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Cardiovascular SCIENCES

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Editorial

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ORIGINAL ARTICLE

Acute Myocardial Infarction with Non-Obstructive Coronary Arteries – Stratifying the Risk of a "new" Clinical Entity using an "Old" Tool

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Abstract

Background: Some of the patients admitted for acute myocardial infarction have non-obstructive coronary artery disease (MINOCA). Their prognosis is not always benign, making it necessary the development of tools for risk stratification of these patients.

Objectives: To describe the characteristics of a sample of patients admitted for suspected MINOCA and to evaluate the prognostic value of GRACE score in this population.

Methods: This was a retrospective, observational, single-center, cohort study involving 56 consecutive patients with MINOCA. During one-year follow-up, patients were assessed for mortality and major adverse cardiovascular events (MACE) – a composite of all-cause mortality and hospitalization due to acute myocardial infarction, heart failure, ischemic stroke, and acute limb ischemia. Statistical analysis was performed using a non-parametric approach, with the Mann-Whitney U test for quantitative variables and ROC curves for assessing the discriminatory power of the Grace score in predicting cardiovascular events. The level of significance was set at 5%.

Results: Of the 56 MINOCA patients included in the study (median age 67 years), 55.4% were female. During the one-year follow-up, mortality rate was 5.5% and 9.1% of patients had MACE. A higher GRACE score was associated with mortality (p = 0.019; AUC 0.907; 95%CI 0.812–1.000; cut off 138) and MACE (p =0.034; AUC 0.790; 95%CI 0.632–0.948; cutoff 114).

Conclusion: The definition of MINOCA includes various diagnoses and prognoses, and the GRACE score is useful for risk stratification of patients with this condition.

Keywords: Myocardial Infarction; Coronary Angiography; Coronary Artery Disease; Magnetic Resonance Spectroscopy/diagnosis; Prognosis.

Introduction

The association between acute myocardial infarction (AMI) and obstructive coronary artery disease, which is found in more than 90% of AMI patients, has been known for a long time.[1] However, nearly 10% of AMI patients do not have obstructive plaques, a finding that has been reproduced in several studies.[2-4] A clinical presentation with symptoms, electrocardiographic and laboratory changes typical of AMI, in the absence of obstructive coronary atherosclerosis, had long been considered as false positive.[5] However, more recent studies have reported that the prognosis of these patients may not be favorable, with rates of mortality and major adverse cardiovascular events (MACE) similar to those of patients with obstructive disease.[6]

For this reason, the term MINOCA (myocardial infarction with non-obstructive coronary arteries) has been introduced to describe AMI patients without significant coronary artery disease, and

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already included in the fourth Universal Definition of Myocardial Infarction.[7]

Several mechanisms have been proposed for the development of MINOCA, including the rupture of a nonobstructive plaque, coronary thromboembolism, other type 2 myocardial infarctions and vasospasm. Myocarditis and Takotsubo syndrome can cause nonischemic myocardial injury, with clinical features similar to those of acute coronary syndrome.[8]

Considering the myriad of possible diagnoses and the lack of scientific evidence,[9] the ideal therapeutic approach to these patients is still uncertain. It has been strongly recommended the investigation, identification, and treatment of the underlying disease. Likewise, the clinical course and prognosis of MINOCA patients is also heterogeneous; while most patients recover from the disease without any cardiac sequelae, a worrying minority of patients have an unfavorable course, with a one-year mortality rate of nearly 5%.[10] Therefore, improving the prognostic stratification of patients with MINOCA is highly needed. The Global Registry of Acute Coronary Events (GRACE) score has been widely used for stratification of in-hospital mortality at 1 and 3 years after acute coronary syndrome.[11-13]

Objectives

The present study aimed to describe characteristics of patients admitted for MINOCA to a single center during a four-year period (from 2014 to 2017). In addition, the study aimed to evaluate the GRACE score for prognostic stratification of patients with MINOCA during a one-year follow-up.

Methods

This was a retrospective, observational, single-center, cohort study that included consecutive patients admitted to a Cardiology unit with a diagnosis of MINOCA, from January 01, 2014 to December 01, 2017. The diagnosis of MINOCA was established by the researchers after review of patients' clinical records, according to the European Society of Cardiology (ESC) criteria:[8] to fulfill the fourth Universal Definition of Myocardial Infarction criteria for AMI;[7] absence of obstructive epicardial coronary artery disease (absence of stenosis greater than 50%); and absence of a clinically overt specific cause for the acute presentation. Patients with suspected myocarditis (pleuritic pain, increase in inflammatory markers, respiratory infection, or gastrointestinal infection in the last four weeks) or with a diagnosis of myocarditis confirmed by cardiac magnetic resonance (CMR) (according to the ESC Working Group criteria),[14] and patients with suspected Takotsubo syndrome (according to the InterTAK diagnostic criteria established in the International Expert Consensus Document on Takotsubo Syndrome)[15] were excluded. A flowchart of patients' selection process is depicted in Figure 1.

Demographic, clinical, laboratory, electrocardiographic, echocardiographic, and angiographic data, as well as information on treatment during hospitalization were collected from patients' medical records.

Dyslipidemia was defined as increased levels of low-density lipoprotein (LDL) cholesterol in patients taking lipid-lowering drug, or LDL levels at admission that would qualify patients for lifestyle changes and/or pharmacological therapy, according to the 2019 ESC guidelines for management of dyslipidemias.[16] All patients had access to echocardiography at hospital admission and prior to discharge, and we also investigated whether patients underwent CMR. CMR was considered of diagnostic value when it enabled the identification of MINOCA etiology or determined an ischemic cause of MINOCA (detection of subendocardial or transmural scarring), even when the mechanism of infarction could not be completely elucidated.

The final diagnosis of MINOCA was established by the investigators after revision of clinical data and results of complementary tests. Cardioembolic stroke was defined as the presence of a predisposing factor (atrial fibrillation without hypocoagulation, thrombophilia, heart valve disease), combined with an image suggestive of intracoronary thrombus that was not adherent to the plaque, or subendocardial or transmural delayed contrast enhancement. Diagnosis of spasm was defined based on documentation of previous spontaneous episodes of rest angina, associated with ST-segment changes that responded promptly to short-acting nitrates.[8] Plaque disruption and spontaneous coronary dissection were confirmed by intracoronary imaging (intravascular ultrasound or optical coherence tomography).[8] Cases where CMR revealed a contrast enhancement pattern compatible with subendocardial or transmural infarction were classified as of ischemic cause with uncertain mechanism. The final diagnosis of MINOCA was classified as unknown when patients did not meet the criteria described above.

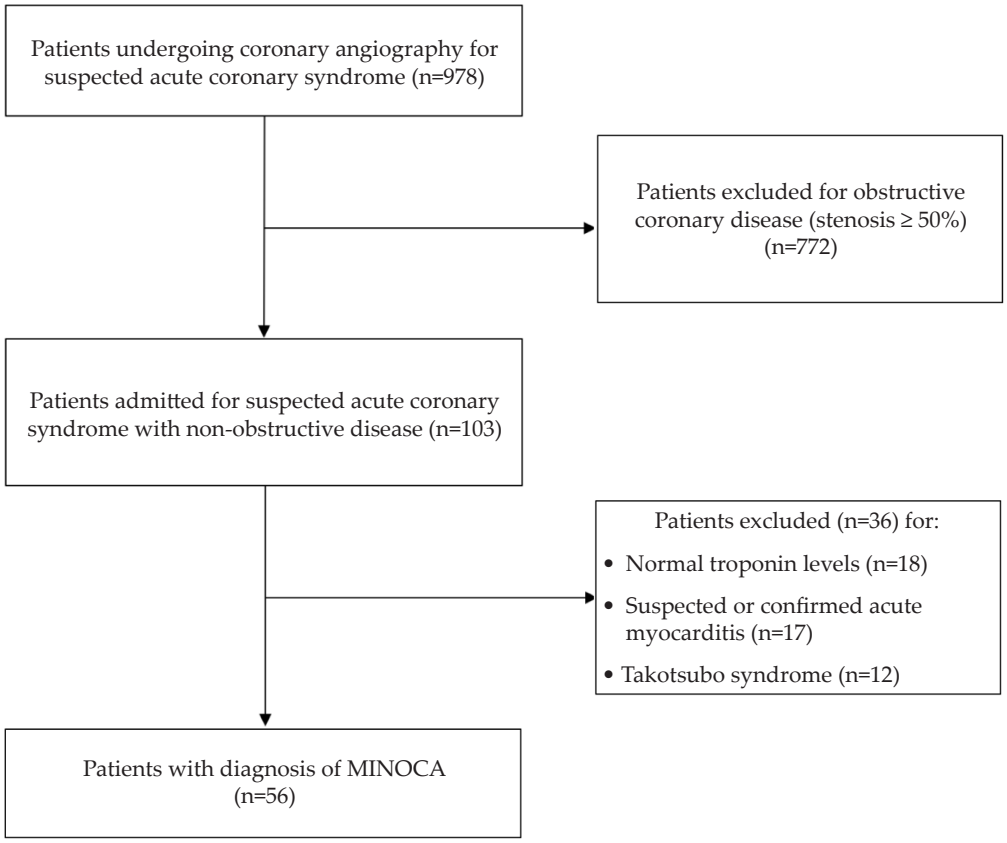

Figure 1 – Flowchart of patient selection process.

The one-year follow-up was conducted by means of review of medical records for the occurrence of the following outcomes – all-cause mortality and MACE (a composite of all-cause mortality and hospitalization due to cardiovascular disease, namely AMI, stroke, acute limb ischemia, or heart failure). The causes of readmission were determined according to medical records.

The GRACE 2.0 risk score was calculated at admission using a validated algorithm.[13]

Statistical analysis

Statistical analysis was performed using the IBM SPSS-statistics, version 25. The level of significance was set at 5%. The sample was described using descriptive statistics. Categorical variables were described as percentage. Normality of quantitative variables was verified by the Kolmogorov-Smirnov test with Lilliefors correction. These variables showed a non-Gausssian distribution and were described as median and interquartile range (IQR). Using a non-parametric analysis, the quantitative variables were analyzed using the Mann-Whitney test. The discriminatory power of the GRACE score for the prediction of cardiovascular events was assessed by ROC curve analysis. The maximum Youden index was used to determine the cutoff points for GRACE score that would best predict the occurrence of primary and secondary outcomes.

Results

Study sample and characteristics at admission

A total of 56 AMI patients that met the inclusion criteria were studied. This corresponded to 7% of admissions for AMI to our center during the study period. Clinical parameters evaluated at admission are described in Table 1. Median age of patients was 67 (IQR 60.5 – 76.3) years, and 55.4% were female. The

Table 1 – Clinical characteristics of patients admitted for acute myocardial infarction with non-obstructive coronary artery disease (MINOCA)

Total, n	**56**
Demographic data	
Median age, years (IQR)	67 (60.5 – 76.3)
Female sex, % (N)	55.4 (31)
Cardiovascular risk factors, % (n)	
Arterial hypertension	69.6 (39)
Type 2 diabetes mellitus	17.9 (10)
Dyslipidemia	71.4 (40)
Smoking habits (previous or current)	16.1 (9)
Obesity	26.8 (15)
Family history of early cardiovascular disease	10.7 (6)
Comorbidities, % (n)	
Atrial fibrillation/flutter	12.5 (7)
Previous stroke	1.8 (1)
Previous AMI	1.8 (1)
Symptoms and vital signs	
Chest pain, % (N)	94.6 (53)
Systolic blood pressure, mmHg (IQ)	144 (132-165)
Heart rate, bpm (IQ)	75 (61-85)
Electrocardiographic changes, % (n)	
Normal electrocardiogram	46.4 (26)
ST elevation	10.7 (6)
ST depression	8.9 (5)
T-wave inversion	30.4 (17)
Pathological q wave	8.9 (5)
Left bundle branch block	3.6 (2)
Laboratory data at admission	
Creatinine, mg/ml (IQ)	0.90 (0.78 – 1.06)
Cholesterol LDL, mg/dl (IQ)	111 (97 – 136)
GRACE score[11]	
Median (IQ)	113.5 (93 – 136)

IQR: Interquartile range; GRACE: Global Registry of Acute Coronary Events

most prevalent risk factors were arterial hypertension (69.6%) and dyslipidemia (71.4%). Only 1.8% of patients had previous AMI. Initial electrocardiogram was normal in 46.4% of patients and 10.7% had ST-segment elevation.

Clinical course during hospitalization

Patients' clinical data during hospitalization, including complementary diagnostic tests and therapy prescribed at discharge are described in Table 2.

During hospitalization, 5.4% of patients had heart failure; 30.9% of patients had abnormal echocardiographic findings of segmental contractility, and 8.2% had reduced ejection fraction (<50%). At discharge, most patients were prescribed angiotensin converting enzyme inhibitors (ACE inhibitors) or angiotensin receptor blockers (ARBs) (72.7%), combined with a betablocker (58.2%), statins (83.6%) or acetylsalicylic acid (61.8%), while 27.3% of patients received double antiplatelet therapy.

Cardiac magnetic resonance and definite diagnosis of MINOCA

Results of CMR are described in Table 2. The causes of MINOCA and values of GRACE score of the patients are described in Table 3. Only 12 patients (21.4%) underwent CMR, which added a diagnostic value in 50% of these patients. In most cases, CMR was performed in outpatient regimen, with a median waiting time of 3.3 months since MINOCA (IQR 1.5 – 10.7).

The cause of MINOCA was determined in 17.9% of the 56 patients. The most common etiology was ischemic disease with unknown etiology (10.7%), followed by vasospasm (5.4%). One case of cardioembolic stroke was detected. No patient underwent intravascular ultrasound or optical coherence tomography, and hence the presence of plaque disruption or spontaneous coronary dissection could not be confirmed.

Events

One patient was lost to follow-up. Among the other 55 patients, the one-year mortality rate was 5.5% and 9.1% developed MACE. Rehospitalization for cardiovascular event occurred in 7.3% of patients. Most events were seen in patients without a definite diagnosis of MINOCA.

Table 2 – Clinical course during hospitalization (including complementary diagnostic tests and drugs prescribed at discharge) of patients admitted for acute myocardial infarction with non-obstructive coronary artery disease (MINOCA)

Clinical course during hospitalization	
Length of hospital stay (median days, IQR)	4 (3-5)
Development of heart failure, % (N)	5.4 (3)
Laboratory data	
Highest troponin I level, ng/mL (IQ)	5.02 (1.55 – 11.09)
Echocardiogram, % (n)	
Changes in segmental contractility	30.9 (17)
Ejection fraction < 40%	4.1 (2)
Ejection fraction 40-50%	4.1 (2)
Ejection fraction >50%	91.8 (45)
Results of coronary angiography, % (n)	
Coronary stenosis	58.9 (33)
Stenosis <50%	41.1 (23)
Myocardial bridging	7.1 (4)
Intracoronary thrombus	3.6 (2)
Slow coronary flow (TIMI-2)	8.9 (5)
Coronary ectasia	3.6 (2)
Results of cardiac magnetic resonance, % (n=12)	
No pathological changes	41.7 (5)
Late gadolinium enhancement pattern suggestive of infarction	50.0 (6)
Myocardial edema	8.3 (1)
Drugs prescribed at discharge, % (n)	
ACE inhibitor/ARBs	72.7 (40)
Spironolactone	1.8 (1)
Betablocker	58.2 (32)
AAS	61.8 (34)
Dual antiplatelet therapy	27.3 (15)
Statin	83.6 (46)

IQR: Interquartile range; ACEI: angiotensin-converting-enzyme inhibitor; ASA: acetylsalicylic acid; ARB: angiotensin receptor blockers

Table 3 – Causes of acute myocardial infarction with non-obstructive coronary artery disease (MINOCA) and respective GRACE score

	% (n)	GRACE score
Cardioembolic stroke	1.8 (1)	138
Vasospasm	5.4 (3)	131 (127 – 147)
Plaque disruption	0 (0)	
Spontaneous coronary dissection	0 (0)	
Ischemic etiology (unknown mechanism)	10.7 (6)	110 (91 – 126)
Without a definite diagnosis	82.1 (46)	112 (93 – 136)

GRACE score

GRACE score at admission was associated with overall mortality (p=0.019) and occurrence of MACE at one year (p=0.034). Higher scores were observed in patients with MACE (Figure 2).

Figure 3 shows the ROC curves for GRACE score in predicting the outcomes studied. The GRACE score showed a high discriminatory power for overall mortality (area under the curve [AUC] of 0.907; 95% confidence interval [CI] of 0.812 – 1.000), and a cut-off of 138 showed high sensitivity and high specificity (maximum Youden index of 0.560) (Figure 3).

The frequencies of occurrence of outcomes according to the GRACE score cut-off points are described in Table 4. Among the patients with GRACE score <114, no patient had MACE after one year of follow-up. Among the patients with GRACE score of 114-137, 13.3% had MACE after one-year follow-up, but the mortality rate was 0%. Among the patients with a GRACE score ≥138, 25% had MACE, with a one-year mortality rate of 25%.

