due to mechanical swinging of the cardiac apex rather than the pathology of the intrinsic conduction pathways). Other situations in which QRS alternans may occur in non-paced rhythms include intermittent sinus pause/ exit block with ventricular escape or junctional escape with bundle branch block (BBB), intermittent BBB on alternate beats, atrial bigeminy with aberrant conduction and ventricular bigeminy. It may also occur during tachyarrhythmias such as bidirectional ventricular tachycardia and supraventricular tachycardias at high rates (e.g., atrioventricular re-entrant tachycardia).

No literature has systematically examined the prevalence of WPW alternans or QRS alternans in a pre-participation, non-emergency setting. However, it remains necessary for medical providers conducting ECG screening to correctly recognize WPW alternans as a form of WPW, distinguish it from other causes of QRS alternans, and thence determine if the underlying cause warrants exclusion from participation.

The Singapore Armed Forces have conducted universal pre-participation ECG screening before military enlistment for all young male Singaporeans to determine cardiac fitness.[11-13] Our primary aim was to systematically determine the prevalence of the WPW alternans pattern and the relevant case characteristics in this pre-participation, non-emergency setting. Our secondary aim was to systematically determine the prevalence of other relevant differential diagnoses presenting as QRS alternans in the same setting.

Methods

One hundred twenty-five thousand one hundred fifty-eight prospective male military recruits were reviewed from January 2016 to December 2019 as part of their determination of fitness to enlist in military service. All individuals attended the same centralized facility and had a supine resting 12-lead ECG. The ECGs were reported by trained clinicians using a standardized algorithm based on International Criteria.[7]

During this period, we observed four cases of WPW alternans on the presenting ECG. We reviewed electronic referrals to the national cardiology tertiary center for suspected WPW ECG patterns and the electronic medical records of the 184 individuals who had received a new WPW pattern or syndrome diagnosis. No other cases of WPW alternans were identified. Separately, we identified 34 individuals who had been diagnosed with WPW prior to attending the pre-participation screening. These cases were excluded from our analysis because their presenting ECGs were unavailable. These 34 individuals had repeat ECGs at our screening center, of which none displayed WPW alternans.

Concurrently, we identified individuals presenting with QRS alternans arising from other etiologies. We determined this through two means: First, by a review of text documentation made for clinical ECG interpretation; Second, by a review of diagnostic codes for cardiac arrhythmias and pericardial tamponade. With the first method, we employed a keyword search and a manual chart review of all documentation. The search terms for the various conditions are listed in Appendix 1 and are based on our facility's standardized ECG interpretation vocabulary. We extracted the electronic medical records for individuals with the relevant diagnosis codes with the second method. This ensured exhaustive identification of individuals with QRS alternans morphology. All individuals identified with WPW alternans and QRS alternans had their ECG manually reviewed.

Approval for data collection and use was granted by the Singapore Armed Forces Joint Medical Committee, and ethical approval was obtained from the local institutional review board.

Statistical analysis

We adopted a descriptive approach, calculating the prevalence of WPW alternans in the overall population and individuals with WPW. We also calculated the prevalence of QRS alternans in the overall population and the individual diagnoses causing QRS alternans. Quantitative analysis was done using Excel (Microsoft 365 Apps). Case details of individuals with WPW alternans are qualitatively presented.

Results

Four individuals (2.2%) had WPW alternans out of 184 individuals with a final diagnosis of WPW pattern or syndrome. In the entire screening cohort, the prevalence of WPW alternans was 0.003%, and the prevalence of WPW was 0.147%.

We also identified 42 other individuals with QRS alternans morphology from medical records review on screening ECG. This comprised 1 individual with intermittent BBB on alternating beats, 9 individuals with atrial bigeminy, and 32 with ventricular bigeminy. No individuals had intermittent sinus pause/exit block with ventricular escape, junctional escape with BBB, or ventricular tachycardia on presenting ECG. No individuals in our cohort had an active diagnosis of pericardial tamponade at the point of screening. Overall, WPW alternans represented 8.7% of individuals presenting with QRS alternans, and QRS alternans had a prevalence of 0.037% in the entire ECG screening population. All of the individuals identified did not have pre-existing cardiac disease. These findings are summarized via a flow diagram in Figure 1.

We present in Table 1 the case details of the four individuals with WPW alternans. At the time of writing, none of the individuals had consented to invasive electrophysiology studies, and none had experienced any sudden cardiac death. All were advised not to engage in physically strenuous activities.

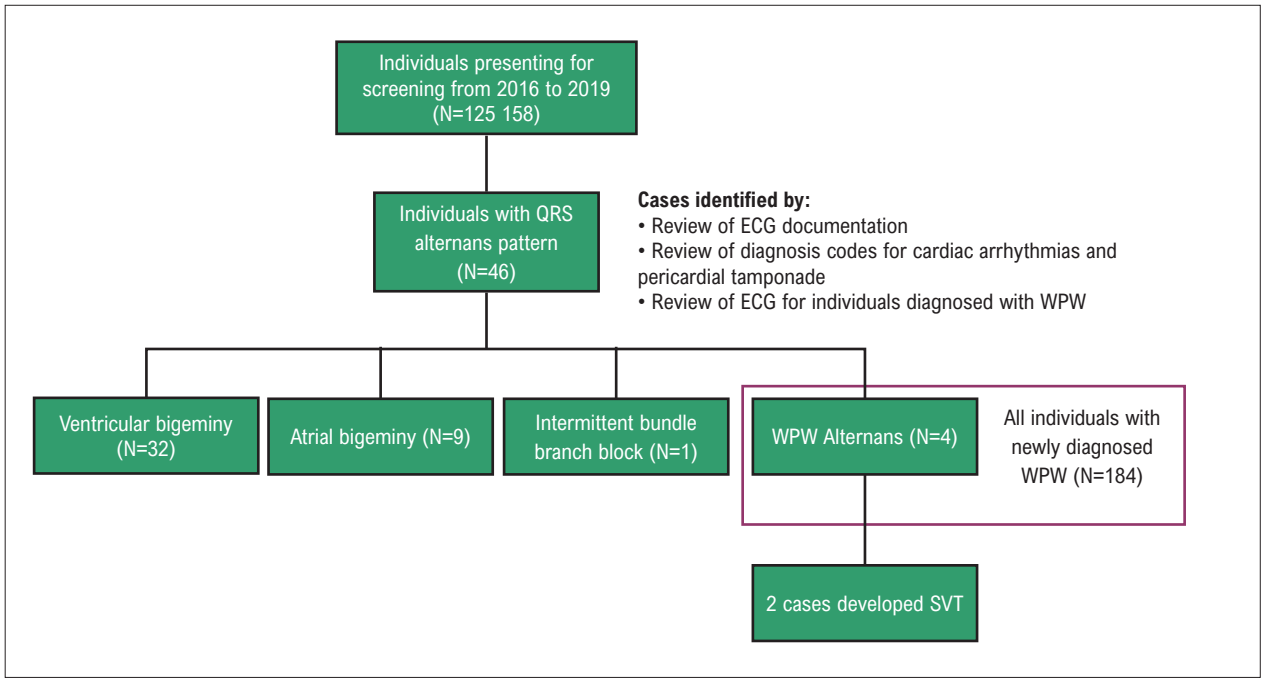

Figure 1 – *Flow diagram of individuals included in the study. ECG: electrocardiographic; WPW: Wolff-Parkinson-White; SVT: supraventricular tachycardia.*

Table 1 – WPW alternans case details

	Case 1	Case 2	Case 3	Case 4
ECG at screening	Please refer to Appendix 2 for ECGs of each case			
Age	19	19	18	18
Symptoms	Palpitations No syncope	Palpitations No syncope	Palpitations No syncope	No symptoms
Presence of supraventricular tachycardia	Yes Had palpitations deemed clinically compatible with supraventricular tachycardia	Yes Developed long RP tachycardia during consult – diagnosed as atrial tachycardia	No	No
Treadmill exercise test	Pre-excited with intermittent pre-excitation	Pre-excited with loss of pre-excitation at maximal HR of 194 bpm	Pre-excited with no sudden loss of pre-excitation	Normal
2D Echocardiogram	Normal	Normal	Normal	Not performed
Other investigations	24 hour Holter: intermittent pre-excitation	Nil	24 hour Holter: intermittent pre-excitation	Nil

ECG: Electrocardiographic ; HR: heart rate; RP: R to P wave interval.

Discussion

Effective pre-participation ECG screening requires recognizing abnormal patterns, including uncommon presentations of ECG abnormalities. Our case series of four individuals with WPW alternans showed a prevalence of 2.2% among WPW cases and 0.003% in the entire cohort. To our knowledge, this is the largest case series of WPW alternans in the literature and the only study that has systematically determined its prevalence. It suggests that WPW alternans may not be as rare as its paucity in the extant literature suggests.

WPW alternans is a form of intermittent pre-excitation, which is conventionally thought to confer a lower risk of supraventricular tachycardia.[15] We did not observe this in our case series - in fact, Case 2 developed episodes of supraventricular tachycardia (SVT) during the screening consultation. He was cardioverted with vagal maneuvers and emergently referred to the national cardiology tertiary

center. Case 4 had recurrent palpitations that the attending cardiologist deemed consistent with paroxysmal SVT. Evidence from Escudero et al.[15] in a recent multicenter pediatric WPW study[16] suggests that intermittent pre-excitation is not entirely risk-free, and such individuals may still have underlying accessory pathways at high risk for developing the SVT. It is thus important that the WPW alternans pattern is adequately recognized at the point of ECG screening and not mistakenly deemed benign. It should be accorded the same treatment as any other case of WPW.

Recognition of WPW alternans may be confounded by other pathologies presenting with the QRS alternans pattern. As expected of a young, pre-participation, non-emergency cohort, no cases of severe acute pathologies such as bidirectional ventricular tachycardia or cardiac tamponade were diagnosed. Ventricular bigeminy was the most common alternative pathology, followed by atrial bigeminy and intermittent BBB on alternate beats. Example ECGs of such conditions gathered from individuals in this cohort art included in Appendix 3. The only way to distinguish WPW from these other pathologies is to examine the ECG for delta waves carefully. As such, examiner physicians must be alert to these other differential diagnoses and consider serial ECGs for further elicitation of delta waves.

The main strength of our study is that it was a comprehensive, population-wide survey conducted over multiple years. It is the first study to systematically examine the epidemiology of the WPW alternans pattern in the ECG screening setting and to document the epidemiology of important differential diagnoses that can also present with QRS alternans. This will aid clinicians performing ECG screening in arriving at a relevant differential diagnosis for the visually striking sign of QRS alternans, as the pathologies observed are not the same as those described in emergency settings.

Our study has some important limitations. First, the ECGs in the study were reviewed by different clinicians, and the study team did not personally review every ECG in the database. There may be inter-individual variation in ECG interpretation between clinicians. Second, we note that WPW has no gender predilection in pediatric age groups[17] but is known to have a male predominance in adults.[18] The relative prevalence of our cohort of adolescent males may thus not be entirely generalizable to female individuals. However, correct recognition of the alternans ECG sign and WPW alternans would still be important for female individuals undergoing ECG screening. Third, we cannot confirm any specific electrophysiologic mechanism of WPW alternans, as none of the individuals identified consented to an invasive electrophysiologic study. Finally, we cannot comment on the long-term sudden cardiac death risk for the individuals with WPW or WPW alternans in this study, given that the individuals examined had only been diagnosed within the last few years. Future studies may include extended follow-up for such individuals to ascertain their sudden cardiac death risk better.

Conclusion

WPW alternans is a variant presentation of intermittent WPW, which occurred in 2.2% of WPW cases in a pre-participation screening cohort. It does not necessarily indicate a low risk for supraventricular tachycardia. Hence, it must be recognized at ECG screening and distinguished from other pathologies that also present with QRS alternans. Common differential diagnoses of QRS alternans observed in our pre-participation, the non-emergency cohort included ventricular bigeminy, atrial bigeminy and intermittent BBB on alternate beats.

Author Contributions

Conception and design of the research: Lim DYZ, Ho WHH; Acquisition of data: Lim DYZ, Ho WHH, Ang WK, Thiagarajan N, Sng GSR, Wang H, Loo WTW; Analysis and interpretation of the data: Lim DYZ, Ho WHH, Wang L; Statistical analysis: Lim DYZ; Writing of the manuscript: Lim DYZ, Ho WHH, Ang WK, Thiagarajan N; Critical revision of the manuscript for important intellectual content: Wang L, Sng GSR, Wang H, Loo WTW, Yang LH, Chow W, Chua TJ, Yeo TJ, Lim P, Chong TTD.

Potential Conflict of Interest

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

Sources of Funding

There were no external funding sources for this study.

Study Association

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

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the SingHealth Centralised IRB under the protocol number 2015/3095. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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*Supplemental Materials

For additional information, please click here.

Original Article

The Relationship between Extracellular Volume Compartments and Matrix Metalloproteinases-2 in Left Ventricular Remodeling after Myocardial Infarction

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Abstract

Background: **Matrix metalloproteinases (MMPs) can affect myocardial extracellular volume (ECV) and its compartments, and this can provide more detailed information about the mechanism of adverse left ventricular (LV) remodeling (AR) after acute myocardial infarction (MI).**

Objectives: **To investigate the role of changes (Δ) in ECV compartments (matrix volume (MVi) and cell volume (CVi)) in the development of AR after MI, and their relationship with MMP-2 expressions.**

Methods: **Ninety-two first MI patients who underwent 3 Tesla cardiovascular magnetic resonance imaging performed 2 weeks (baseline) and 6 months post-MI. We measured T1 mapping with MOLLI sequences. ECV was performed post-gadolinium enhancement. ECV and LV mass were used to calculate MVi and CVi. AR was defined as an increase of ≥ 12% in LV end-diastolic volume in 6 months. MMPs were measured using a bead-based multiplex immunoassay system at first day (baseline) and 2 weeks post-MI. P <0.05 was accepted as statistically significant.**

Results: **Mean ECV and mean MVi baseline levels were higher in AR group compared to without AR group (42.9±6.4 vs 39.3±8.2%, p= 0.037; 65.2±13.7 vs 56.7±14.7 mL/m², p=0.010; respectively). CVi levels was similar between groups. A positive correlation was found between baseline levels of MMP-2 and baseline levels of ECV (r=0.535, p<0.001) and MVi (r=0.549, p<0.001). Increased ΔMVi levels was independently predictor of AR (OR=1.03, p=0.010). ΔMVi had superior diagnostic performance compared to ΔECV in predicting AR (ΔAUC: 0.215±0.07, p<0.001).**

Conclusion: **High MVi levels are associated with AR, and ΔMVi was independently predictor of AR. This may be associated with MMP-2 release due to increased inflammatory response.**

Keywords: **Myocardial Infarction/metabolism; Ventricular Remodeling; Myofibroblasts/cytology; Matrix Metaloproteinase; TI Mapping/cytology.**

Introduction

Acute myocardial infarction (MI) initiates an inflammatory response involving the interaction of the extracellular matrix (ECM) and neurohumoral activation and then progresses with fibroblast increase.[1] Fibroblasts produce the structural proteins of the ECM and can cause cytokine storms and overproduction of matrix metalloproteinases (MMPs) in extreme inflammatory responses.[2] These factors contribute to the production and accumulation of excess ECM proteins, causing a maladaptive effect on the structural and functional properties of the heart and resulting in adverse left ventricular (LV) remodeling (AR).[3]

The developmental process of AR is associated with the expansion of the interstitial matrix and dynamic changes in the ECM network.[4] Extracellular space increases when healthy myocardium is replaced by fibrosis or scar tissue.[5] ECM enlargement is converted

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to quantitative values via T1 values and extracellular volume (ECV) fraction assessed by T1 mapping by cardiovascular magnetic resonance imaging (CMRI).[6] In addition, indices derived from the ECV and myocardial volume (LV matrix volume and cell volume) allow the assessment of the reversibility of changes in cellular and extracellular compartments.[7] MMPs, which are zinc-dependent proteolytic enzymes, play a major role in the modulation of the ECM and thus have prognostic significance in LV remodeling.[8] However, we could not find any previous study evaluating the contribution of changes in cellular and extracellular compartments to the development of AR after MI and the relationship between these changes and MMPs. Therefore, in this study, the prognostic role (Δ) of T1 mapping including LV matrix volume and cell volume with AR development in patients with first acute ST-segment-elevation MI (STEMI) and its relationship with MMP-2 were investigated.

Materials and Methods

Study population

This research was conducted between June 2015 and June 2018 as a multicenter, prospective study in accordance with the principles of the Declaration of Helsinki and was approved by the local ethics committee (Decision Date/No: 24.06.2013/106). Written consent was obtained from all patients. Based on previous studies, the rate of AR development at the 6th month of follow-up after MI was assumed to be 30% and the estimated sample size was at least 46 patients, with an alpha value of 0.05 and 0.80 power.

A total of 567 patients over 18 years of age who were admitted to the emergency department with the diagnosis of STEMI for the first time and who underwent primary percutaneous coronary intervention (pPCI) were evaluated. It was found that 351 patients did not meet the inclusion criteria and they were excluded from the study. Ninety-two patients who underwent pPCI within 12 hours from the onset of chest pain and whose T1 mapping was evaluated by CMRI at the 6th month of follow-up after MI were included in the study (Figure 1). The diagnosis of STEMI was made according to the third universal definition for MI[9] and treatment was planned according to the most recently updated guidelines of the European Society of Cardiology (ESC).[10]

Study exclusion criteria were previous history of coronary artery disease, delayed admittance (>12 hours), cardiogenic shock (systolic blood pressure of ≤90 mmHg), need for hemodynamic support, previous history of silent ischemia/infarction, systemic inflammatory disease or autoimmune disease, chronic corticosteroid or anti-inflammatory medication use, pregnancy/delivery/breastfeeding in the last 3 months, myocardial reinfarction following emergency or elective coronary artery bypass grafting after angiography, failed pPCI, fear of MRI, and claustrophobia.

Study Protocol

All pertinent data were noted within the files of the patients as they were obtained in the course of follow-up, including demographic data and data on clinical, laboratory, and radiological results. Calculation of the Global Registry of Acute Cardiac Events Risk (GRACE) Score was used by the official calculator (www.gracescore.org). In the course of follow-up, CMRI was conducted for all participating patients at 2 weeks (baseline) and at 6 months after STEMI using the same devices (Magnetom Skyra 3-T scanner, Siemens Medical Systems, Erlangen, Germany) at all participating centers. The data thus obtained were gathered to be assessed by one individual with considerable experience in reading CMRI results; this individual was blinded to the specific patient data and all relevant outcomes. To evaluate MMPs, assessments for these patients were performed on the first day (baseline) and at 2 weeks after STEMI. Serum were held at -80 °C until they were assayed. After collecting serum from whole samples, the parameters of interest were quantified by the same laboratory staff using the same device in a single session in the Tissue Typing Laboratory and Genetic Diagnosis Center of the relevant hospital.

Laboratory testing

Venous blood samples were taken at the time of admission and centrifuged at 1500 rpm for 10 minutes, and complete blood count (CBC) and biochemistry parameters were analyzed. CBC parameters were measured with a Sysmex XN-1000 hematology analyzer (Sysmex Corporation, Kobe, Japan) and hemoglobin measurements were taken by photometric method. Total cholesterol was measured by the homogeneous enzymatic colorimetric method (Hitachi Modular P800 autoanalyzer, Roche Diagnostics Corp., Indianapolis, IN, USA) and low-density lipoprotein (LDL) cholesterol levels were determined with Friedewald's method.[11] Serum cardiac troponin I (cTn-I) levels were measured on a Dimension analyzer (Dade Behring Diagnostics, Amersfoort, the Netherlands) with a one-step enzyme immunoassay method based on the sandwich principle.

Measurements of MMP-2 were repeated twice. Previously frozen serum were allowed to thaw on ice and MMP-2 values were subsequently analyzed with the assistance of a bead-based multiplex immunoassay system (Bio-Plex Pro Human Inflammation Panel, Bio-Rad Laboratories, Hercules, CA, USA). To measure and quantify the development of selected sandwich immunocomplexes, the Bio-Plex MAGPIX System (Bio-Rad) was applied for the relevant bead sets. Final concentrations of analytes were determined with the help of Bio-Plex Manager v.5.0 software (Bio-Rad). Blood samples were taken at similar times in order to prevent the effect of daily rhythm on expression differences of inflammatory markers. Therefore, 46 patients who applied in the early hours (8:00-12:00 A.M.) were examined for MMP-2 expressions.

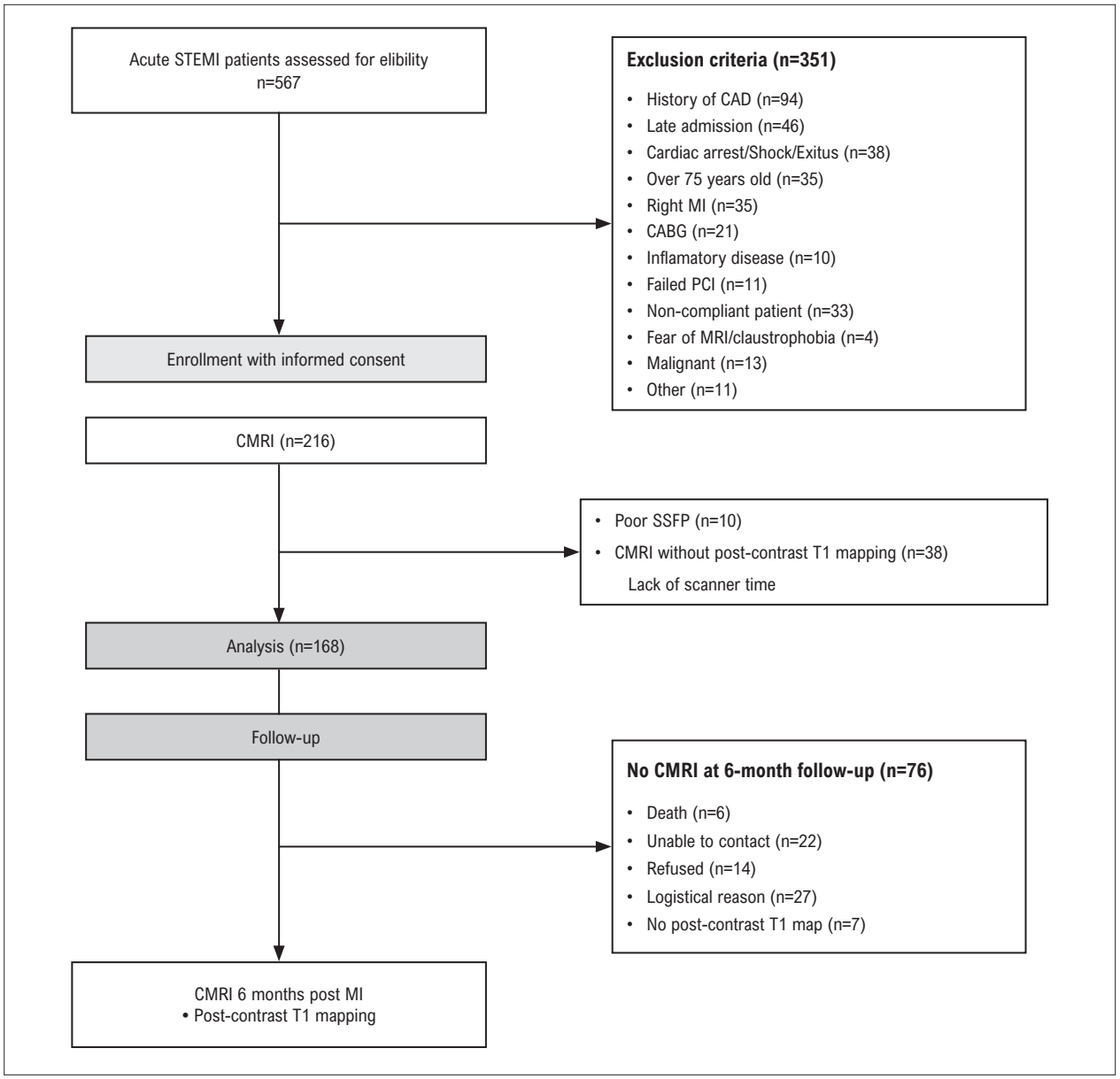


Figure 1 – *Flow diagram of the cohort study. CMRI: cardiac magnetic resonance imaging; SSFP: steady-state free precession. STEMI: STsegment-elevation MI; CAD: coronary; CABG: coronary artery bypass grafting; MI: myocardial infarction; PCI: percutaneous coronary intervention.*

Cardiac magnetic resonance imaging

In the process of obtaining the CMRI data, a single view with 4 chambers and cine short-axis sections (slice thicknesses of 6 mm at 10-mm intervals) was obtained, as well as a single view with 2 chambers. Evaluations of the LV systolic function indices were performed with the application of retrospective electrocardiogram gated turbo fast low angle shot (turbo-FLASH) sequences with echo time (TE) of 1.42 ms, repetition time (TR) of 39 ms, flip angle of 57°, and voxel size of 1.67 × 1.67 × 6 mm. The CMRI data obtained in this way were subsequently transferred in their entirety to a workstation. Thereafter, LV end-systolic volume (ESV) and LV end-diastolic volume (EDV) were determined by a reader employing Siemens syngo.via VA30 imaging software. In this process, the endocardial borders of the end-systolic and end-diastolic phases of short-axis stack images, which encompassed the LV within a range of space from the mitral annular line to the apex, were manually traced with exclusion of the papillary muscles. For cine images, the first phase was taken to be the end-diastolic phase, and the end-systolic phase was visually identified based on the cessation of inward LV motions.[12] Infarct size was performed by the volume summation of hyperenhancement per-slice, and presented as percentage of total LV mass.

The definition of AR was applied in light of widely accepted threshold LVEDV values (ΔLVEDV >12%).[13]

T1 mapping

T1 maps were obtained both prior to and 15 minutes after the processing of gadolinium contrast. Three short-axial slices (apical, middle, and basal) were considered while obtaining the T1 mapping with the application of a modified look-locker inversion-recovery (MOLLI) investigational prototype sequence (Siemens Healthcare, Malvern, PA, USA)[14,15] together with incorporation of an automatic registration algorithm as detailed in a previous publication.[16] In the process of acquiring T1 MOLLI cardiac-gated data, a total of 3 inversion-recovery prepared look-locker experiments were carried out according to a single protocol.[14] For the steps described here, the applied CMRI parameters included bandwidth of ~1090 Hz/pixel, flip angle of 35°, echo time of (TE) 1.1 ms, initial experimental T1 of 100 ms, TI increment of 80 ms, matrix of 192 × 124 pixels, spatial resolution of 2.2 × 1.8 × 8.0 mm, slice thickness of 8 mm, and scan time of 17 heartbeats.