Discussion

Characteristics of our patients with diagnosis of MINOCA are similar to those described in several international studies.[2-4,6,17-19] A recent systematic review of records of patients with MINOCA reported a mean age of 55 years,[6] and higher prevalence of female

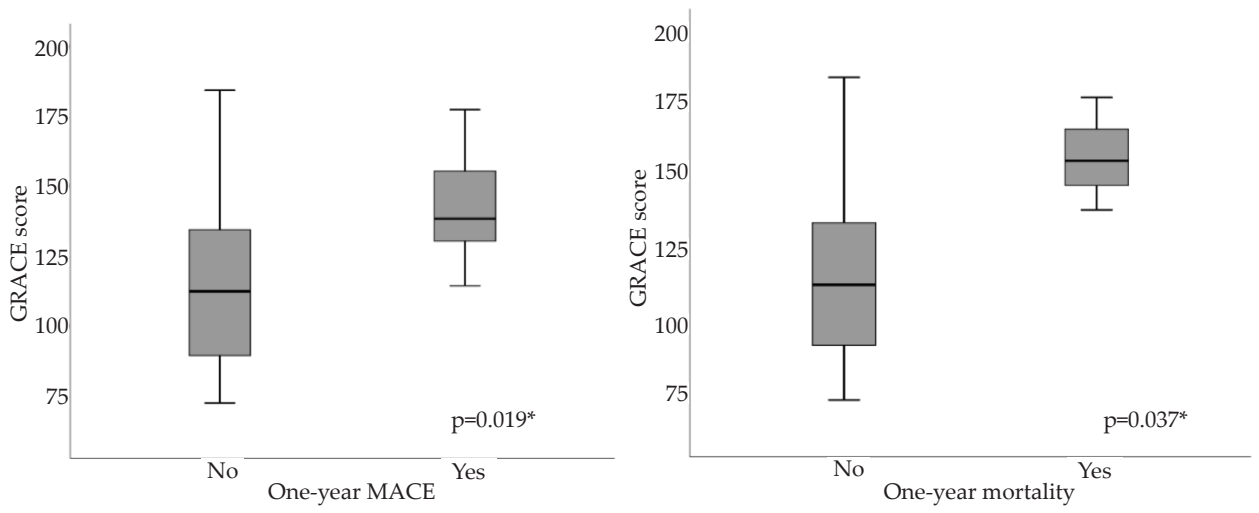

Figure 2 – Boxplot of the distribution of GRACE score for patients who had (or not) major adverse cardiovascular event (MACE) and patients who died (or survived) in one year * Mann Whitney test

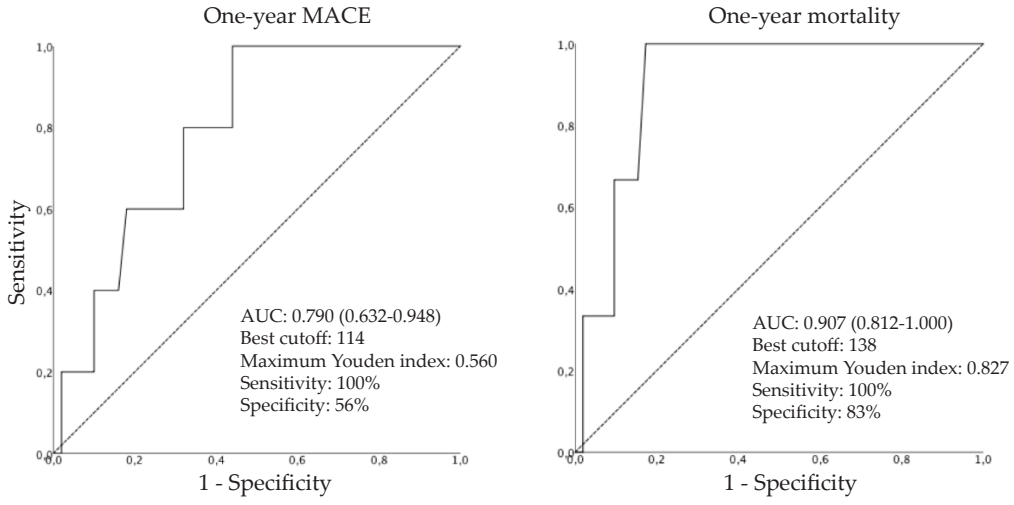

Figure 3 – ROC curves of GRACE score in predicting overall mortality and major adverse cardiovascular events (MACE) in one year; AUC: area under the curve.

Table 4 – One-year rates of major adverse cardiovascular events stratified according to GRACE score

	GRACE score			Total
	<114	114-137	≥138	
Number of patients	28	15	12*	55*
Mortality (n)	0% (0)	0% (0)	25.0% (3)	5.5% (3)
MACE (n)	0% (0)	13.3% (2)	25.0% (3)	9.1% (5)

** One lost to follow-up (% of follow up: 98%)*

patients, [2-4,6,17-19] suggesting sex-related or hormone effects on the pathophysiology of the disease.[8] However, contrary to our findings, some international studies have described a lower frequency of classical cardiovascular risk factors in these patients.[18,19] Our study showed a high prevalence of dyslipidemia and arterial hypertension in our sample, which was already reported in a previous Portuguese study.[17] As compared with the population of the Portuguese Registry of Acute Coronary Syndromes,[20] our sample shows some similarities, such as mean age (66 ±13 years), and prevalence of arterial hypertension (66.9%) and dyslipidemia (57.2%), and differed especially in sex distribution and prevalence of smoking (28.5%), diabetes mellitus (31.9%), and history of AMI (17.9%). These findings may reflect a higher prevalence of MINOCA associated with atherosclerotic disease in the Portuguese population, which is difficult to be confirmed in our study due to the small proportion of patients whose cause of MINOCA could be confirmed, despite similar mortality rates to other series.[21]

In our sample, the prognosis was similar to that previously described in other observational studies. Kang et al.[10] also reported an annual MACE rate of 7.8%, which was comparable to that observed in the comparative sample of acute coronary syndrome patients with one or two-vessel disease. Pasupathy et al.,[6] in a systematic review of studies on MINOCA patients, described a 12-month all-cause mortality rate of 4.7%. More recently, the COAPT study[22] presented even more worrying results – an all-cause mortality rate of 3.9% and 12.6% likelihood of occurrence of the composite endpoint of cardiac death and cardiovascular rehospitalization within one year.

A variable clinical course has been reported in previous studies; while most patients have a favorable course, without myocardial function sequelae, a significant proportion of patients develop MACE in short term. In light of the difficulty in establishing an etiological diagnosis in all patients, and the clinical dilemma in identifying which patients would require a closer follow-up and more aggressive secondary prevention therapy, the prognostic stratification is crucial. Numerous studies have proposed several prognostic markers, but with heterogeneous results – female sex, history of smoking, atrial fibrillation, previous AMI, ST-segment elevation at admission,[18,23] age, diabetes, previous stroke, peripheral arterial disease, chronic obstructive pulmonary disease, neoplasms, reduced ejection fraction, levels of LDL, creatinine and C-reactive protein,[18] and number of coronary arteries with stenosis less than 50%.[24]

The GRACE score is an ideal prognostic stratification tool in these patients. The instrument allows an objective quantification of the risk, making it more practical for clinicians when compared with a wide range of markers difficult to be integrated. Also, there is ample scientific evidence on the use of this risk stratification score in acute coronary syndrome.[11-13] Also, it has been widely use in clinical practice even for risk stratification of patients with MINOCA, before being submitted to catheterization.[12] Our study showed that the GRACE score is associated with one-year MACE. The cut-off points revealed by our statistical analysis are similar to those suggested by the ESC guidelines on the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation.[12] The authors suggest that MINOCA patients with a GRACE score < 109 would be classified as "low risk", a GRACE score of 109-139 would indicate an "intermediate risk" (already at a high risk of one-year MACE) and those with a GRACE score ≥140 would be classified as "high risk" (at high risk of one-year mortality). Therefore, an AMI patient, regardless of the presence of obstructive coronary artery disease, would be categorized into a risk group (low, intermediate, or high). However, independent of such classification, the active investigation for the etiologic diagnosis and appropriate therapy is always indicated.

CMR is an essential tool in the diagnosis of MINOCA. When performed in the acute phase of the disease (ideally in the first seven days of presentation),[25] the test allows the diagnosis in up to 87% of patients, changes the diagnosis made by cardiologists in nearly 52% of patients, and contributes to the definition of the best therapeutic strategy for the patient.[26] In our study, CMR had a lower diagnostic value, since it was performed in outpatient regimen in most cases, and did not allow the detection of perilesional edema using T2-weighted sequences or changes in segmental contractility in acute phase.[8,27] The low percentage of patients who underwent CMR in our study may be explained by the low accessibility of this test in our center. Similarly, although intravascular ultrasound and optical coherence tomography are essential tools for diagnosis of plaque disruption and spontaneous coronary dissection,[8] these are not readily accessible in clinical practice in our institution.

In the present study, secondary prevention therapy was prescribed at discharge based on clinical suspicion of the disease and following the current ESC recommendations.[8] Most patients were prescribed ACE inhibitors, ARBs, betablocker, and statins. However, considering the lack of robust scientific evidence, the benefit of using traditional therapies in secondary prevention in this population, with different diagnosis, is questionable. The MINOCA BAT trial aims to randomly assign more than 5,600 MINOCA patients to receive ACE inhibitor/ARBs plus betablocker versus placebo and evaluate one-year mortality rate and other cardiovascular events in one year. The use of these medications in this population can be considered reasonable according to recent findings reported in an observational study of MINOCA patients recorded in the SWEDEHEART registry,[28] suggesting long-term beneficial effects of ACE inhibitors and ARBs, and possibly betablockers in preventing cardiovascular events in these patients.

Limitations

This was a single-center, retrospective study, and limitations inherent to this study design should be considered, including a possible selection bias of patients. The small sample size and the short study period may affect the strength of our findings. In addition, since this was a retrospective study based on clinical records, a possible underreporting of endpoints cannot be ruled out. The low rate of identification of the cause of MINOCA may also bias the results, since it is not possible to determine the number of patients whose MINOCA was not related to vessel disease (as in case of myocarditis and Takotsubo syndrome). Besides, the cause of death of patients with definite diagnosis of MINOCA was unknown, which may limit the interpretation of the results.

Conclusions

This study highlights the diversity of causes and heterogeneous prognosis of MINOCA, which depends on the etiology and, in most cases, is not benign. The GRACE score at admission was shown a useful tool to identify those patients with a less favorable prognosis, with a good discriminatory ability in predicting the occurrence of events during the follow-up of our sample.

Future perspectives

Due to the heterogeneity of patients with MINOCA, multicenter studies using specific protocols for the etiological diagnosis, prognosis and therapeutic guidance are needed to establish the best therapeutic strategies tailored to the prognosis of each patient.

Author contributions

Conception and design of the research: Carvalho P, Caçoilo M; Afreixo V; Bastos JM; Acquisition of data Carvalho P, Caçoilo M; Analysis and interpretation of the data Carvalho P, Caçoilo M; Afreixo V; Bastos JM; Statistical analysis Caçoilo M; Afreixo V; Writing of the manuscript Carvalho P; Caçoilo M; Critical revision of the manuscript for intellectual content Carvalho P, Caçoilo M, Afreixo V, Bastos JM, Ferraz L, Vieira M, Santos L, Gonzaga A, Ferreira R, Adrega T, Faustino A, Briosa A.

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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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EDITORIAL

Back to The Future: How To Define Prognosis in MINOCA?

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Editorial referring to the article: Acute Myocardial Infarction with Non-Obstructive Coronary Arteries – Stratifying the Risk of a "new" Clinical Entity using an "Old" Tool

Myocardial Infarction with non-Obstructive Coronary Arteries (MINOCA) is the final diagnosis in 6-10% of all acute coronary syndromes (ACS). It is mostly present in female individuals. MINOCA was defined by the European Society of Cardiology (ESC) in 2017, and the Fourth Universal Definition of Myocardial Infarction (2018) further reinforced this concept.[1,2]

Dreyer et al.,[3] analyzing Medicare data in the United States, determined an incidence for MINOCA of 5.9%. Lower rates of one-year MACE (1.7% vs 27.6%), mortality (12.3% vs 16.7%) and re-hospitalization for ACS (1.3% vs 6.1%) were observed in MINOCA compared with ACS with coronary obstruction. Although the prognosis of MINOCA seems to be better than conventional ACS, a better understanding of which conditions are associated with better or worse prognosis within the MINOCA spectrum is needed.

In this issue of the International Journal of Cardiovascular Sciences, Carvalho et al.,[4] applied the GRACE score in 56 patients with suspicion of MINOCA and found an excellent discriminatory accuracy for mortality (AUC 0.907; 95%CI 0.812–1.000; p = 0.019) and occurrence of MACE (AUC 0.790; 95%CI 0.632-0.948; p < 0.05). They also showed a higher event rate for each GRACE score cut off (< 114, 114-137 and >= 138).

Yin et al.,[5] recently published data regarding the use of the GRACE score in a retrospective cohort of MINOCA patients in Shangai and found a worse prognosis for patients with higher GRACE score (> 140 points) compared with those at low/intermediate risk defined by the score. The occurrence of MACE was higher in those with high GRACE score (21.9% vs 10.2%; p < 0.01), and this difference was driven particularly by the component cardiac mortality (7.5% vs 1.4%; p < 0.05). Also, they found an AUC of 0.710 (95% CI 0.625–0.796, p < 0.001).

Results of both studies reinforce the use of the GRACE score for MINOCA in daily practice. As the GRACE score may help in stratifying patients before coronary angiography, it has already been used in most centers for all patients who present with suspected ACS, including MINOCA, as the final diagnosis of MINOCA will be made only after the coronary profile is established. Thus, in some cases, the score prevents the patient from being submitted to unnecessary tests.

But what explains the prognostic value of GRACE risk score in MINOCA?

This question should be answered from two perspectives. The first regards the pathophysiological mechanism of MINOCA. In a series of MINOCA patients,[6] cardiac magnetic resonance and optical coherence tomography (OCT) revealed an ischemic nature of the disease in 63.8% of patients. In this scenario the performance of GRACE score would be kept. In the study by Carvalho et al.,[4] cardiac magnetic resonance was performed in only 21.4% of the patients and OCT was not performed, and the underlying mechanism of the disease was established in only 17.9% of the cases.

Second, despite being a poor predictor of anatomical severity[7], the GRACE score will always be a good predictor of insult severity, regardless of anatomy.

Keywords

Cardiovascular Diseases; Myocardial Infarction; Acute Coronary Syndrome; Coronary Artery Disease; Coronary Angiography; Magnetic Resonance/diagnostic imaging.

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The individual components of the GRACE score provide prognostic information that are not specific of ACS. In fact, age, heart rate, systolic blood pressure, the Killip class (presence of pulmonary edema or cardiogenic shock), troponin and even ST changes play a general role in the prognosis and accurately predict mortality; the outcome depends more on patients' susceptibility to the stress event than on atherosclerotic burden per se. For example, the GRACE score was also shown to provide good prognostic information in Takotsubo cardiomyopathy[8,9] and pulmonary embolism.[10]

Finally, in a significant proportion of cases, MINOCA may not be indissociable from ACS and may be interpreted as a continuum in atherosclerotic disease.[11] In this case, patients should be advised and counseled appropriately, beyond the aspects of coronary heart disease. New studies evaluating the relation of other classical prognostic factors to atherosclerosis in MINOCA are warranted.

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ORIGINAL ARTICLE

The Correlation between Cardiac Enzymes and Cardiotrophin-1 Levels in Patients with Acute Coronary Syndrome

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Abstract

Background: In the current era, there is always search for better cardiovascular biomarkers to early diagnose the disease.

Objectives: We aimed to investigate the association between a novel biomarker, cardiothropin-1 (CT-1), and standard markers of myocardial ischemia in patients with acute coronary syndrome (ACS) in Turkey.

Patients and Methods: In this prospective cohort study, patients who were admitted to our institution between July 2012 and July 2013 with the diagnosis of ACS were included. The standard markers of myocardial necrosis and CT-1 were evaluated at the time of admission and after 6 hours. Changes in laboratory parameters were statistically tested and correlated with routinely used markers of myocardial ischemia. The distribution of the data was analyzed by the Kolmogorov-Smirnov test. Proportional analysis and changes in laboratory parameters were evaluated with Chi-Square test and Fisher Exact test. Statistical significance was defined as $p<0.05$.

Results: The study enrolled 24 patients (14 male, 10 female) with ST-segment elevation myocardial infarction (STEMI) and 16 patients (9 male, 7 female) with non-ST-segment elevation myocardial infarction (NSTEMI) with elevated cardiac enzymes such as creatine kinase (CK), creatine kinase-MB (CK-MB) and Troponin-T (Tn-T). The average age of the patients was 61.45 ± 11.04 years. Increasing CT-1 levels were correlated with the increasing CK ($p=0.035$ and $p=0.018$, respectively), CK-MB ($p=0.006$ and $p=0.096$, respectively), and Tn-T ($p=0.041$ and $p=0.000$, respectively) at first and at the 6th hour measurements. The CT-1 values were found to be more increased in the STEMI group ($p=0.0074$).

Conclusion: CT-1 is one of the novel biomarkers for cardiac injury. It is correlated with standard markers of myocardial ischemia and the results suggest that CT-1 can be used as a new biomarker.

Keywords: Myocardial infarction; Acute coronary syndrome; Cardiotrophin-1; Atiral fibrillation; Troponin-T.

Introduction

Cardiovascular diseases are the major causes of mortality and morbidity, especially among the aging population.[1] Studies have reported that one out of every five deaths in the United States is caused by coronary atherosclerosis.[2] It is expected that CAD will take the number 1 place in the list of 2020 causes of death prepared by the World Health Organization[3] Similar studies examining coronary artery disease (CAD) associated mortality in European countries (an average of 30 countries) report that the aforementioned

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rates among individuals between 45 and 74 years of age were 2.3 per thousand in men and 0.72 per thousand in women.[4] CAD is a pathological process mainly caused by atherosclerosis.[5] Other factors such as arteritis may also lead to coronary pathologies.[6,7] The process starts with fatty streaks in the early stages of life[6], and ischemia usually results from acute rupture of vulnerable plaques[8] or as a result of long-lasting decreased coronary blood flow due to increasing coronary obstruction.[6]

The 19-year long follow-up data of the Cardiac Disease and Risk Factors in Turkish Adults (TEKHARF) study determined the CAD associated mortality rate as 7.5 per thousand in men and 3.9 per thousand in women between 45 and 74 years of age. It is obvious that there would be a hike in CAD incidence and recurrent cardiovascular events due to the extension of the average lifespan, increasing treatment options and higher rates of risk factors in senior patients.[4]

Each of the endogenous and exogenous risk factors such as age, gender, smoking, hypercholesterolemia, family history, diabetes mellitus and hypertension significantly increases the risk of CAD. However, there are studies indicating the development of atherosclerosis in some patients with CAD despite the lack of mentioned risk factors. Such findings lead scientists to investigate new risk factors and markers for atherosclerosis (9). Biochemical markers such as C-reactive protein, fibrinogen and homocysteine have been determined to be associated with atherosclerosis already in the past years.[9]

New biomarkers are sought for the early diagnosis of cardiovascular diseases to initiate treatment as early as possible in order to prevent or at least minimize mortality and morbidity, and better quality of life. One of these newly investigated biomarkers in recent years has been Cardiotrophin-1 (CT-1) molecule .[10]

CT-1 is a molecule with many endocrine and paracrine functions beyond being a simple cardiac biomarker. Early detection and follow-up of CT-1 levels may be helpful in predicting cardiac remodeling and determining treatment intensity.[11] Liao et al.,[12] administered CT-1 to their cohort and showed that CT-1 might have a protective effect against ischemia/reperfusion injury when added before or after stimulated ischemia and re-oxygenation,[12] Moreover, CT-1 release is increased to protect cardiomyocytes from ischemia and reperfusion injury in case of hypoxia. In a study conducted by Freed et al., authors found that CT-1 levels were high in the infarct area following acute myocardial infarction in mice .[13]

In this study, we sought to investigate the association between CT-1 and other well-known markers of myocardial ischemia in patients with ACS.

Patients and Methods

The study was conducted with 40 patients between July 2012 and July 2013 in Turkey. Forty patients who were presented to the emergency clinic and diagnosed with acute coronary syndrome (ACS) were included in the research. Exclusion criteria were patients under 18 years of age, with acute renal failure at the time of admission, advanced left ventricular systolic dysfunction (having ejection fraction (EF) of 30% or less), chronic inflammatory disease, presence of malignancy, presence of acute infection, severe liver failure (alanine aminotransferase (ALT) > 3X upper limit of normal), uncontrolled hypertension (diagnosed with hypertension and having blood pressure values above 140/90 mmHg with effective dose medical treatment) or severe mitral and/or aortic valve disease. The study was approved by the institutional medical research ethics committee (ref. no: 2012-13/3, dated July 12, 2012) and conducted in accordance with the Declaration of Helsinki. The patients were transferred to the intensive care unit of the cardiology department and received medical or interventional treatment following being diagnosed with ACS.

A detailed anamnesis was obtained from the patients and their physical examinations were performed. Five cc blood samples for CT-1 measurement were drawn in EDTA-containing tubes in addition to the appropriate amount for routine analysis from each patient from the antecubital fossa veins. Samples were transferred into storage at -80 °C at the laboratory. Venous blood plasma samples from patients' admission and 6 hours after admission are incubated in microtiter wells coated with polyclonal anti-human CT-1 antibody.

Electrocardiograms (ECG) and echocardiographies of the patients were evaluated on admission and during the follow-up. Echocardiographies were performed by physicians who were blind to the groups. Patients were divided into three different subgroups of ACS as STEMI (ST-Elevation Myocardial Infarction), NSTEMI (Non-ST-Elevation Myocardial Infarction) and unstable angina pectoris (USAP) according to ECG findings and cardiac enzyme levels.

The development of atrial fibrillation (AF), acute renal failure and death were observed as complications during

the hospital stay. Also, patients developing acute renal failure, which was determined as 50% increase in urea/creatine levels from the admission values were recorded.

Cardiotrophin-1 measurement using the ELISA method

After a total of 2-hour incubation, biotin-labeled monoclonal anti-human CT-1 antibody was added. Following one hour of incubation, streptavidin-horseradish peroxidase conjugate was added. After a total of 30 minutes of incubation, substrate (H_2O_2-tetramethylbenzidine) was added. The reaction was terminated with an acidic solution after 15 minutes of incubation. Absorbance was measured at a wavelength of 450 nm. Absorbance is directly proportional to the CT-1 concentration. CT-1 concentrations of patient samples were calculated by plotting absorbance versus standard concentrations. CT-1 protein levels were read manually by CT-1 kit, in the DNM-9602 Micro Plate Reader manual reading device. It was read at 450 nm wavelength by the ELISA method. All data evaluations in the reading process were performed manually.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for Social Sciences for Windows (SPSS Inc., Chicago, Illinois, USA) 22.00 software. Continuous variables with a normal distribution are described using the average and standard deviation and those that did not show normal distribution is described using the median and interquartile range. Categorical variables are given as number and percentage. The distribution of the data was analyzed by the Kolmogorov-Smirnov test. Normally distributed variables are analyzed with paired samples T test to compare continuous variables. Continuous values without normal distribution were analyzed with Wilcoxon Signed-Rank test and Mann-Whitney U test. Proportional analysis and changes in laboratory parameters in blood drawn at different time intervals were evaluated with Chi-Square test and Fisher Exact test. Pearson correlation was used for analysis of the correlation between the variables. Statistical significance was defined as $p<0.05$.

Results

Forty patients were included in the study. There were 23 males and 17 females (57.5% - 42.5%, respectively). The mean age of the patients was 61.45 ± 11.04 years. The overall incidence for diabetes mellitus was 27.5%. Hypertension was present in 70% of the patients. Dyslipidemia which was described as LDL-C ≥140 mg/dL, HDL-C <40 mg/dL, triglycerides ≥150 mg/dL was detected in 12.5%. Among the patients 10% had a positive family history of heart disease and 37.5% of the patients were current or former smokers.

There were 24 patients with ≥1 mm ST elevation in at least two leads on the ECG with elevated cardiac enzyme levels, and they were allocated into the STEMI group. Approximately one-third of patients with NSTEMI may have present elevated troponins.[14] Sixteen patients whose cardiac enzyme levels were elevated without ST elevation (with dynamic ST-T change) were included in the NSTEMI (n: 10) / USAP (n: 6) group (Figure 1). The demographic data of the patients (Patients' age, gender, medical history, smoking habits, diabetes, and hypertension status, familial cardiac history, and the drugs that they are taking) in STEMI and NSTEMI/USAP groups are presented separately in Table 1 and Table 2.

When the CT-1 level distribution in patients with ACS was evaluated in two groups as STEMI and NSTEMI/USAP, the variability of CT-1 levels in the STEMI group was higher than that of the NSTEMI group (Figure 2).

The blood biochemistry, cardiac enzymes and CT-1 values of the patients were measured at the time of admission and after 6 hours. The mean aspartate aminotransferase (AST) (N: 0-35 U/L), creatine kinase (CK) (N: 30-170 U/L) values were found increased at the 6th hour and the increases were found to be statistically significant ($p<0.01$). Similarly, creatine kinase-MB (CK-MB) (N: 5 to 25 IU/L) value was increased after 6 hours of admission. Troponin-T (N: 0-0.10 ng/mL (0-0.10 µg/L) and CT-1 values were found increased at the 6th hour and the increase of the markers were found to be statistically significant ($p<0.01$) (Table 3). Hence, myocardial enzymes (CK, CK-MB and Troponin-T) of all patients were significantly increased at the the 6th hour control when compared with the admission values ($p<0.01$). Moreover, the CT-1 levels were also increased approximately three folds with respect to admission values at the 6th hour control ($p<0.01$).

The CT-1 levels were correlated with the routine biomarkers of CAD, and we detected a statistically significant, positive correlation between Tn-T, CK, CK-MB values, and CT-1 values at the time of admission as well as at the 6th hour controls (Table 4, Table 5, Table 6).

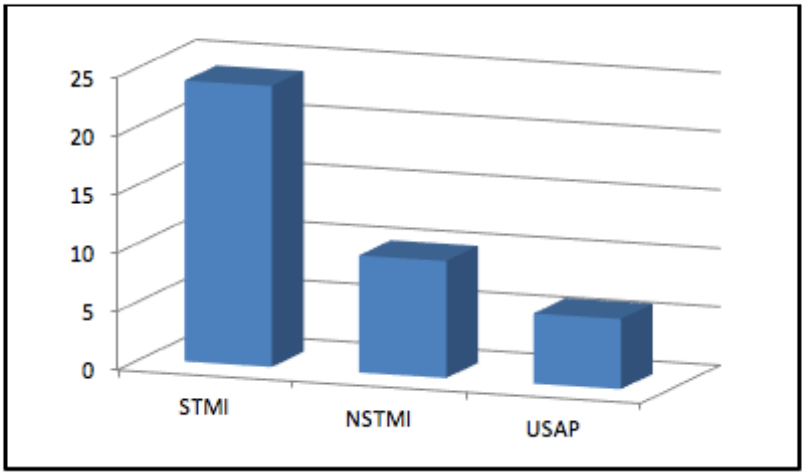

Figure 1 – Patient distribution (ST-segment elevation myocardial infarction (STEMI)/Non-ST-segment elevation myocardial infarction (NSTEMI)/Unstable angina pectoris (USAP)).

Table 1 – Demographic and basic clinical characteristics of patients with STEMI (n: 24)

Gender (n, %) (male/female)	**14/10 (58.3, 41.7)**
Age (Year) (Mean ± SD)	62,25 ±8,3
Diabetes mellitus (n, %)	6 (25)
Hypertension (n, %)	15 (62,5)
Dyslipidemia (n, %)	2 (8,3)
Smoking (n, %)	4 (16,6)
Coronary artery disease (n, %)	10 (41,6)
Family History (n, %)	4 (16,6)
ACE inh/ARB (n, %)	17 (70,8)
B-blocker (n, %)	5 (20,8)
Statin (n, %)	4 (16,6)
Acetylsalicylic Acid (n, %)	5 (20,8)
Calcium Channel Blocker (n, %)	5 (20,8)

STEMI: ST-segment elevation myocardial infarction, ACE inh: Angiotensin-converting enzyme inhibitor, ARB: Angiotensin Receptor Blocker, B-blocker: Beta blocker

Table 2: Demographic and basic clinical characteristics of patients with NSTEMI / USAP (n: 16)

Gender (n, %) (Male/Female)	**9/7 (56.2, 43.8)**
Age (Year) (Mean ± SD)	60.25 ± 3,5
Diabetes mellitus (n, %)	5 (31.2)
Hypertension (n, %)	13 (81.2)
Dyslipidemia (n, %)	3 (18.7)
Smoking (n, %)	0 (0)
Coronary artery disease (n, %)	5 (31,2)
Family History (n, %)	7 (43.7)
ACE inh/ARB (n, %)	9 (56.2)
B-blocker (n, %)	2 (12.5)
Statin (n, %)	7 (43.7)
Acetyl Salicylic Acid (n, %)	7 (43.7)
Calcium Channel Blocker (n, %)	5 (31.2)

NSTEMI: non-ST segment elevation myocardial infarction, ACE inh: Angiotensin-converting enzyme inhibitor, ARB: Angiotensin Receptor Blocker

Coronary angiography was performed in all patients. Percutaneous coronary interventions were performed in 34 patients (22 patients with STEMI, 9 patients with NSTEMI, 3 patients with USAP), 3 patients underwent coronary artery bypass surgery (2 patients with STEMI, 1 patient with NSTEMI) and medical therapy was given to 3 patients (3 patients with USAP). Among 40 patients diagnosed with ACS, 4 patients developed new-onset AF during hospitalization. Although the general features (gender, family history, smoking habits) of these 4 patients with newly diagnosed AF did not differ from the non- AF population, hypertension and CAD on angiography were significantly more prevalent in these cases (Table 7). Moreover, the Tn-T

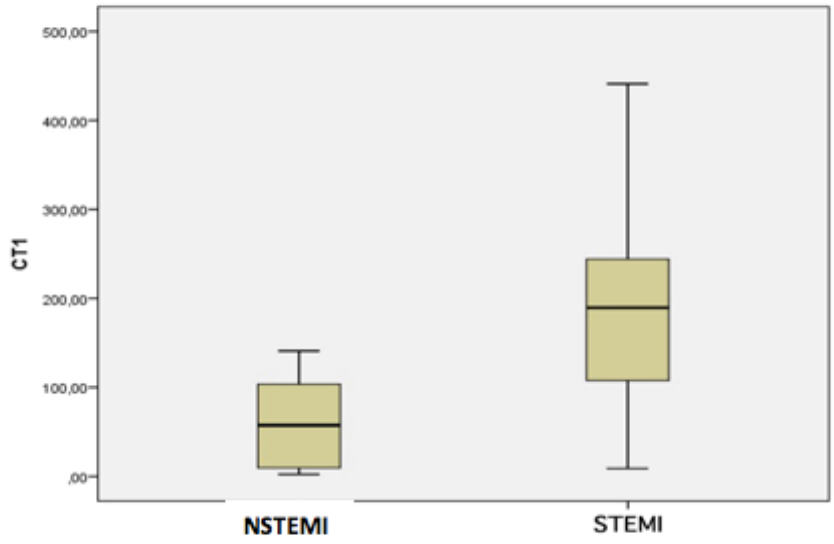

Figure 2 – Distribution of CT-1 levels in patients with acute coronary syndrome (ACS).
CT1: Cardiotrophin-1; NSTEMI: Non-ST-elevation myocardial infarction; STEMI: ST-elevation myocardial infarction.

Table 3 – Changes in laboratory values at 0 and 6 hours of all subjects included in the study

	0. hour	6. hour	p value
WBC (K/Ml)	10.68 ± 4.01	11.62 ± 3.29	0.024*
HG (g/dl)	12.90 ± 1.77	12.46 ± 1.84*	0.022
AST (IU/L)	48.77 ± 13.34	56.45 ± 18.32	0.0045*
ALT (IU/L)	26.85 ± 11.89	29.13 ± 8.01	0.0071*
CK (IU/L)	Range: 254-493 Median: 372.5	Range: 416-829 Median: 712.3	0.0082**
CK-MB (IU/L)	48.08 ± 24.5	90.18 ± 33.14	0.0065*
Tn-T (ng/mL)	Range: 1354-2462 Median: 1758.4	Range: 2519-6128 Median: 4732.6	0.0092**
CT-1 (pg/mL)	132.04 ± 48.1	322.19 ± 98.12	0.0084*

WBC: White blood cell count, HG: Hemoglobin, AST: Aspartate amino transferase, ALT: Alanine amino transferase, CK: Creatine kinase, CK-MB: Creatine kinase-Muscle Brain, Tn-T: Troponin-T, CT-1: Cardiotrophin-1, p<0.01 statistically significant.
**: paired T-test was used, **: Wilcoxon Signed-Rank test was used.*

values at the time of admission were higher in the AF group (p<0.01). However, the CT-1 values were not significantly different in patients developing AF and the remaining patients without AF (Figure 3) which was attributed to the small number of patients with the AF group (4 patients).

During the follow-up of the patients in the coronary intensive care unit, complete atrioventricular block developed in 2 patients and rhythm control was achieved with temporary cardiac pacemakers. One patient developed nodal rhythm. There was no need for a permanent pacemaker. One patient developed ventricular tachycardia and with electrical cardioversion rhythm control was achieved (Figure 4).

Mortality occurred in 1 patient with acute myocardial failure and renal insufficiency (cardiorenal syndrome). Cardiorenal syndrome was developed during the follow-up period in the coronary intensive care unit. Hemodynamic stability was achieved with inotropic and intra-aortic balloon pump support. Hemodialysis was necessitated and adequately performed. Unfortunately,

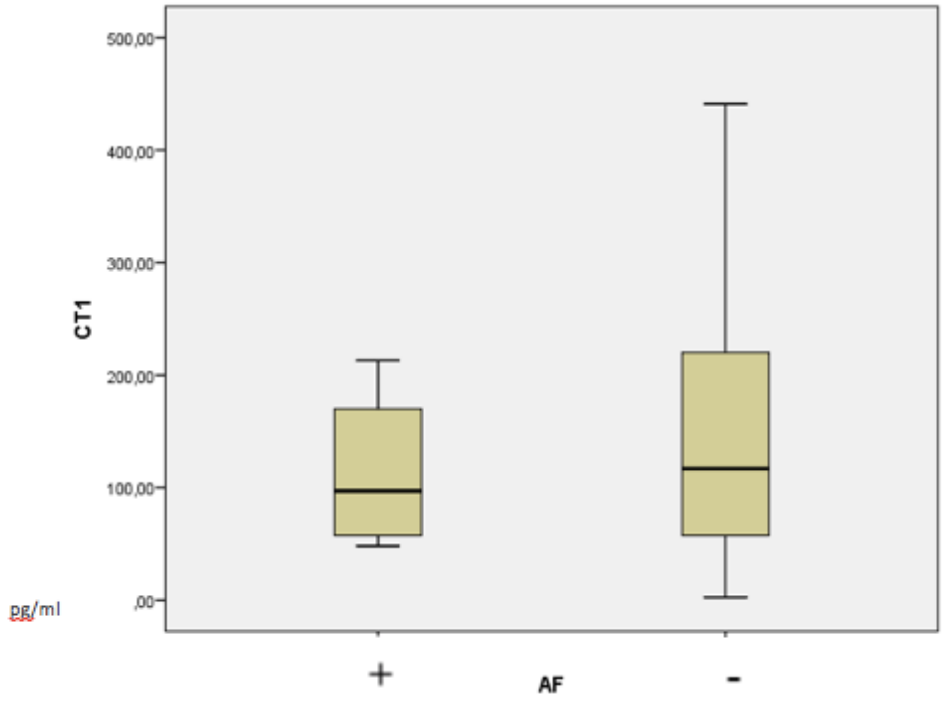

Figure 3 – Distribution of CT-1 levels in patients with atrial fibrillation (AF).
CT1:Cardiotrophin-1; VAR: It is a Turkish word, the figure is revised and the word is removed; YOK: It is a Turkish word, the figure is revised and the word is removed.