ECV measurement

Regions of interest (ROIs) were taken from the remote myocardium at a location 180° from the infarct zone, from the infarct zone across the full area of the recorded injury, and from the LV blood pool. These specified ROIs were copied with the application of T1 mappings before and after administering a contrast agent. In this process, manual corrections were also applied to maintain the margins of separation from tissue interfaces. ECV values were calculated based on the ratios of relevant T1 infarct area values previously obtained before and after administering the contrast agent in each ROI. As a result, registrations among T1 maps were not necessary to obtain ECV calculations with accuracy. Equation (1) was used here for ECV, wherein $\lambda = \Delta R1_{myocardium}/\Delta R1_{blood}$, $\Delta R1 = R1_{post\text{-}contrast} - R1_{pre\text{-}contrast}$, and $R1 = 1/T1$. Hematocrit (HCT) was also evaluated while these scans were being performed.

$$ECV = (1\text{-}HCT) \times \lambda \qquad (1)$$

Matrix volume index were calculated by the product of LV myocardial volume (LV mass divided by specific gravity of myocardium [1.05 g/mL]) and ECV or (1 – ECV) for cellular volumes index.[17] Examples of these measurements of T1 maps, and ECV and compartments are provided in Figure 2.

Statistical analysis

Categorical variables were presented as numbers and percentages, and comparisons between groups were performed using chi-square, Yates correction, and Fisher tests. The normal distribution of numerical variables was evaluated with Kolmogorov-Smirnov tests and results with normal distribution were shown as mean±standard deviation while those with non-normal distribution were shown as median (interquartile range (IQR)). Intergroup comparisons of numerical variables were performed with Student t-tests or Mann-Whitney U tests. The change in CMRI parameters between 2 weeks and 6 months was evaluated with the paired T test or Wilcoxon test according to the normality distribution. To compare the considered CMRI parameters, a mixed model for repeated measures (MMRM) was established with the aim of comparing CMRI parameters and levels

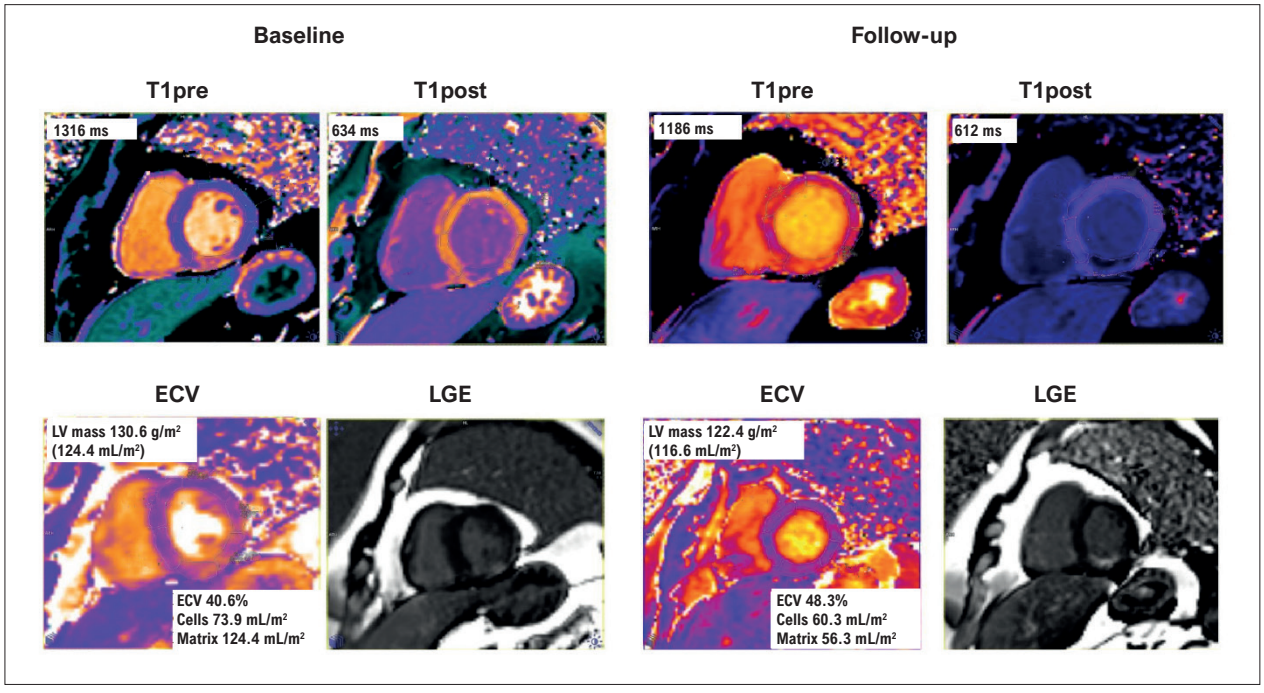


Figure 2 – *T1 maps and ECV values post-MI periods. CVi: cell volume index; ECV: extracellular volume; MVi: matrix volume index.*

of MMP-2 between the groups in the post-MI period. The correlation between numerical variables were tested by Spearman correlation analysis. Effects on AR were evaluated by conducting univariable logistic regression analysis. Potential risk factors associated with AR ($p<0.25$) were included in these multivariable logistic regression models.[18,19] In stepwise multivariable regression models, potential risk factors and changes of CMRI parameters from 2 weeks to 6 months post-MI were included. Receiver operating characteristic (ROC) curve analysis was conducted to establish a diagnostic discrimination of T1 mapping parameters on AR. IBM SPSS Statistics (IBM Corp., Armonk, NY, USA) was used for all analyses and $p<0.05$ (*) was accepted as statistically significant.

Results

A total of 567 patients who were admitted to the emergency department with the diagnosis of STEMI were evaluated (mean age: 56.7±15.2 years, 14.3% women). Ninety two patients who met the exclusion criteria and evaluated for CMRI were included in the analysis (mean age: 54.1±9.0 years), and patients were mostly male (90.2%) with a representative risk profile for cardiovascular disease. Demographic, clinical and CMRI characteristics are shown in Tables 1 and 2. AR was detected in 32.6% (n=30) of all patients at 6-months after MI. The median cardiac troponin I, and median high-sensitivity C-reactive protein levels were higher in the AR group compared to without AR group. There was no significant difference between the demographic and other clinical characteristics of the patients with and without AR groups (Table 1).

In the acute post-MI period, mean T1 levels in the infarct zone myocardium was not significantly different between the with and without AR groups. Mean ECV and mean MVi levels were higher in AR group compared to without AR group. At 6 months post-MI, mean ECV and mean MVi levels were higher in AR group compared to without AR group (Table 2).

Dynamic changes in CMRI at 6 months post-MI were summarized in Table 3. Accordingly, there was a similar reduction in native T1 values in the infarct zone myocardium after 6 months in with and without AR groups, while there was higher increase of ECV levels in AR group. MVi levels was significantly increased after 6 months in patients AR group, while there was not significantly different in without AR group. CVi levels was significantly decreased in both AR and without AR groups, and this decrease was similar between groups.

In regression model I examining the relationship between AR and dynamic changes at 6 months post-MI, an increased ΔLVMi levels and increased ΔECV levels were independently predictor of AR. In regression Model II, MVi and CVi derived from them were added instead of LVMi and ECV. Accordingly, an increased ΔMVi levels was independently predictor of AR. Model II had higher performance in explaining AR possibility compared to Model I (Model I: Nagelkerke $R^2=0.537$ vs Model II: Nagelkerke $R^2=0.615$) (Table 4). In addition, ΔMVi had superior diagnostic performance compared to ΔECV and ΔLVMi in predicting AR (Figure 3).

Median MMP-2 levels at first day post-MI was higher in AR group compared to without AR group [33241.6 (IQR: 18811.3-60196.5) vs 21333 (IQR: 16043.3-28784.3) pq/mL, $p=0.026$], while there was not significantly different at 2 weeks post-MI [32811.3 (IQR: 19906.7-51487.2) vs 25572.8 (IQR: 16831-46611.6) pq/mL, $p=0.340$]. Median MMP-2 levels was not significantly different at 2 weeks compared to the first day post-MI in AR group (33241.6 vs 32811.3 pq/mL, $p=0.809$), while increased in without AR group (21333 vs 25572 pq/mL, $p=0.046$). A positive correlation was found between baseline levels of MMP-2 and baseline level of LVMi, ECV and MVi (Figure 4) (Table 5).

Discussion

The main findings of this study were that, in acute STEMI patients who developed AR at the 6-month follow-up, 1) The ECV values increased more prominently after 6 months, 2) This increase was in the direction of the matrix volume, 3) A positive correlation was found between MMP-2 levels and ECV and MVi levels, 4) ΔMVi in 6-month follow-up was superior to ΔECV in predicting AR, 5) The regression model in which MVi was included was superior in explaining AR.

Quantitative T1 mapping measures pixel-based T1 relaxation time in the myocardium. T1 relaxation time varies depending on the differentiation around the tissue and it reflects pathological processes at tissue level.[20] In patients with heart failure, T1 relaxation times have been reported to be positively correlated with fibrosis detected by biopsy.[17] Increased amounts of myocardial fibrosis disrupt the structure of the myocardium and cause systolic and diastolic dysfunction.[21] This is characterized by the excessive accumulation of ECM proteins. Increases in total myocardial water, edema, and collagen deposition due to inflammatory response result in increased native T1 values.[22] Decreases in native T1 values in STEMI patients, regardless of AR development, may be associated with preserved healing capacity, resorption of edema, and necrotic tissue in the infarcted myocardium. Segmental fibrosis develops in the area of necrosis, and replacement or interstitial fibrosis develops in non-necrotic areas after MI. High ECV values reflect excessive collagen deposition, scarring, and extensive interstitial fibrosis[5] and may be important indicators of AR.[23] This is consistent with the fact that ECV was an independent predictor in the regression model I established in the present research. Moreover, the elimination of native T1 supports the idea that the extracellular space has a more prognostic role in AR development.[22,24]

T1 mapping has introduced a new concept in cardiology practice by allowing the myocardium to

Table 1 – Demographic and laboratory findings

Variables	Total population n=92	Adverse remodeling		p
		Yes n=30	No n=62	
Demographic findings				
Age, years	54.1±9.0	53.4±8.5	54.4±9.3	0.623
Male gender, n(%)	83(90.2)	25(83.3)	58(93.5)	0.241
BMI, kg/m^2	26.7±4.3	27.0±3.7	26.5±4.6	0.704
BSA, m^2	1.9±0.2	1.9±0.2	1.9±0.2	0.997
Hypertension, n (%)	40(43.5)	12(40.0)	28(45.2)	0.661
Diabetes, n (%)	27(29.3)	9(30.0)	18(29.0)	0.999
Dyslipidemia, n (%)	24(26.1)	10(33.3)	14(22.6)	0.315
Smoking, n (%)	46(50.0)	19(63.3)	27(43.5)	0.113
Clinical findings				
Heart rate, bpm	76.9±16.8	75.2±12.6	77.8±18.7	0.509
SBP, mm Hg	123±15.5	124.1±14.7	122.4±16.1	0.657
DBP, mm Hg	77.2±12.2	77.8±11.2	77.0±12.8	0.785
Symptom-to-balloon time, mins	312.2±68.4	304.6±67.2	317.4±69.8	0.535
Door-to-balloon time, mins	28.1±8.8	27.2±8.4	29.5±9.0	0.358
IRA, n(%)				
LAD	67(72.8)	22(73.3)	45(72.6)	0.999
Cx	25(27.2)	8(26.7)	17(27.4)	
Grace score	128.5±30.4	131.1±24.0	127.3±33.2	0.529
Pre-PCI TIMI flow, n(%)				
0	54(58.7)	18(60.0)	36(58.1)	0.848
1	15(16.3)	5(16.7)	10(16.1)	
2	2(17.5)	5(16.7)	12(19.4)	
3	6(6.5)	2(6.7)	4(6.5)	
Post-PCI TIMI flow >2, n(%)	90(97.8)	29(96.7)	61(98.4)	0.999
Laboratory findings				
cTn-I, ng/L	46.4(37.7-57.8)	56.5(50.4-60.0)	41.7(35.5-48.0)	<0.001
Hemoglobin, g/dL	13.8±1.5	14.0±1.8	13.6±1.4	0.375
WBC, x10^9/L	12.3±3.3	12.4±3.2	12.2±3.4	0.829
Lymphocytes, x10^9/L	2.3±0.8	2.2±0.8	2.4±0.8	0.149
Neutrophils, x10^9/L	8.4±2.1	8.8±1.9	8.2±2.2	0.190
Monocyte, x10^9/L	0.7±0.2	0.8±0.2	0.7±0.2	0.884
Platelets, x10^9/L	301.7±60.7	318.6±54.0	293.5±62.5	0.062
Glucose, mg/dL	112(75-140)	114(100-149)	107(83-139)	0.390
Total cholesterol, mg/dL	197(160-220)	191(155-211)	200(164-240)	0.264
LDL, mg/dL	132(100-157)	119(101-144)	136(100-170)	0.261
HDL, mg/dL	41.3±9.2	41.7±9.5	41.1±9.1	0.781
C-reactive protein, mg/L	24.2(13-31.3)	28.0(16-41.2)	18.3(11.7-26.3)	0.024
Discharge therapy, n(%)				
ACE/ARB	90(97.8)	30(100.0)	60(96.8)	0.816
Beta blockers	90(97.8)	29(96.7)	61(98.4)	0.999
Statins	91(98.9)	30(100.0)	61(98.4)	0.999

Numerical variables are shown as mean±standard deviation or median (IQR). Categorical variables are shown as number (%). ACE: angiotensin-converting enzyme; ARB: angiotensin II receptor blocker; BMI: body mass index; BSA: body surface area; Cx: circumflex artery; DBP: diastolic blood pressure; HDL: high-density lipoprotein; IRA: infarct-related artery; LAD: left anterior descending artery; LDL: low-density lipoprotein; PCI: percutaneous coronary intervention; SBP: systolic blood pressure; TIMI: thrombolysis in myocardial infarction.

Table 2 – Acute and follow-up CMR results

Variables	Total population n=92	Adverse remodeling		p
		Yes n=30	No n=62	
Second weeks				
LVEF, %	46.8±9.6	46.5±9.6	47.0±9.6	0.818
LVEDV, mL	155(130.1-172.5)	153(135-176.7)	157.6(129-170)	0.723
LVESV, mL	83.4(60.1-112.5)	93.5(70.7-128)	78.3(60-102)	0.207
LVMi, g/m^2	144(130-165)	147(133-176)	143(128-162)	0.257
Infarct size, % of LV	15(11-22)	18(12-21)	15(10-21)	0.407
Native T1, ms				
Pre-contrast	1411.0±148.8	1421.2±162.8	1406.5±142.8	0.692
Post-contrast	490.8±88.2	493.5±90.7	489.5±87.7	0.837
ECV, %	40.1±7.4	42.9±6.4	39.3±8.2	0.037
MVi, mL/m^2	59.5±14.9	65.2±13.7	56.7±14.7	0.010
CVi, mL/m^2	88.0±15.0	86.3±13.6	88.9±15.6	0.447
Sixth months				
LVEF, %	47.7±9.7	42.9±10.3	50.0±8.5	0.001
LVEDV, mL	155.4(130-180.9)	180.7(159-227)	140(125.6-162.3)	<0.001
LVESV, mL	79(59.7-116.1)	115.6(80-164)	68.9(54.4-90.7)	<0.001
LVMi, g/m^2	126(116-144)	138(122-166)	123(112-137)	0.002
Infarct size, % of LV	12(8-16)	15(10-18)	11(7-15)	0.035
Native T1, ms				
Pre-contrast	1309.4±135.7	1325.2±117.0	1302.4±136.7	0.490
Post-contrast	455.3±82.1	438.7±69.4	463.3±86.9	0.179
ECV, %	45.8±6.2	49.7±6.1	44.0±5.4	<0.001
MVi, mL/m^2	60.5±15.2	70.7±12.1	55.6±11.8	<0.001
CVi, mL/m^2	70.6±11.0	70.9±12.2	70.4±10.4	0.851

Numerical variables are shown as mean±standard deviation and median (IQR). CVi: cell volume index; ECV: extracellular volume; LVEDV: left ventricular end-diastolic volume; LVEF: left ventricular ejection fraction; LVESV: left ventricular end-systolic volume; LVMi: left ventricular mass index; MVi: matrix volume index.

be separated into its cellular compartment (mostly myocytes) and interstitial compartment (mostly collagen or edema). The ECV reflects a relative volume ratio of total myocardial volume. However, it does not sensitively reflect dynamic changes in myocardial tissue when change of cellular and extracellular components.[17] Thus, evaluating ECV by dividing it into matrix and cell volume indices can provide more detailed information about the mechanism of AR and make the new paradigms of cardiac vulnerability easier to understand and apply. In previous studies of different cardiac diseases, enlarged cell and matrix models were established, a decrease in their levels was detected with medical treatment as per the relevant guidelines, and the decrease was associated with improvement in cardiac volume and functions.[7,17] In our study, although the symptom to balloon time did not differ in patients who developed and did not develop AR post MI, and all patients received guideline treatment, and a significant decrease was found in cell volume index. In addition, there was no significant difference in infarct size in the second week between the two study groups. However, similar reduction in CVi was observed among those who developed AR despite receiving similar treatment, but high incremental variation in the MVi was concluded to be an independent predictor of AR. This finding is consistent with the mechanisms through which myocyte recovery may precede adaptive remodeling in the extracellular component.[7,25] In addition, this may show that cell volumes normalize earlier than matrix volumes. On the other hand, high MMPs levels may contribute to the late normalization of matrix volume, which may be associated with a later improvement in infarct size at 6 months in patients with AR.[26]

The regression model including ECV showed less diagnostic performance compared to the regression model including ECV components. On the other hand,

Table 3 – Dynamic changes in injured myocardium according to presence of adverse remodeling

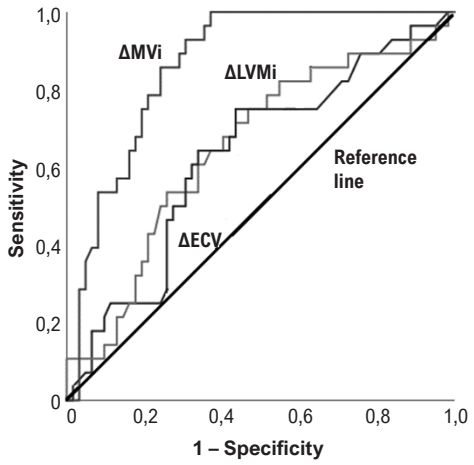
Variables	Adverse remodeling	Second weeks	Sixth months	p[1]	p[2]
LVMi, g/m²	No	143(128-162)	123(112-137)	<0.001	0.011
	Yes	147(133-176)	138(122-166)	<0.001	
Infarct size, % of LV	No	15(10-21)	11(7-15)	<0.001	0.715
	Yes	18(12-21)	15(10-18)	<0.001	
Native T1 infarct, ms	No	1406.5±142.8	1302.4±136.7	<0.001	0.378
	Yes	1421.2±162.8	1320.2±117	0.005	
ECV, %	No	39.3±8.2	44.0±5.4	<0.001	0.027
	Yes	42.9±6.4	49.7±6.1	<0.001	
MVi, mL/m²	No	56.7±14.7	55.6±11.8	0.480	0.007
	Yes	65.2±13.7	70.7±12.1	<0.001	
CVi, mL/m²	No	88.9±15.6	70.4±10.4	<0.001	0.164
	Yes	86.3±13.6	70.9±12.2	<0.001	

Numerical variables are shown as mean±standard deviation or median (IQR). p[1]: Second weeks vs sixth months within remodeling groups. p[2]: Comparison of the changes in follow-up (Adverse remodeling groups: No vs. Yes). CVi: cell volume index; ECV: extracellular volume, LVMi: left ventricular mass index; MVi: matrix volume index.

Table 4 – Multivariable associations of T1 mapping parameters with adverse remodeling at six months post-MI

Variables	Univariable			Multivariable		
	OR	95% CI	p	OR	95% CI	p
Model I						
cTn-I	1.05	1.01-1.09	0.011	1.28	1.05-1.55	0.013
C-reactive protein	1.07	1.01-1.12	0.017	1.15	1.01-1.32	0.044
ΔLVMi	1.28	1.12-1.48	0.010	1.36	1.14-1.78	0.012
ΔInfarct size	1.02	0.98-1.06	0.249	-	-	-
ΔNative T1 infarct	1.01	0.97-1.06	0.154	-	-	-
ΔECV	1.04	1.01-1.08	0.025	1.05	1.02-1.09	0.041
				Nagelkerke R^2=0.537, p<0.001		
Model II						
cTn-I	1.05	1.01-1.09	0.011	1.32	1.12-1.56	0.014
C-reactive protein	1.07	1.01-1.12	0.017	1.15	1.03-1.30	0.020
ΔInfarct size	1.02	0.98-1.06	0.249	-	-	-
ΔNative T1 infarct	1.01	0.97-1.06	0.154	-	-	-
ΔMVi	1.06	1.01-1.11	0.004	1.03	1.01-1.06	0.010
ΔCVi	0.97	0.95-0.99	0.089	-	-	-
				Nagelkerke R^2=0.615, p<0.001		

Co-founder factor, including age, male gender, smoking, lymphocytes, neutrophils and platelet parameters, were adjusted in all analysis. Δ: the change of T1 mapping parameters from 2 weeks to 6 months post-MI. CI: confidence interval; CVi: cell volume index; ECV: extracellular volume; LVMi: left ventricular mass index; MVi: matrix volume index; OR: odds ratio.



	ΔMVi	ΔLVMi	ΔECV
AUC±SE	0.865±0.04	0.650±0.03	0.640±0.06
95% CI	0.793-0.938	0.527-0.774	0.526-0.753
Sensitivity	93.30%	76.70%	73.30%
Specificity	69.40%	56.50%	53.20%
p	<0.001	0.023	0.034

Pairwise comparison of ROC Curves

	AUC±SE	p
ΔMVi vs ΔLVMi	0.215±0.047	<0.001
ΔMVi vs ΔECV	0.225±0.006	<0.001
ΔLVMi vs ΔECV	0.010±0.008	0.812

Figure 3 – *Diagnostic performance of ΔECV, ΔLVMi and ΔMVi in predicting AR. AUC: area under the curve; ΔAUC: difference of area under the curve; CI: confidence interval; ECV: extracellular volume; LVMi: left ventricular mass index; MVi: matrix volume index; SE: standard error.*

the lower diagnostic performance of ECV compared to both cellular and extracellular components in ROC analysis supports that ECV may be less sensitive to tissue changes. The superior diagnostic performance of MVi in predicting AR compared to ECV and CVi may indicate that it may be more sensitive to tissue changes. All of the findings presented here highlight the importance of cardiac fibroblasts in changes in the dynamic structure of the extracellular matrix, including diffuse fibrosis (matrix volume).[27] The association of cardiac fibroblasts with changes in the collagen cycle highlights the dynamic nature of the extracellular matrix. MVi quantification could add more predictive information and support reversibility in AR development, especially considering its association with MMPs. In clinical practice, MVi can provide detailed information on the mechanism of AR by better reflecting myocardial tissue changes. Therefore, MVi may be a guide in terms of unfavorable prognosis after STEMI. It may also be important in terms of endpoints.[17] Because both focal fibrosis and extensive fibrosis have been shown to be univariate predictors of outcome.[28] Previous research has shown that cardiac fibroblasts constitute 60-70% of all myocardial cells, exerting crucial influence in processes of myocardial repair to ensure the continuation of post-injury cardiac functions. Enhanced pro-fibrotic and pro-inflammatory profiles might lead to gradual increases in the stiffness of the myocardium as well as decreased myocardial compliance alongside ventricular systolic and diastolic dysfunction. This process has its foundation in the early activation of MMPs.[29,30] MMP-2 can be self-activated in the ECM by the action of free radicals produced by activated tissue macrophages.[31]

An excessive inflammatory response may result in excessive production of MMP-2, and this, in turn, may play a role in AR by causing cardiac vulnerability.[32] The mechanism of this process may be oriented toward ECV enlargement (mainly with increases in matrix volume) as a result of excessive MMP-2 production due to excessive inflammatory response. Therefore, MMP activation may represent a viable therapeutic target for regulating ECM transformation during the pathological process of AR development after MI.

This study, which represents a cohort of patients who had experienced STEMI for the first time, has certain limitations. Although the findings of this small sample are in line with the literature, a larger sample could provide more consistent results. On the other hand, the pathophysiology of AR is complex. Changes in the remote zone myocardium, microRNAs, and cytokines may play important roles, and these could not be evaluated in this study. The consideration of these factors in future studies could further illuminate the association of change in the compartments of ECV with inflammation.

Conclusion

This study provide further evidence for the pathophysiological significance of tissue characteristics and LV remodeling in the setting of acute STEMI. We conclude that change of matrix volume, superior to change of ECV, after acute MI period were independently predictor of AR, reflecting increased interstitial fibrosis. Increased levels of MMP-2 at the onset of acute MI play an important role in the change in matrix volume, and therefore may be a therapeutic target.

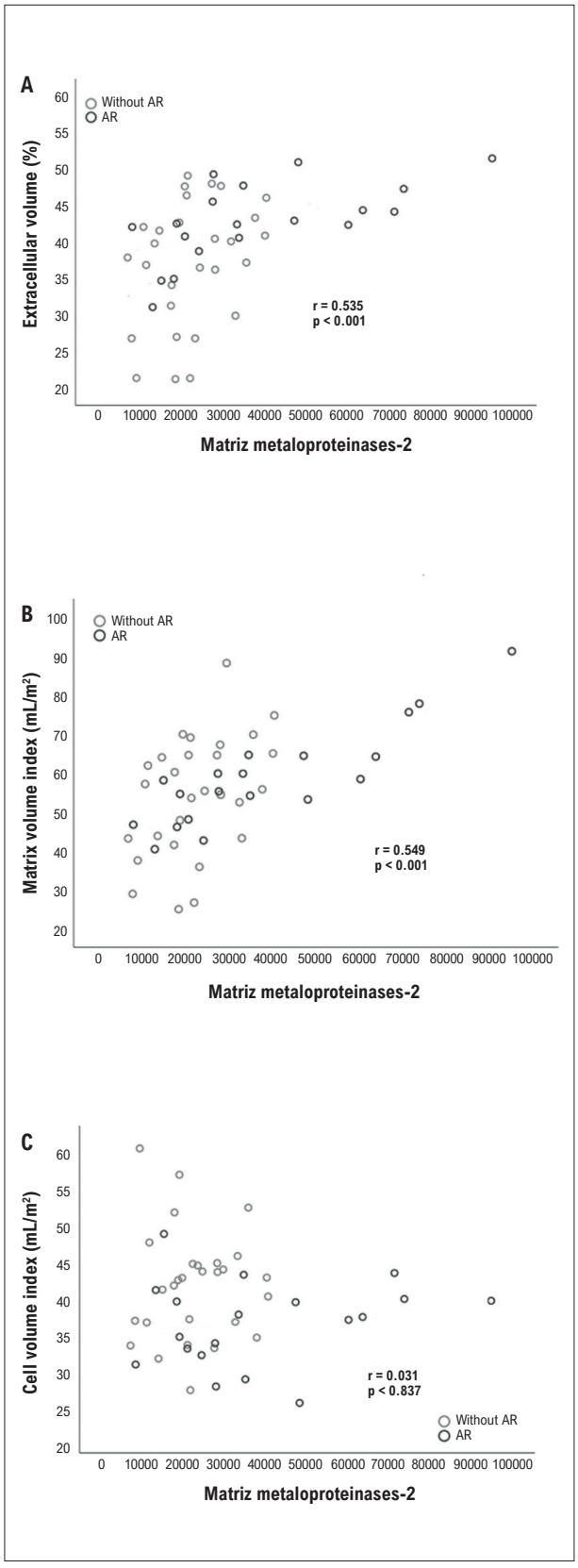


Figure 4 – *Relationship between matrix metalloproteinase-2 and ECV (A), VMi (B), and CVi (C). AR: adverse cardiac remodeling; CVi: cell volume index; ECV: extracellular volume; MVi: matrix volume index.*

Table 5 – The relationship between matrix metalloproteinases-2 and CMR parameters

Variables	First day post-MI MMP-2		2 weeks post-MI MMP-2	
	r	p	r	p
2 weeks				
LVMi	0.301	0.047	0.089	0.551
Infarct size	0.024	0.878	0.221	0.144
Native T1 infarct	0.135	0.367	0.166	0.263
ECV (%)	0.535	<0.001	0.355	0.014
MVi	0.549	<0.001	0.325	0.029
CVi	0.031	0.837	0.143	0.338

CVi: cell volume index; ECV: extracellular volume; LVMi: left ventricular mass index; MMP-2: matrix metalloproteinases-2; MVi: matrix volume index.

Author Contributions

Conception and design of the research and Writing of the manuscript: Eyyupkoc F; Acquisition of dat and Statistical analysis: Eyyupkoc F, Eyerci N, Altintas MS, Felekoglu MA, Bite HI, Hidayet S, Sivri S, Demirtas B, Ates OF; Analysis and interpretation of the data: Eyerci N, Altintas MS, Felekoglu MA, Bite HI, Hidayet S, Sivri S, Demirtas B, Ates OF; Critical revision of the manuscript for important intellectual content: Eyerci N, Ates OF.

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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Prognosis after Myocardial Infarction – A Deep Look into Myocardial Tissue

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Short Editorial related to the article: The Relationship between Extracellular Volume Compartments and Matrix Metalloproteinases-2 in Left Ventricular Remodeling after Myocardial Infarction

Adverse cardiac remodeling after acute myocardial infarction (MI), regardless of primary percutaneous coronary intervention, is strongly associated with the development of heart failure and poor prognosis. Since demographic and clinical characteristics are not sufficiently sensitive to predict adverse remodeling after MI, more precise parameters are needed to identify individuals at risk of progression to ventricular dysfunction and heart failure, potentially allowing an early and intensive prognosis modifying therapy.

New biomarkers of adverse cardiac remodeling have emerged, such as matrix metalloproteinases (MMP) 2 MMP-2, MMP-6, MMP-9.[1] There is an increasing awareness of the importance of interstitium in the pathophysiology of cardiac diseases beyond cardiac myocytes. In fact, the cardiac interstitium represents one-third of the total myocardial volume. It contains two-thirds of the total number of cells in the myocardium, mainly fibroblasts.[2] Fibroblasts are responsible for maintaining interstitial homeostasis, and the production of MMP.[3] Interstitial expansion is associated with adverse effects on myocardial function in multiple entities.[4-6]

CMR is nowadays an important method to evaluate the myocardium. Parametric mapping is a CMR technique that directly quantifies the T1 relaxation time of each voxel within a CMR image, building a visual map and allowing a non-invasive evaluation of myocardial tissue.[7] The correlation between T1 values and extracellular volume (ECV) with collagen volume fraction has been validated with myocardial biopsy.[8]

Ferhat Eyyupkoca et al.[9] showed that there is a significant difference in tissue characteristics between patients with and without adverse remodeling from the early period after the acute phase of MI. Interestingly, in the early CMR, left ventricular volumes and systolic function were similar between patients with and without adverse remodeling, emphasizing the importance of additional markers, as the study of extracellular space, for predicting outcomes. ECV and matrix volume (MVi) assessed by CMR were significantly different in the exam done at two weeks, and the magnitude of the difference was even higher after 6 months reflecting the adverse remodeling. Although ECV increased in the follow-up in both groups, the matrix volume index just increased in the adverse remodeling group, highlighting its added value in the comprehensive study of extracellular space compared to ECV. Furthermore, the model with ΔMVi performed better than the ΔECV model, showing better sensibility and specificity to predict adverse remodeling. On the other hand, the cell volume index decreased in both study groups without difference among them. A strong point of this work is the evidence of the good correlation between MMP-2 and MVi, and ECV, which contributes to strengthening the association between CMR and biomarkers of fibrosis and myocardial tissue changes.

In the era of increasing available biomarkers and imaging parameters, it is paramount to thoughtfully use all the information to apply the most efficient approach to predict prognosis in clinical practice. Considering the elevated incidence of MI and the onus of the development of heart failure for patients and health systems, a model that anticipates maladaptive remodeling can influence myocardial remodeling with the early implementation of pharmacological interventions. With the progressive widespread of CMR and mapping technique, this may soon assume the screening role for adverse remodeling after MI. In this issue of the Journal, Ferhat Eyyupkoca et al. contribute to increasing the accuracy of the evaluation of MI patients by adding MVi to CMR analysis, which is easy to obtain from routinely used mapping sequences and may be easily adopted at CMR units. This promising parameter needs further validation in bigger samples and more heterogeneous populations.

Keywords

Infarto Agudo do Miocárdio; Remodelação Ventricular; Ressonância Magnética; Metaloproteinases

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Gender Disparity in First and Senior Authorship in Brazilian Cardiology Journals

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Abstract

Background: **Despite the importance of women in clinical research, no assessment has been made of the fraction of women in a leadership positions in the Cardiology journals of the SBC.**

Objectives: **To assess the fraction of female authors in the International Journal of Cardiovascular Sciences (IJCS) and the *Arquivos Brasileiros de Cardiologia* (ABC Cardiol) over the last decades.**

Methods: **We searched the original articles of the ABC Cardiol, from 2000 to 2019, and of the IJCS, from 2010 to 2019. We surveyed the number of first and senior female authors and the total number of original articles from 2010 to 2019. We calculated the total proportion of female authorship and compared the first quinquennium with the second. Only data from the ABC Cardiol were analyzed to assess the temporal evolution of the two decades. We used the chi-square test to assess the differences within each journal and between them. The IBM® SPSS® software was used in the analyses. The level of significance adopted was 5%.**

Results: **From 2010 to 2019, 1,157 original articles were published in the ABC Cardiol and 398 in the IJCS. We observed that women are more prevalent as first authors in the IJCS compared to the ABC Cardiol, but men prevail as senior authors in both journals. From 2010 to 2019, there was no significant change in the proportion of female authorship. Throughout the decades analyzed for the ABC Cardiol, there was a projection of linear growth of female authorship, with the slope of the line being greater in the first authorship than in senior authorship.**

Conclusions: **There is gender disparity, with lower female representativeness in authorship in the articles from the Brazilian Cardiology journals analyzed: *Arquivos Brasileiros de Cardiologia* and International Journal of Cardiovascular Sciences. We believe that based on these results, more efforts should be implemented in the search for gender equity in the cardiology scientific production published by these journals.**

Keywords: **Scientific Publications; Authorship and Co-Authorship in Scientific Publications; Gender Analysis; Disparity; Gender Equity.**

Introduction

Women in Academic Medicine are still underrepresented and face great professional challenges. Although the progressive growth in the proportion of women who graduated in Medicine, they are less likely to occupy leadership positions in Academic Medicine, have lower chances of being recognized as specialists and leaders, and have lower chances of being invited for presentations in national medical conferences or receiving prestige awards.[1,2] Ouyang et al.[3] used an extensive database of publications and concluded that although female representation in the research published in the area of Cardiology has increased in the last four decades, there is a persistent gap in women's representation in research at all levels, whether as first authorship, senior authors and concerning the number of publications. Another interesting observation made by Asghar et al.[4] was that female authors are more likely to have a female mentor when compared with their male colleagues. These authors concluded that women in leadership positions might positively influence other women in their departments and motivate a more intense involvement with scientific research.

Moraes, Kovacs[5] traced a parallel between Brazil and the USA, noting that, although women represent half the population, only one-third of cardiologists are women,

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even with cardiovascular diseases comprising about 30 percent of the causes of death in Brazil and one-third of deaths among women worldwide. According to the report of Elsevier entitled *The Researcher Journey Through a Gender Lens*[6], upgraded in November 2020, gender inequity can be observed in terms of publications, citations, scholarships awarded and collaborations. In all countries included in the study, the percentage of women who published in international journals is lower compared to men. There is still a gender difference in article citation: female authorship works are less often cited than those authored by men. When we assess higher scientific impact studies, i.e., randomized clinical trials (RCTs), Mehran et al.[7] observed a progressive increase in the number of female first authors of cardiology RCTs from 2011 to 2020; going from 20 percent of the articles to 30 percent at the end of the decade. The authors credit this increase to defending female empowerment and equal gender representation.

Oliveira et al.[8], in their document named "Carta das Mulheres," published by the *Arquivos Brasileiros de Cardiologia* (ABC Cardiol), recognize the importance of promoting practices aimed at the consolidation of Cardiology among Brazilian women to increase the opportunity of healthcare from the female standpoint, allowing for integration and exchange of experiences which improve daily clinical practice. Launched in 1948, the ABC Cardiol is one of the main vehicles for disseminating Brazilian scientific research in cardiovascular sciences. The International Journal of Cardiovascular Sciences (IJCS) was incorporated by the Brazilian Society of Cardiology in 2015 and was preceded by the Revista Brasileira de Cardiologia, created in 2010 by the Society of Cardiology of the State of Rio de Janeiro (SOCERJ). Altogether these journals publish a great part of Brazilian scientific production in cardiology, especially the products of stricto sensu postgraduate programs. Despite the substantial importance of women for healthcare and clinical research worldwide, there is no assessment of the fraction of women in first author and senior author positions in the Cardiology journals kept by the Brazilian Society of Cardiology, namely ABC Cardiol and IJCS. The assessment of this profile and its variation throughout the last two decades may allow for the identification of authorship disparities between men and women in Brazilian journals in the area of cardiology and enable the development of strategies aimed at reducing the barriers to female representativeness in medical leadership, as well as in the academic promotion in the area of cardiology. The purpose of this article is to evaluate the role of women as authors of cardiology scientific articles in the journals of the Brazilian Society of Cardiology so that these data can serve as the basis to increase women's inclusion in cardiology scientific production.

Methods

We carried out a cross-sectional study, where a bibliographic search of all original articles published in the ABC Cardiol was performed between 2000 and 2019, and of all the original articles of the IJCS, between 2010 and 2019, in the websites of those journals.[9,10] Data collection was carried out between December 2020 and February 2021 in the database of the websites of each journal. The gender of the authors was determined by the analysis of the first and senior authors' names. In cases of uncertainty regarding gender, we searched for the author's name on the respective institution's website or social media.

In all stages, data were independently assessed by two or more researchers and discrepancies were resolved by consensus.

Eligibility criteria for the selection of articles

The following inclusion criteria were used for selecting articles in this review: 1) original articles, 2) publications made between 2000 and 2019 for the ABC, and 3) publications made between 2010-2019 in the IJCS. The articles were excluded if they were editorials, mini-editorials, reviews or special articles.

Data collection

After searching and excluding the irrelevant articles, the researchers independently collected the data from the selected studies according to a predefined script. The number of female authors of the articles, the number of male authors of the articles, the number and identification of all women as first authors of the articles, and the number and identification of all women as senior authors of the articles.

Statistical analysis

Numerical data were used to determine the absolute number of first and senior female authors and the total number of original journal articles from 2010 to 2019 for the ABC Cardiol and the IJCS. Categorical variables were presented as absolute numbers and percentages. From the results obtained, the total proportions of female authorships were calculated according to the journals and the temporal evolution within the decade of the authorships by comparing the first quinquennium with the second.

The proportions of female and male authorships were compared between the first half of the period and the second half.

In the case of the data from ABC Cardiol, two decades (2000 to 2019) were analyzed, whereas, for the IJCS, only the period from 2010 to 2019 was analyzed because the IJCS was created in 2010. The chi-square test was used to analyze the differences in proportions of authorships inside each journal and between both journals. Analyses were performed with IBM® SPSS® Statistics version 21. The level of significance adopted was 5%.

Bioethical aspects

Only public data available on the websites of the cardiology journals were used in this research, in compliance with item 3 of CSN Resolution no. 510/2016, which states that research using public domain data does not require evaluation by the CEP/CONEP system.

Results

Table 1 presents the number of original articles found between 2010 and 2019 for the ABC Cardiol and the IJCS according to authorship and gender. During that period, 1,157 original articles were published in the ABC Cardiol and 398 in the IJCS. We observed a predominance of male first authors in the ABC Cardiol (666 male authors; 58%), whereas, in the IJCS, there is a discrete predominance of female first authors (212 female authors; 53%). This difference between the journals is statistically significant ($p = 0.001$; Table 1), indicating that the predominance of women as first authors is greater in the IJCS compared to the ABC Cardiol.

When we analyze senior authorship, we note that men prevail as senior authors in both journals. However, the number of men as senior authors in the ABC Cardiol is significantly higher than that of men as senior authors in the IJCS (873 authors in the ABC Cardiol - 75% vs. 235 authors in the IJCS - 59%; p value < 0.001; Table 1).

Table 2 compares authorship gender in the IJCS from 2010 to 2019 by dividing the decade into two quinquenniums. We observed that the was no significant change in the proportion of female authorship, both in the first position of the article (55% in the first quinquennium vs. 52% in the second; $p = 0.2$) and in a senior position (42% in the first quinquennium vs. 40% in the second; $p = 0.8$).

Table 3 compares authorship gender in the ABC Cardiol from 2010 to 2019, splitting the decade into two quinquennials. We observed no significant change in the proportion of female authorship both in the first position of the article (42% in the first quinquennium vs. 42% in the second; p=1) and in a senior position (25% in the first quinquennium vs. 24% in the second; $p = 0.8$).

Table 4 compares authorship gender in the ABC Cardiol over time, considering the decade from 2000 to 2009 to 2010 to 2019. We observed a significant increase in the proportion of female authorship both in first (33% in the 2000s vs. 42% in the 2010s; $p < 0.0001$) and in a senior position (20% in the 2000s vs. 25% in the 2010s; $p = 0.006$).

Figures 1 and 2 show the temporal evolution, year by year, of first and senior female authorships, respectively, in the journals analyzed from 2010 to 2019. Both Figures show a variable distribution throughout the period analyzed, without establishing a standard profile of female authorships, regardless of the position in both cardiology journals.

Figures 3 and 4 represent the temporal evolution, year by year, of first and senior authorship, respectively, throughout the two decades analyzed for the articles published in the ABC Cardiol journal. We observe a seasonality concerning the number of female authorships in the first (Figure 3) and in the senior position (Figure 4) of authors of original articles published in the analyzed period without configuring a clear change trend.

Discussion

This study aimed to investigate gender diversity in the publications of the main journals for Brazilian research in cardiovascular sciences in the last decades. Our findings showed gender disparity in article authorship, in first (45% of female authors) and senior positions (29% of female authors), indicating a minor female representation. However, our results suggest a discrete increase in female participation in main authorship positions during the last decades, which is obviously below the desired gender equality.

The academic environment has witnessed a greater number of female scientists in Brazil in various fields, as demonstrated by the 2016 census of the Directory

Table 1 – Number and percentage of original articles published in the *Arquivos Brasileiros de Cardiologia* and the International Journal of Cardiovascular Sciences according to author gender, from 2010 to 2019

Articles	Total of original articles	First female authorship (%)	First male authorship (%)	Senior female authorship (%)	Senior male authorship (%)
ABC Cardiol	1,157	491 (42%)	666 (58%)	284 (25%)	873 (75%) *
IJCS	398	212 (53%)	196 (47%)	163 (41%)	235 (59%) *
TOTAL	1,718	771 (45%)	947 (55%)	494 (29%)	1,224 (71%)

*ABC Cardiol: Arquivos Brasileiros de Cardiologia; IJC: International Journal of Cardiovascular Sciences. * comparison between senior male authorship ABC Cardiol vs. IJCS: p < 0,001.*

Table 2 – Number and percentage of original articles published in the International Journal of Cardiovascular Sciences according to authorship gender from 2010 and 2019, divided according to the quinquenniums of the decade

Articles	Total of original articles	First female authorship (%)	First male authorship (%)	Senior female authorship (%)	Last male authorship (%)
IJCS 2010-2014	160	88 (55%)	72 (45%)	67 (42%)	93 (58%)
IJCS 2015-2019	238	124 (52%)	112 (48%)	96 (40%)	142 (60%)

IJCS: International Journal of Cardiovascular Sciences.

Table 3 – Number and percentage of original articles published in the *Arquivos Brasileiros de Cardiologia* according to the gender of the author from 2010 to 2019 divided according to the decade quinquenniums

Articles	Total of original articles	First female authorship (%)	First male authorship (%)	Senior female authorship (%)	Senior male authorship (%)
ABC Cardiol 2010-2014	656	279 (42%)	377 (58%)	163 (25%)	493 (75%)
ABC Cardiol 2015-2019	501	212 (42%)	289 (58%)	121 (24%)	380 (76%)

ABC Cardiol: Arquivos Brasileiros de Cardiologia.

Table 4 – Number and percentage of original articles published in the *Arquivos Brasileiros de Cardiologia* according to authorship gender comparing the 2000s with the 2010s

Articles	Total of original articles	First female authorship (%)	First male authorship (%)	Senior female authorship (%)	Senior male authorship (%)
ABC Cardiol 2000-2009	1,026	340 (33%)	686 (77%)	202 (20%)	824 (80%)
ABC Cardiol 2010-2019	1,157	491 (42%)	666 (58%)	284 (25%)	873 (75%)

ABC Cardiol: Arquivos Brasileiros de Cardiologia.

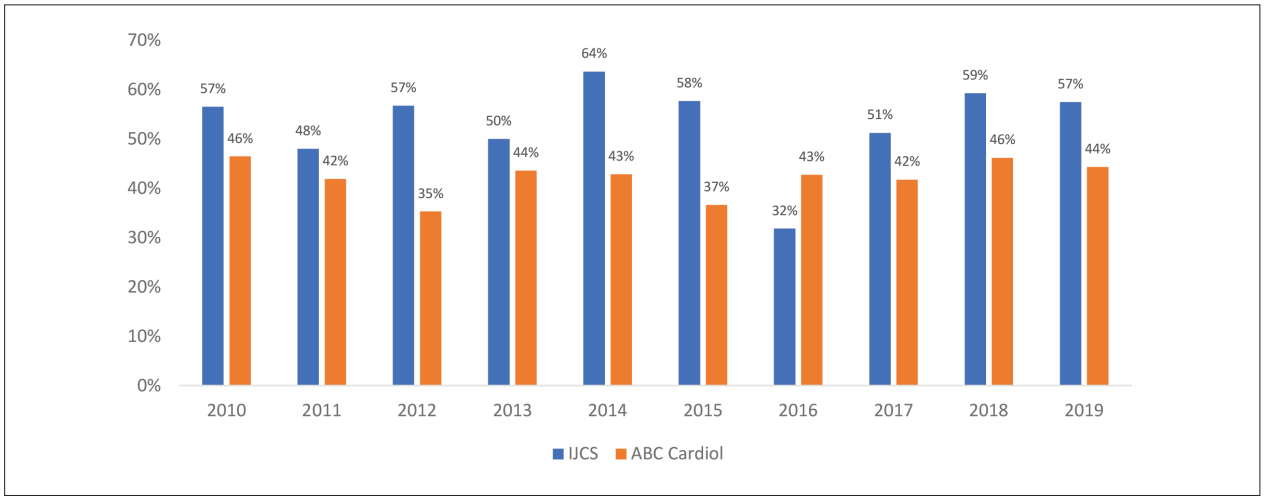

Figure 1 – *Evolution of the proportion of the first female between 2010 and 2019 in the IJCS and ABC Cardiol. ABC Cardiol: Arquivos Brasileiros de Cardiologia; IJCS: International Journal of Cardiovascular Sciences.*

of Research Groups of the Brazilian National Council for Scientific and Technological Development (CNPq),[11] which shows that about 50% of the researchers are female. Nevertheless, female representation decreases as they advance in a scientific career, especially in leadership positions, reaching 45% of the total Brazilian research group leaders. This study corroborates this fact, as it showed female underrepresentation in the different authorship positions, reaching levels that are closer to gender equity in first female authorship (45% of the total articles published by the ABC Cardiol and the IJCS) and more evident disparity in leadership positions, as in senior authorship (only 29% of the total articles published by the ABC Cardiol and the IJCS) of Brazilian scientific production, in the field of cardiovascular sciences, over the last decades. We also highlight that the IJCS presents greater female representation, both in first and senior authorship, compared with the ABC Cardiol, considering the total number of original articles published in the last decade. Our data corroborate those found by Mehran et al.,[7] who showed in 2019 that women authored 30% of the articles on randomized trials in cardiology. Among the main causes of gender disparity in academic performance are implicit biases and stereotype threats.[12] Women and other ethnic and social groups usually do not fit the perceptions of the qualities of successful scientists, triggering negative cultural stereotypes, even unintentionally, of weak scientific performance, which has no relation with true capacity. The impact of these attitudes and judgments, especially concerning gender, ends up implicitly influencing the academic environment, where men usually predominate in prestigious positions.[12,13] In addition, the important

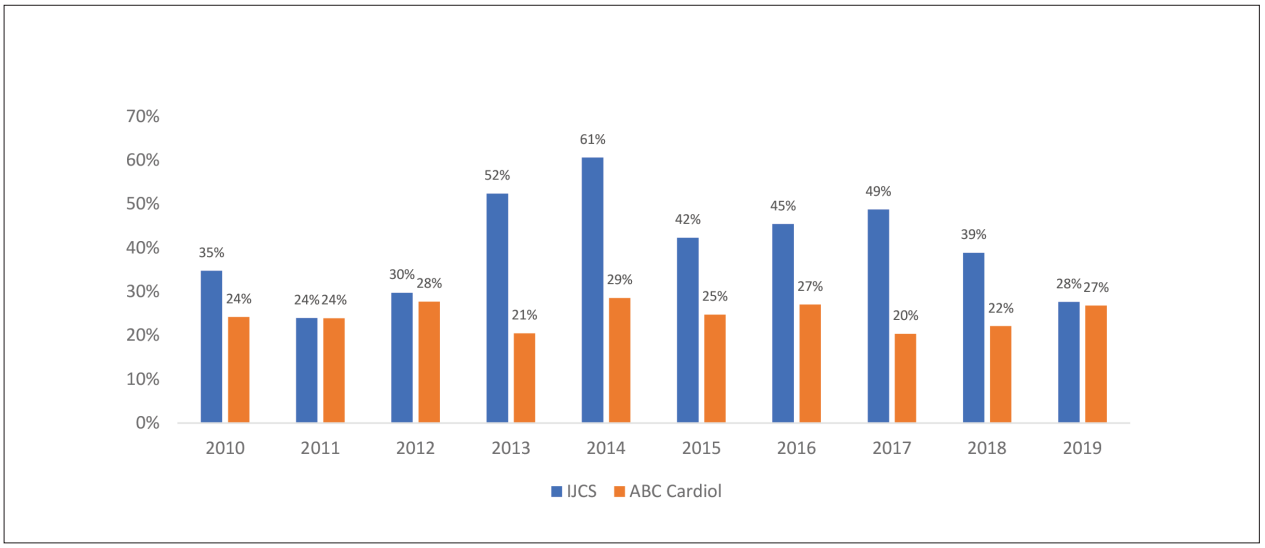

Figure 2 – *Evolution in the proportion of senior female authorship between 2010 and 2019 in the IJCS and ABC Cardiol. ABC Cardiol: Arquivos Brasileiros de Cardiologia; IJCS: International Journal of Cardiovascular Sciences.*

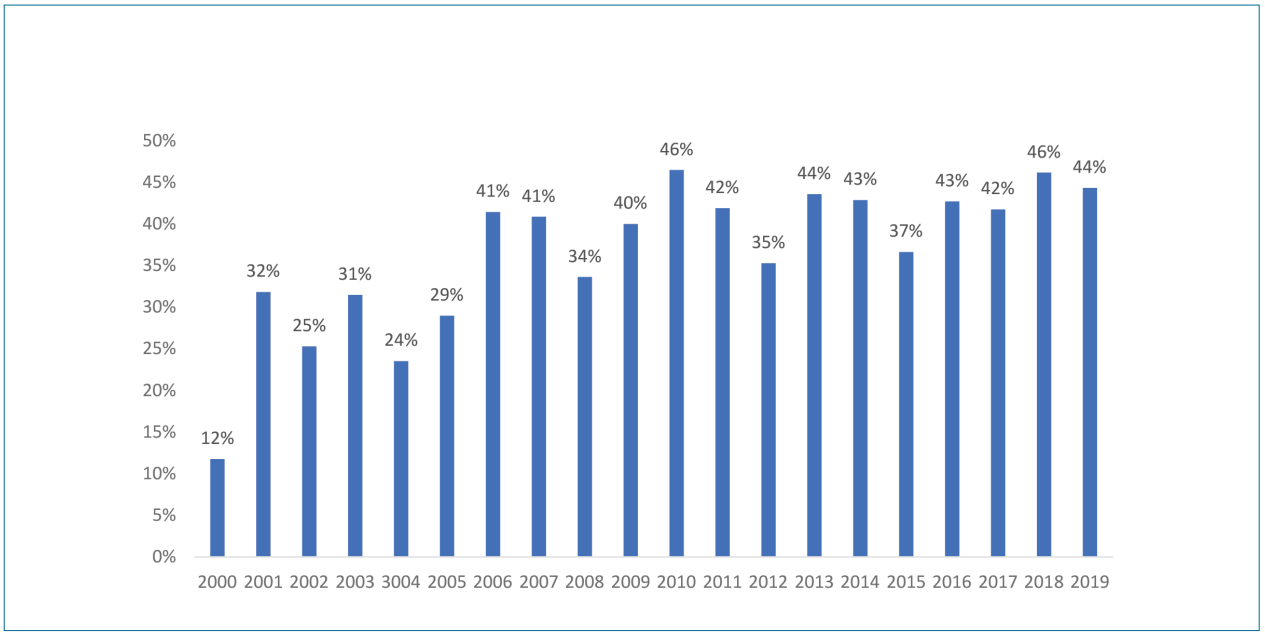

Figure 3 – *Temporal evolution of the proportion of first female authorship in the period 2000 and 2019, in the ABC Cardiol journal. ABC Cardiol: Arquivos Brasileiros de Cardiologia.*

work developed by the Parent in Science movement[14] (https://www.parentinscience.com/) indicates that motherhood is one of the main factors for the underrepresentation of women in science, accounting for a decrease in the production of scientific articles and deposit of patents, for instance. Another factor that exacerbates gender disparity in the COVID-19 pandemic context is that women have not occupied leadership roles in international clinical trials. Chatterjee, Werner[15] analyzed 1,548 related to the pandemic and concluded that only 27.8% of them were led by women, corresponding to less than one-third of the clinical trials on COVID-19 carried out by women. It is also important to point out that the survey done in Brazil during social isolation related to COVID-19 (April and May 2020) showed that women with children had their academic productivity more negatively affected by the pandemic.[16] Thus, this study did not include the pandemic period in the analysis (publications from 2020 to 2021) because we believe that it deserves differentiated attention and will be the focus of a future study of the group, which is already in progress.