Table 3 – Changes in laboratory values at 0 and 6 hours of all subjects included in the study

	0. hour	6. hour	p value
WBC (K/Ml)	10.68 ± 4.01	11.62 ± 3.29	0.024*
HG (g/dl)	12.90 ± 1.77	12.46 ± 1.84	0.022*
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CK (IU/L)	Range: 254-493 Median: 372.5	Range: 416-829 Median: 712.3	0.0082**
CK-MB (IU/L)	48.08 ± 24.5	90.18 ± 33.14	0.0065*
Tn-T (ng/mL)	Range: 1354-2462 Median: 1758.4	Range: 2519-6128 Median: 4732.6	0.0092**
CT-1 (pg/mL)	132.04 ± 48.1	322.19 ± 98.12	0.0084*

WBC: White blood cell count, HG: Hemoglobin, AST: Aspartate amino transferase, ALT: Alanine amino transferase, CK: Creatine kinase, CK-MB: Creatine kinase-Muscle Brain, Tn-T: Troponin-T, CT-1: Cardiotrophin-1, p<0.01 statistically significant.
**: paired T-test was used, **: Wilcoxon Signed-Rank test was used.*

the patient died on the 12th day of hospitalization at the cardiology intensive care unit. The control CT-1 levels were above the average values on admission and at the 6th hour control in this patient.

We have not come across any other complications (mechanical, ischemic and neurological complications etc.) of myocardial infarction, Hence, we could not evaluate the relationship between CT-1 levels and complications of myocardial infarction. However, according to the correlation between CT-1 levels and routine biomarkers for CAD a positive, significant correlation was observed with standard biomarkers of myocardial ischemia and CT-1 (Tables 3-6).

Table 4 – Correlation analysis for 0-hour CT-1

0.hour CT-1	r value	p value
0.hour CK	0.335	0.035
0.hour CK-MB	0.427	0.006
0.hour Tn-T	0.085	0.041
6.hour CK-MB	0.396	0.011
6.hour CK	0.372	0.018
6.hour Tn-T	0.064	0.096
6.hour CT-1	0.702	0.000

CK: Creatine kinase, CK-MB: Creatine kinase MB, Tn-T: Troponin-T, CT-1:Cardiotrophin-1

Table 5 – Correlation analysis for Cardiotrophin-1 at the 6th hour

6. hour CT-1	r value	p value
0.hour Tn-T	0.003	0.047
0.hour CT-1	0.702	0.000
6.hour CK	0.656	0.000
6.hour CKM-B	0.683	0.000
6.hour Tn-T	0.011	0.046

CK: Creatine kinase, CK-MB: Creatine kinase MB, Tn-T: Troponin-T, CT-1:Cardiotrophin-1

Table 6 – Correlation analysis for the 6th hour Troponin-T

6. hour Troponin-T	r value	p value
0.hour Tn-T	0.976	0.000
0.hour CT-1	0.064	0.036
6.hour CT-1	0.011	0.044
6.hour CK	0.042	0.795
6.hour CK-MB	0.683	0.000

CK: Creatine kinase, CK-MB: Creatine kinase MB, Tn-T: Troponin-T, CT-1:Cardiotrophin-1

Discussion

To the best of our knowledge, the current research is one of the preliminary studies in the literature comparing CT-1 levels with other cardiac markers in patients presenting to the clinic with ACS. The results of our study indicate that the CT-1 levels were significantly higher in the STEMI group compared to the other subgroups of ACS who were admitted to the hospital with chest pain.

C-reactive protein, metalloproteinases, brain natriuretic protein (BNP) have been considered biomarkers of atherothrombotic risk, platelet activation and cardiac insufficiency. One of these newly investigated biomarkers in the recent years has been the CT-1 molecule. This cytokine performs growth and differentiation activities through a unique receptor system comprising the interleukin 6 (IL-6) receptor and glycoprotein 130 (Gp130). Although the CT-1 molecule is found in the liver, adipose tissue and respiratory system, its predominant effect is on the heart as it is synthesized by the myocardium. It acts in myocardial protection by triggering proliferation with cell survival, shows its hemodynamic effects and endocrine properties, and finally prepares the heart for pathological conditions. It actually induces myocyte hypertrophy and collagen synthesis. Studies have shown that CT-1 inhibits cardiomyocyte apoptosis and plays a role in the survival and proliferation of embryonic cardiomyocytes.[10] In previous studies, CT-1 protein was also found to be associated with hypertension, congestive heart failure and CAD.[15]

Khan et al.,[16] showed that CT-1 levels would be a prognostic biomarker in patients with acute myocardial infarction to indicate death and cardiac insufficiency. In one of our patients, cardiac arrest occurred on the 12th day of hospitalization and subsequently death. When the features of this patient at the first admission were examined, it was observed that the control CT-1 levels were above the average values on admission and at the 6th hour control, and that cardiac systolic dysfunction and cardiogenic shock were accompanied by acute renal insufficiency.

There is a close relationship between hypertension and ACS.[17] CAD has 2-3 times higher incidence in hypertensive patients compared with normotensive people. Twenty-eight (70%) of the 40 patients included in the study had hypertension. We failed to find a significant correlation between the hypertensive patients and CT-1 levels in our cohort, most probably attributed to the small sample size.

In another study by Martinez et al.,[18] on rats, a linear correlation was found between myocardial fibrosis and increased CT-1 levels. These findings showed that CT-1 level may provide useful prognostic value in heart failure. In our study, especially in patients with STEMI, CT-1 levels increased more than the other ACS groups, supporting its myocardial protective effects in terms of prognosis.

Table 7 – Comparison of demographic characteristics and laboratory values of new atrial fibrillation in patients after myocardial infarction

	AF Developers N:4	Non-AF Patients N:36	p value*
Age	Range: 48-78 Median:68	Range: 42-75 Median: 65.4	0.23*
Gender Male Female	(n, %) 2 (50) 2 (50)	21 (58.3) 15 (41.6)	0.027** 0.019**
Diabetes mellitus (n, %)	1 (25)	10 (27.7)	0.012**
Hypertension (n, %)	4 (100)	24 (66.6)	0.032***
Dyslipidemia (n, %)	1 (25)	4 (11.1)	0.11**
Smoker	1 (25)	14 (38.8)	0.014**
Family history	0 (0)	4 (11.1)	
Coronary artery disease history	2 (50)	9 (25)	0.0093**
WBC (K/µl)	Range: 9.2-14.5 Median: 11.5	Range: 9.58-15.3 Median: 10.8	0.21*
HG (g/dl)	Range: 8-13.4 Median: 12.8	Range: 8.6-14.4 Median: 13.6	0.25*
AST (IU/L)	Range: 30-52 Median: 40.3	Range: 34-63 Median: 55.6	0.025*
ALT (IU/L)	Range: 20-27 Median: 22.8	Range: 22-35 Median: 32.1	0.034*
CK (IU/L)	Range: 200-320 Median: 251	Range: 375-594 Median: 402	0.031*
CK MB (IU/L)	Range: 35-72 Median: 33.4	Range: 42-87 Median: 62	0.021*
Tn- T (ng/ml)	Range: 10020-10940 Median: 10502	Range: 952-1402 Median: 1024	0.0081*
CT-1 (pg/ml)	Range: 97-114 Median: 108	Range: 110-203 Median: 157.4	0.014*

WBC: White blood cell count, HG: Hemoglobin, AST: Aspartate amino transferase, ALT: Alanine amino transferase, CK: Creatine kinase, CK-MB: Creatine kinase MB, Tn-T: Troponin-T, CT-1: Cardiotrophin-1, p<0,01 statistically significant.
: Mann Whitney U test was used, **: Fisher exact test was used, * Chi-square test was used.*

Altun et al. found a positive correlation between CT-1 levels and recurrence of AF after cardioversion in 32 patients with AF (19). In our study, AF was detected in 4 patients; but CT-1 levels were not different between groups with and without AF. In Altun et al.,[19] series a correlation between chronic fibrosis and CT-1 levels was detected, and it was proposed that increased CT-1 levels might be useful in detecting AF recurrence after cardioversion.[19] AF was new onset in our 4 patients, and it could be the reason for not increasing CT-1 levels. The other reason for failure to detect a significant correlation might be the small number of patients experiencing AF in our cohort. On the contrary, our findings of not increasing CT-1 levels in acute onset AF may be a distinct marker and have prognostic value to rule out long-standing myocardial fibrosis as previously stated by Calabro et al.[20]

The Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZON-AMI) study investigated the relationship between occult and overt infarction and cytokines in patients with STEMI who received paclitaxel-eluting stent implantation. The aim of this study was to determine whether biomarkers would be useful in predicting stent thrombosis after drug-eluting stent implantation. The study was the first to be conducted in this respect. Patients included in the study were followed up for a total of 3 years. A total of 26 biomarkers were measured at the beginning of the study and during the follow-up. In multivariate analysis, CT-1 was found to be associated with the target vessel

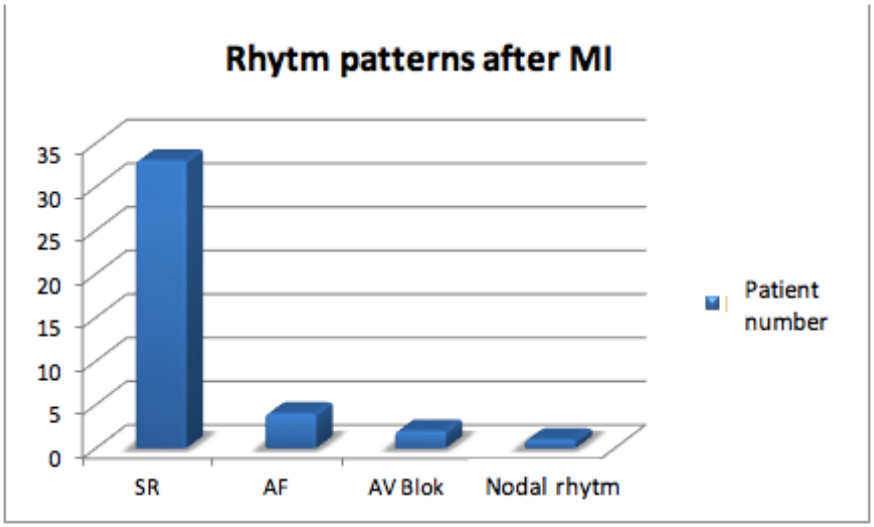

Figure 4 – Electrocardiogram (ECG) recordings of patients after myocardial infarction (MI).

revascularization independent to other biomarkers in late stent thrombosis.[21]

In their study, Bortolotti et al. showed that the most important cytokine that increases the survival of cardiac mesenchymal cells as graft in vivo had been the CT-1 (11). All these findings show how important CT-1 is in cardiac remodeling. Cardiac functions after acute myocardial infarction are very important in determining medical treatment. In this study, our aim was to focus on early markers of cardiac injury, determine the molecules that will increase the risk of early cardiac events and decide on the treatment plan.

Limitations

The major limitations of the study are small cohort size and short period follow up of the patients. Despite the small number of patients, the correlation analysis indicated the adequacy of CT-1 as a reliable marker in patients with ACS. Definitely additional serial blood tests at the follow-up would have added to the scientific strength of the manuscript.

Conclusion

Due to the increased incidence of cardiovascular events in the community, which leads to a long hospitalization and the increased incidence of mortality, there is an ongoing search for novel prognostic biomarkers. CT-1 was found to be increased in correlation with routine biomarkers CK, CK-MB and the levels of troponin also in our study, and high blood levels were detected especially in patients with STEMI. However, multicenter studies including a higher number of patients and patients from different regions of the world are warranted to better confirm the findings with CT-1.

Author contributions

Conception and design of the research: Polat U, Aydinlar A, Caliskan S, Boyuk F, Unal O. Acquisition of data: Polat U. Analysis and interpretation of the data: Polat U, Aydinlar A, Caliskan S, Boyuk F, Unal O. Writing of the manuscript: Polat U. Critical revision of the manuscript for intellectual content: Polat U, Aydinlar A, Caliskan S, Boyuk F, Unal O.

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 Doctoral submitted by Ufuk Polat, from Uludag University Faculty of Medicine.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Uludag University Faculty of Medicine under the protocol number 2012-13/3. 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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EDITORIAL

Cardiotrophin-1 in Patients with Acute Coronary Syndromes: Does it Have a Role?

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Editorial referring to the article: The Correlation between Cardiac Enzymes and Cardiotrophin-1 Levels in Patients with Acute Coronary Syndrome

Acute coronary syndromes are among the most common diagnoses in the emergency department (ED). It has been estimated that 300,000 to 400,000 cases are seen each year in Brazil.[1] The diagnosis of acute myocardial infarction (AMI) is made on the basis of symptoms, electrocardiogram, and biological markers of myocardial necrosis. Troponins are the most specific cardiac markers, and in the era of highly sensitive assays, they have been shown to make the exclusion of AMI in the ED more rapid, being particularly helpful in patients with atypical presentations.[2]

Cardiotrophin-1 (CT-1) is a member of the interleukin-6 superfamily of proinflammatory cytokines. It is expressed in many tissues, including heart and vessels. CT-1 is upregulated in cardiac fibroblasts and cardiomyocytes in response to mechanical, humoral, metabolic, and hypoxic stress (Figure 1).[3] It is elevated in the myocardium and plasma of heart failure (HF) patients and has also been associated with hypertension, diabetes, cardiac hypertrophy, and fibrosis, both in patients and experimental studies.[3,4] CT-1 is expressed after an AMI and seems to be involved in the healing and remodeling process that occurs after myocardial infarction.[5,6] In the study by Freed et al.,[5] CT-1 was able to initiate each of the processes related to scar formation, including fibroblast migration and proliferation, and collagen synthesis.[5]

This new biomarker may have prognostic and therapeutic implications in clinical practice. In one study, CT-1 was a predictor of death or HF after AMI.[7] CT-1 and NT-proBNP predicted events independently of age, sex, previous AMI, serum creatinine, and Killip class (area under the curve of 0.62 for CT-1 and of 0.77 for NT-proBNP). When both were used, the AUC was improved to 0.84.[7] CT-1 may additionally have a therapeutic role. In one experimental study, administration of CT-1 to rats seven days before the induction of AMI attenuated apoptosis and improved hemodynamics.[8]

In this issue of IJCS, Polat et al.,[9] sought to investigate the association between CT-1 and traditional markers of myocardial ischemia.[9] The authors found a positive correlation of CT-1 with creatine kinase (CK), creatine kinase-MB (CK-MB), and troponin T, at admission and also at six hours . The increases in CT-1 levels were especially higher in patients with ST-elevation myocardial infarction (STEMI). We congratulate the authors for bringing up recent data on this new biomarker and for confirming the results of previous work.[10] However, one strong limitation in this study is the absence of a control group, without myocardial ischemia. As pointed out before, CT-1 may be elevated in non-ischemic conditions.[3,4] This lack of specificity limits the utility of this biomarker as a diagnostic tool for myocardial ischemia. Additionally, there is no head-to-head comparison of CT-1 with troponin, the gold standard biomarker in this setting.

New biomarkers are more than welcome and the authors are to be congratulated for bringing knowledge on CT-1. To be established in clinical practice, however, new biomarkers need to add information to traditional ones and, in this regard, studies comparing CT-1 with troponins have not been done. Until now, troponins remain the gold standard in the diagnosis of AMI.

Keywords

Coronary Artery Disease; Myocardial Infarction; Electrocardiography/methods; Biomarkers; Cytokines.

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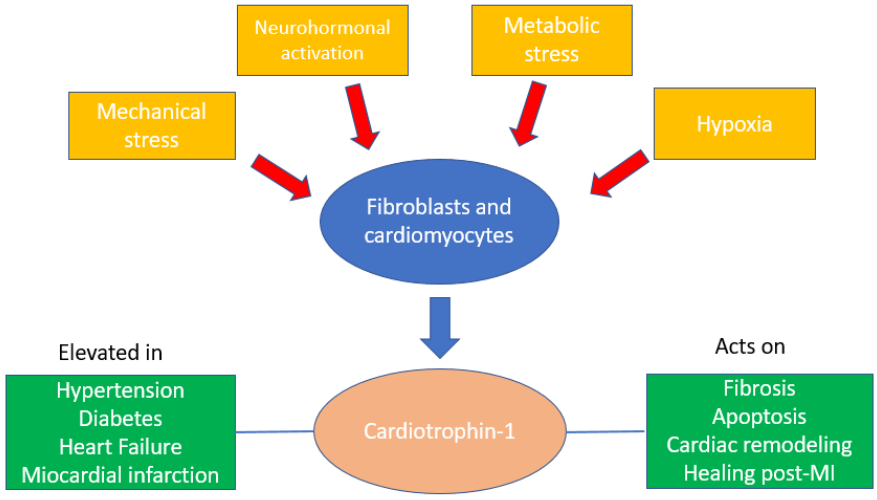

Figure 1 – Summary of known stimuli for cardiotrophin-1 upregulation in the heart and its relationship with cardiovascular diseases. MI: myocardial infarction

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ORIGINAL ARTICLE

Pericardial Effusion and Cardiac Tamponade: Etiology and Evolution in the Contemporary Era

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Abstract

Background: Pericardial effusion is a relatively common finding and can progress to cardiac tamponade; etiological diagnosis is important for guiding treatment decisions. With advances in medicine and improvement in the social context, the most frequent etiological causes have changed.

Objectives: To evaluate the clinical and laboratory characteristics, etiology, and clinical course of patients with pericardial effusion and cardiac tamponade.

Materials and methods: Patients with pericardial effusion classified as small (< 10 mm), moderate (between 10-20 mm), or severe (> 20 mm) were included. Data from the clinical history, physical examination, laboratory tests, and complementary tests were evaluated in patients with pericardial effusion and cardiac tamponade. The significance level was set at 5%.

Results: A total of 254 patients with a mean age of 53.09 ± 17.9 years were evaluated, 51.2% of whom were female. A total of 40.4% had significant pericardial effusion (> 20 mm). Pericardial tamponade occurred in 44.1% of patients. Among pericardial effusion patients without tamponade, the most frequent etiologies were: idiopathic (44.4%) and postsurgical (17.6%), while among those with tamponade, the most frequent etiologies were postsurgical (21.4%) and postprocedural (19.6%). The mean follow-up time was 2.2 years. Mortality was 42% and 23.2 in those with and without tamponade, respectively (p=0.001).

Conclusions: There is an etiological difference between pericardial effusion patients with and without cardiac tamponade. An idiopathic etiology is more common among those without tamponade, while postinterventional/postsurgical is more common among those with tamponade. The tamponade group had a higher mortality rate.

Keywords: Pericardium; Pericarditis; Cardiac Tamponade/therapy; Pericardial Effusion/therapy.

Introduction

Pericardial effusion is a common finding in clinical practice and could be due to systemic disease or a cardiac problem. Some patients with pericardial effusion also have cardiac tamponade, which is characterized by a drop in cardiac output, jugular venous distension, muffled heart sounds, arterial hypotension, and systemic hypoperfusion. Cardiac tamponade is a serious condition that requires rapid intervention.[1-8]

Some of the etiologies of pericardial effusion include neoplasm, infection, and tuberculosis in developing countries. It has been closely related to immunodepression, iatrogenesis, connective tissue diseases, and postsurgical complications. Moreover, the etiology of many patients is idiopathic.[1] There has been a significant increase in cardiac procedures in recent decades, both diagnostic and therapeutic, in addition to the more frequent use of anticoagulants or antiplatelet agents. This has led to an increased incidence of pericardial effusion after procedures such as cardiac catheterization, angioplasty, arrhythmia ablation, and implantation of pacemakers and percutaneous prostheses.[1,9-14]

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The most frequent etiologies differ depending on the type of cohort studied, as well as the region where in which the study was conducted. In addition, with advances in medicine and improvement in the social context, the most frequent etiologies have changed.[1-10] The present study, conducted at a tertiary cardiology center, selected patients who had pericardial effusion with or without cardiac tamponade and evaluated their clinical, laboratory, and etiological characteristics, in addition to their clinical course.

Material and methods

This retrospective cohort study included patients diagnosed with pericardial effusion with or without cardiac tamponade who were treated in the outpatient or inpatient unit of a tertiary cardiology center in the city of São Paulo between March 2007 and March 2018. The inclusion criteria were a diagnosis of pericardial effusion with or without cardiac tamponade. The included patients were admitted through the Brazilian Unified Health System. We assessed the patients' medical records and contacted them to assess survival. From the medical records, we evaluated clinical data (blood pressure, heart rate, jugular venous distension, pericardial friction, paradoxical pulse, Kussmaul's sign, edema, and ascites), laboratory data, and echocardiography, as well as pericardial biopsy and analysis of pericardial fluid in patients with cardiac tamponade. At the discretion of the attending physician, pericardial biopsy was indicated for patients with refractory recurrent pericarditis, as well as those with suspected neoplastic disease or tuberculosis. We also evaluated postprocedural complications, which were defined as pericardial effusion or tamponade after an angioplasty, ablation, or pacemaker procedure. Patients with recurrent pericardial effusion or tamponade were also evaluated.

The size of the pericardial effusion was quantified with two-dimensional echocardiography and was divided into small effusion (size in the M mode < 10 mm and visualized only in the posterior part of the left ventricle), moderate (size between 10 and 20 mm and encompassing the entire heart), or major (echo-free spaces > 20 mm).[7] Cardiac tamponade was diagnosed using the clinical picture (decreased cardiac output, hypotension, muffled heart sounds, jugular venous distension, hypoperfusion) and echocardiogram to confirm the presence of pericardial effusion. All echocardiograms were performed at our service.

This study was approved by the Ethics Committee of the Hospital das Clínicas of the University of São Paulo Faculty of Medicine (CAPPesq: 2,885,227, 11/09/2018).

Statistical analysis

Initially, all variables were analyzed descriptively. Quantitative variables were analyzed as minimum and maximum values and by calculating the mean and standard deviation. For qualitative variables, absolute and relative frequencies were calculated. Data normality was assessed using the Kolmogorov-Smirnov test. An unpaired Student's *t*-test was used to compare means between the two groups. The chi-square test or Fisher's exact test was used to test homogeneity. The Kaplan-Meier curve was used to study survival. SPSS 17.0 was used for the calculations; a 5% significance level was used for the tests.

Results

A total of 254 patients (mean age 53.09 [SD,17.9] years; 51.2% female) diagnosed with pericardial effusion or cardiac tamponade were included. Table 1 lists the patients' clinical characteristics. A total of 40.4% of the patients had a significant pericardial effusion (> 20 mm) and 112 (44.1%) had cardiac tamponade. The group with tamponade had a higher percentage of effusion > 20 mm than the group without tamponade (Table 2). The group with tamponade had a significantly higher percentage of complications, such as jugular venous distension, pericardial friction, paradoxical pulse, Kussmaul's sign, and muffled heart sounds. Table 3 compares the group characteristics.

In the overall sample, idiopathic pericardial effusion was the most frequent etiology (84 patients, 33.1%), followed by postsurgical (49 patients, 19.3%), neoplastic (43 patients, 16.9%), and postprocedural complications (angioplasty, ablation and pacemaker)(22 patients, 8.7%). Table 4 shows all observed etiologies. When the etiologies were compared according to the presence or absence of tamponade, the most frequent ones in the group without tamponade were idiopathic (44.4%), post-cardiac surgery (17.6%), and neoplasm (16.2%), whereas in the group with tamponade, the most frequent etiologies were postsurgical (21.4%), postprocedural (19.6%), idiopathic (18.8%), and neoplastic (17.9%) (Table 5).

When the groups were compared regarding the need for pericardiocentesis, recurrence, and medication type,

Table 1 – Clinical and demographic characteristics of the total population

Variable	(n=254)
Age years (mean ± SD)	53.09 ± 17.95
Female n (%)	130 (51.2)
Hypertension n (%)	120 (49.2)
Diabetes n (%)	53 (21.7)
Jugular venous distension n (%)	99 (42.7)
Pericardial friction n (%)	28 (12.1)
Paradoxical pulse n (%)	63 (27.3)
Kussmaul's sign n (%)	64 (27.7)
Muffled heart sounds n (%)	95 (41.1)
Edema n (%)	71 (30.7)
Systolic blood pressure mmHg (SD)	119.27 (25.01)
Heart rate, mean (SD)	88.94 (22.31)
Ascites n (%)	8 (3.5)

Table 2 – Classification of effusion by echocardiography according to the patient's clinical condition (presence or absence of clinical tamponade)

Variable	(n=254)	Cardiac tamponade		p
		No (n=142)	Yes (n=112)	
Pericardial effusion n (%)				0.042*
<10	75 (29.8)	39 (27.6)	36 (32.4)	
10-20	75 (29.8)	51 (36.2)	24 (21.6)	
>20	102 (40.4)	51 (36.2)	51 (46.0)	

** Likelihood ratio test - descriptive probability level*

the group with tamponade had a significantly higher percentage of pericardiocentesis and death (Table 6). The overall mortality rate was 31.5% (80 patients), being significantly higher in the group with tamponade (42%) than the group without it (23.2%)(P=0.001). Patient follow-up time ranged from 0 days to 10.5 years (mean 2.22 years, SD 2.70 years; median 1.07 years). According to the Kaplan-Meyer curve, there was a significant difference in survival time between the groups (log rank test: P=0.004), which was shorter in the group with tamponade (Figure 1).

Discussion

The most frequent etiologies of pericardial effusion in our sample were idiopathic, followed by post-cardiac surgery and neoplastic. However, when we separated the groups according to the presence or absence of cardiac tamponade, the most frequent etiology in patients without tamponade was idiopathic, followed by post-cardiac surgery and neoplastic, similar to the general group. However, in those with tamponade, the most frequent etiology was post-cardiac surgery, followed by

Table 3 – Clinical and demographic differences between patients with and without cardiac tamponade

Variable	(n=254)	Cardiac tamponade		p
		No (n=142)	Yes (n=112)	
Age years (mean + SD)	53.09 (17.95)	51.54 ±17.70	55.06±18.16	0.120*
Female n (%)	130 (51.2)	74 (52.1)	56 (50.0)	0.738†
Hypertension n (%)	120 (49.2)	66 (49.3)	54 (49.1)	0.980†
Diabetes n (%)				0.690§
Yes	53 (21.7)	29 (21.6)	24 (21.8)	
Previous pericarditis n (%)	15 (6.2)	13 (9.7)	2 (1.8)	0.011†
Fever n (%)	20 (8.2)	13 (9.7)	7 (6.4)	0.344†
Radiotherapy n (%)	14 (5.7)	6 (4.4)	8 (7.3)	0.336†
Mean height (SD)	163.07 (12.45)	163.10 (11.74)	163.04 (13.35)	0.971*
Mean weight (SD)	70.25 (18.70)	69.66 (18.82)	71.03 (18.61)	0.577*
Mean BMI (SD)	26.01 (5.79)	25.93 (5.99)	26.11 (5.55)	0.821*
Jugular venous distension n (%)	99 (42.7)	44 (34.1)	55 (53.4)	0.003†
Pericardial friction n (%)	28 (12.1)	4 (3.1)	24 (23.3)	<0.001†
Paradoxical pulse n (%)	63 (27.3)	8 (6.3)	55 (53.4)	<0.001†
Kussmaul's sign n (%)	64 (27.7)	16 (12.5)	48 (46.6)	<0.001†
Muffled heart sounds n (%)	95 (41.1)	32 (25.0)	63 (61.2)	<0.001†
Edema n (%)	71 (30.7)	39 (30.5)	32 (31.1)	0.922†
Mean SBP (SD)	119.27 (25.01)	122.29 (21.85)	115.76 (27.95)	0.070*
Mean DBP (SD)	73.45 (15.05)	76.51 (13.91)	69.92 (15.61)	0.002*
Mean HR (SD)	88.94 (22.31)	88.38 (17.88)	89.64 (26.83)	0.694*
Ascites n (%)	8 (3.5)	4 (3.1)	4 (3.9)	1.000§

**Student's t-test - descriptive probability level*
† Chi-square test - descriptive probability level
‡ Likelihood ratio test - descriptive probability level
§Fisher's exact test - descriptive probability level

postprocedural, idiopathic, and neoplastic. Mortality was higher in the group with cardiac tamponade.

The frequency of pericardial effusion etiologies varies in the literature according to geographic distribution, selection criteria, and type of medical service, ie, a tertiary, secondary, or primary reference center. We found a number of different etiologies for pericardial effusion.[6] Corey et al.,[7] evaluated 57 patients with pericardial effusion > 10 mm, finding that the most frequent etiology was infectious (27%), followed by neoplastic (23%). In a study of 322 patients with pericardial effusion > 10 mm by Sagrista et al.,[8] the most frequent etiology was idiopathic (29%), followed by iatrogenic (16%), and neoplastic (13%); 37% of the sample had cardiac tamponade. A 2003 study by Levy et al.,[9] evaluated 204 patients with pericardial effusion, and the most frequent etiologies were idiopathic (48%), infectious (16%), and neoplastic (15%). In our study of 254 patients with pericardial effusion, most had an idiopathic etiology (33.1%), followed by postsurgical (19.3%), neoplastic (16.9%) and postprocedural (8.7%). However, when patients with and without tamponade were analyzed separately, we found a difference in etiology: in patients without tamponade, the most frequent causes were

Table 4 – Etiology of pericardial effusion and cardiac tamponade: overall study population

Etiology	(n=254) n (%)
Idiopathic	84 (33.1)
Post-cardiac surgery	49 (19.3)
Cancer	43 (16.9%)
Lung neoplasm	19 (7.5)
Breast neoplasm	5 (2.0)
Lymphoma	6 (2.4)
Other neoplasms	13 (5.1)
Postprocedural	22 (8.7)
Collagenous	13 (5.1)
Tuberculosis	13 (5.1)
Post-acute myocardial infarction	7 (2.8)
Renal	6 (2.4)
Bacterial	6 (2.4)
Acquired immunodeficiency syndrome	5 (2.0)
Aortic dissection	3 (1.2)
Hypothyroidism	2 (0.8)
Chylopericardium	1 (0.4)

Table 5 – Relationship between etiology and the presence or absence of tamponade

Variable	(n=254)	Cardiac tamponade		p*
		No (n=142)	Yes (n=112)	
Etiology	n (%)	n (%)	n (%)	<0.001
Tuberculosis	13 (5.1)	8 (5.6)	5 (4.5)	
Cancer	43 (16.9)	23 (16.2)	20 (17.9)	
Collagenous	13 (5.1)	7 (4.9)	6 (5.4)	
Postprocedural	22 (8.7)	0 (0.0)	22 (19.6)	
Postsurgical/pericardiectomy	49 (19.3)	25 (17.6)	24 (21.4)	
Idiopathic	84 (33.1)	63 (44.4)	21 (18.8)	
Other	30 (11.8)	16 (11.3)	14 (12.5)	

Table 6 – Absolute frequencies (%) of the variables (intervention and recurrence) in the clinical course of 254 patients according to the presence or absence of tamponade

Variável	(n=254)	Cardiac tamponade		p*
		No (n=142)	Yes (n=112)	
Pericardiocentesis	194 (76.4)	99 (69.7)	95 (84.8)	0.005
Recurrence	14 (5.5)	8 (5.6)	6 (5.4)	0.924
Non-hormonal anti-inflammatory	188 (74.0)	100 (70.4)	88 (78.6)	0.142
Colchicine	34 (13.4)	23 (16.2)	11 (9.8)	0.138
Corticoid	111 (43.7)	60 (42.3)	51 (45.5)	0.601
Death	80 (31.5)	33 (23.2)	47 (42.0)	0.001

** Chi-square test - descriptive probability level*

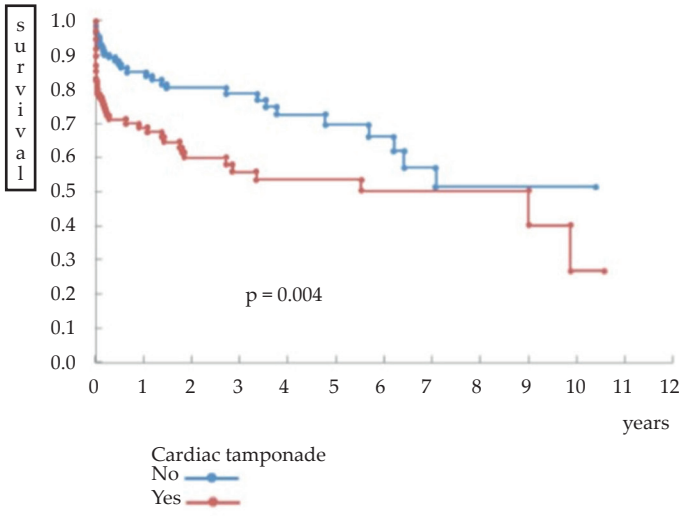

Figure 1 – Kaplan-Meier survival curve according to the presence or absence of cardiac tamponade.
(Yes = with tamponade; No = without tamponade)

idiopathic (44.4%), postsurgical (17.6%), and neoplastic (16.2%), whereas in patients with tamponade, the most frequent causes were postprocedural (19.6%), idiopathic (18.8%), and neoplastic (17.9%).