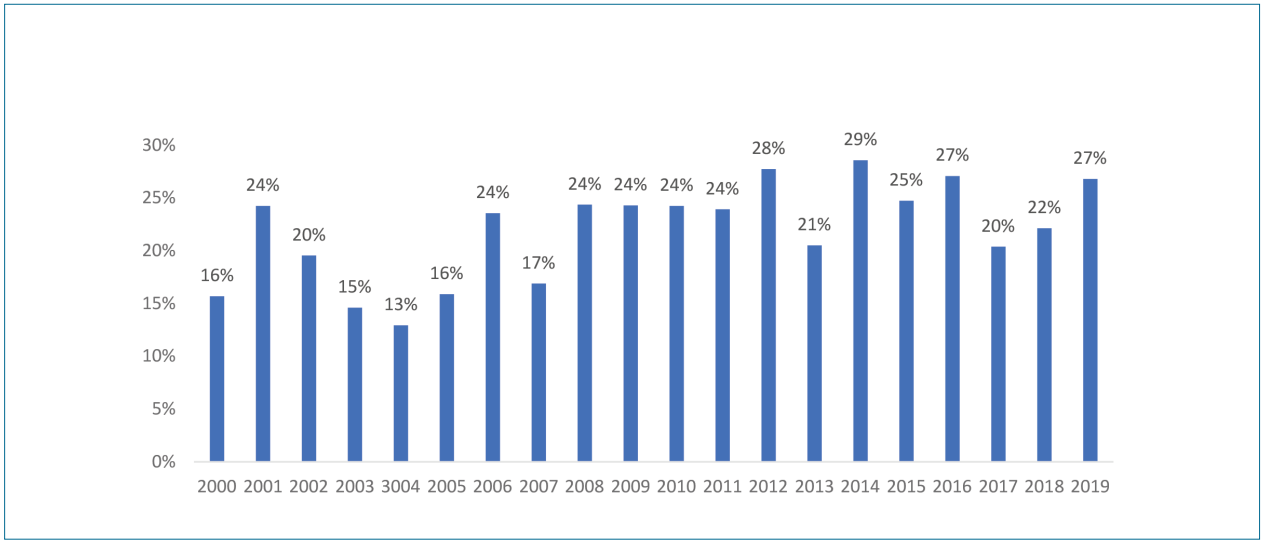

Figure 4 – *Evolution in the proportion of senior female authorship between 2000 and 2019 in the ABC Cardiol. ABC Cardiol: Arquivos Brasileiros de Cardiologia.*

On the other hand, over the last years, several initiatives have been promoted aimed at making changes that minimize gender disparity in Brazilian science. One example is the inclusion of the period corresponding to maternity leave in the Brazilian national resumé database, "Curriculo Lattes," which makes the selection of researchers based on this tool more inclusive.[17] In this interface, although far from ideal, we showed a growing linear projection in female representation over the years, especially in first-position authorship in the publications of ABC Cardiol. From an optimistic perspective, possibly with the positive impact of the initiatives abovementioned, we can project greater participation of women in leadership positions and the main authorship positions of scientific publications.

This data survey on the order of authorship by gender in the main Brazilian research journals today in the cardiovascular sciences field showed an underrepresentation of women in scientific production. We hope this study stimulates reflections upon the big challenge in the search for gender equity for a more diverse community and a more inclusive science.

Among the limitations found in carrying out this study was that the study did not consider

the authors' ages and or graduation years. These data may be important since there has been a progressive increase in the number of female doctors. This could cause a greater proportion of men with master and doctorate degrees compared with female medical doctors, which is still more critical because, in Brazil, these courses have a direct connection with scientific production.[18] Another limitation is that it was impossible to correlate the scientific production at a regional level, identifying the areas in Brazil where gender disparity is greater and should be studied more. However, the results from this study are the only first to point out the necessity of actions that increase women's inclusion in cardiology scientific production authorship.

Conclusion

There is gender disparity, with lower female representativeness in authorship in the articles from the Brazilian Cardiology journals analyzed: *Arquivos Brasileiros de Cardiologia* and International Journal of Cardiovascular Sciences. We believe that from these results, more effort should be put into the search for gender equity in the scientific production on Cardiology published by these journals.

Author Contributions

Conception and design of the research: Mesquita CT, Lacerda AG, Fernandes FA; Acquisition of data: Alves VPV, Amorim LEO, Coutinho BA, Dalben LR, Veloso VD, Mello LLC, Fernandes FA, Urel ICAB; Analysis and interpretation of the data and Critical revision of the manuscript for important intellectual content: Mesquita CT, Lacerda AG, Frantz EDC, Fernandes FA; Statistical analysis: Mesquita CT, Fernandes FA; Writing of the manuscript: Mesquita CT, Lacerda AG, Frantz EDC, Oliveira GMM, Fernandes FA.

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

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The First Step

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Short Editorial related to the article: Gender Disparity in First and Senior Authorship in Brazilian Cardiology Journals

George Eliot and George Sand, 19th-century novelists, were pen names for Mary Ann Evans and Amandine Aurore Lucile Dupin, respectively. In common, two women who, to achieve recognition for their texts, used male names in their works, as portrayed by Nodari in his article published in 2021.[1] Far beyond historical knowledge, analyzing gender disparity in scientific production transcends literature and must be understood as the result of a process of formation and development of society. The patriarchal, white model with financial privileges is unquestionable, which, combined with a vision of the "man with reason and the woman with emotion",[2] helped to build the model of science that, in a wrong way, kept women away from the scientific field.

To think of this model as something belonging to the past is inadequate. Data from the National Household Sample Survey (PNAD) from the Brazilian Institute of Geography and Statistics (IBGE) in 2019 exposes a social reality that reflects on the formation of the scientist.[3] Women spend twice as much time on housework per week compared to men of the same age group (21.4 versus 11 hours), earn less than their male peers (77% of male income), and in those aged between 25 and 49 years old who live in the same household with a child up to three years old, the percentage of insertion in the labor market is lower than that of men in the same situation (59.6% versus 89.2%).[3]

Despite the growing number of women in medicine and the younger generalist university education, cardiology is still a specialty with a male predominance.[4,5] In 2020, the male/female ratio was 2.21, unlike other specialties such as dermatology, pediatrics and endocrinology, with ratios lower than 1.[4] This pattern observed in Brazil is also found in the United States[6] and Europe,[7] with low global female representation in cardiology or leadership positions within the specialty.

After the specialization, the path goes towards the postgraduate course for teacher training with the consequent and natural leadership in research areas. Again, the scenario does not change; women represent 46% of the superior faculty.[3] This data is, in practice, reflected in the study by Oliveira-Ciabati et al., which showed that more than 60% of the professors at the University of São Paulo are male, which also contributes to the increase in gender disparity in schools publications.[2]

In this context, the study published by *Arquivos Brasileiros de Cardiologia* is fundamental for understanding the Brazilian academic environment.[8] In it, the authors approach in a very elucidative way the gender disparity in the publications of *Arquivos Brasileiros de Cardiologia* (ABC Cardiol) and the International Journal of Cardiovascular Sciences (IJCS) from 2000 to 2019.

Among the 1555 articles published in journals that represent the largest sources of studies in cardiology in the country, the authors observed that women predominated only in the first authorship and only in the IJCS journal (53%), while men predominated in the first authorship in the ABC Cardiol (58%) and as senior authors in both (75% in ABC Cardiol and 59% in IJCS).[8] Generally, it is known that the first author reflects the main responsible for the article in question, while the last author, or senior, reflects the leader of the research line responsible for the most comprehensive work, capable of generating other publications.

Another observation made by the authors refers to the temporal evolution of gender predominance in authorship fields. Despite being underrepresented in magazines, between 2000 and 2019, in ABC, there was an increase in the first female authorship of articles, from 12% to 44%. As the last author, and therefore senior authors, the increase was more modest, from 16% in 2000 to 27% in 2019, in the same jornal.[8]

Among the factors highlighted by the authors that may contribute to this gender disparity are the stereotyped view that only men represent the successful scientist and motherhood.[5,8] Although the first may be unconscious and the second inherent to the genre, both must be considered in the discussion about the disparity in scientific publications and neither, in isolation, is consistent with the observed results.

The pattern noted in the study[8] is not unique to national publications.[7] It can also be observed in randomized clinical trials in cardiology indexed in PubMed between 2011 and 2020[9] and in the American College of Cardiology/ American Heart guidelines Association – ACC/AHA), the Canadian Cardiovascular Society (CCS), and the European Society of Cardiology (ESC), between 2006 and 2020.[10] In both studies that evaluated the publications mentioned, the underrepresentation of women remains in the main authorship or as a research leader.

Finally, the gender inequality found in scientific publications has a multifactorial origin and complex interrelationships, probably reflecting the behavior of society. Existing inequities prior to higher education

Keywords

Gender Inequality; Authorship; Publications; Cardiology.

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training, inequalities in income and opportunities due to inconsistent stereotypes, motherhood, double shifts and structural sexism are just a few obstacles on women's winding path to scientific authorship or leadership. To change this scenario, it is necessary to recognize the problem, and in this way, the contribution of the study[8] is essential. The path toward equity is long, but the first step has been taken.[8]

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Original Article

Hospital Mortality from Myocardial Infarction in Latin America and the Caribbean: Systematic Review and Meta-Analysis

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Abstract

Background: **Most cardiovascular deaths occur in low- and middle-income countries and myocardial infarction is one of the main life-threatening conditions.**

Objective: **We assessed all-cause in-hospital mortality in patients admitted for myocardial infarction (STEMI and NSTEMI) in Latin America and the Caribbean from 2000 onward.**

Methods: **We systematically searched in electronic bibliographic databases for cohort studies which reported in-hospital mortality due to STEMI and NSTEMI. A meta-analysis was performed and a p-value < 0.05 was considered significant.**

Results: **We identified 38 studies (29 STEMI, 3 NSTEMI and 6 both). Pooled STEMI in-hospital mortality was 9.9% (95% CI: 9.1 – 10.7). Heterogeneity was not trivial (I^2 = 74% and prediction interval = 6.6 – 14.5). The percentage of reperfusion therapy and decade explain part of the heterogeneity (I^2 = 54%). The higher the rate of reperfusion therapy, the lower the in-hospital mortality (coefficient = -0.009, 95% CI: -0.013 to -0.006, p<0.001). This mortality was higher in the first decade as compared with the second (coefficient = -0.14, 95% CI: -0.27 to -0.02, p=0.047). Pooled NSTEMI in-hospital mortality was 6.3% (95% CI: 5.4 – 7.4) and heterogeneity was null.**

Conclusion: **Pooled STEMI in-hospital mortality in low- and middle-income countries was high in comparison with rates reported in high income countries. To improve these estimates, higher use of reperfusion therapy must be pursued. Pooled NSTEMI in-hospital mortality was similar to the ones found in high-income countries; however, it was based on few studies and most of them were carried out in two countries.**

Keywords: **Cardiovascular Diseases/mortality; Myocardial Infarction/mortality; Poverty/ statistics & Numeral data; Latin America; Caribbean Region; Systematic Review; Meta-Analysis.**

Introduction

Cardiovascular diseases (CVDs) are the main cause of mortality among adults worldwide. Over three quarters of CVD deaths occur in low- and middle-income countries.[1] As a result, in Latin American and the Caribbean, where these countries prevail,[2] CVD represent a significant burden on their economies.[3] In the Sustainable Health Agenda for the Americas 2018-2030, the Pan American Health Organization (PAHO) declared that decrease in the CVD burden is one of its goals since these disorders are the main noncommunicable diseases.[4]

Ischemic heart disease is responsible for most deaths caused by CVD as well as for premature death and disability.[5] One of its main clinical manifestations is myocardial infarction, a common life-threatening emergency. It is classified as ST-segment elevation myocardial infarction (STEMI) or non-ST-elevation myocardial infarction (NSTEMI), and both have different prognosis and therapy.[6]

Management of myocardial infarction has improved in last decades. In STEMI, fibrinolytic agents and aspirin, along with percutaneous coronary intervention and more powerful new antiplatelet agents, have decreased hospital mortality rates to 5-6%. Likewise, in NSTEMI, early revascularization associated with anticoagulation and new antiplatelet agents has also improved the outcomes.[7,8]

In order to evaluate the contemporary management of myocardial infarction in low- and middle-income countries, we carried out a systematic review to assess all-cause in-hospital mortality in patients admitted for STEMI and NSTEMI in hospitals in Latin America and the Caribbean from 2000 onward.

Methods

This systematic review was performed according to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) checklist.[9] The protocol was registered in the

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International Prospective Register of Systematic Reviews (PROSPERO, number CRD42019109184).

Terminology

In this systematic review, the Latin America and the Caribbean region was defined as the geographic composed of all countries in the American continent, except the USA, Canada and the Bermuda Islands.[10] The region has a population of 645 million; 82% live in urban areas. Brazil and Mexico are the most populous countries, accounting for more than a half of the total population, and Argentina, Colombia, Peru, Venezuela and Chile for about one third. The Caribbean region accounts for less than 10% of the population and approximately 70% of this concentrates in Cuba, Haiti and Dominican Republic.[10] The list of all countries may be accessed in the Supplementary Material.

Selection criteria

This systematic review included studies that met the following inclusion criteria: (1) included male and female adults who are 18 years old and older; (2) carried out in countries in Latin America and the Caribbean; (3) collected data from patients admitted from 2000 onward; (4) prospective or retrospective cohort studies; and (5) reported all-cause in-hospital mortality due to STEMI and/or NSTEMI.

Exclusion criteria consisted of studies (1) whose samples were a specific group of the target population (such as older adults, women, diabetics); (2) whose samples were a group with a specific condition (such as patients who underwent a specific reperfusion therapy, who were in cardiogenic shock, who did not undergo reperfusion therapy); and (3) studies based on administrative data. In studies using before-after cohorts to evaluate the effect of implementing a management protocol, we selected the second period, as it would provide more recent data. For repetitive cohorts, we considered the ones with original and more recent data. We were careful to avoid double counting of patients included in different cohorts.

Search strategy

A systematic search was carried out in the following electronic databases: MEDLINE, Embase, Web of Science, Latin America and Caribbean Health Science Literature (LILACS), National Center of Cuba Medical Information (CUMED), Caribbean Health Sciences Literature (MEDCARIB) and Institutional Repository for Information Sharing/Pan America Health Organization (IRIS/PAHO). The search strategy combined terms related to "myocardial infarction" and "Latin America and the Caribbean" and was restricted to studies published from 2000 onward (Supplementary Material), and was not limited by language. A manual search of the references of selected articles was also conducted.

All reports identified in the different sources were exported to EndNote, gathered in a same file, and duplicates were removed.

Study selection and data extraction

The first step of study selection comprised the screening of reports, in agreement with eligibility criteria, through reading titles and abstracts. The second step involved the confirmation of eligibility through reading the full texts of the selected studies. In this step, reasons for exclusion were registered and, if there was any doubt, the authors were contacted. Two independent reviewers (L.A. and V.R.) selected the studies, and disagreements were resolved by consensus.

We extracted study characteristics (first author, year of publication, country, time period, sample size, type of cohort, local of recruitment, number of health centers, funding health system); patient characteristics (demographic characteristics and risk factors – hypertension, diabetes, smoking and dyslipidemia); STEMI-related data (III/IV Killip classes, ischemic time and reperfusion therapy percentage and type) and to NSTEMI studies (biomarker of myocardial injury, risk score, antithrombotic therapy and myocardial revascularization); and in-hospital mortality. This process was conducted by two reviewers independently (L.A. and V.R.) and disagreements were resolved by consensus.

Risk of bias assessment

The overall risk of bias in included studies was assessed by the Quality in Prognosis Studies (QUIPS) tool which consists of six domains.[11] In this review, we used three of them that address representativeness of the study sample, loss to follow-up, and the outcome measurement. In order to rate representativeness, we considered high-risk studies those that, at least, conducted in a single intensive care unit or did not perform consecutive recruitment (or not reported); low-risk studies those with population-based samples; and moderate-risk studies those that did not meet the previous criteria. We rated loss to follow-up as low risk (< 10%), moderate risk (10 – 20%) or high risk (> 20%).

Studies that had at least one domain rated as high risk were classified into overall high risk of bias, while the ones that had all domains rated as low risk were classified into overall low risk of bias. Studies that did not meet the previous criteria were classified into overall moderate risk of bias. Two independent reviewers (L.A. and V.R.) conducted this evaluation and disagreement was solved by consensus.

Data analysis

We performed independent meta-analyses to assess STEMI and NSTEMI in-hospital mortality. Mortality was exhibited as proportion (number of deaths divided by the total number of patients at risk in the period under evaluation). Pooled estimates were calculated by using the random effect models (due to heterogeneity, which is expected in observational studies like ours) with logit transformation and inverse variance method (as a sensitive analysis, GLM was adjusted and the difference in results was unnoticeable). We used the DerSimonian and Laird method to estimate the between-study variability.

Heterogeneity across studies was evaluated by I^2 statistics,[12] Cochran test and 95% prediction interval. This interval gives a better picture of the mortality variability expected among different populations considered in the random effect models, that is, the clinical relevance of heterogeneity.[13,14] To identify potential sources of heterogeneity, we conducted subgroup analysis (country, decade of the study) and meta-regression.

We also conducted sensitivity analysis (excluding studies with some characteristics, studies with a small sample size, high bias risk studies and outlier studies) to evaluate heterogeneity and the robustness of results.

Small-study effects, which has publication bias as one of the causes,[15] were evaluated by funnel plot that was constructed with the logit transformation of mortality against the sample size. The use of sample size is more accurate to evaluate proportion studies than the use of a measure of precision.[16] This effect, which is observed by asymmetry on funnel plot, was evaluated analytically by the Peters test that is also based on sample size.[17] R software meta package was used to perform all analyses.[18,19] A P value below < 0.05 was considered statistically significant.

Results

Search results

Our search strategy identified 9,244 reports (1st September 2018; updated on 15th April 2020). After the exclusion of duplicates, we screened 7,597 reports through title and abstract analysis of which 381 full texts were assessed for eligibility. We included one study carried out by our research group that had not been published up to the date of the search update and five reports found by screening the reference list of each full text included in the review. We could not get access to 14 full text articles despite exhaustive search. This process resulted in 38 studies: 29 on STEMI, three on NSTEMI and six that evaluated both (Supplementary Figure 1).

Study characteristics

A total of 28,878 individuals from 35 STEMI studies[20-54] and a total of 2,377 individuals from nine NSTEMI studies[20,26,30,32,39,46,55-57] were included in this review. STEMI studies were conducted in Brazil (n=15), Cuba (n=6), Argentina (n=5), Mexico (n=3), Colombia (n=2), Chile (n=1), Paraguay (n=1), Peru (n=1) and Puerto Rico (n=1), while NSTEMI ones were conducted in Brazil (n=6), Argentina (n=2) and Colombia (n=1). Most studies were multicenter prospective cohort studies and emergency rooms were the most frequent locals of recruitment.

Study	Start Year	Country	Patients	Mortality % (95% CI)	Weight
Cano, 2004	2000	Colombia	234	15.0 (10.6 – 20.2)	2.7%
Gálvez, 2002	2001	Cuba	105	13.3(7.5 – 21.4)	1.7%
Nazzal, 2008	2001	Chile	924	8.5 (6.8 – 10.5)	3.6%
García-Castillo, 2005	2002	Mexico	4,555	10.0 (9.1 – 10.9)	4,5%
Poutriel, 2009	2002	Cuba	388	13.9 (10.4 – 18.1)	3.1%
Medina, 2013	2003	Cuba	1,729	12.7 (11.1 – 14.3)	4.3%
Piegas, 2013	2003	Brazil	950	8.1 (6.4 – 10.0)	3.6%
Sánchez, 2006	2003	Puerto Rico	184	12.5 (8.1 – 18.2)	2.2%
Santos, 2006	2003	Brazil	78	6.4 (2.1 – 14.3)	0.8%
Pereira, 2009	2004	Brazil	103	17.5 (10.7 – 26.2)	1.9%
Reis, 2007	2004	Brazil	148	14.9 (9.6 – 21.6)	2.2%
Soares, 2009	2004	Brazil	158	9.5 (5.4 – 15.2)	1.8%
Takada, 2012	2004	Brazil	268	6.0 (3.5 – 9.5)	1.9%
Blanco, 2007	2005	Argentina	385	14.0 (10.7 – 17.9)	3.2%
Silveira, 2016	2005	Brazil	938	8.6 (6.9 – 10.6)	3.7%
Teniente-Valente, 2009	2005	Mexico	144	4.9 (2.0 – 9.8)	1.1%
Correia, 2014	2007	Brazil	152	10.5 (6.1 – 16.5)	1.8%
Klinger, 2015	2008	Colombia	106	15.1 (8.9 – 23.4)	1.8%
Berenstein, 2014	2009	Argentina	47	8.5 (2.4 – 20.4)	0.7%
Pérez, 2013	2009	Argentina	705	8.8 (6.8 – 11.1)	3.4%
Caluza, 2012	2010	Brazil	205	6.8 (3.8 – 11.2)	1.7%
Quadros, 2016	2010	Brazil	1,973	7.5 (6.4 – 8.8)	4.1%
Alves, 2020	2011	Brazil	530	8.9 (6.6 – 11.6)	3.1%
Aurelio, 2014	2011	Argentina	476	8.0 (5.7 – 10.8)	2.9%
Figueira Filho, 2018	2011	Brazil	520	14.0 (11.2 – 17.3)	3.5%
García, 2013	2011	Cuba	644	7.8 (5.8 – 10.1)	3.2%
Lana, 2017	2011	Brazil	788	9.1 (7.2 – 11.4)	3.5%
Rodríguez-Londres, 2014	2011	Cuba	2,493	7.0 (6.0 – 8.1)	4.2%
Martinez-Sanchez 2016	2012	Mexico	4,258	8.7 (7.9 – 9.6)	4.5%
Casillo, 2018	2013	Cuba	1,427	9.1 (7.7 – 10.7)	4.0%
Marino, 2016	2014	Brazil	138	11.6 (6.8 – 18.1	1.8%
Oliveira, 2019	2014	Brazil	707	9.9 (7.8 – 12.3)	3.5%
Gagliardi, 2016	2015	Argentina	1,759	8.8 (7.5 – 10.2)	4.1%
Gonzales, 2020	2015	Paraguay	313	12.8 (9.3 – 17.0)	2.9%
Chacón-Diaz, 2018	2016	Peru	396	10.9 (8.0 – 14.3)	3.0%
Pooled estimative (random model)			**28,878**	**9.9 (9.1 – 10.7)**	**100.0%**
Prediction interval				**(6.6 – 14.5)**	
Heterogeneity: $I^2 = 74\%$, $p < 0.01$					

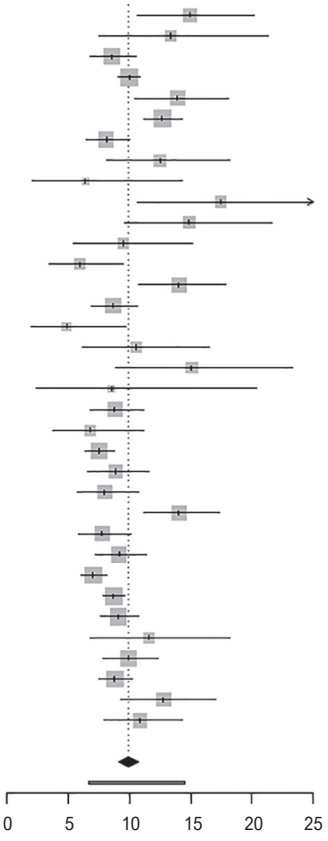

Figure 1 – *Pooled in-hospital mortality in patients admitted due to STEMI in Latin America and the Caribbean from 2000 onward.*

Median study period was 18 months (IQR: 12 – 37 months) for STEMI studies and 10 months (IQR: 12 – 37 months) for NSTEMI studies. Characteristics of the selected studies are shown in Supplementary Table 1 (STEMI) and Supplementary Table 2 (NSTEMI).

In STEMI studies, mean age varied from 55 to 65 years old and most individuals were males (56% or more in each study). Regarding patient selection, some studies used specific ischemic times as inclusion criterion (up to 12, 24, 36, 48 and 72 hours). Patient delay time was reported in less than 50% of the studies while system delay time was reported in very few studies. The percentage of reperfusion therapy varied considerably across studies, from 21% to 99%; around 60% of them showed percentages below 70%. In the first decade, the most frequent reperfusion therapy was fibrinolysis (streptokinase). Primary percutaneous coronary intervention was more frequent in the second decade; however, when fibrinolysis was an option, a fibrin-specific agent was chosen. The main cause of no reperfusion therapy was the fact that patients looked for assistance 12 hours after symptom onset. System delay time and under-diagnosis were also mentioned.