Our study found that cardiac procedures, such as angioplasty, pacemaker implantation and arrhythmia ablation, are important in the etiology of cardiac tamponade, and these procedures are increasingly performed. Recent studies indicate the growth of this etiology. A 2016 study by Orbach et al.,[10] of patients with cardiac tamponade found that the main etiology was percutaneous cardiac intervention (36%), followed by neoplasia (23%), infectious and inflammatory causes (15%), and mechanical complications of myocardial infarction (12%).

In cancer patients, pericardial effusion can develop through various mechanisms, such as direct extension or metastatic dissemination, or as a complication of systemic tumor treatment with radiotherapy and chemotherapy, although it may also be due to an opportunistic infection. Thus, neoplastic diseases are a significant etiology of pericardial effusion or tamponade.[11-16] In our study,

neoplasia was a frequent cause of pericardial effusion, with or without cardiac tamponade. This etiology was found in 43 (16.9%) of our patients, the most frequent types being lung cancer (44.2%), lymphoma (13.9%), and breast cancer (11.6 %). In a 2013 review article by Burazor et al.,[11] pulmonary effusion varied between 34% and 76% in cancer patients, with breast cancer as the etiology in 15% to 17%. We should be aware that pericardial effusion can be one of the first manifestations of cancer, and pericardial fluid analysis and biopsy can be the key to diagnosing the primary tumor.

Despite progressive improvement in tuberculosis prevention, this etiology is still prevalent in our country. In tuberculous pericarditis, a bacillus is found upon direct examination in only 40% to 60% of patients undergoing pericardiocentesis. High adenosine deaminase activity is also diagnostic, with high sensitivity and specificity.[2] Our data showed an overall incidence of approximately 5.1%. An etiology of tuberculosis is highly dependent on region. In a review article by Mayosi[21], tuberculosis was the etiology in 69.5% of African pericardial effusion cases, compared to 3.8% in non-African countries.[22-23] Our results were comparable to non-African countries.

In evaluating the clinical course of patients, mortality is related to etiology and the presence or absence of tamponade. Our study found an overall mortality of 31.5% during follow-up, with a significantly higher mortality rate in patients with tamponade (42% vs. 23.2% p=0.001). We observed a new scenario for the etiology and clinical course of pericardial effusion. Burazor et al.,[11] highlighted the correlation between pericardial effusion and worse prognosis in cancer patients in their review of studies conducted between 1977 and 2007: 86% of cancer patients with pericardial effusion died in the first year and almost one-third died in the first month. It should be pointed out, however, that cancer therapy was not very advanced early in the review period.[11] A 2016 study by Orbach et al.,[10] of patients with pericardial effusion of various etiologies found that patients with iatrogenic pericardial effusion had a favorable evolution compared to those whose pericardial effusion was due to neoplasia, coagulation disorder, or infarction. These authors found the following mortality rates for hospitalized pericardial effusion patients according to etiology (total number; mortality after 30 days and 1 year of follow-up, respectively): inflammatory and infectious (8.3%; 16.7% and 16.7%), postsurgical complication (10.3%; 13.8% and 17.20%), neoplasia (15.8%; 36.8% and 68.4%), coagulopathy and bleeding (40%; 60% and 80%), and infarction (70%; 80% and 80%). This disease still has a high mortality rate, especially in cases of cardiac tamponade.

Study limitations

This single-center study was conducted in a tertiary hospital and based on the analysis of medical records. Although all echocardiograms were performed in our service, it should be pointed out that they were not performed by the same observer, which could have biased the classification of pericardial effusion. Due to the convenience sampling and lack of sample size estimation, any statistical inferences are exploratory.

Conclusions

In the present study, which was carried out in a tertiary cardiology hospital, the most frequent etiologies were idiopathic, followed by post-cardiac surgery, neoplastic, and as a postprocedural complication. A significant percentage of the patients (44.1%) had cardiac tamponade. Among those without tamponade, the most frequent etiologies were idiopathic, postsurgical, and neoplastic, while among those with tamponade, the most frequent etiologies were postsurgical, post-procedural, idiopathic, and neoplastic. Mortality was high overall (31.5%) and significantly higher in the group with tamponade. Patients with tamponade had shorter survival than those without it.

Author contributions

Conception and design of the research: Queiroz CM, Cardoso J, Fernandes F. Acquisition of data: Queiroz CM, Cardoso J, Dias RR, Mady C. Analysis and interpretation of the data: Queiroz CM, Cardoso J. Statistical analysis: Cardoso J. Writing of the manuscript: Queiroz CM, Cardoso J, Ramires FJA, Ianni BM, Buck PC. Critical revision of the manuscript for intellectual content: Cardoso J, Ramires FJA, Ianni BM, Hotta VT, Buck PC, Dias RR, Mady C, Fernandes F.

Potential Conflict of Interest

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

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Study Association

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

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the *Hospital das Clínicas da* FMUSP under the protocol number 2.885.227. 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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EDITORIAL

The Importance of Early Diagnosis and Treatment for Pericardial Effusion and Cardiac Tamponade

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Editorial referring to the article: Pericardial effusion and cardiac tamponade: etiology and evolution in the contemporary

Pericardial effusion has several etiologies, such as primary pericardial diseases, cardiac surgery, trauma and systemic conditions, including hypothyroidism, renal failure, chronic neoplastic infiltration, autoimmune inflammation, systemic lupus erythematosus, and rheumatoid arthritis . Queiroz et al.,[2] published an interesting paper on 254 patients with pericardial effusion at a quaternary institution, 40.4% with severe pericardial effusion and 44.1% with cardiac tamponade. Retrospective cohorts of critically ill patients are rare in the literature. The most frequent etiology was idiopathic, but postoperative, neoplasia, and postinterventional procedures were also common. Although the main etiology is idiopathic in developed countries, infectious causes are prominent in developing countries, such as tuberculosis, which reaches a frequency above 60%.[3] During the current COVID-19 pandemic, SARS-CoV-2 is of great importance in etiological investigation.

In Queiroz et al.,[2] pericardial effusion was diagnosed by echocardiography, a widely available and inexpensive method that can be performed at bedside. In addition to clinical and epidemiological aspects, Doppler echocardiography, magnetic resonance imaging, nuclear medicine tests, and laboratory analysis of the pericardial fluid could provide additional information about the etiology. However, the gold standard diagnostic exam is pericardial biopsy, which is indicated for diagnostic investigation in patients with persistent pericarditis refractory to clinical treatment and no definitive diagnosis.

Keywords

Pericardium/ abnormalities; Pericardial Effusion/ therapy; Cardiac Tamponade/ therapy; Echocardiography/ methods.

Cardiac tamponade is the most serious and potentially lethal spectrum of pericardial effusion. It is defined as a significant accumulation of fluid that exceeds the distension capacity of the pericardial fibroelastic tissue, leading to progressive compression of all cardiac chambers due to increased intrapericardial pressure, reduced cardiac filling volume and greater ventricular interdependence.[4] Its development depends on the speed of accumulation and the causal factor: acute cardiac tamponade occurs within minutes, resulting in cardiogenic shock, while subacute cardiac tamponade occurs over days or weeks. Regional cardiac tamponade occurs when a localized effusion or hematoma produces regional compression in a single chamber.[5]

Clinical diagnosis of cardiac tamponade is based on Beck's triad (arterial hypotension, jugular distension, and muffled heart sounds) and the presence of paradoxical arterial pulse. Doppler echocardiography shows changes that appear prior to the clinical syndrome. These changes include cava dilation with little respiratory variation, diastolic collapse of the right ventricle free wall, right atrium, left atrium, and, rarely, the left ventricle, increased tricuspid flow and reduced mitral flow during inspiration, and the opposite at expiration. Right atrial collapse is a more sensitive sign, while right ventricle collapse is the more specific.[6]

In Queiroz et al.,[2] the patients were followed-up for 2.22 years and, as expected, the tamponade group had a worse prognosis. Cardiac tamponade treatment consists of draining the pericardial fluid to reduce intrapericardial pressure and, thus, improve patient hemodynamics. Pericardial drainage can be performed through a percutaneous puncture and placement of a drainage catheter, through open surgical drainage with

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or without pericardiectomy, or through video-assisted pericardioscopy.[7,8] Catheter drainage may require a few days and the catheter should not be removed until the drainage falls below 20-30 ml/24 h. The advantage of surgical drainage is that it allows pericardial biopsy, which is recommended in cases of recurrence after catheter drainage, as well as in cases of clots or effusions inaccessible by the percutaneous route.[9] A recent study proposed a prediction score consisting of systolic blood pressure < 100 mmHg (1.5 points), effusion diameter [1-2 cm (0 points), 2-3 cm (1.5 points), > 3 cm (2 points)], right ventricular diastolic collapse (2 points), and mitral inflow velocity variation > 25% (1 point). The need for pericardial drainage was high in patients with scores ≥ 4.[10] These four variables can be easily obtained at bedside and facilitate the difficult decisions required to improve patient outcomes.

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ORIGINAL ARTICLE

Clinical Characteristics and Mid-Term follow-up of Elderly Patients with Severe Aortic Stenosis not Eligible for TAVI

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Abstract

Background: The treatment for symptomatic severe aortic stenosis (AS) is the correction of valve stenosis by surgical valve replacement and more recently by transcatheter aortic valve implant (TAVI). However, in some high risk surgical patients, TAVI is not possible for technical or clinical reasons or due to the unavailability of the endoprosthesis.

Objective: The aim of this study was to evaluate a mid-term follow-up of symptomatic severe AS patients who are not eligible for TAVI trials, as well as to identify the clinical features of these patients.

Methods: This was an observational, retrospective study conducted with 475 symptomatic severe AS patients, evaluated by the Heart Team between 2000 and 2017. Inclusion criterias were: patients considered not to be eligible for TAVI. The Shapiro-Wilk test was applied to evaluate normality. Non-paired t and Mann-Whitney tests were applied for continuous variables, while the chi-squared and Fischer exact tests were applied for categorical variables, with a level of significance of p<0,05.

Results: The heart team evaluated 475 patients: 25 (5.26%) died before any intervention could be proposed; 326 (68.3%) were submitted to TAVI, so the study population consisted of 124 patients not eligible for TAVI. Of these, 31 (25%) underwent surgery and 93 (75%) remained in clinical treatment. In a mean 56 months- follow-up the mortality in clinical group was 46.2%. In the surgical group the mortality was 23.9% (in-hospital 12.9% and late mortality 11% in a mean 47.4 months follow-up). The patients that died presented a significantly lower left ventricle ejection fraction (LVEF), a smaller valve area, and a larger end-systolic diameter of the LV.

Conclusion: The mortality of the clinical group's patients was significantly higher than the surgical mortality (46.2% vs. 12.9%; p=0.021). The patients of the clinical group were older, weighed less, and had a higher incidence of renal failure and a higher STS score.

Keywords: Aortic valve stenosis, TAVI, transcatheter prosthesis implant, aortic valve replacement.

Introduction

Degenerative aortic stenosis (AS) is the most common form of valve disease in the Western world, especially in the population over 75 years of age,[1-3] with a progressive increase in prevalence with advancing age.[3,4] It merits particular attention for its clinical importance and its growing socio-economic impact.

The natural history of the disease consists of a prolonged latent period of low morbidity and mortality.[2] However, when symptoms of angina, syncope, or cardiac insufficiency develop, the average survival drops, and there is a progressive increase in the risk of sudden death.[2] However, in clinical practice, at least 30% of patients with symptomatic AS aged 75 or older do not undergo surgery due to their advanced

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age and comorbidities that increase the risk of surgery.[5] Without surgery, the rate of survival after three years of severe symptomatic AS is 30%.[6,7] Patients in their 80s who remain in clinical treatment have a survival rate of 65.8% at one year and 41.8% at two years, regardless of the associated symptoms.[8]

Transcatheter aortic valve implantation (TAVI) has gained prominence among the treatment options for AS. Studies have shown an increasing role of this method. In high-risk patients, TAVI is not inferior to conventional surgery.[9-12] In the intermediate-risk patients, TAVI, and surgical treatment have been shown to have equal mortality rates, though TAVI can have better results than surgery when transfemoral access is possible.[13-15] In low-risk patients, TAVI is also comparable or even better than surgery in patients with mean age of 73 years.[16,17]

It is still the case that the vast majority of patients who are referred for TAVI are those for whom surgery presents a high risk. However, some are not clinically or anatomically fit to undergo any intervention at all, surgical or percutaneous.

Besides, TAVI is not available to patients in Brazilian hospitals belonging to the Unified Health System (SUS) except for those included in research trials. Therefore, for patients who are excluded from such trials, for those that surgical treatment is clinically or technically contraindicated or for those who do not agree to undergo surgery, clinical management is the only possible option.

Objectives

To evaluate the mid-term clinical follow-up of patients with severe symptomatic AS who are not eligible for TAVI research trials and to identify the clinical characteristics of these patients.

Methods

This is a retrospective observational study to evaluate patients with severe symptomatic AS who were attended in the valve disease outpatient clinic at a tertiary cardiac hospital between 2000 and 2017.

Severe AS were defined as an aortic valve area ≤ 1.0 cm^2, transaortic mean pressure gradient (ΔP) ≥ 40 mmHg or peak aortic jet velocity ≥ 4.0 m/s in the presence of normal or reduced left ventricle function. Patients with valve area ≤ 1.0 cm^2, a mean gradient lower than 40 mmHg and low ejection fraction (EF), were submitted to dobutamine stress transthoracic echocardiogram, in line with the criteria defined by the Brazilian Society of Valve Disease and the American Society Echocardiography.[18,19]

Clinical, epidemiological, laboratory, and echocardiography characteristics were evaluated, along with findings from tomography and cinecoronariography. The stratification of perioperative risk used scoring from the Society of Thoracic Surgeons (STS) and EuroSCORE II.

Inclusion criteria: patients with severe AS, symptomatic, considered not to be eligible for TAVI by the Heart Team and thus referred for aortic valve replacement surgery or conservative treatment due to anatomical difficulties or clinical criteria.

Exclusion criteria: patients with severe AS, symptomatic, considered to be eligible for TAVI by the Heart Team.

Statistical analysis

Statistical analysis was carried out using the program Statistical Package for Social Sciences (SPSS), version 19.0. The Shapiro–Wilk test was used to assess normality. Continuous variables with a normal distribution were described by their mean and standard deviation, while continuous variables with a non-normal distribution were described using their median and interquartile range. Significant differences were determined using the unpaired *t*-test for normally distributed variables and the Mann–Whitney test for non-normally distributed variables. Categorical variables were presented as percentages using the chi-squared and Fisher exact tests. Statistical significance was defined as $p < 0.05$.

Results

Between 2000 and 2017, a total of 475 patients with a diagnosis of severe AS were evaluated by the local heart team. Of these, 25 (5.26%) patients died before an intervention could be proposed, and 326 (68.3%) underwent TAVI. The remaining 124 patients who were not eligible for TAVI were included in this study. Thirty-one (25%) underwent valve replacement surgery and 93 (75%) remained in clinical treatment (Figure 1).

The main clinical characteristics of the 124 patients included in this study are provided in Table 1, while Table 2 provides echocardiographic results. The mean age was 80.66 ± 6.37 years, with women making up the majority of the study group and 44.5% were in functional class III. The mean STS score was 6.8 ± 5.27%, and the

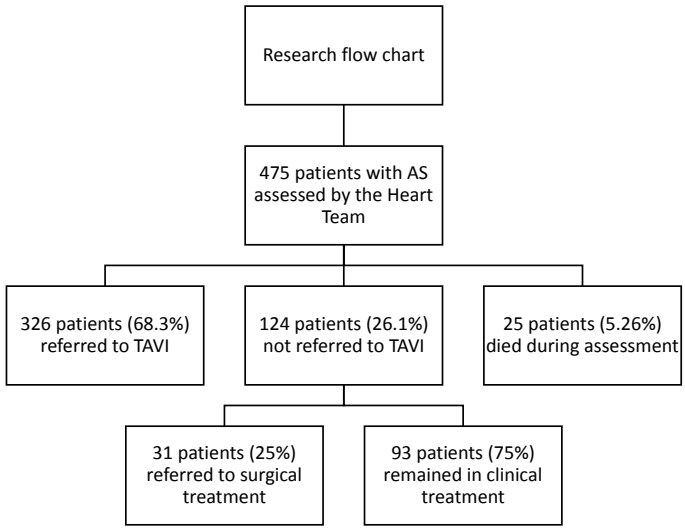

Figure 1 – Research flowchart

mean EuroSCORE II was 17.3 ± 11.03%. In addition, 31 (25.6%) patients had moderate to severe mitral insufficiency. Mean left ventricle ejection fraction (LVEF) was 53% ± 18.25% and mean creatinine clearance (CrCl) was 48.37 ± 17.67 mL/min.

The clinical reasons for inegibility for TAVI–trials were as follows: presence of a thrombus in the left ventricle, severe chronic obstructive pulmonary disease (COPD), coronary disease with indication for surgery, symptomatic carotid disease, contraindication for antiplatelet drugs and life expectancy less than one year (16.5%).

The anatomical contraindications for TAVI included inadequate vascular access due to severe calcification, reduced arteries diameters or severe aortic/iliofemoral tortuosity, insufficient height of the coronary arteries relative to the valvar plane and bicuspid aortic valve.

Of these 124 patients, 31 (25%) underwent conventional valve replacement and 93 (75%) remained in clinical treatment. The main reasons for patients did not go for surgery are: life expectancy less than one year and refusal of surgical procedures.