Table 1 – In-hospital mortality estimation following univariate and multivariable meta-regression analysis

Characteristic	Mortality % (95% CI)	
Crude Analysis		
Reperfusion therapy rate		
20%	14.4 (12.3 – 16.8)	
30%	13.2 (11.6 – 15.0)	
40%	12.1 (11.0 – 13.4)	
50%	11.1 (10.3 – 12.0)	
60%	10.2 (9.5 – 10.8)	
70%	9.3 (8.7 – 9.9)	
80%	8.5 (7.8 – 9.2)	
Decade		
First	10.7 (9.6 – 11.9)	
Second	9.1 (8.2 – 10.1)	
Country (N of studies)		
Chile (1)	8.5 (5.3 – 13.5)	
Mexico (3)	8.6 (6.5 – 11.4)	
Argentina (5)	9.6 (7.6 – 12.1)	
Brazil (15)	9.6 (8.3 – 11.0)	
Cuba (6)	10.0 (8.2 – 12.1)	
Peru (1)	10.9 (6.5 – 17.5)	
Puerto Rico (1)	12.5 (7.0 – 21.2)	
Paraguay (1)	12.8 (7.7 – 20.5)	
Colombia (2)	15.0 (10.1 – 21.7)	
Adjusted Analysis		
	First decade	**Second decade**
Reperfusion therapy rate		
20%	15.0 (12.8 – 17.5)	13.3 (11.2 – 15.8)
30%	13.8 (12.1 – 15.7)	12.3 (10.6 – 14.2)
40%	12.7 (11.4 – 14.2)	11.3 (10.0 – 12.7)
50%	11.7 (10.7 – 12.9)	10.4 (9.4 – 11.5)
60%	10.8 (9.9 – 11.8)	9.5 (8.8 – 10.4)
70%	9.9 (9.4 – 10.9)	8.8 (8.0 – 9.5)
80%	9.1 (8.2 – 10.2)	8.0 (7.3 – 8.9)

CI: confidence interval.

In NSTEMI studies, mean age varied from 63 to 65 years old and most individuals were males (60% or more in each study). No study presented any risk scores or reported exclusive use of troponin as biomarker of myocardial injury. Five studies reported information about dual antiplatelet and anticoagulation therapy and only two reported data on early coronary revascularization.

Risk of bias

Overall risk of bias in STEMI studies was 14%, 49% and 37% for low, moderate and high-risk studies, respectively, and 22%, 56% and 22% for low, moderate and high-risk studies on STEMI, respectively (Supplementary Table 3). The selection bias (representativeness domain) was the primary concern while outcome measurement and loss to follow-up did not represent any risk.

STEMI outcomes

Mortality rates varied substantially across the studies, from 4.9% to 17.5%. Pooled in-hospital mortality was 9.9% (95% CI: 9.1 – 10.7) (Figure 1). Width of the prediction interval (6.6 – 14.5) showed non-trivial heterogeneity across studies. Percentage of variance not explained by sampling error (I^2 statistics) was 74% (p <0.001). Univariate meta-regression revealed that the higher the percentage of reperfusion therapy, the lower the in-hospital mortality (coefficient -0.010, 95% CI: -0.014 to -0.006, p<0.001; residual I^2 = 56%) (Supplementary Table 4 and Supplementary Figure 2). The linear effect on mortality rate is on the logit scale; thus, to improve the interpretation of results, mortality estimates for some reperfusion percentages are shown (Table 1). Subgroup analysis also identified lower in-hospital mortality in the second decade (2010 to 2020) by comparison with the first decade (2000 to 2009) of this review (9.1%, 95% CI: 8.2 – 10.1 *vs* 10.7%, 95% CI: 9.6 – 11.9; p=0.036) (Table 1 and Supplementary Table 4). Considering mortality by country, the lowest in-hospital mortality was in Chile (8.5, 95% CI: 5.3 – 13.5) while the highest was in Colombia (15%, 95% CI; 10.1 – 21.7) (Table 1); however, no statistical difference was found among counties (p=0.47) (Supplementary Table 4).

In the multiple meta-regression model, only reperfusion rate and decade kept independently associated with in-hospital mortality (Supplementary Table 4). Regardless of the decade, logit of mortality decreased linearly when reperfusion rate increased (coefficient -0.009, 95% CI: -0.013 to -0.006, p<0.001). Regardless of the reperfusion

rate, logit of mortality was higher in the first decade by comparison with the second one (coefficient -0.14, 95% CI: -0.27 to -0.02, p=0.047). Mortality estimates varied from 15% to 9.1% in the first decade and from 13.3% to 8% in the second decade, depending on reperfusion rate (Table 1). Difference in mortality throughout decades varied from 1.7 percentage point for 20% reperfusion rate to 1.1 percentage point for 80% rate (Table 1). Finally, heterogeneity decreased and was partially explained by these characteristics (residual I^2=54%).

Sensitivity analyses excluding retrospective cohort studies, studies with a small sample size (below 100 patients), studies which used patient delay ischemic time < 12 h as inclusion criterion and high bias studies did not affect much overall results (Supplementary Table 5). None of the studies individually impacted results.

NSTEMI outcomes

NSTEMI mortality ranged from 4.9% to 8.6% across the studies, except one study whose rate was 16.5% (outlier study). Pooled NSTEMI in-hospital mortality was 7.2% (95% CI: 5.5 – 9.3) (Figure 2). The width of prediction interval (3.2 – 15.2) showed a substantial heterogeneity across studies. Percentage of variance not explained by sampling error (I^2 statistics) was 63%. In sensitivity analysis (Supplementary Table 6), heterogeneity was totally explained (I^2=0%) by exclusion of the outlier study (which is also a high bias one). As a result, the pooled estimate decreased to 6.3% (95% CI: 5.4 – 7.4) and the prediction interval narrowed to 5.1 – 7.7. Exclusion of one study with high bias risk and of three studies with a small sample size (below 100 patients) did not affect results. None of the studies individually impacted results, except the outlier study as previously mentioned.

Small-study effects

Visual inspection of funnel plot did not suggest small-study effects on STEMI mortality since asymmetry was not observed (Supplementary Figure 3), but it was not supported by the Peters test (p = 0.04). However, after the imputation of two hypothetical studies by the trim-and-fill method (sensitivity analysis), pooled mortality did not change much (9.7%; 95% CI: 8.9 – 10.5). Regarding NSTEMI studies, we did not have enough studies to assess this effect.

Discussion

In this systematic review, we investigated in-hospital mortality due to myocardial infarction (STEMI and NSTEMI) in Latin America and the Caribbean over the two last decades. Pooled in-hospital mortality was 9.9% and 6.3% for STEMI and NSTEMI, respectively, after exclusion of the outlier study with high-bias risk. To the best of our knowledge, it is the first systematic review that evaluated mortality due to myocardial infarction in this geographical area.

In-hospital mortality rate for STEMI varied among studies. The main source of this heterogeneity was the reperfusion therapy whose association with mortality has been well-established. The same fact is observed in Europe, where registries carried out by several countries showed mortality rates that ranged from 4% to 13% while reperfusion therapy also varied much.[58] Therefore, low use of this therapy, which was observed in many studies in our review, is a concern in terms of the quality of medical care. The main reasons for this situation were patient delay in seeking medical care, besides system delay and under-diagnosis. These issues can be solved mainly with implementation of well-structured system of care which involves prehospital evaluation, triage, and transfer together with standardized protocols. This structure can improve access to tertiary care facilities, decrease the number of "eligible, but untreated" patients and shorten time-to-treatment.[59] Educational measures about chest pain in the population must also implemented. Favorable results of these strategies were described by studies conducted in Latin American countries.[22,50,60]

Pooled in-hospital mortality rate for STEMI is higher than the ones found in registries in high-income countries, such as 5.1% and 7%[61,62] in the United States and 6.8% in Canada.[63] This difference may be due to low perfusion therapy percentages. This fact is also supported by the study that evaluated outcomes in STEMI patients in clinical trials which found negative association between mortality and gross national income.[64] This association was independent of other predictors, such as severity of cases, ischemic time and perfusion management.

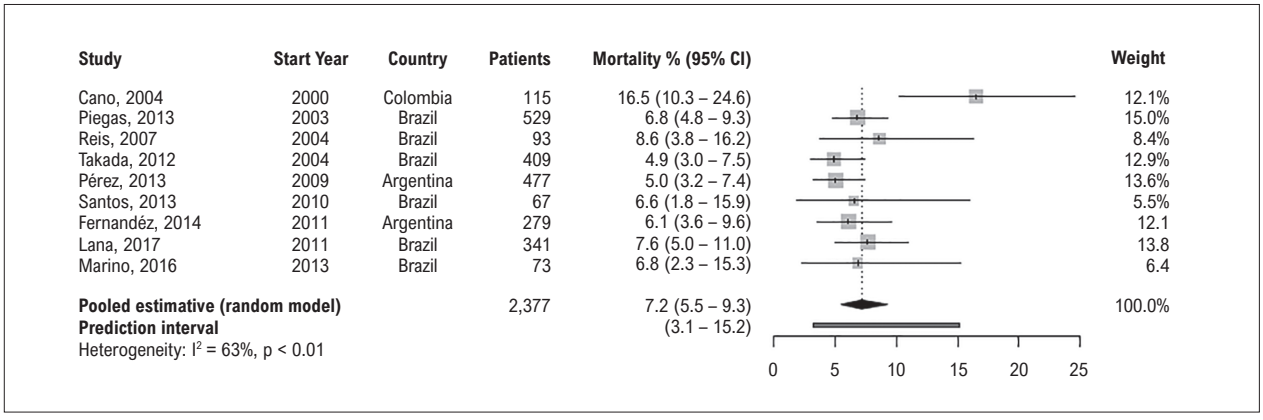

Figure 2 – *Pooled in-hospital mortality in patients admitted due to NSTEMI in Latin America and the Caribbean from 2000 onward.*

Another source of heterogeneity that we found in STEMI studies was related to the period in which studies were carried out. In the first decade of this review, we observed higher mortality than in the second one, which may be due to predominant use of non-fibrin-specific agents for fibrinolysis and less anti-thrombotic therapy. It should be highlighted that the result of this source of heterogeneity was very close to the arbitrary limit of statistical significance.

Finally, in-hospital mortality varied among the countries where the studies were carried out, but this source of heterogeneity was not statistically significant. Although the Latin America and the Caribbean are composed of low- and middle-income countries, there are differences in their gross national incomes and health systems.[64] In this case, the fact that this systematic review did not have enough statistical power any power may have influenced the result.

Two large STEMI registries conducted in Latin America (Mexico and Brazil) should also be highlighted. They reported in-hospital[60] and 30-day cardiovascular mortality[65] rather than all-cause in-hospital mortality, as in our review.[60,65] In the Mexican registry, 71% of patients received reperfusion therapy and cardiovascular mortality was 9.4% (after implementation of management protocol). This rate is also higher than the ones found in registries in high income countries. In the Brazilian registry, reperfusion therapy was used in 88% of patients while 30-day cardiovascular mortality was 3.4%. This rate was lower than the ones observed in high income countries although it considered only cardiovascular deaths. Reasons for this fact may include the participation of referral cardiac care centers, besides sampling and recruitment methods under use.

There are limitations to be considered. Some studies used different limits of ischemic times due to patient delay as an inclusion criterion (others did not mention whether they used it). Since ischemia time is associated with mortality, these studies could select patients with different prognosis. Likewise, lack of data on ischemia time (patient delay and system delay) in studies did not allow to evaluate it as a source of heterogeneity since mortality is not only associated with performing reperfusion therapy, but also with the time period in which it is performed. Other potential sources of heterogeneity, such as mean age and proportion of females were not also evaluated due to lack of information. Finally, concern about representativeness of studies should be considered. This systematic review of STEMI studies included only nine countries, and most studies were conducted in well-structured health services which usually have better results.

In-hospital mortality for NSTEMI across studies did not change after excluding the one outlier study, with a high bias risk. Pooled estimates were similar to the mortality rates of large registries, such as 5% in the GRACE study and 7.6% in the Kaiser registry.[62,66] However, there are caveats to be considered in these analyses. The shortage of data on in-hospital mortality from NSTEMI alone is due to the fact that most studies have combined mortality from NSTEMI with from other conditions like unstable angina. In addition, the studies were carried out mainly in two countries (Brazil and Argentina), which can harm generalization of the estimate in the region. The studies did not report any risk score; therefore, we could not evaluate and compare the severity level of the population under study.

Finally, the overall risk of bias was classified into high and moderate risk according to the selection bias. Therefore, attention must be paid to sampling methods in order to avoid biased estimate. In addition, definition of the representativeness domain in this review was arbitrary, which was a limitation. As a result, these facts should be taken into account when in-hospital mortality estimates are considered.

Conclusion

Pooled STEMI in-hospital mortality in low- middle-income countries was high in comparison with rates found in high income countries. To improve these estimates, it is fundamental to increase the percentage of reperfusion therapy, which can be reached by focusing on organization of the health care system and population education. Pooled NSTEMI in-hospital mortality was similar to the ones found in high-income countries; however, it was based on few studies and most of them were carried out in two countries. Therefore, regarding NSTEMI data, more registries from different countries must be addressed to obtain a more accurate estimate. Finally, researchers must focus on quality of both sampling and recruitment methods in order to avoid bias risk and, consequently, improve estimates.

Author Contributions

Conception and design of the research and Writing of the manuscript: Alves L, Polanczyk CA; Acquisition of data: Alves L, Ribeiro V; Analysis and interpretation of the data and Critical revision of the manuscript for important intellectual content: Alves L, Ziegelmann P, Polanczyk CA; Statistical analysis: Alves L, Ziegelmann P, Polanczyk CA.

Potential Conflict of Interest

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

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Study Association

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Ethics approval and consent to participate

This article does not contain any studies with human participants or animals

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*Supplemental Materials

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High Mortality for Myocardial Infarction in Latin America and the Caribbean: Making the Case for Systems of Care Implementation in Brazil

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Short Editorial related to the article: Hospital Mortality from Myocardial Infarction in Latin America and the Caribbean: Systematic Review and Meta-Analysis

Ischemic heart disease (IHD) is the leading cause of death worldwide, and while in high-income countries (HIC), substantial declines in mortality rates for IHD were observed in the last decades, the same did not occur in low- and middle-income countries (LMIC).[1] The final event in the chain of IHD is myocardial infarction (MI), which can be classified based on the electrocardiogram in ST-segment elevation MI (STEMI), and non-ST-segment elevation MI (NSTEMI) - the first having higher lethality.[2] Mortality rates for both MI presentations can be reduced by timely diagnosis and treatment according to current guidelines, including reperfusion therapy for STEMI.[3] In HIC, such as the US, STEMI in-hospital mortality varied from 3.5% for individuals receiving primary percutaneous coronary angioplasty to 14.9% for those receiving no reperfusion, while in European countries, mortality as low as 2.5% has been reported.[3,4]

In this issue of the Journal, the article "Hospital Mortality from Myocardial Infarction in Latin America and the Caribbean: Systematic Review and Meta-Analysis" brings a welcome addition regarding MI in-hospital mortality in LMIC from Latin America and the Caribbean from 2000 to 2020.[5] Using sound methodology, the authors made a meta-analysis of data from 38 studies, mostly conducted in Brazil, Cuba, and Argentina: 35 for STEMI with 28,878 individuals, and 9 for NSTEMI with 2,377 individuals. Pooled analysis demonstrated that in-hospital mortality for STEMI was 9.9% (95%CI: 9.1–10.7), with moderate to high heterogeneity (I^2=74%). Chile had the lowest mortality (8.5%; 95%CI: 5.3-13.5), and Colombia the highest (15%; 95%CI: 10.1-21.7), with Brazil showing a mortality of 9.6% (95%CI: 8.3-11.0); however, no statistical difference was found among countries (p=0.47). For NSTEMI, in-hospital mortality was 7.2% (95% CI: 5.5 – 9.3), also with moderate to high heterogeneity (I^2 = 63%), explained (I^2=0%) by the exclusion of one outlier study.[5]

The results above described are robust because mortality reduction for STEMI was associated with known factors that improve outcomes, which also partly explained the heterogeneity: higher reperfusion rate (coefficient=-0.009, 95% CI: -0.013 to -0.006, p<0.001) and temporal advances in treatment, with higher mortality in 2000-2009 compared to 2010-2020 (coefficient=-0.14, 95% CI: -0.27 to -0.02, p=0.047).[2] However, it should be acknowledged that the in-hospital mortality reported is probably lower than the actual numbers, as included studies were conducted in more organized health facilities, where patients may have had better access to treatment than the total MI population of the region.

Still, the gaps in STEMI in-hospital mortality between HIC and Latin America/Caribbean reinforces the possibility of reducing MI mortality in LMIC by providing better access to care. By integrating and organizing health facilities and providers in a region, MI care systems bring better access to reperfusion, evidence-based medication, and intensive care, leading to improved outcomes and optimizing resources.[6]

In the Brazilian context, IHD is the first cause of mortality, accounting for 12% of all deaths.[7] Hospitalizations due to MI rose 54% from 2008 to 2019 in public hospitals - with 12.9% in-hospital mortality in 2019, making MI a major public health issue.[7] Of note, disparities in MI care occur within the country: in a registry of 4782 patients from selected public and private hospitals, in-hospital mortality was 3.4%, but higher in public hospitals.[8] Higher mortality was also shown in a Brazilian city in public (19.5%) compared to private hospitals (4.8%).[9]

As such, implementing the MI system of care in Brazil from the public health perspective is fundamental to reduce MI mortality. In 2011, the Ministry of Health launched the ordinance 2.994 to promote the organizations of MI systems of care. While initial experiences have successfully reduced in-hospital mortality (4-6% of absolute reduce), they have been restricted to some geographical areas.[10-12] In 2021, pre-hospital components of the system were also regulated in the ordinance 2.777, which includes the use of telemedicine for the use of telemedicine for ECG analysis and clinical support, and pre-hospital thrombolysis.

Many challenges for implementing the MI systems of care have been described. They relate to late diagnosis, inadequate referral strategies and/or health infrastructure,

Keywords

Myocardial Infarction; Epidemiology; Mortality; Acute Coronary Syndrome; Public Health Policy

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insufficient funding, and delays in seeking care.[6] Telemedicine support for ECG diagnosis and clinical care, organization of referral hubs, enhanced pre-hospital care – including pre-hospital thrombolysis – and public campaigns about MI symptoms are strategies to overcome these barriers.[6,13] A recent meta-analysis showed that including telecardiology as part of MI systems of care was associated with a 37% reduction in mortality.[13] Moreover, the involvement of different stakeholders, including health policymakers and pre-hospital and hospital healthcare providers, is another essential part of a successful implementation strategy.[6]

Laying in the fundamental principles of SUS of universality and equity, the extension of the MI system of care across every Brazilian municipality urges if we want to reduce mortality by MI, the number one cause of death in our country.

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Review Article

The Benefits of Exercise in Breast Cancer

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Abstract

Breast cancer is the most prevalent cancer among women, accounting for nearly 30% of all cancers, while in men, it represents only 1% of cases. Breast cancer is the main cause of death for cancer, and its incidence and mortality vary according to patients' ethnicity, geographic region, and socioeconomic status. Due to the low prevalence of breast cancer among men and the scarcity of studies in the literature, exercises have been prescribed based on extrapolations from studies on female patients. Scientific evidence has suggested beneficial effects of physical exercises on breast cancer prevention, treatment, and post-treatment. In addition to combatting sedentary behavior, it is essential to maintain a healthy body weight, limit alcohol consumption, and follow a balanced diet, rich in fruit, vegetables, grains and fibers, and limited in red meat. The effects of exercises are not restricted to breast cancer, but extend to controlling modifiable risk factors, and reducing the incidence of cardiovascular diseases, and all-cause and cardiovascular mortality.

Introduction

Breast cancer is the most incident cancer among women in the world, with approximately 2.3 million new cases in 2020, corresponding to 24.5% of all types of cancer.[1] In Brazil, apart from non-melanoma skin cancer, breast cancer is the most common among women, with the highest rates in the south and in the southeast regions.[2] The highest occurrence in these regions may be attributed to the highest human development index and life expectancy, high prevalence of white race, life style, later pregnancy and less children.[3,4] For 2022, it is estimated 66,280 new cases of breast cancer in Brazil.[2]

Keywords

Breast Neoplasms; Exercise Movement Techniques; Exercise; Diet, Healthy

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With respect to mortality, breast cancer is the main cause of death for cancer among the female population in Brazil, except for the north region, where colon cancer ranks the first. The highest mortality rates are observed in the south and southeast regions and the rates increase from the age of 40 years of age.[5] In places where mortality rates are low, like the north of Brazil, the possibility of underdiagnosis of breast cancer cannot be excluded.

Genetic causes, including BRCA1 and BRCA2 mutations, are responsible for 5-10% of all cases of breast and ovarian cancer, with a greater contribution of environmental factors and lifestyle in the pathogenesis of these tumors.[6] The BRCA 1 and BRCA2 genes produce tumor suppressive proteins. These proteins repair damaged DNA and thereby play a role in maintaining genetic material stability in each cell. When mutation or alteration occurs in one of these genes, the activity of the protein product can be altered, and the DNA damage may be not properly repaired. As a result, the cells are more likely to develop genetic changes that may lead to cancer development.[7]

The adoption of a healthy lifestyle is important for prevention of breast cancer, including an adequate diet (higher consumption of fruit, vegetables and whole grains, and lower consumption of red meat), weight control, reduction of alcohol intake, and regular physical exercises (PE).[8] The effects are not restricted to the prevention, but also to disease control, since experimental studies have demonstrated influence on tumor formation kinetics, growth and recurrence.[9]

The third consensus of the World Cancer Research Fund[10] and the Brazilian Society of Oncology guidelines on physical activity[11] address the importance of women being physically active, involving several types of physical activities, from household chores (e.g. gardening), occupational, and recreational activities, to those systematically categorized as PE, whose frequency, intensity, time and type (aerobic, resistance and combined) are determined by prescription.

Mechanisms of action of physical exercises in tumor progression

PE promote different organic and biological mechanisms that can be involved in the control of the development of several tumors. These responses originate from metabolic and hormonal changes, in addition to modulation of systemic inflammation.[12] However, the potential of directly affecting tumor progression has been recently related to

changes in vascularization and blood flow in tumors,[13] the use of substrates by neoplastic cells, protein interactions between cancer and muscle tissue, and to the regulation of immune function by PE.[14-16]

Tumor microenvironment acts in the cooption and deviation of the action of immunoinflammatory and stromal cells.[17] While the acute and transient action of lymphocytes and macrophages is a controlling and repair factor of tissue damage, chronic inflammation and macrophage infiltration into the tissue promote tumor progression.[18]

The development of anticancer therapy has been based on hallmarks (biological capabilities acquired by human cells during the development of tumors) proposed by Weinberg in 2000.[19] Also based on these concepts, possible mechanisms of action and adaptation by which PE can influence these marks of tumor development have been studied (Figure 1).

Results of preclinical studies indicate that these molecular effects resulting from each exercise session overcome the control of hormonal factors and insulin.[20] During exercise, these factors act immediately on tumor metabolism, and long-term training leads to metabolic and immunogenic adaptations that contribute to slow tumor progression.[21]

Evidence that PE inhibits malignant tumor progression emerged from animal models.[12,22,23] Recently, clinical studies have identified cellular and molecular actions that are similar to exercise in patients with cancer, including breast cancer.[24,25] However, there are still no studies that clearly determine the clinical relevance of these findings.

Physical exercise in breast cancer prevention

One of the first and largest prospective studies on PE and breast cancer was the "Nurses Health Study". This study evaluated 121 701 nurses aged between 30 and 55 years, during a follow-up period of 16 years, and showed that women who engaged in moderate or vigorous physical activity for seven or more hours per week had a nearly 20% lower risk of breast cancer than those who engaged in such physical activity for less than one hour per week (relative risk 0.82; 95% confidence interval [CI] 0.70-0.97). This benefit was observed in both premenopausal and postmenopausal women.[26]

Literature has suggested that women who exercise regularly have 10-25% lower risk of breast cancer compared with those who do not.[27,28] This association seems to be stronger for activity sustained over the lifetime and after menopause, for women who are normal weight, have no family history of breast cancer, and are parous.[29] Available evidences of the impact of PE on breast cancer reduction in BRCA1 and BRCA2 mutation carriers are limited, and larger studies are warranted.[30]

A meta-analysis published in 2013 of 31 prospective studies found a significant association between physical activity and reduction of breast cancer risk, with a combined relative risk (RR) with 95 % CI of 0.88 (0.85-0.91), highlighting the importance of prevention. Dose-response analysis suggested that the risk of breast cancer decreased by 2 % for every 25 metabolic equivalent (MET)-h/week increment in non-occupational physical activity (approximately 10 hours per week in household activities), 3 % for every 10 MET-h/week increment in recreational activity (equivalent to 4 h/week of walking in 3Km/h), and 5 % for every 2 h/week increment in moderate and vigorous recreational activity.[31] Other studies have corroborated these results, suggesting greater risk reduction of breast cancer with higher levels of PE.[28,32] The exact dose and the type of exercise needed to reduce breast cancer risk have not been clearly determined.

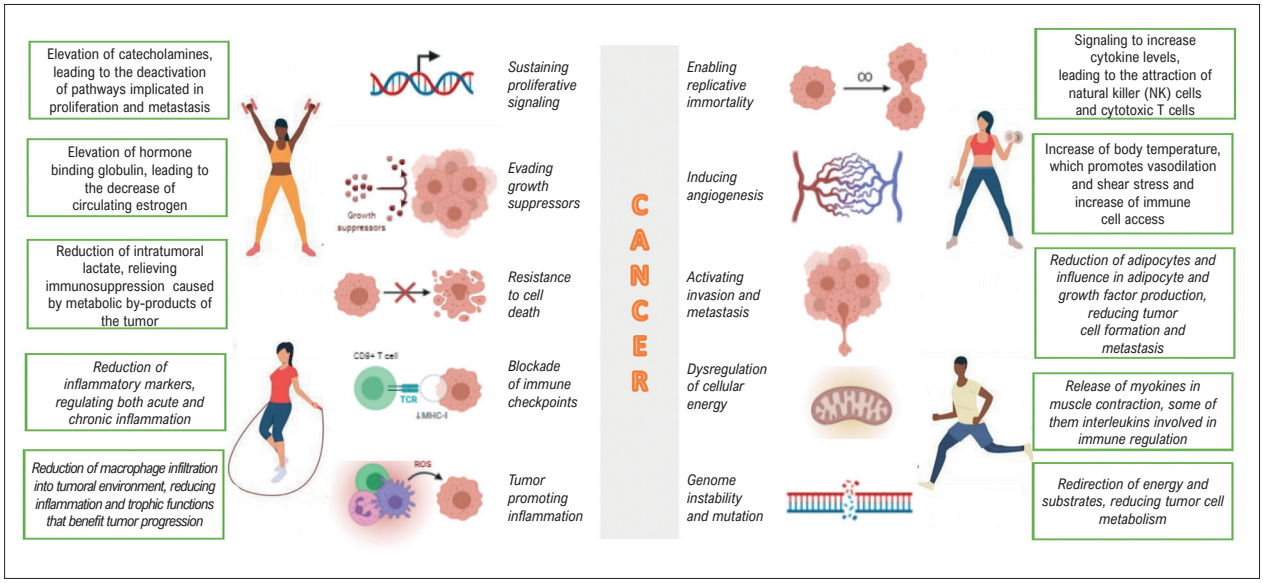

Figure 1 – *Scheme of the mechanisms by which physical education can affect the hallmarks of cancer in breast cancer. Adapted from "Hallmarks of cancer", by BioRender.com*

In an umbrella review[33] about physical activity and cancer incidence and mortality, the results suggested a reduction of breast cancer risk in the general population. However, classification of physical activity across studies were heterogeneous and most reviews were based on observational studies, mainly cohort studies, in which the control of selection bias is difficult, since healthy habits tend to cluster. For example, a person with a healthy lifestyle eat well, has close to ideal body weight and is nonsmoker. To minimize limitations of this type of study, guidelines have been established based on cohort studies with larger samples of the population.[33]

The role of PE in breast cancer prevention seems to be linked to reductions in estrogen activity, insulin resistance, inflammation, and oxidative stress.[34] Estrogen is related to reduction of cellular proliferation and tumor development. PE increase sex hormone-binding globulin, and reduce circulating levels of estrogen, as described in Figure 1. They contribute to the reduction of fat mass, mainly by visceral fat reduction, improvement of cellular insulin sensitivity and consequent decrease of insulin serum levels. Insulin is involved in the activation of aromatase and estrogen elevation, in addition to exerting mitogenic effects. In addition, PE have immunomodulatory effects, increasing both innate and acquired immunity and improving DNA repair mechanisms, thereby reducing the risk of breast cancer.[35]

More research is needed to fully understand the mechanisms by which physical activity can reduce breast cancer risk.

General recommendations for physical activity in the prevention and control of breast cancer

In 2020, the World Health Organization (WHO) and the Brazilian Ministry of Health recommended for the general adult population (18-64 years old) and for breast cancer survivors, 150-300 minutes of moderate-intensity physical activity, at least 75–150 minutes of vigorous-intensity aerobic physical activity; or an equivalent combination of moderate- and vigorous-intensity activity throughout the week.[11,36,37]

Table 1 summarizes the description of different intensities of physical activity based on the Physical Activity Guidelines for the Brazilian Population.

It is important to differ physical activities (voluntary body movements, with energy expenditure resting levels) from PE (planned, structured, and repetitive physical activity, essentially aimed to improve cardiorespiratory fitness, strength, flexibility and balance). It is recommended that PE be supervised by a physical educator or a physical therapist, and all programs include aerobic components (walking, cycling, dancing, jogging, swimming), muscle-strengthening activities (strength training, Pilates, functional exercise) and range of motion exercises (stretching, yoga, tai-chi).[11]

Aerobic exercises increase the levels of peripheral beta-endorphins, which are correlated with decreased systemic sympathetic activity and improvement in serotonergic activity, reflected in the activity of neuromuscular junctions. Resistance training exercise promote better synchronization, recruitment and excitability of motor units. Finally, flexibility exercises can lead to a better control of articular structures and soft parts.[38,39]

Now we describe particularities of physical activities and PE during treatment and follow-up periods of survivors after breast cancer treatment.

Physical exercises during breast cancer treatment

Breast cancer treatment should be individualized according to patients' age, hormonal status, comorbidities,

Table 1 – Description of physical activity intensities for the prevention and control of breast cancer

Intensity	Description	Examples
Light <3 metabolic equivalents (METs)	Requires minimum effort, with small increase in HR and RR increase. On a 0-10 scale, perceived exertion ranges from 1 to 4. One can breathe calmly, talk, or even sing during exercise	Standing or sitting, washing dishes, doing arts and crafts
Moderate 3 – 5.9 METs	Requires greater physical effort, with perceptible but moderate increments in RR and HR. On a 0-10 scale, perceived exertion ranges from 5 to 6. One can talk with difficulty but not sing	Walking at > 5 Km/h; cycling at < 5 Km/h, double tennis, and ballroom dancing
Vigorous > 6 METs	Requires great physical effort with large increments in RR and HR. On a 0-10 scale, perceived exertion ranges from 7 to 8. One is not able to talk during the exercise.	Running, slope walking, bicycling at > 16 km/h, aerobic dancing

Source: Adapted from Physical Activity Guidelines for the Brazilian Population.37 HR: heart rate; RR: respiratory rate.

lifestyle, and personal choices, as well as to fundamental pillars in determining the prognosis: the extent of the disease (cancer staging) and the type of the tumor. In general, treatment can be divided into local therapy (surgery, radiotherapy, and breast reconstruction) and systemic therapy (chemotherapy, hormone therapy and biological therapy).[40]

Chemotherapy is associated with fatigue, anorexia, anemia, neutropenia, thrombocytopenia, peripheral neuropathies and, in some cases, cardiotoxicity.[41,42] The side effects of hormone therapy include weight gain, arthralgia, myalgia, bone loss, effects on the cardiovascular system and changes in the lipid profile.[43] Sequelae of radiation therapy include cardiac and pulmonary damage, lymphedema, brachial plexopathy and secondary malignant diseases.[44] Associated to these physical repercussions, emotional changes including depression, anxiety, low self-esteem, and negative body image can occur, since the disease affects an important symbol of femininity, sexuality and maternity.[45]

Six months after the diagnosis, approximately 90% of women present at least one of the adverse symptoms of the antineoplastic therapy; 60% have multiple symptoms that affect not only patient therapy and quality of life, but also survival rates. Six years after treatment, up to 30% of women still have complaints related to the therapies.[46]

Physical activity is safe and can be performed at different stages of cancer treatment, resulting in better quality of life, and improved global function, and lower psychological symptoms related to disease and its treatment.[47,48]

Pain is one of the most common symptoms in breast cancer patients; 30-60% of patients have moderate to severe symptoms, that may lead to activity restrictions and limitations in physical activity during and after therapeutical interventions.[39,49] Pain manifestations tend to decrease with physical training, with direct implications for strength gain, better cardiorespiratory capacity and flexibility, and also for lower rates of fatigue, length of hospital stay, anxiety, depression, sleep disorders, nausea and vomiting.[50,51] Figure 2 summarizes the final clinical effects of PE during treatment and in other breast cancer stages.

Van Waart et al.[52] demonstrated that, in patients undergoing chemotherapy, an aerobic training program was associated with enhanced physical functioning, with maintenance of cardiorespiratory fitness, facilitating the return to work during and after treatment, in addition to reducing the incidence of nausea and vomiting as with the group that did not undergo physical training.[52]

In addition, a multicentric study[53] evaluated the effect of physical activity in 301 patients during breast cancer chemotherapy and demonstrated improvements in health-related fitness in the three groups of exercise intervention: STAN group (three sessions of 25–30 min/week of vigorous-intensity aerobic exercise), HIGH group (three sessions of 150 min/week of vigorous-intensity aerobic exercise, and the COMB group (aerobic exercise plus a resistance exercise program). The higher dose of aerobic exercise intervention (HIGH group) was more effective in improving life quality and aerobic capacity, and in controlling pain and endocrine symptoms (e.g. hot flashes). However, the COMB group was superior to the HIGH and STAN groups in muscular strength gain.[53]

In chemotherapy patient, resistance exercise programs are associated with improved self-esteem, muscular strength, and body composition, without causing or

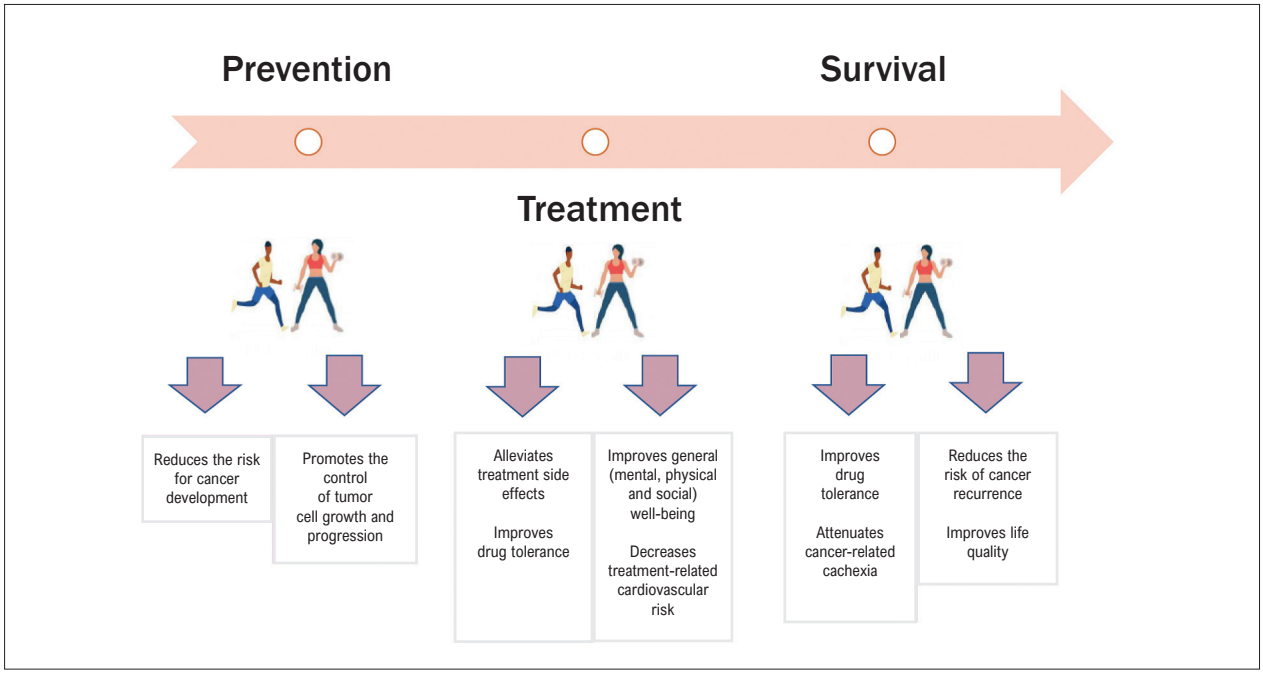

Figure 2 – *Clinical results of exercise in breast cancer timeline.*

aggravating lymphedema or other complications in those who underwent surgery.[54,55] Before initiating upper limbs exercises, it is recommended to assess the mobility of the arms. In addition, specific examination for the presence of peripheral neuropathies, musculoskeletal disorders, and risk of fractures, especially in patients on hormone therapy and in those with metastatic bone disease is advisable.[46,56,57]

The combination of the three exercise programs proposed (aerobic, resistance and flexibility exercise) have largely contributed to the control of pain and fatigue. Improvement of cardiorespiratory function, due to increased aerobic capacity (maximal oxygen consumption) in combined exercise training programs may be explained by the ventilation perfusion matching and oxidative capacity of skeletal muscle.[55] This can play an important role in the management of structural disorder related to chemo- and radiation-induced toxicity.[46]

Chemotherapeutic agents that also cause direct and indirect cardiotoxicity, with acceleration of general and vascular aging, and consequent decline of cardiopulmonary reserve. Both the disease and the therapy can contribute to weight gain and reduction of physical activity,[58] potentially increasing the risk for cardiovascular diseases (CVD). Studies on secondary prevention have corroborated the improvement of cardiopulmonary function with physical training programs in breast cancer women.[59]

Cardiotoxicity, associated with psychoemotional factors, affects autonomic balance and consequently cardiovascular mortality.[60] In patients treated at initial stages of the disease, a sustained increment in sympathetic function and reduction in parasympathetic effect on the sinoatrial node have been reported.[61] Other reports have pointed out a reduction in heart rate variability and baroreflex sensitivity among women with a history of breast cancer.[61-63]

In addition to autonomic regulation, another important factor for the development of CVD is endothelial dysfunction. A recent meta-analysis[64] evaluated 163 patients from four studies (two on breast cancer, two on prostate cancer). Aerobic exercise improved vascular function and peak oxygen consumption. These data reinforce the importance of PE as an adjuvant therapy in breast cancer treatment, especially regarding the management of the side effects.

With respect to overall and specific mortality, evidence accumulated so far suggests a favorable effect of moderate to vigorous physical activity, and preliminary evidence indicates associations of physical activity with risk reduction of breast cancer recurrence and progression.[11] A recent study evaluated systematic reviews on physical activity and reduction of all-cause mortality and breast cancer mortality, considering the dose-response relationship (also regardless of body mass index); the certainty of evidence was moderate. Regarding associations of the domain or the type of physical activity with mortality, the certainty of evidence was classified as low and, so far, it was not possible to identify physical activity modalities that had the greatest impact on the outcome. The same study evaluated risks and benefits, patients' values and preferences, resources required to meet the recommended physical activity, equity, acceptability of the recommendation, and the strength of the recommendation of PE to increase breast cancer survival was classified as "strong".[11] Future studies may change the quality of available evidence; it remains an open field of research.

Physical exercises in breast cancer post-treatment

PE have been strongly recommended for breast cancer survivors and associated not only with improvement of quality of life, but also with possible increased survival.[65-67] A prospective study that included 2987 women with stage I, II, or III breast cancer between 1984 and 1988, followed up until death or June 2002, showed that physical activity after breast cancer diagnosis can reduce the risk of death for the disease. The greatest benefit occurred in women who performed the equivalent of walking three to five hours per week at an average pace.[65]

After the end of treatment, the main objective is to rehabilitate patients to return to their usual activities. Regular exercises can contribute to physical and psychological well-being and improved quality of life, consisting of one of the main recommendations to prevent chronic degenerative conditions; it would not be different for patients who had recently faced cancer treatment.[68] Evidence has shown that PE have a positive impact on survival and minimize breast cancer-related morbidity.[65] Despite favorable data, the practice of PE is limited by barriers like fatigue, lack of motivation, loss of self-confidence, inadequate follow-up, lack of family support and lack of instructions.

Encouraging women in the post-treatment period to adopt a healthy lifestyle – by avoiding excess alcohol and increasing fruit and vegetable intake and physical activity volume, is important to improve their quality of life and health.[69] Increased exercise levels represent a modifiable health behavior that can ameliorate sequalae of the disease and help women to return to their health status before cancer diagnosis and treatment.[70] Thus, current recommendations of PE for breast cancer survivors are based on the return, as soon as possible, to habitual daily activities, on the maintenance of metabolic expenditure during and after therapies, and on the classical recommendation of weekly aerobic exercises.[57]

Also, it has been demonstrated that physical inactivity is related to weight gain after the diagnosis which, in turn, has been associated with lower survival in some studies.[71,72] More physically active women are less likely to gain weight after the diagnosis, improving the chance of survival.[65,73]

Obesity is related to increased mortality rates for breast cancer (13-20%) and all-cause mortality (14-70%).[74-77] Obesity was also associated with a twice greater chance of post-menopausal contralateral breast cancer and a nearly 60% greater occurrence of other cancers.[76] Therefore, maintaining normal body mass index can reduce the risk of a new breast cancer in the postmenopausal period, other cancers, and all-cause mortality.[75,76,78]

Giallauria et al.[61] evaluated whether exercise training improved autonomic function in women with a history of primary invasive breast cancer. Fifty-one patients enrolled in the DIANA clinical trial were divided into two groups. Group 1 (n = 25) that followed a formal exercise program of moderate intensity – three sessions/week on a bicycle or treadmill at 70 ± 2% VO_2 peak for 12 weeks, followed by one session/week until one-year follow-up. Group 2 while a control group (n = 26) did not perform any formal training. At baseline and at one-year follow-up, all patients underwent cardiopulmonary exercise stress test. Heart rate recovery (HRR) was calculated as the difference between heart rate at peak exercise and heart rate at the first minute of recovery. Compared with control group, group 1 showed significant improvement of VO_2 peak (from 12.4 ± 2.9 to 14.3 ± 3.3 mL/kg/min; $p<0.001$) and in HRR (from 17.6 ± 6.4 to 23.0 ± 8.3 beats/min; $p<0.001$). The authors concluded that moderate-intensity exercise is associated with improvement of autonomic function in breast cancer survivors.[62]

Evidence suggests that PE can also promote physiological and psychological benefits in cancer survivors.[70,79] A meta-analysis of randomized controlled trials by Fong et al.[70] reported that PE had positive effects on physical functions, body weight and quality of life in patients after treatment for breast cancer.[70] Additionally, results from another systematic review[66] indicated that PE can have beneficial effects on overall and on certain domains of quality of life, like body image, self-esteem, emotional well-being, sexuality, sleep disorder, social functioning, anxiety, fatigue and pain.[66] Also, a Cochrane database systematic review that included 63 trials and 5761 women evaluated the effects of PE in patients in the post-treatment period and in a control group. Once again, it was shown that that physical activity interventions resulted in improvements in quality of life, emotional health, anxiety, physical function, muscular strength, and fatigue. Besides, relatively few adverse events were reported in the trials, suggesting that PE are safe in this population.[67]

To be safe, exercise prescription requires the understanding, by the multidisciplinary team (physical educators, physical therapists, among others), of the peculiarities, implications and consequences of cancer treatment.[57] Prescriptions should be made according to pre-treatment physical performance and comorbidities of cancer survivors, therapeutic response and negative immediate and persistent effects of treatment.[57] Special attention should be given to peripheral neuropathies and secondary musculoskeletal diseases, regardless of the treatment time. Patients on hormone therapy should be assessed for the risk of fractures. It is also recommended evaluating the mobility of arms and shoulders before initiating upper limb exercises. It is important to consider the needed time for wound healing, which may be eight weeks or longer in mastectomies.[57]

Individuals with bone metastatic disease will required individualized exercise programming aiming at determining safety limits before initiating the PE. Rehabilitation of these patients include adaptations in pre-established programs, with reductions in impact, intensity, and volume, due to the increased risk posed by bone frailty and fractures.[57] In addition, individuals with known CVD (secondary to cancer or not) also require initial individualized examination regarding the safety of the exercise programs, closer supervision, and shorter intervals. Guidelines' recommendations on exercise and rehabilitation should be followed, especially considering cardiovascular and pulmonary contraindications.[57]

Cancer survivors should be physically active. However, exercise prescription including exercise frequency, intensity, type and duration has been based on limited literature data. Table 2 summarized recommended exercise prescription for breast cancer patients in the post-treatment.[47,57]

The progression of PE should be slower in cancer survivors as compared with healthy individuals, particularly if the prescribed exercises result in greater fatigue and unexpected adverse effects, which serves as an alert to individual's capacity thresholds. There are no maximum loads for weight training exercises for these patients. Attention should be paid to symptoms in the arms and shoulders, including lymphedema, resulting in load decrease or interruption of specific exercises according to the symptom reported.[57]

Despite all the benefits of regular physical activity described above, there is no consensus or clear standard of the magnitude of their benefits, the way of administration or the most effective PE for this population. Further research is needed to establish the ideal exercise prescription. Studies so far have evaluated the effects of different exercise modalities, frequencies, intensities and durations on specific outcomes in breast cancer survivors, which make generalization and standardization of results difficult.

Finally, we reinforce the need of all health professionals involved – physicians, physical educators, physical therapists, psychologists, and nutritionists – be aware of the importance of encouraging these women to regularly exercise after breast cancer treatment, highlighting the benefits and excellent cost-effectiveness.

Conclusion

Regular exercise/physical activity should be encouraged among women, targeting primary prevention, improvement of life quality and reduction of mortality among survivors, although studies have not reported the strength of evidence for breast cancer control. It is also important to highlight the important role of PE in reducing the incidence of CVD, which reinforces the importance of encouraging these women to be physically active. Although attention should be paid to some details in exercise prescription to breast cancer patients, in general, it is not very different from that made to the general population. Future studies are needed to better guide individualized prescriptions for these patients.

Table 2 – Recommended prescription of physical exercises in the post-treatment of breast cancer

	Frequency	Intensity	Duration/performance	Quality
Aerobic	Patient should start exercises twice a week and progressively increase until 3-5 times a week	Patient should be instructed about effort perception. If exercises are well tolerated (without symptoms or side effects), the intensity of exercises should not be different from that in healthy population. Intensity should be from moderate to vigorous	Exercise duration should be increased according to patient tolerance. A target of 75min/week of vigorous exercise or 150min/week of moderate exercise should be aimed	Rhythmic, prolonged exercises that use large muscle groups. Examples: swimming, walking, bicycling, dancing
Resistance	2-3 days a week	Moderate intensity (60-70% maximum repetitions)	Sets of 8 - 12 repetitions	Programs should include weights, resistance training equipment, functional tasks with weights, using the main large muscle groups
Flexibility	Exercises can be performed daily, according to patient's condition			Programs should include stretching exercises. Attention to body parts with restricted mobility due to treatment

Source: Adapted from the American College of Sports Medicine guidelines for exercise testing and prescription.[47]

Author Contributions

Conception and design of the research: Campos MSB, Feitosa RHF, Mizzaci CC, Flach MRTV, Siqueira BJM; Acquisition of data: Campos MSB, Feitosa RHF, Mizzaci CC, Flach MRTV, Siqueira BJM; Analysis and interpretation of the data, Writing of the manuscript and Critical revision of the manuscript for important intellectual content: Campos MSB, Feitosa RHF, Mizzaci CC, Flach MRTV, Siqueira BJM, Mastrocolla LE.

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Intracardiac Metastasis of Colonic Adenocarcinoma 12 Years After Primary Tumor Control and Without Any Sign of Other Metastasis: A Case Report

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Introduction

Thrombus, vegetation and tumor are the main diagnoses for intracardiac masses.[1] Malignant cardiac tumors are rare and cardiac metastasis are around 20 times more frequent than primary tumors.[2] Cardiac metastases originate from lymphatic or blood dissemination,[3] mediastinum direct invasion or tumoral growth inside inferior vena cava or pulmonary veins[4-6] and can lead to obstruction of the right or left outflow or inflow tract or arrhythmias.[7] Frequently, symptoms are similar to other prevalent cardiovascular diseases, such as dyspnea, chest pain, palpitations and edema,[8] but sometimes a cardiac mass is found out incidentally during an image exam performed for an unrelated indication.[1] We aim to describe an uncommon case of intracardiac metastasis from colonic adenocarcinoma 12 years after the end of the primary tumor treatment.

Case presentation

A 61-years-old man was admitted, in January 2020, at the emergency department of a Brazilian tertiary hospital due to a sudden crisis of dyspnea, sweating, pallor and dizziness. On physical examination, the patient had symmetric lower limbs edema, elevated jugular venous pressure and systolic heart bruit in the right ventricular outflow tract. His medical history included hypertension, *diabetes mellitus*, chronic kidney disease and colonic adenocarcinoma treated by surgical resection and chemotherapy in 2005. In 2007, a hepatic metastasis was also properly resected and, in 2009, he received the last dose of chemotherapy. He was regularly followed up with colonoscopy and carcinoembryonic antigen assessment, without any sign of recurrence.

The initial evaluation ruled out acute myocardial infarction and showed hypochromic and microcytic anemia, worsening renal function, and severe thrombocytopenia ($16 \times 10^3/\mu L$). A transthoracic echocardiogram described a huge mass in the right ventricle with extension to the right atrium and pulmonary trunk (figures 1A and B). Computed Tomography (CT) scan showed no evidence of pulmonary or abdominal masses. There was only a minor elevation of the carcinoembryonic antigen (CEA) (previous: 2.9 ng/mL in 2019, current: 6.5 ng/mL). A myelogram showed a hyperproliferative bone marrow, so the hypothesis of thrombocytopenia was attributed to peripheral platelets destruction by the tumor itself or by immunological mechanism.

A cardiac magnetic resonance (CMR) showed an intracavitary mass in the right ventricle, occupying most part of its cavity. The mass didn't have intrinsic contractility and was apparently fixed in the ventricular wall, without local invasion. The outflow tract of the right ventricle was almost completely occupied by the tumor, tricuspid valve opening was significantly restricted and there was systolic abnormal leftward motion of interventricular septum. Dimensions of the mass were 8.4 cm (craniocaudal), 4.4 cm (anteroposterior) and 5.7 cm (longitudinal). Tissue characterization showed heterogeneous appearance in all sequences. At cineresonance, the mass exhibited hyposignal in comparison with myocardium, isosignal in T1 and hyposignal in T2, without signal changes in sequences with fat suppression. In perfusion sequences, heterogeneity and discrete contrast enhancement could be seen. In late gadolinium enhancement, a peripheric hypersignal with a hyposignal hole suggested the mass could have a necrotic

Keywords

Adenocarcinoma; Neoplasm Metastasis; Genes, Tumor Suppresor; Heart Neoplasms; Colonic Neoplasms; Carcinoembryonic Antigen; Thrombocytopenia; Diagnostic, Imaging/methods

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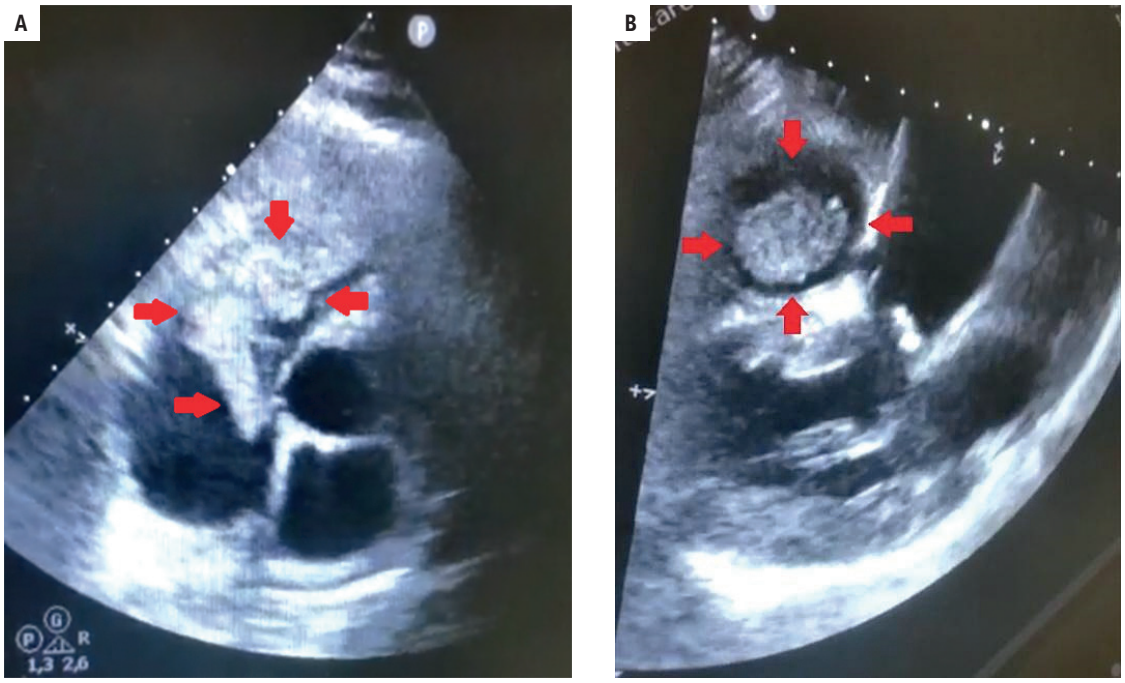

Figure 1 – *Echocardiography. Intracavitary mass (arrows) identified by transthoracic echocardiogram in four chambers view (A) and parasternal long axis view (B).*

core or a thrombotic component (figures 2 A-E). Because of the severe thrombocytopenia, anticoagulation therapy was not initiated.