Table 3 shows the characteristics of clinical and surgical patients. In the clinical group the patients were older, weighed less, had a lower CrCl, and higher STS risk score. There was no difference between the groups in terms of the EuroSCORE. Patients referred to surgery had more symptoms. The mean LVEF, mean gradient and mean aortic valve area were similar between both groups, as well as the LV end-diastolic and end-systolic diameters.

The total mortality of the 124 non-TAVI eligible patients with severe AS was 39.5% (49 patients). Concerning the 93 patients who remained in clinical treatment, 42 (46.2%) died within 56 months of average follow-up. Meanwhile, the 30-day mortality among the operated patients was 12.9%. Late mortality within the surgical sub-group was 11% within an mean 47.4 months follow-up.

Patients who died had a lower LVEF and more severe AS, as indicated by valve area and end-systolic diameter of the left ventricle.

Discussion

In our midst there is few data on the patients outcomes with severe symptomatic AS, who remained in clinical treatment or underwent valve replacement surgery despite the high surgical risk. Evaluating these patients is of considerable importance since the Brazilian population is aging significantly, with the prevalence of aortic stenosis rising as a consequence.

The PARTNER I study showed that TAVI was more effective than clinical treatment for inoperable patients. The follow up showed a mortality of 38,9% in 3- to 5 years in the TAVI group, against a mortality of 66,7% in the clinical group. In addition, the clinical group had a higher rate of rehospitalization within five years (87.6% vs. 47.6%)[10].

Table 1 – Clinical characteristics of the study population (124 patients ineligible for TAVI)

Variable	Measurement
Age (years)	80.66 ± 6.37
Gender (%)	
Male	37%
Female	63%
Weight (kg)	65.88 ± 15.3
STS score (%)	6.8 ± 5.27
EuroSCORE (%)	17.3 ± 11.03
NYHA (n = 124)	
I	16%
II	33.6%
III	44.5%
IV	5.9%
Serum creatinine (mg/dL)	1.23 ± 0.48
Creatinine clearance (mL/min)	48.37 ± 17.67
Hemoglobin (mg/dL)*	12.75 (10.86 – 14.64)
Hematocrit (%)*	39.1 (33.34 – 44.86)
Atrial fibrillation (%)	0.7%
COPD (%)	9.2%
DAPT contraindication (%)	2.6%
Life expectancy of < one year (%)	16.5%
Symptomatic carotid disease (%)	7.6%
Neoplasia (%)	5.6%

STS: Society of Thoracic Surgeons. NYHA: New York Heart Association. COPD: Chronic Obstructive Pulmonary Disease. DAPT: Dual Anti-Platelet Therapy.
** Expressed as median ± interquartile range (Q1 – Q3).*

Table 2 – Baseline echocardiographic findings

Variable	Measurement
LVEF (%)	55.84 ± 15.35
Mean aortic-valve gradient (mmHg)	53 (34.75–71.25)
Max. aortic-valve gradient (mmHg)	80.5 (51–110)
Aortic valve area (cm^2)	0.81 ± 0.27
LVEDD (mm)	51.43 ± 7.72
LVEDV (mL)	127.56 ± 45.96
LVESD (mm)	33.1 ± 8.32
LVESV (mL)	64.41 ± 23.35
Thrombus (%)	1.7%
Bicuspid valve (%)	4.3%
Mitral insufficiency	
Absent/Discrete	74.3%
Moderate	16.2%
Severe	9.4%

LLVEF: left ventricle ejection fraction. LVEDD: left ventricle end-diastolic diameter. LVESV: left ventricle end-systolic volume. LVESD: left ventricle end-systolic diameter. LVEDV: left ventricle end-diastolic volume.
**Expressed as median ± interquartile range (Q1–Q3).*

This study evaluated 475 elderly patients with severe and symptomatic AS. The institution's Heart Team was responsible for deciding between conservative treatment, transcatheter prosthesis implantation, or surgical treatment. In doing so, they considered both the inclusion protocols in use at the institution and the clinical and technical contraindications for TAVI.

It is well-known in cardiology that patients with severe and symptomatic AS have a reduced survival rate following the onset of the classic symptoms of heart failure, syncope, or angina.[2] The only treatment that reduces mortality is correcting the valve obstruction.[20] Until recently, the only option was valve replacement surgery. However, due to the age of patients with calcific AS and associated comorbidities, many symptomatic patients remain in clinical treatment. TAVI has recently emerged as an alternative to valve replacement surgery in patients of advanced age or patients with a technical contraindication to surgical intervention.[10]

In this study, 124 of 475 patients (26%) were ineligible for TAVI trials for technical or clinical reasons by the Heart Team decision. In the literature, the factors for which patients are not referred to valve replacement include age, left ventricular systolic dysfunction, and the presence of comorbidities, such as renal failure, COPD, and coronary disease. Of these factors, age and left ventricle function appear to have the greatest negative impact on the decision to operate.[20] In this study, the main reasons for choosing clinical treatment were the patient's refusal to undergo valve disease correction, associated comorbidities, technical contraindication, and low life expectancy (futile treatment). Some patients also had a

Table 3 – Comparison between clinical treatment and surgical treatment groups

	Clinical treatment (93 patients)	Surgical treatment (31 patients)	*p*
Age (years)	81.91 ± 6.1	76.87 ± 5.71	< 0.01
Sex (%)			
Male	34.1%	45.2%	0.272
Female	65.9%	54.8%	
Weight (kg)	64.2 ± 16.2	70.5 ± 11.6	0.011
STS score (%)	7.2 ± 5.23	5.7 ± 5.31	0.004
EuroSCORE (%)	17.8 ± 10.7	15.9 ± 12	0.206
NYHA (%)			
I - II	53.5%	38.7%	
III-IV	46.5%	61.3%	0.023
Serum creatinine (mg/dL)	1.26 ± 0.54	1.14 ± 0.28	0.674
Creatinine clearance (mL/min)	45.17 ± 17.5	56.6 ± 15.4	0.002
Hemoglobin (mg/dL)*	12.7 (11.3 – 14)	12.8 (11.2 – 4.3)	0.95
LVEF (%)	55.74 ± 15.92	56.1 ± 13.8	0.961
Mean aortic-valve gradient (mmHg)	45 (36 – 57)	50.5 (40.5 – 62.5)	0.249
Max. aortic-valve gradient (mmHg)	75.5 (60 – 88.7)	76.5 (69.7 – 95.5)	0.273
Aortic valve area (cm^2)	0.82 ± 0.24	0.79 ± 0.34	0.26
LVEDD (mm)	51.2 ± 7.9	52.14 ± 7.28	0.567
LVESD (mm)	33.22 ± 8.6	32.6 ± 7.08	0.975

STS: Society of Thoracic Surgeons. NYHA: New York Heart Association. LVEF: left ventricle ejection fraction. LVESD: left ventricle end-systolic diameter. LVEDD: left ventricle end-diastolic diameter.
** Expressed as median ± interquartile range (Q1–Q3).*

technical contraindication to surgery, such as porcelain aorta, or contraindications to TAVI such as significant peripherical artery disease or inadequate aortic annulus size. The Heart Team's evaluation considered invasive treatment to be futile in 16.5% of the patients analyzed; in this population, the life expectancy was less than one year.

Besides, this was a group with elevated risk of mortality, which was confirmed by the high incidence of death before an intervention could be proposed (5.26%). Since these patients were elderly and had severe and symptomatic AS, most of the 475 patients assessed by the Heart Team were referred for TAVI (68.3%), while 19,5% remained in clinical treatment for several reasons mentioned earlier, and only 6.5% could be referred for surgery. Despite the high surgical mortality (12.9%), it was significantly less than for patients who remained in clinical treatment (46,2%). In this sample, it is noteworthy that the surgical mortality was closer to the EuroSCORE projection (17.3 ± 11.03 %). Our data are consistent with the literature, which reports surgical mortality of up to 14% for octogenarians.[21]

The high mortality observed in the clinical sub-group is not a surprising finding. It is well established in the literature on the natural history of AS that shows a 2-3 year patient survival after symptoms begin (angina and dyspnea).[22]

TAVI is an innovative procedure that uses a minimally invasive technique, reduces symptoms and improves the quality of life in elderly patients with severe symptomatic AS.[10] However, this procedure is not yet covered by most private health insurance providers in Brazil nor by SUS, the country's publicly funded health care system .

Although the sample size of this study was fairly small, it represents the reality of elderly symptomatic aortic patients who remain in clinical treatment.

In this study, 26.1% of elderly patients with symptomatic aortic stenosis were ineligible for TAVI research trials, and only 6.5% could be referred to surgery. The authors would like to note that the patients who remained in clinical treatment may have indeed been able to undergo TAVI if the procedure had been available from SUS since the inclusion criteria in the research protocols were more rigid than those for TAVI in clinical practice.

Limitations

This retrospective and observational study evaluated patients with severe AS and high surgical risk who were not eligible for TAVI. It did not discuss the patients late follow-up who underwent TAVI, which could enrich the results obtained. However, since the SUS represents the healthcare reality for most of our country's population, it is important to study the patients' outcomes excluded from the research protocols.

Conclusion

Of the 475 patients with severe symptomatic AS evaluated by the Heart Team, 124 (26.1%) patients were ineligible for TAVI for technical or clinical reasons. Of these, 75% remained in clinical treatment, and 25% were referred to surgery. The clinical mortality was significantly higher than the surgical mortality (46.2% vs. 12.9%; p=0.021). The patients who remained in clinical treatment were older, weighed less, had a higher incidence of renal failure and higher STS risk score.

Author contributions

Conception and design of the research: Ramos AIO, Rezende MO. Acquisition of data: Rezende MO, Dos Santos NSS, Targino DVD, Francischini MS, Andrade AIA, Souza CS, Maldi CP. Analysis and interpretation of the data: Ramos AIO, Andrade AIA, Rezende MO. Statistical analysis: Ramos AIO, Andrade AIA, Rezende MO. Writing of the manuscript: Ramos AIO, Rezende MO, Andrade AIA, Dos Santos NSS, Siqueira DAA, Le Bihan David, Pinto IM. Critical revision of the manuscript for intellectual content: Ramos AIO.

Potential Conflict of Interest

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

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

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EDITORIAL

Clinical Characteristics and Mid-Term Follow-Up of Patients with Severe Aortic Stenosis and Those not Eligible for TAVI

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Editorial referring to the article: Clinical Characteristics and Mid-Term follow-up of Elderly Patients with Severe Aortic Stenosis not Eligible for TAVI

Aortic stenosis is an insidious disease with a long-term period of latency. It progresses rapidly after symptoms appear, esulting in a high mortality rate (approximately 50% in the first 2 years) in untreated symptomatic patients,[1] with sudden death being common in these individuals.

Approximately 30% of the patients aged 75 years or over are not candidates for surgical procedure[2] due to their advanced age, female sex, functional class, operatory emergency, ventricular dysfunction, pulmonary hypertension, previous heart surgery, associated coronary artery disease, among others. In the age range of patients in their 80s, those who remain in clinical treatment have a survival rate of 65.8% in the first year and 41.8% in the second year of follow-up.[3]

Transcatheter aortic valve replacement implantation (TAVI) has become the primary therapy for these patients. It initially demonstrated a non-inferiority as regards patient mortality in one year of follow-up when compared to valve replacement surgery in high-risk patients. In addition, when compared to standard therapy, it has proven that it is necessary to treat 5 patients to prevent 1 death in the period of one year of follow-up.[4] In the years that followed, it also showed its non-inferiority for intermediate[5,6] and low[7,8] surgical risk patients, according to Society of Thoracic Surgery (STS), when compared to conventional surgery.

Keywords

Aortic Valve Stenosis/surgery; Elderly; Mortality; Transcatheter Aortic Valve Replacement/methods.

According to the guidelines from the American Heart Association (AHA), the American College of Cardiology (ACC), and Society of Thoracic Surgery (STS),[9] the recommendation for TAVI has been reclassified as Class I; Evidence Level A, in high-risk patients, as well as a treatment option for intermediate-risk patients, classified as Class IIa; Evidence Level B. The most recent European guideline[10] is, in fact, more liberal in the indication in almost all of the elderly patient scenarios.

In the context of symptomatic severe degenerative aortic stenosis, most patients are elderly and have a predisposition for associated comorbidities. Thus, the deterrents, both for the surgical as well as the less invasive procedures, become more present and significant. Under ideal conditions, TAVI has proven to be the therapy of choice. Nevertheless, some anatomical, clinical, and mainly economic conditions have limited a broader adoption of this technique, which has transformed cardiology as we know it today, in turn engendering a new health challenge in society today.

In an attempt to evaluate the clinical evolution of patients who are not eligible for TAVI, Resende et al.,[11] published a retrospective observational study, which included the analysis of a databank of 475 patients with severe aortic stenosis who were evaluated by the Heart Team to define the proper therapy to be implemented between 2000 and 2017. Considering that 5.26% of the patients died and that 68.3% were recommended for TAVI, the remaining 124 patients were considered for the aim of this study. Of these, 25% were recommended for valve replacement surgery, while in "75% were opted" for the conservative clinical treatment.

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The results showed that, in the conservative group, the mortality rate was significantly lower when compared to the conventional surgery (46.2% vs. 12.9%; p=0.021). The clinical factors that stood out concerning this outcome were low weight, advance age, and worsened renal function. These factors are also commonly related to a worse outcomes at any stage of treatment. However, it is also well-known that the worse the scenario, the more benefit a potentially curative strategy can have upon one's quality of life or life expectancy.

TAVI became an ineligible procedure in the Resende et al.[11] series, considering the following clinical and anatomical factors: a life expectancy of less than one year, the presence of thrombosis in the left ventricle, important symptomatic carotid artery disease, contra-indication for antiplatelet therapy, severe COPD, coronary artery disease with recommendation for surgery, vascular trajectory inadequate due to tortuosity or calcification, and bicuspid aortic valve. It is known, however, that science and technology advance quickly and that many of these frontiers and limits have been overcome. The history of interventionist cardiology has proven this to us, especially in the field of structural pathologies. Nevertheless, the proper recommendation of TAVI, which is based on clinical criteria, adequate diagnostic confirmation, classification of severity, specific anatomical evaluation, and surgical risk, is essential for the success of the procedure. The best decision-making process always resides in the interdisciplinary teamwork and discussion among qualified and trained professionals. Two clinical findings presented here are considered to be absolute contra-indications to this procedure: a life expectancy of less than 1 year and the presence of thrombosis in the left ventricle. Others, however, such as peculiar situations of the trajectory and bicuspid aortic valve, have already been conducted in routine procedures in centers with greater experience and volume.

It is important to highlight that, for the case of bicuspid aortic valves, the elderly of over 80 years of age correspond to nearly 20% of the surgical cases. Some anatomical characteristics of this pathology, such as the oval form of the ring, the size, and the unequal calcification of the leaflets, confer less predictable results for the use of TAVI. But a recent meta-analysis of 13 observational studies containing data from 758 patients with bicuspid valves showed a 95% success rate for the device.[12]

Despite the limitations inherent to the study conducted by Resende et al.,[11] as this is an observational design with intrinsic selection biases, the clinical and anatomical aspects presented and the deterrents of TAVI reflect the hold-ups of the real world of healthcare practice in Brazil. Clinical judgment conducted by a Heart Team appears to be of utmost importance in choosing the proper therapy. Therefore, we should continue to work in such a way that more patients can be benefitted and receive universal access to this revolutionary, highly safe, and effective treatment. We are also eager for the possibility of adopting this procedure as a routine technique within the public healthcare network and for all individuals who fulfill the necessary clinical and anatomical criteria to be able to receive this treatment.

The challenges for the incorporation of new technologies are immense. But when science, good judgement, medical management focused on results, and the decision-making body walk hand-in-hand, the goals are more easily achieved. And the natural consequences and those benefitted from these actions are and always will be the patients and society in general.

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ORIGINAL ARTICLE

Stroke and Myocardial Infarction: Effects of the "Hiperdia" and "Mais Médicos" Programs on the Hospitalizations Trends in Brazil

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Abstract

Background: Stroke and acute myocardial infarction (AMI) are cardiovascular diseases commonly characterized by the development of atheromatous plaques associated with major complications and high mortality rates.

Objective: To identify an epidemiological trend in hospitalizations due to stroke and AMI and to analyze the relationship between health programs applied in Primary Health Care, gender and the Federative Unit.

Methods: Ecological study with a time series design between 1998 and 2018, collecting data from all federal units in Brazil stratified by, gender and place of residence. There were analyzed Hospitalization Authorizations (AIH) for stroke and MI, consulting the Hospital Admissions System (SIH) of the Informatics Department of the National Health Service with $p < 0.05$.

Results: From 1998 to 2018, the rate of hospitalization for AMI increased in Brazil approximately 42.58 events per 100 thousand inhabitants annually ($p<0.001$), while hospitalizations for stroke declined 32.17 cases ($p=0.03$). This pattern was observed in both sexes in AMI and stroke. There is also evidence of the effect of the Hiperdia ($p<0.001$) and Mais Médicos ($p=0.001$) program in reducing stroke and Hiperdia cases in mitigating the evolution of AMI cases ($p = 0.0001$).

Conclusion: Although these diseases remain as an important cause of death, stroke hospitalization has reduced significantly in the period evaluated. National programs as the Hiperdia and Mais Médicos showed an impact in the acute cases of strokes and AMI.

Keywords: Stroke; Myocardial Infarction; Hospitalizations; Hiperdia, Primary Health Care; Medically Underserved Area.