Aiming to confirm the mass etiology and unblock the blood flow, a surgical resection was scheduled. During the surgery, signs of extensive myocardial involvement were identified. The right ventricle wall was invaded and occupied by a large mass of soft tissue. Through the right atrium, a large amount of friable tumor material was removed (figures 3 A-C). Due to the impossibility of complete removal of the mass through the right atrium, right ventriculotomy was performed attempting to completely resect the lesion, with partial success due to wall invasion. A transesophageal echocardiogram was performed during the surgery and showed an improvement in cardiac dynamics after partial tumor removal.

The surgical sample consisted of many irregular, soft and extensive necrotic fragments. Histologically, the lesion was represented by an adenocarcinoma-type malignant neoplasm of mucosecretory/mucinous aspect,[9] with extensive areas of necrosis and autolysis, both inside and on the surface of the fragments (Figure 4 A-B). It was not possible to assess myocardial infiltration, since cardiomyocytes were not identified in the various fragments examined. The immunohistochemical study showed: negative CK7, CD20 and KRAS; CDX2 and β-catenin positive; high rate of cell proliferation (Ki-67 => 50%). The final diagnosis was cardiac metastasis from colonic adenocarcinoma. The microscopic aspect of the lesion was similar to the primary colonic tumor resected in 2005 and to the liver metastasis removed in 2007.

The patient was discharged a few weeks after the surgery, with no more cardiovascular symptoms, normal platelet levels and renal recovery. One cycle of palliative chemotherapy was prescribed, but treatment was interrupted because of dropping in platelet counts. One month later he was readmitted to the hospital with signs of decompensated heart failure. Right pleural effusion was identified, and echocardiogram showed a mass occupying a large part of the right ventricle. Therefore, the patient, his family and medical team decided for palliative support. He died a few weeks later.

The supplementary material shows the timeline of events since the admission until the patient's death.

Discussion

Malignant cardiac tumors are rare, particularly the primary ones. Cardiac metastases originate mainly from lung, breast and esophageal carcinomas, melanomas, lymphomas and leukemias.[3] Due to their low incidence, cardiac tumors are not commonly investigated in oncology practice, although they have been gaining greater importance due to improvement in cancer diagnosis and longer patients survival.[10]

Clinically, cardiac tumors often evolve silently for years, being underdiagnosed,[11] or can cause constitutional symptoms, obstruction of intracardiac blood flow, valve dysfunction,

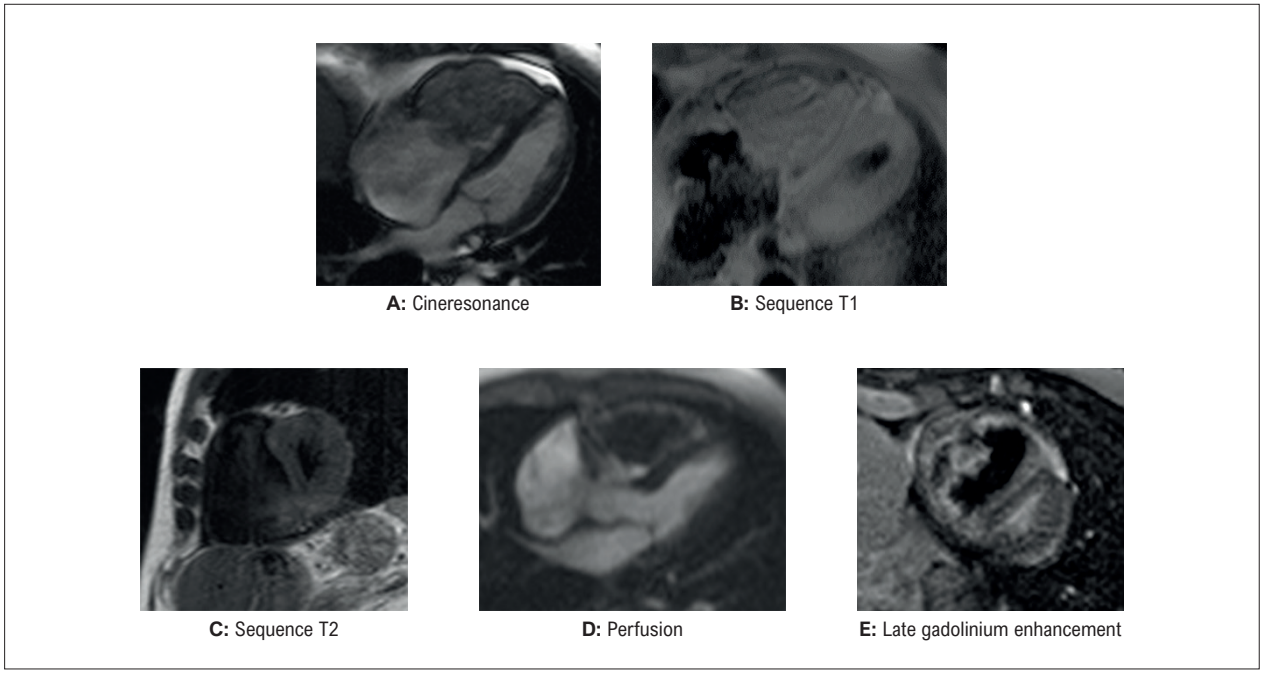

Figure 2 – *Cardiac magnetic resonance. Intracavitary mass in different sequences in CMR.*

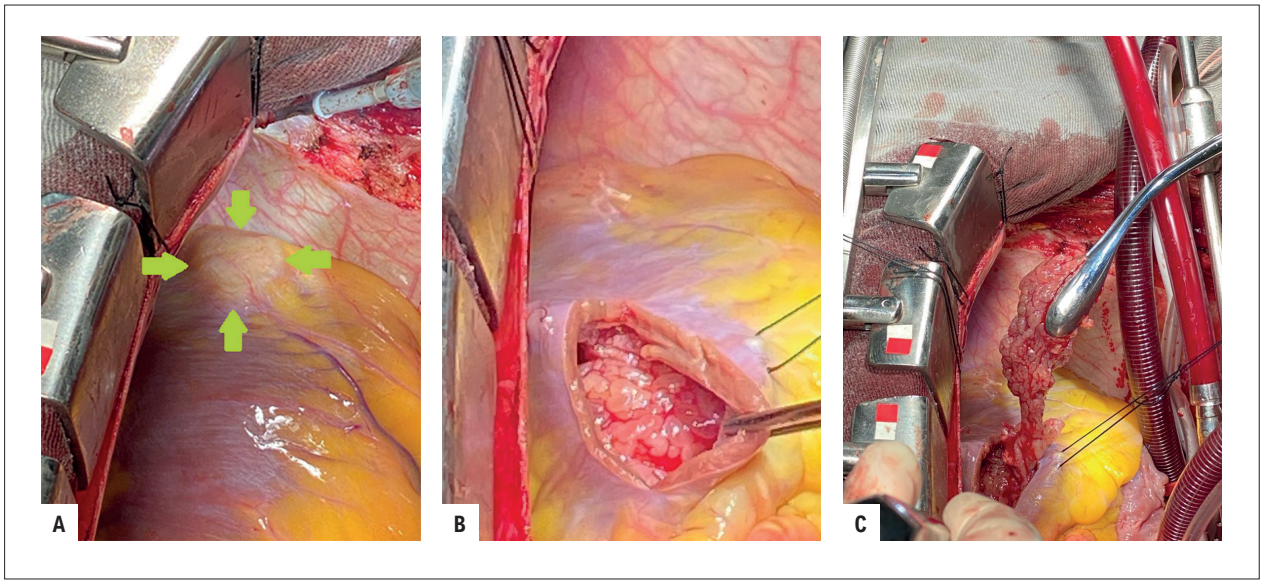

Figure 3 – *Per operative view. A. Tumoral invasion in the right ventricle wall. B. A soft tissue and polypoid mass is seen in right ventricle cavity. C. Tumor being removed from the ventricle.*

arrhythmias, pericardial effusion and embolization.[12] Secondary cardiac implants are frequently associated with the terminal phase of a widespread malignancy or, less commonly, can be the initial manifestation of a newly diagnosed or newly recurrent malignancy.[13] When neoplastic infiltration forms a large intracardiac mass, the patients present with hemodynamic instability and have a worse prognosis before, during or after surgical intervention.[5] Infiltration of the cardiac wall by malignant cells can result in a catastrophic and symptomatic event for the patient, impairing cardiac dynamics.[14]

Although cardiac metastases can be suspected in life, they are rarely diagnosed before death.[15] In autopsy studies, endocardial metastases from colorectal tumors are detected in 1.4 to 7.2% of the patients with this malignancy.[16] In the review by Oneglia et al.[10] heart metastases were found in 3.2% of autopsied patients with known colorectal carcinoma.[10]

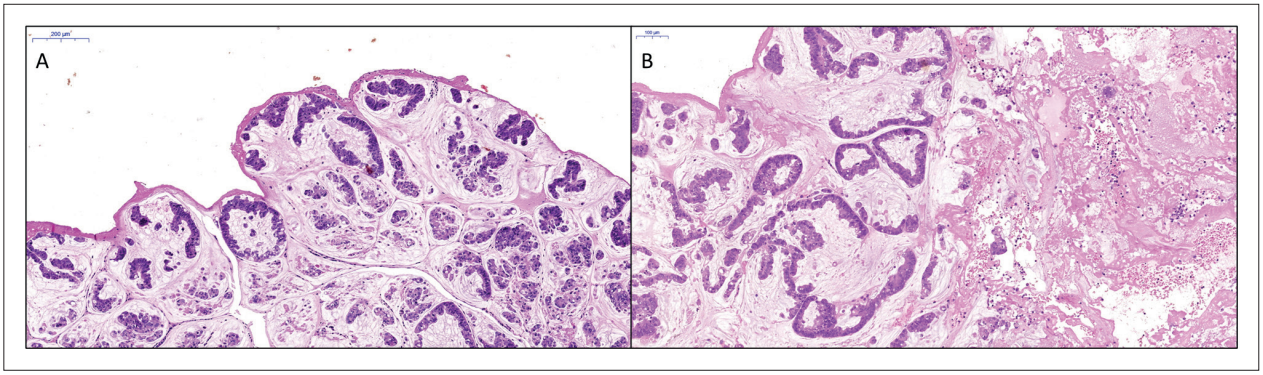

Figure 4 – *Microscopic aspects of the lesion. A. Several malignant glands associated with abundant mucous substance. On the surface, there is a thin fibrin layer. B. On the left side of the figure, there are malignant glands inside abundant mucous substance; on the right side, there is extensive necrotic material mixed with fibrin and blood cells.*

Preoperative differential diagnosis of cardiac masses is not always easy or possible, even with advanced propaedeutic facilities.[17] Echocardiography is usually the first tool used for the diagnosis of cardiac tumors.[1] CT scans and CMR are important to provide anatomic information and to visualize infiltration or extension of the tumor.[15] In many patients, the precise diagnosis is only confirmed after anatomopathological examination of the surgically removed sample. When the lesion is in the atrium and/or the right ventricle, endomyocardial biopsy may be attempted. However, it does not always allow definitive diagnosis, especially due to the difficulty in obtaining representative portions of the lesion. In the present case, the preoperative diagnosis by endomyocardial biopsy could be possible only if a fragment like that showed in the Figure 4A could be obtained. The extensive tumor necrosis, especially in the superficial portions of the fragments, make the sampling of cells and neoplastic glands by endomyocardial biopsy less attainable.

The incidence of colorectal and other malignancies has been increasing in recent years.[9] With better cancer treatments and longer patient's survival, cardiac metastases are expected to increase. In this setting, medical staff will be faced with the decision as to perform or not a surgery, for diagnosis or for palliation and improvement of the patient's hemodynamics.

Screening for cardiac metastases is not currently recommended for patients with malignancies. However, oncologic patients presenting with cardiopulmonary symptoms should be evaluated for secondary cardiac implants.[15] Possible benefits from cardiac surgery may be counterbalanced by perioperative morbimortality[18] and patients, cardiologists, cardiovascular surgeons, and oncologists should be involved in making the final decision about the best treatment in each specific scenario.[15]

Despite of all the strategies, the median overall survival for patients with unresectable metastatic colorectal cancer who receive best supportive care alone is approximately five to six months. In general, patients with cardiac metastases have a 5-year survival rate of only 7%.[19] With the improvement of early detection, development of modern diagnostic tools, advances in chemotherapeutic regimens and radiation techniques and refinement of preoperative care, cancer patient survival is expected to increase.[15]

Author Contributions

Conception and design of the research: Faé IG, Ruiz GZL, Almeida Junior RS, Conceição PA, Passaglia LG, Oliveira CRA; Acquisition of data: Faé IG, Irffi GP, Almeida Junior RS, Conceição PA, Oliveira CRA; Analysis and interpretation of the data: Faé IG, Ruiz GZL, Falchetto EB, Passaglia LG, Brasileiro Filho G, Gelape CL, Oliveira CRA; Writing of the manuscript: Faé IG, Ruiz GZL, Irffi GP, Conceição PA, Passaglia LG; Critical revision of the manuscript for important intellectual content: Faé IG, Falchetto EB, Passaglia LG, Brasileiro Filho G, Gelape CL, Oliveira CRA.

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

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Study Association

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

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Hospital das Clínicas da Universidade Federal de Minas Gerais under the protocol number CLM-78-2021. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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*Supplemental Materials

For additional information, please click here.

Left Ventricular Thrombosis and Pulmonary Thromboembolism in an Asymptomatic Covid-19 Patient

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COVID-19 (coronavirus disease) is the clinical syndrome associated with Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection. Although respiratory failure is the most apparent feature of the disease, venous and arterial thrombosis are well-recognized complications. COVID-19 patients are known to activate multiple systemic coagulation and inflammatory responses that are vital for host defense but can lead to deleterious situations, mainly in those admitted to the intensive care units. We report here a case of multiple embolic events with left ventricular thrombosis and co-incidence of pulmonary thromboembolism in a patient with asymptomatic COVID-19 infection and no pre-existing cardiovascular disease.

Research Letter

A 48-year-old-man presented to the emergency room with abdominal pain and vomiting of 12-hour duration. He had a history of porto-splenic venous thrombosis ten years before admission that was treated with 6 months of oral anticoagulation and felt to be due to moderate protein C deficiency, which was not confirmed in subsequent laboratory tests. Vital signs were normal, he was afebrile and no remarkable findings were found on physical examination except for pain on palpation in the left flank. The reverse transcriptase polymerase chain reaction (RT-PCR) test for COVID-19 was negative. Blood tests showed significant elevation of acute phase reactants (c-reactive protein: 138.3 mg/L, fibrinogen > 500mg/dL and leukocites 12.99 10^3/μL). Coagulation parameters where in normal range: phrotrombin time (PT) 12.1 seconds, partial thromboplastin time (PTT) 36.3 seconds, prothrombin activity (PA) 86%, international normalized ratio (INR) 1.08 and platelets 326.000/μL.

Keywords

COVID-19/complications; SARS-COV-2; Pulmonary Embolism; Ventricular Dysfunction Left; Infarction, Myocardial; Severe Acute Respiratory Syndrome/complications; Diagnostic, Imaging/methods.

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The abdominal ultrasound-scan did not show releant findings, so a computed tomography (CT) scan study was completed. CT abdominal scan found multiple infarcts in the right kidney (Figure 1A) and isolated in spleen (Figure 1B), furthermore, a filling defect in the left ventricle was observed (Figure 2A). Transthoracic echocardiogram confirmed the presence of a pedunculated hyperechogenic and homogeneous mobile mass (3.1x2cm) with regular borders (Figures 2A, 2B, 2C), anchored to the middle third of the septum of left ventricle (LV). Anatomy of LV was normal, with normal dimensions and normal ejection fraction without wall motion abnormalities.

CT chest scan also revealed pulmonary thromboembolism, with a filling defect originating from the right main pulmonary artery (Figure 1C), associated with pulmonary infarction in the right upper lobe; and brain CT found a subacute ischemic lesion in the right parieto-occipital junction (Figure 1D). With the diagnosis of pulmonary thromboembolism and probably left ventricular thrombus with multiple embolic lesions, the patient underwent cardiac surgery to remove the mass. Although electrocardiogram was normal and cardiac troponins were in normal range, an

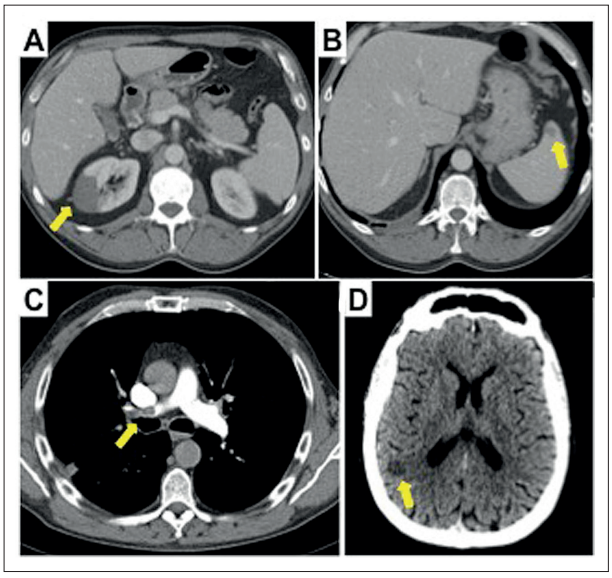

Figure 1 – *A) Abdominal computed tomography (CT) scan. Infarct in the right kidney (arrow). B) Abdominal CT Scan. Infart in the spleen). C) Cerebral CT Scan. Ischemic lesion in the right parieto-occipital junction (arrow). D) Chest CT Scan. Filling defect originating from the right main pulmonary artery (arrow).*

invasive coronary angiogram was performed preoperatively, and revealed no atherosclerotic coronary artery disease or coronary embolism. Intraoperative transesophageal echocardiogram showed dilation of the pulmonary trunk, with the presence of an image compatible with thrombus in the right pulmonary branch (Figure 2F), in addition, interatrial communication and patent foramen ovale were ruled out after negative echo bubble study. 2 days after admission, a new RT-PCR test for COVID-19 was done, with a positive result (Alpha variant [B.1.1.7], commonly known as the British variant). A few days later the presence of COVID-19 IgG was confirmed. The patient had no infectious symptoms at any time. The majority of the mass could be removed with surgery (Figure 2G), and pathological anatomy confirmed that it was thrombus (Figure 2H). The subsequent evolution was favorable under anticoagulation with enoxaparin. New laboratory tests to assess the presence of a coagulopathy disorder showed mild protein C deficiency.

The presence of cardiac left ventricular thrombus is a relatively common condition in patients with myocardial infarction (MI) (15-25%) and in the setting of dilated cardiomyopathy (up to 36%) when detected with optimal imaging modalities.[1,2] However, there are only anecdotal reports in structurally normal LV even in the presence of a thrombophilia.[3-5]

Coagulopathy, in the form of venous and arterial thrombosis, is one of the most severe sequelae of the SARS-CoV-2 infection, and has been associated with poor outcomes. Reports of a high incidence of thrombosis despite prophylactic and therapeutic dose anticoagulation raise question about a pathophysiology unique to COVID-19. Proposed hypotheses include a severely heightened inflammatory response that leads to thrombo-inflammation, through mechanisms such as cytokine storm, complement activation, and endothelitis.[6-9] It has also been suggested that the virus itself can possibly activate the coagulation cascade.[10]

Though thrombosis is frequently seen in the setting of critically ill COVID 19 patients, major thromboembolic events are rare in patients with asymptomatic or mild infections.[11] However, to the best of our knowledge, there are no previous reports of thrombosis in multiple locations, including LV thrombi, in a completely asymptomatic patient from the infectious point of view without pre-existing cardiovascular disease. We believe that in our patient, the presence of a previous coagulopathy, has played a relevant role in this rare form of presentation of a patient with COVID-19.

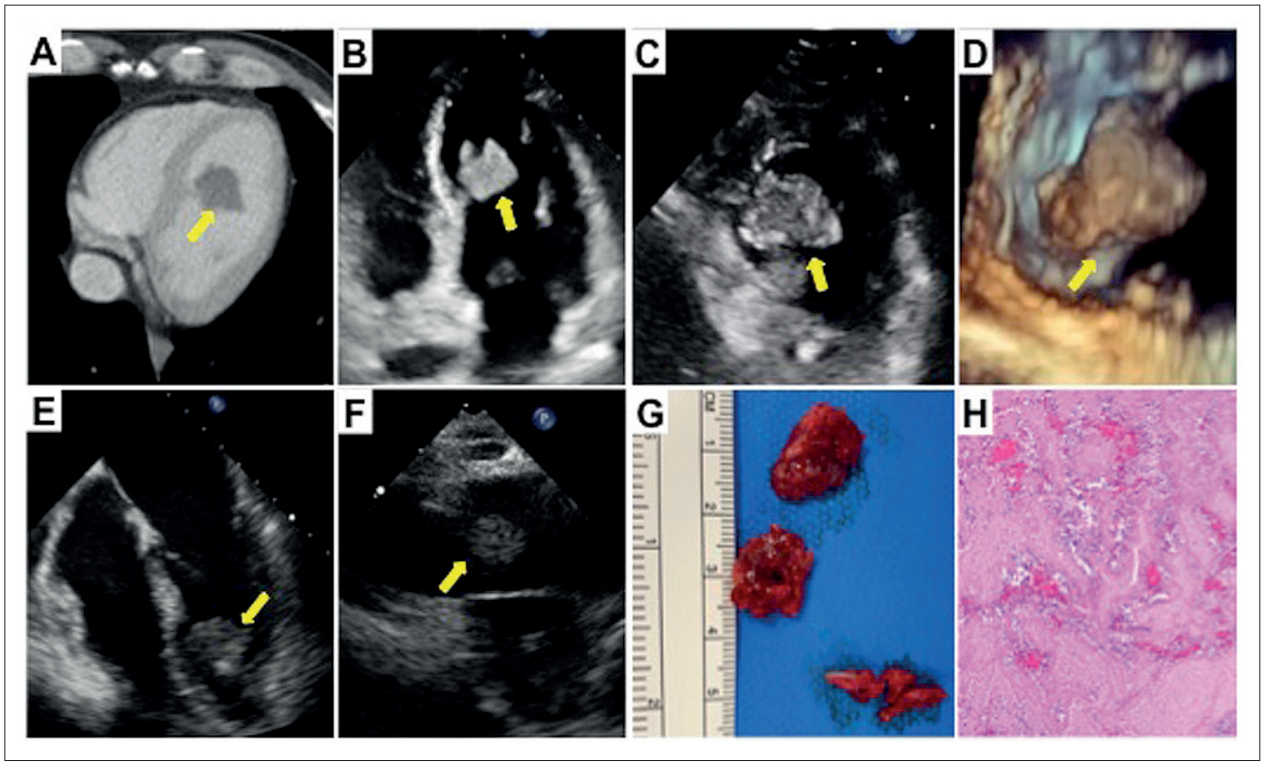

Figure 2 – *A) Chest computed tomography (CT) Scan. Filling defect in the left ventricle (arrow). B) 2D-Transthoracic echocardiogram. 4-axis-view. Pedunculated hyperechogenic mass (arrow). C) 2D-Transthoracic echocardiogram. The mass (arrow) in short-axis-view. D) 3D-Transthoracic echocardiogram. Mass anchored to the septum of left ventricle (arrow). E) 2D-Transesophageal echocardiogram. 4-chamber-view. Mass anchored to the septum of left ventricle (arrow). F) Thrombus in the right pulmonary branch (arrow). G) Surgical piece removed from the left ventricle. H) Pathological anatomy of the thrombus.*

Author Contributions

Conception and design of the research: Lorenzo N; Acquisition of data: Lorenzo N, Hernandez V, Montes A, Rivero F, Reyes G, Aguilar R; Analysis and interpretation of the data: Lorenzo N, Hernandez V, Aguilar R; Writing of the manuscript: Lorenzo N, Aguilar R; Critical revision of the manuscript for important intellectual content: Lorenzo N, Hernandez V, Aguilar R.

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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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Caseous Calcification of the Mitral Annulus: A Post-Heart Transplant Diagnosis

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Introduction

Caseous calcified mitral annulus is a non-neoplastic cardiac lesion considered to be a variant of mitral annular calcification that should be suspected when heart masses are detected by echocardiogram, chest x-ray or other radiologic studies.[1-3] The majority of the patients is asymptomatic, but signs and symptoms of mitral regurgitation, systemic embolization and atrioventricular blocks have been described.[3] The diagnosis is confirmed by anatomopathologic examination. The prognosis is good. Here, we present a caseous calcification of the mitral annulus case diagnosed after the pathologic analysis of explanted heart.

Case report

A 35-year-old man with diagnosis of heart failure (stage III by New York Heart Association Classification) secondary to rheumatic heart disease was admitted at a tertiary public University Hospital for heart transplantation. He had been having recurrent hospitalizations due to chronic heart failure. Physical examination showed edema of the lower limbs, lateral dislocation of apex heartbeat, irregular heart rhythm, presence of the third heart sound, and early systolic and mid-diastolic murmur at the apex of the heart. The chest x-ray revealed a hyperdense lesion localized at the heart next to the mitral valve (Figure 1 and 2). Transthoracic echocardiogram done 3 years before heart transplantation disclosed both right and left atria enlarged, mitral byoprothesis unremarkable and aortic valve regurgitation. Transthoracic echocardiogram performed 2 months before transplantation showed enlargement of both atria and ventricles, moderate bioprosthetic mitral valve insufficiency and moderate aortic valve insufficiency and stenosis (data not shown). In both echocardiograms no calcified lesion was seen around mitral valve annulus.

At the age of 15, the patient went through a bioprosthetic mitral valve replacement to treat the rheumatic mitral valve disease, requiring two subsequent reoperations (age 21 and 23). For the last three years, despite optimal medical therapy, his heart function had continually deteriorated. There were no other comorbidities in his past medical history.

Laboratory findings showed a reduced kidney function (serum creatinine of 3,0 mg/dL and estimated glomerular filtration rate of 25.7 mL/min/1.73m^2). Electrocardiogram was remarkable for atrial fibrillation.

The main diagnostic hypothesis was advanced heart failure caused by bioprosthetic mitral valve dysfunction. For a heart mass visualized on the x-ray, some possibilities were considered: mitral annular calcification, calcified myxoma, other cardiac neoplasms or pseudoneoplasms, cardiac abscess, tuberculosis, calcified amorphous tumor or calcified valvar vegetations. The precise diagnosis is obviously essential for the appropriate treatment.

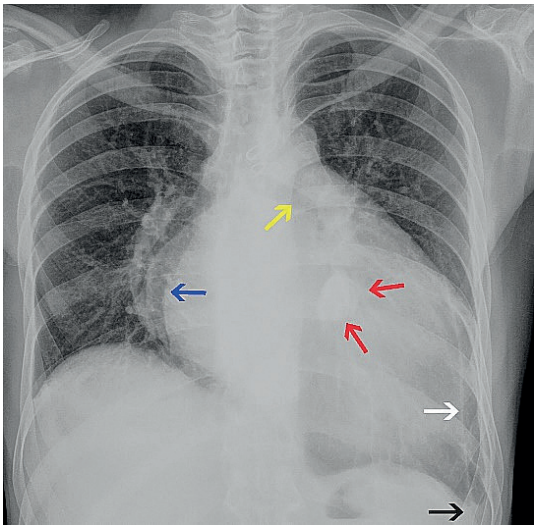

Figure 1 – *Chest radiography – posteroanterior view. Enlarged heart. Next to the mitral valve, there is an ovulated hyperdense lesion (red arrows) measuring about 3,5cm x 2,0cm. The double density sign (blue arrow) and elevation of the left bronchus (yellow arrow) indicate left atrial enlargement. The left costodiaphragmatic recess is obliterated (black arrow), and a calcified line is noted at the left hemithorax seemingly along the pleura (white arrow).*

Keywords

Mitral Valve Insufficiency; Calcinosis; Heart Neoplasms/surgery; Heart Transplantation; Cardiomyopathies; Diagnostic, Imaging/methods

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Management and diagnosis

Given the progressive cardiac failure, the patient went through heart transplantation. During the patient's first postoperative days, severe hemodynamic instability and acute heart failure suggested primary graft rejection. Despite pharmacological intervention for primary graft dysfunction, the patient died after three days of heart transplantation.

The explanted heart weighed 515 grams and measured 10.5 x 9.5 x 8.0 cm. All for chambers were significantly dilated. A bioprosthetic valve was present on the left atrioventricular orifice; the other three valves were native, including a mixed stenotic and regurgitant aortic valve showing fusion and shortening of the leaflets, highly suggestive of rheumatic heart disease. On the anterior portion of the myocardium, at the left atrioventricular junction, there was a gray-yellow, oval mass of 3.3 x 2.3 cm, with well-demarcated and regular borders and thin peripheric calcification. After cutting, a small amount of pasty content (similar to caseum) leaked (Figure 3). Microscopically, the lesion was involved by a fibrotic tissue with calcium deposits, mild mononuclear cell infiltration, and peripheral multinucleated giant cells. In the center of the lesion, there was abundant amorphous and basophilic material (Figure 4). All these findings are consistent with caseous calcification of the mitral annulus (CCMA). In the left ventricle myocardium, there were a few and small macrophage and lymphocyte aggregates suggestive of Aschoff nodules.

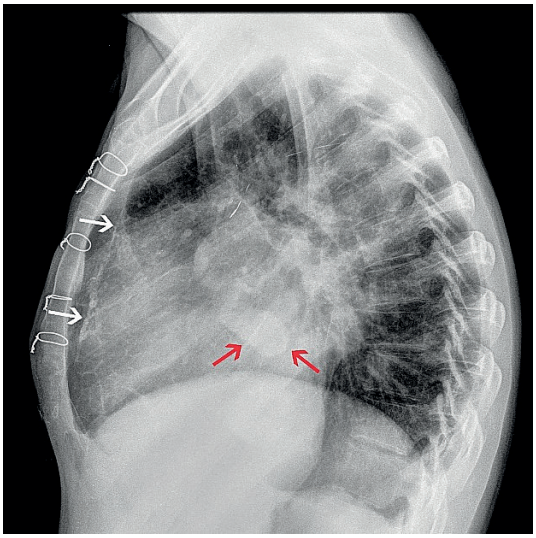

Figure 2 – *Chest radiography – lateral view. The hyperdense heart lesion (red arrows) and the calcified pleural line (white arrows) are visible.*

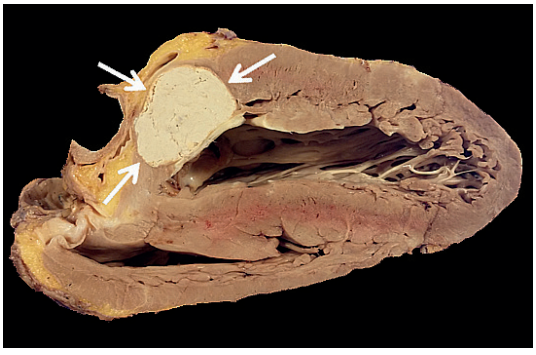

Figure 3 – *Macroscopic view of the lesion. Explanted heart with a partially regular border lesion of 3,3 x 2,3 cm (white arrows). The lesion content has a pasty and chalky aspect and was minimally detached during the cutting of the specimen heart. It is involved by a fibrotic capsule without continuity with the ventricle cavity.*

Discussion

Calcification of mitral annulus (CMA) is a chronic degenerative lesion that affects mainly older people, especially women and patients with end-stage disease or abnormalities in calcium metabolism.[1,2] Usually asymptomatic, CMA is commonly recognized by echocardiography. Caseous calcification of mitral annulus (CCMA) is a rarely CMA variant represented by a round intramyocardial mass containing abundant pasty or putty-like material composed by fatty acids, cholesterol and calcium;[1,4,5] rarely, the lesion appears to arise from de mitral valve leaflet.[5] Also generally asymptomatic and more prevalent in the elderly, CCMA can be suspected by echocardiography, which shows a mass with distinct borders and a central echolucent area suggestive of liquefaction in the annular mitral region.[4,5] In the current case, CCMA was not clinically suspected.

In echocardiography examinations, CCMA is seen in 0.04% to 0.07% of the general population and in 0.06% of CMA patients.[5-7] Its ethiopatogenesis is largely unknown. We consider the concomitant rheumatic disease in our patient as merely coincidental.

In most patients, the lesion is clinically asymptomatic. When present, the most common signs and symptoms relate to mitral insufficiency.[4] In the current case, it is difficult to attribute the clinical manifestations to the CCMA, since many of them could be clearly explained by heart failure due to rheumatic disease and atrial fibrillation. In the asymptomatic patients, an incidental echocardiogram may arise the suspicion. In our patient, two echocardiograms were not able to detect the lesion. In some patients, the diagnosis is made at autopsy[4] or in an explanted heart, as occurred in this case.

Caseous calcification of mitral annulus' diagnosis is established by anatomopathological examination. Macroscopically, CCMA is a round lesion with distinct borders and a central area containing caseous material, ranging from 1.5 to 4.0 cm.[8] In general, it is found around mitral annulus. Histologically, the lesion contains

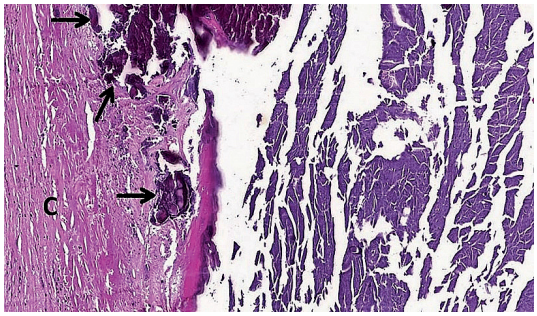

Figure 4 – *Microscopic view of the lesion – hematoxylin and eosin, magnification of 200x. On the left, there is the fibrotic tissue of the capsule (C) with calcium deposits (black arrows). A wide amorphous and basophilic material is seen on the right half.*

a fibrous layer of connective tissue with calcium deposits, inflammatory mononuclear cells and multinucleated giant cells surrounding an abundant amorphous material.

The most important differential diagnoses include cardiac myxoma, which is usually mobile, pedunculated and located along interatrial septum, abscess and pseudoaneurysms, whose content, although pasty, lacks calcium deposits, and cardiac calcified amorphous tumor, a lesion composed of dense collagenous fibrous tissue with calcium nodules, without pasty constituent.[9-13]

The therapeutic approach, in general conservative, is guided by the clinical repercussions. In patients with mitral regurgitation, cardiac surgery is indicated.[5] Besides being a curative intervention, surgery is the method to obtain sample for morphological diagnosis. Sometimes, the lesion regress spontaneously.[4] The prognosis, usually good, depends on its size, location and growth pattern.

Author Contributions

Conception and design of the research: Chaves BJ, Brasileiro Filho G; Acquisition of data: Chaves BJ, Duarte MB, Azevedo PHR, Brasileiro Filho G; Analysis and interpretation of the data: Chaves BJ, Duarte MB, Passaglia LG, Gelape C, Brasileiro Filho G; Writing of the manuscript: Chaves BJ, Duarte MB, Brasileiro Filho G; Critical revision of the manuscript for important intellectual content: Chaves BJ, Duarte MB, Passaglia LG, Gelape C, Azevedo PHR, Brasileiro Filho G.

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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Bulky Mitral Annulus Caseous Calcification in an Atypical Location

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Hospital Cuf Viseu,[2] *Viseu – Portugal*

Abstract

Mitral annular calcification (MAC) is a commonly observed chronic and degenerative fibrotic process of the base of the mitral valve, usually deemed as an incidental finding. Although initially, MAC was thought to be a consequence of an age-related degenerative process, recent findings suggest other independent contributive mechanisms, such as atherosclerosis and abnormal calcium-phosphorus metabolism.

Caseous calcification of the mitral annulus (cMAC) is a rarely described variant of MAC, characterized by an ovoid, focal mass with internal caseous fluid-like calcifications and debris.

Differentiating a cMAC from other cardiac masses attached to the mitral annulus may be challenging. A single imaging modality, such as transthoracic echocardiography, may not be sufficient for a clear diagnosis. Therefore, a multimodal imaging approach is necessary, including cardiac tomography computerized imaging and cardiac magnetic resonance (CMR).

MAC and cMAC typically affect the posterior mitral annulus, with very few cases in the literature describing the involvement of the anterior annulus. We present a rare case of an anterior mitral annulus caseous calcification found in a CMR performed to evaluate a left atrial mass identified on a transthoracic echocardiogram.

Clinical case

An 84-year-old woman with a known medical history of hypertension and dyslipidemia was referred to our unit to perform a cardiovascular magnetic resonance (CMR) for further evaluation of a left atrial mass depicted by transthoracic echocardiography, which was performed in the context of hospitalization by an ischemic stroke.

CMR revealed a very large mass on the left anterolateral auriculoventricular groove that was hypointense in all fast spin-echo sequences (Figure 1) and exhibited no perfusion or evidence of contrast uptake in early enhancement sequences (Figure 2). The mass was slightly darker than the myocardium in the cine sequences (steady-state free precession). Delayed enhancement sequences (Figure 3) showed a small, enhanced border surrounding an important non-enhanced core.

Based on the existing literature, although the atypical location, the mass characteristics on CMR could be compatible with caseous calcification of the mitral annulus (cMAC).[1-3] To confirm this hypothesis, the patient was then submitted to an additional cardiac computerized tomography (CT) scan (prospective acquisition without contrast, covering all heart), that showed a calcified mass with less attenuation in the central part (Figure 4), features typically found on caseous calcification of the anterior mitral annulus.

Discussion

Mitral annular calcification (MAC) is a commonly observed chronic and degenerative fibrotic process of the base of the mitral valve, usually deemed as an incidental finding.[4] MAC is more prevalent in the elderly, particularly in women.[5] The prevalence of MAC varies from 5% to 42%, depending on the imaging modality used.[6]

MAC is defined as the accumulation of calcium along the annulus. Although initially, MAC was thought to be a consequence of an age-related degenerative process, recent findings suggest other independent contributive mechanisms, such as atherosclerosis and abnormal calcium-phosphorus metabolism.[4,6] MAC may occur in younger patients with advanced renal disease or other metabolic disorders that result in abnormal calcium metabolism.[5] The contributing factors include age-related factors, cardiovascular risk factors, increased mitral valve stress (hypertension, aortic stenosis, and hypertrophic cardiomyopathy), abnormal calcium-phosphorus metabolism, congenital disorders (Marfan syndrome, Hurler syndrome) and female sex.[4]

The prognosis of MAC relates to the association with cardiovascular adverse events and mortality and the mitral valve dysfunction it can cause. MAC has been independently associated with all-cause and cardiovascular mortality, with an increased risk of coronary heart disease events and incident heart failure. Moreover, the association with stroke occurs in multiple cohorts, partially related to the risk of atrial fibrillation due to progressive valvular dysfunction. MAC is also associated with an increased prevalence of conduction system delays, including atrioventricular block, bundle branch block, and intraventricular conduction delay. MAC generally has little or no impact on left ventricular inflow hemodynamics or mitral valve function. Limited data suggest that MAC may

Keywords

Cardiac Imaging Techniques; Tomography, X-Ray Computed; Stroke.

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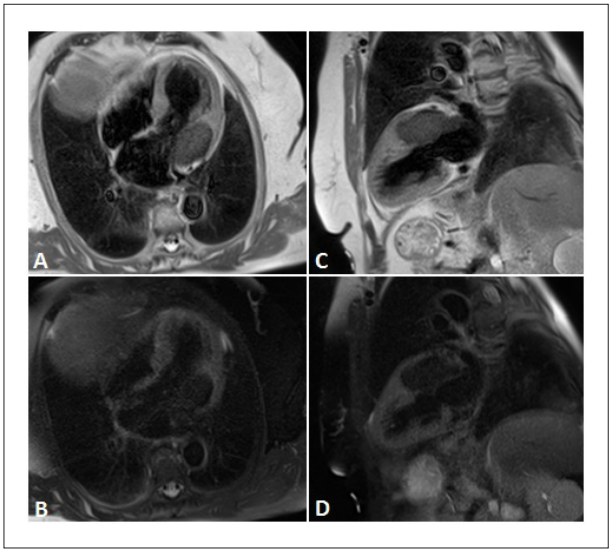

Figure 1 – *Fast spin echo (FSE) images in 2 and 4 chamber long axis views. (A, B): T1 FSE showing a hypointense mass relative to the myocardium (arrow). (C,D): T2 FSE with fat saturation pulse showing almost absence of signal in the mass location.*

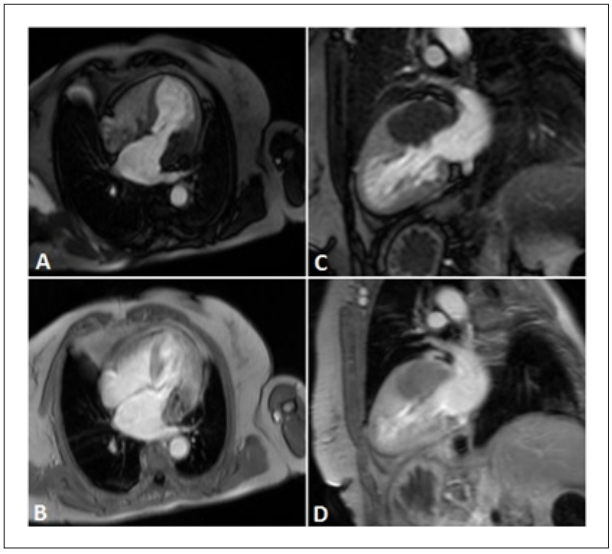

Figure 2 – *First pass perfusion (A, C) and early enhancement sequence (B, D) images in 2 chamber and 4 chamber long axis views, demonstrating absence of perfusion or contrast accumulation in the mass.*

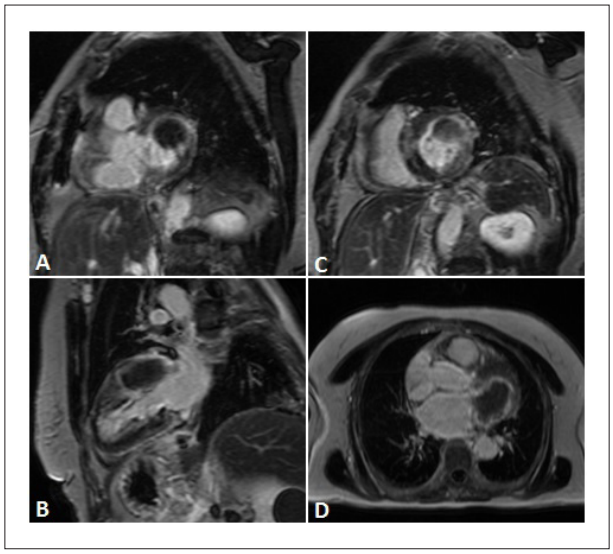

Figure 3 – *Delayed enhancement patterns in different planes: (A, C) - short axis; B - 2 chamber long axis; D - transaxial basal slice. All show only a small rim of enhancement at the mass periphery.*

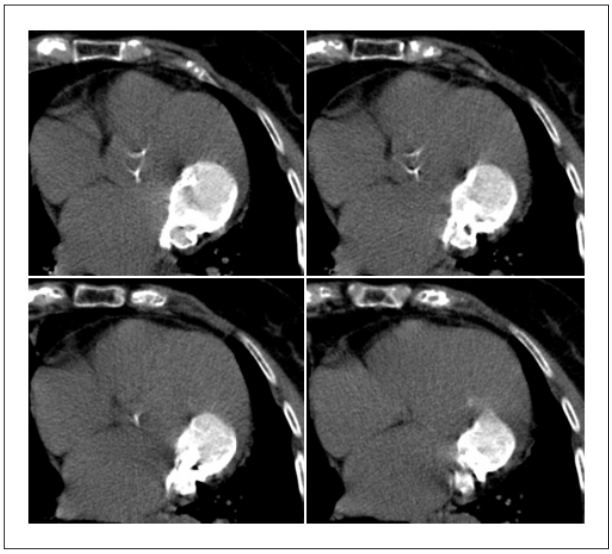

Figure 4 – *Cardiac CT images in contiguous axial planes, showing a large calcified mass with low central attenuation.*

exacerbate mitral regurgitation, and rarely association with mitral stenosis has been reported. Lastly, MAC may be an important factor in the development of mitral valve endocarditis by acting as a nidus for infection.[4,6]

cMAC is a rarely described variant of MAC, characterized by an ovoid, focal mass with internal caseous fluid-like calcifications and debris.[1] The terminology of cMAC is peculiar, as the term caseous usually refers to a type of necrosis often encountered in tuberculosis. The most common clinical presentation is the incidental finding of an intracardiac mass during cardiac imaging.[5] The echocardiographic prevalence is 0.6% in patients with MAC, and the overall prevalence is up to 0.07% in the general population.[7] cMAC tends to occur in older patients and is associated with hypertension.[8]

cMAC may mimic cardiac masses such as tumors (most commonly myxoma), abscesses and vegetations. Differentiating a cMAC from other cardiac masses attached

to the mitral annulus may be challenging due to its variable imaging characteristics depending on its stage of evolution. A single imaging modality, such as echocardiography, is often insufficient for a correct diagnosis. Therefore, the multimodal image approach is mandatory.[4,5]

Due to the elevated calcium content, MAC is generally hypointense on CMR. Nevertheless, the calcium salts and proteinaceous fluid in caseous MAC can generate a high signal on T1 weighted spin-echo sequences (Table I).[1,2]

MAC and cMAC commonly affect the posterior mitral annulus, with very few cases in the literature describing the involvement of the anterior annulus.[3,7] cMAC can lead to mitral valve disease (regurgitation or stenosis) or systemic embolization. In this clinical case, the condition that motivated the diagnostic approach was a stroke. The postulated mechanisms of embolization include embolization of small calcified parts, ulceration of the surface complicated by thrombus formation, and subsequent embolization or fistulization of the caseous necrosis in the lumen of the left atrium or left ventricle.[5,9] Most authors agree that surgical treatment is indicated in symptomatic patients with cCMA associated with mitral valvular dysfunction, embolic manifestations, or when it is impossible to rule out the possibility of a tumor.[9]

In conclusion, MAC is an incompletely understood disorder with clinical and prognostic implications. Although the presence of cMAC may pose a diagnostic dilemma, understanding this entity allows for establishing an accurate diagnosis.[1]

Author Contributions

Conception and design of the research: Correia JL, Correia M; Writing of the manuscript: Correia JL; Critical revision of the manuscript for important intellectual content: Correia M.

Potential Conflict of Interest

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

Sources of Funding

There were no external funding sources for this study.

Study Association

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

Ethics approval and consent to participate

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

Table 1 – Cardiac magnetic resonance appearances found in the reported cases of caseous calcification of the mitral annulus

Pre-contrast T1-weighted	Pre-contrast T2-weighted	Pre-contrast BSSFP	First pass perfusion	Delayed Enhancement
Dark	Black	Slightly darker than myocardium	Not perfused	Enhanced border surrounding a non-enhanced core

BSSFP: balanced steady state free precession. Adapted from from Monti et al.[2]

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Acute Myocarditis after mRNA COVID-19 Vaccine: A Correspondence

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Dr. DY Patil University,[2] *Pune – India*

Dear Editor,

We would like to share ideas on the publication "Acute Myocarditis Following mRNA COVID-19 Vaccine."[1] Gomes et al. examine the potential side effects of COVID-19 vaccination and the current state of acute myocarditis. COVID-19 immunization will probably cause heart abnormalities. We agree that this is a possibility. However, it should be noted that there is frequently inadequate information on the health/cardiac status of the troublesome cases before immunization. Although a post-vaccination analysis, which includes an EKG, can confirm the presence of myocarditis, it is impossible to establish a link between heart disease and the COVID-19 vaccine. There is still a potential that you will have medical issues simultaneously. Dengue fever, for example, can induce cardiac problems if it co-occurs.[2]

Keywords

Myocarditis; mRNA; COVID-19; Vaccine.

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Reply

Dear Editor,

We thank Mungmunpuntipantip and Wiwanitkit for their letter regarding our paper entitled "Acute Myocarditis Following mRNA COVID-19 Vaccine".[1]

We agree that although there is a temporal relationship between vaccination and the development of myocarditis, it is not possible to establish causality. However, after we reported this clinical case, case series were published regarding myocarditis following the BNT162b2b mRNA vaccine (Pfizer-BioNTech).[2,3]

In the report by Mevorach et al.,[2] with 136 cases of post-vaccination myocarditis, the observed risk was 2.35 times higher compared to unvaccinated persons, and one fatal case occurred. In another report with 54 cases by Witberg et al.,[3] the incidence of myocarditis up to 42 days following vaccination was 2.13 per 100.000 persons, all experiencing spontaneous recovery. In both series, the highest incidence was amongst young males.

It should be outlined that the occurrence of myocarditis following COVID-19 vaccination is rare and self-limited in the vast majority of cases.[4] Therefore, this presumed complication must not alter the vaccine's superior benefit/ risk relationship.

Daniel Gomes
Rita Santos
Pedro Freitas
Mariana Paiva
Jorge Ferreira
Marisa Trabulo

References

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Erratum

September 2020 Issue, vol. 115(3), pages 478-479

In the Short Editorial "Oxygen Consumption and Cardiorespiratory Fitness. The Difference between Chronological and Biological Age", with DOI: https://doi.org/10.36660/abc.20200582, published in the journal Arquivos Brasileiros de Cardiologia, 115(3): 478-479, in page 478, correct the DOI for: https://doi.org/10.36660/abc.20200648

July 2022 Issue, vol. 119 (1), pages 143-211

In the "Brazilian Society of Cardiology Guideline on Myocarditis – 2022", with DOI number: https://doi.org/10.36660/abc.20220412, published in the journal Arquivos Brasileiros de Cardiologia, 119(1):143-21, on pages 143 and 147, correct the name of the author Marcelo Imbroise Bittencourt to: Marcelo Imbroinise Bittencourt.

October 2022 Issue, vol. 119 (4), pages 638-680

In the " Brazilian Society of Cardiology Guidelines on the Analysis and Issuance of Electrocardiographic Reports – 2022", with DOI number: https://doi.org/10.36660/abc.20220623, published in the journal Arquivos Brasileiros de Cardiologia, 119(4):638-680, on page 655 (Item 6.1.4.2 Sokolow-Lyon Index), correct the phrase "This index should not be used in athletes" to: "Alone, this index should not be used in athletes."

On page 665 (Item 12.1.2 Abnormal ECG Findings (Group 2)), correct the phrase "QRS duration ≥ 160 ms" to: "QRS duration ≥ 140 ms;".

December 2022 Issue, vol. 119(6), pages 883-890

In the Original Article "Coronary Tortuosity as a New Phenotype for Ischemia without Coronary Artery Disease", with DOI: https://doi.org/10.36660/abc.20210787, published in the journal Arquivos Brasileiros de Cardiologia, 119(6): 883-890, in page 884, the correct figure is in the link: http://abccardiol.org/supplementary-material/2022/11906/2021_0787_fig-01 corrigida.jpg

DOI: https://doi.org/10.36660/abc.20220846

Erratum

June 2020 Issue, vol. 114 (6), pages 1027-1028

In Short Editorial "Catheter Ablation Without Use of X-rays to Treat Atrial Fibrillation and Atrial Arrhythmia" with DOI: https://doi.org/10.36660/abc.20200159, published in the Journal Arquivos Brasileiros de Cardiologia, 114(6):1027-1028, on page 1027, change DOI to: https://doi.org/10.36660/abc.20200451.

DOI: https://doi.org/10.36660/abc.20210747