Introduction

Stroke and acute myocardial infarction (AMI) are considered cardiovascular diseases (CVD) and their pathophysiological process is generally characterized by the development of atherosclerotic plaques in vessels, whose detachment and/or rupture lead to lumen occlusion, interrupting blood flow in the brain or heart and this process being influenced by several risk factors, notably systemic arterial hypertension (SAH).[1]

CVDs are currently the largest cause of mortality in the world,[2] in addition to being among the diseases with the greatest financial impact.[1] Its prevalence is linked to the increase in life expectancy, which causes more people to reach the age groups at risk for developing such diseases.[3]

AMI is the most frequent and fatal manifestation among cardiovascular diseases[4] and, when it does not result in death, it can generate physical repercussions and psychosocial impacts.[5] Annually, more than 2.4 million deaths are registered in the United States and more than 3.9 million in Europe.[6,7] In Brazil, the standardized average mortality rate was 108.14 deaths for 10^5 men and 61.49 women between 1980-2009,[8] with an economic impact of R$ 22.4 billion.[9]

Ischemic stroke produces a high rate of morbidity and mortality and sudden neurological dysfunction with

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severe motor, sensory and psychocognitive sequelae,[10] being the second leading cause of death globally, with 5.5 million deaths in 2016 and a prevalence of 80.1 million people, showing a similar occurrence between the genders up to 55 years and significantly higher in men between 55 and 75 years.

These health conditions are associated with modifiable risk factors that can be the focus of specific actions to expand medical and pharmaceutical assistance, as well as non-specific health promotion, especially in Primary Health Care (PHC) services. As an example, in the context of the *Sistema Único de Saúde* (SUS), the programs *Hiperdia*, *Mais Médicos* and the *Programa de Acesso e Melhoria da Qualidade* (PMAQ) can be mentioned. Due to the need to monitor and implement public policy strategies for prevention, this study seeks to estimate the trend of cases of ischemic stroke and AMI hospitalization in the Brazilian population and, in the absence of stationarity, to specify the influence that health programs developed in Primary Health Care (PHC).[11]

Method

This is an ecological study with a design of time series and analytical approaches between the years 1998 and 2018. The information collected comprises all the federative units (FU) in Brazil. In order to study the number of hospitalizations for ischemic stroke and AMI, the Hospitalization Authorizations (HA) resulting from the disease were analyzed.

Thus, the study was carried out by consulting the *Sistema de Informação Hospitalar* (SIH) of the *Departamento de Informática do* SUS (DATASUS),[12] which contains secondary data without the patients' personal identification. It is noteworthy that the SIH information is available to the public, thus exempting the appraisal of the ethics committee.

In order to obtain the number of hospitalization cases due to stroke and AMI, the functions of epidemiological information and general hospital morbidity by place of residence were used for the codifications of the International Classification of Diseases in its 10th version, which are: G45 (cerebrovascular accident transient ischemic and related syndromes), I66 (occlusion and stenosis of cerebral arteries that do not result in cerebral infarction), I65 (occlusion and stenosis of pre-cerebral arteries that do not result in cerebral infarction), I63 (cerebral infarction); and I21 (acute myocardial infarction). Demographic data were collected from the database of the *Instituto Brasileiro de Geografia e Estatística* (IBGE).[13]

Statistical Analysis

There was a stratification of data about hospitalizations for stroke and AMI according to Federative Unit (UF) and gender. The incidence rate was obtained by means of the ratio between the number of stroke cases and AMI per year and the estimated population for each year, on a scale for each 100,000 (10^5) inhabitants. To avoid possible errors in the collection of information, an audit was carried out by a second group of researchers in a random sample from the bank. Because of this, the outcomes were defined as the incidence of hospitalization due to stroke and the incidence of hospitalization due to AMI for the estimated population for the years of the study time series.

A polynomial sequence and regression graph was constructed to analyze data trends, which aims to discover the best outcome curve (Y), with the independent variable year (X). In order to prevent serial correlation between the coefficients of the equation, it was preferred to use the difference between the year and the midpoint of the historical series, rather than the gross values of the years, and the Prais-Winsten method of regression. Therefore, considering the period between 1998 and 2018, the adjusted year (X-2008) constituted the independent variable. Each equation had estimated the adjusted determination coefficient (R^2_{ajus}) that reveals the explanatory proportion of the model.

To estimate the impact of programs developed in PHC in SUS, three national policies were taken into account: *Hiperdia*, which was implemented in 2002 and expanded medical and pharmaceutical assistance to people with hypertension and diabetes, being used in this study, mainly, as confusion control since there is already evidence of its effectiveness;[14] the *Mais Médicos* program, which started in 2013 and aimed to increase the number of medical professionals in PHC in the municipalities; and PMAQ, which also started the first cycle in 2013, aspiring to evaluate, monitor and stimulate the quality of services provided at PHC via technical and financial support.

Each program consisted of a dichotomous variable (before/after) the implementation and was independent of the trend of hospitalizations for stroke and AMI in Brazil. Its effects were estimated using the Generalizable Estimation Equations, an extension of the Generalizable

Linear Models (MLG) for correlated data. A robust covariance matrix and an autoregressive work correlation matrix (ARIMA) were used to estimate the effects of independent variables, depending on the quality of the model based on the model's Quasi-Likelihood Criteria (QIC). The gamma link function was used to connect the independent variables and the outcome in the model. The observation of the sign of the model coefficients (B) would allow identifying the effect of the independent variables and their significance being estimated by Wald's chi-square test ($\chi 2$). R® was used to adjust the polynomial curves and construct the MLG. A significance level of 5% was considered to minimize a type I error in the curve adherence and modeling processes.

Results

The analysis of hospitalizations in Brazil reveals an increase in those resulting from AMI with an incidence rate of 42.58 cases per 100 thousand inhabitants per year. Among the genders (Figure 1A), there are also increasing rates, with 30.14 cases per 100 thousand inhabitants per year for women and, to a greater extent, men with a rate of 55.96 cases per 100 thousand inhabitants per year. The equation has excellent adherence to the almost linear growth of cases, $R^2_{ajus} > 0.80$ (Table 1).

In this context, hospital admissions for stroke in Brazil decreased in the period studied (Figure 1B), with a decline rate of 32.17 cases per 100 thousand inhabitants per year.

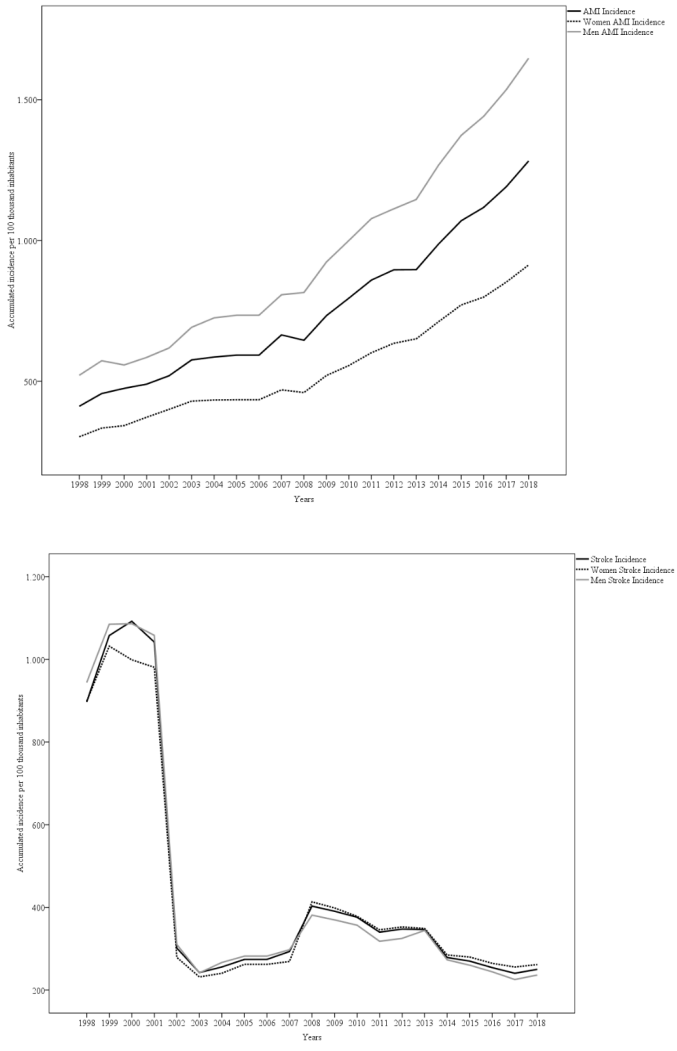

Figure 1 – Trend of acute myocardial infarction (AMI) and ischemic stroke in the Brazilian population between 1998 and 2018. Graph A reveals the trend of general AMI and by sex. Graph B reveals the trend of general stroke and gender.

Table 1 – Modeling the trend of total hospitalizations according to sex for acute myocardial infarction and stroke in Brazil between 1998 and 2018

		AMI				Stroke			
		Model	Trend	p	R^2_{adjus}	Model	Trend	p	R^2_{adjus}
Brazil	Men	55.96x+1009.11	Crescent	<0.001	0.81	-34.67x+464.34	Decrescent	0.02	0.23
	Woman	30.14x+574.10	Crescent	<0.001	0.81	-30.33x+457.15	Decrescent	0.04	0.20
	Total	42.58x+781.42	Crescent	<0.001	0.85	-32.17x+462.67	Decrescent	0.03	0.21

AMI: Acute myocardial infarction; p: probability; R^2_{adjus}: Adjusted coefficient of determination.

This decreasing trend is also observed in both genders, for women the reduction is 30.33 cases annually for every 100 thousand inhabitants. Among male individuals, there is a reduction of 34.67 cases annually for every 100 thousand inhabitants. Stroke cases showed an abrupt decline after 2002 without linearity, R^2_{ajus}<0.30 (Table 1).

Among the FUs, almost all of them had an increasing trend of hospitalizations for AMI, except for Amapá. Among those that grew the most were Santa Catarina, Piauí and Rio Grande do Sul, which respectively increased 2.53, 2.43 and 2.35 cases per 100 thousand inhabitants per year. For stroke cases, the FUs that most declined were Rio Grande do Sul, Santa Catarina and Tocantins with 6.17, 3.57 and 2.80 cases per 100 thousand inhabitants each year (Table 2).

The incidence of hospitalizations for stroke and AMI are affected by health programs developed in primary care (Table 3). It can be seen that the reduction in stroke cases was influenced by the Mais Médicos program (p<0.0001) and more strongly by Hiperdia (p<0.0001), regardless of the actions produced by the PMAQ (p=0.35). Regarding AMI, despite its increasing tendency, Hiperdia (p=0.03) mitigates the evolution of cases as well as there is a marginal significance of the influence of the Mais Médicos Program (p=0.059). There was, again, no significant impact of the PMAQ (p=0.35).

Discussion

Few studies analyze the incidence of cerebrovascular diseases in the Brazilian population over long time series. This study covers the entire national territory and uses data from a 20-year time series (1998-2018) of SUS relevant for monitoring the outcomes studied. As a result, it was shown that hospitalizations for AMI increased throughout the series and, conversely, stroke cases declined. Although there was an antagonistic scenario of the outcomes, it can be inferred that the national programs of Hiperdia and Mais Médicos influenced the mitigation of acute cases of both stroke and AMI after their implementation.

The psychological, financial, social and quality of life impact caused by CVDs is undeniable, causing investments in the area to end up generating greater welfare for the population and economy for the state. Stevens B. et al.,[9] analyzed the costs of cardiovascular diseases in Brazil and AMI had the greatest impact among the diseases surveyed, with a cost of 22.4 billion reais compared to 56.2 billion spent on cardiac conditions and the average cost for each case of AMI was of 7,777.[9]

This contrasts with the reduction in hospitalizations for stroke, which was also observed by other researchers. Ramirez et al. found that hospitalizations for ischemic stroke and age-adjusted had a reduction,[14] as well as Johnson et al.,[11] found that the global incidence and mortality of stroke adjusted for age decreased 8.1% and 36.2%, respectively, from 1990 to 2016 in the United States.[11] In Brazil, a decline in hospitalization for ischemic stroke was observed from 2002, year of the implementation of Hiperdia. Between 1998 and 2001, the incidence was 37.87/10^5 inhabitants, being 9.98/10^5 between 2002 and 2005, a reduction of 73.64%.[15]

The study by Dantas et al.,[16] analyzed hospitalizations for stroke in the period from 2009 to 2016 through AIH in DATASUS and observed an increase in absolute numbers of 12.1%, explained by the population increase in the period (8.2%), extended life expectancy and aging of the population. However, in this same study, data adjusted for age showed an average reduction of 11.8%

Table 2 – Modeling the trend of hospitalization for acute myocardial infarction and stroke in the states of Brazil between 1998 and 2018

	Acute Myocardial Infarction (AMI)				Stroke			
FU	Model	Tend	p	R^2_{adjus}	Model	Tend	p	R^2_{adjus}
AC	0.89x+14.50	Crescent	<0.001	0.71	-1.14x+18.49	Stationary	0.12	0.02
AL	0.88x+16.42	Crescent	<0.001	0.51	-1.92x+24.00	Stationary	0.12	0.03
AM	1.57x+20.54	Crescent	<0.001	0.68	1.69+18.73	Crescent	0.001	0.40
AP	0.24x+10.52	Stationary	0.06	0.09	-1.25x+8.14	Stationary	0.09	0.05
BA	1.73x+25.90	Crescent	<0.001	0.84	-0.77x+13.75	Stationary	0.58	0.09
CE	1.12x+24.70	Crescent	<0.001	0.63	-0.35x+6.99	Decrescent	0.002	0.34
DF	1.53x+31.30	Crescent	<0.001	0.47	-0.29x+8.64	Stationary	0.13	0.02
ES	2.10x+38.14	Crescent	0.001	0.41	-1.15x+18.17	Decrescent	0.003	0.32
GO	1.64x+26.93	Crescent	<0.001	0.76	-0.99x+17.70	Stationary	0.10	0.04
MA	0.59x+10.86	Crescent	0.001	0.39	-1.99x+22.13	Decrescent	0.003	0.33
MG	1.86x+45.36	Crescent	<0.001	0.98	-1.45x+16.30	Decrescent	0.004	0.31
MS	1.95x+30.87	Crescent	<0.001	0.76	-1.14x+15.80	Decrescent	0.004	0.30
MT	1.93x+30.13	Crescent	<0.001	0.68	-1.01x+12.07	Decrescent	0.01	0.19
PA	0.90x+14.88	Crescent	<0.001	0.72	-0.90x+8.60	Decrescent	0.01	0.20
PB	0.74x+23.33	Crescent	0.007	0.26	-0.32x+6.69	Stationary	0.18	0.005
PE	1.79x+28.45	Crescent	<0.001	0.73	0.31x+7.05	Stationary	0.40	0.06
PI	2.43x+27.40	Crescent	<0.001	0.78	-0.19x+19.94	Stationary	0.67	0.10
PR	2.29x+42.69	Crescent	<0.001	0.86	-1.81x+28.24	Decrescent	0.04	0.11
RJ	0.93x+37.65	Crescent	<0.001	0.58	-0.71x+14.70	Decrescent	0.04	0.11
RN	2.33x+29.58	Crescent	<0.001	0.63	-1.79x+23.89	Stationary	0.09	0.50
RO	1.80x+18.54	Crescent	<0.001	0.64	-1.51x+13.84	Decrescent	0.04	0.11
RR	0.70x+10.80	Crescent	0.001	0.38	0.17x++1.15	Crescent	0.001	0.40
RS	2.35x+59.96	Crescent	<0.001	0.84	-6.17x+63.01	Decrescent	0.04	0.12
SC	2.53x+52.62	Crescent	<0.001	0.88	-3.57x+41.69	Decrescent	0.01	0.22
SE	1.74x+25.65	Crescent	<0.001	0.48	-1.52x+10.07	Decrescent	0.02	0.15
SP	2.24x+49.73	Crescent	<0.001	0.97	-0.53x+12.09	Stationary	0.056	0.09
TO	0.46x+20.26	Crescent	0.01	0.19	-2.80x+19.87	Decrescent	0.04	0.11

FU: Federation unity; p - probability; R^2_{adjus}: Adjusted coefficient of determination; AC: Acre; AL: Alagoas; AM: Amazonas; AP: Amapá; BA: Bahia; CE: Ceará; DF: Distrito Federal; ES: Espirito Santo; GO: Goiás; MA: Maranhão; MG: Minas Gerais; MS: Mato Grosso do Sul; MT: Mato Grosso; PA: Pará; PB: Paraíba; PE: Pernambuco; PI: Piauí; PR: Paraná; RJ: Rio de Janeiro; RN: Rio Grande do Norte; RO: Rondônia; RR: Roraima; RS: Rio Grande do Sul; SC: Santa Catarina; SE: Sergipe; SP: São Paulo; TO: Tocantins.

Table 3 – Adjusted model of the relationship between cases of AMI and stroke in the Brazilian population and public health programs for primary care

	B	Standard Error	95%CI of Wald		Hypothesis testing		
			Lower	Upper	Wald's x^2	df	p
Stroke							
Interception	1112.02	42.171	1029.36	1194.67	695.31	1	<0.001
Year	10.56	4.303	2.13	19.00	6.02	1	0.01
Mais Médicos							
After	-111.23	28.919	-167.91	-54.54	14.79	1	<0.001
Before	0						
Hiperdia							
After	-781.02	39.424	-858.29	-703.74	392.45	1	<0.0001
Before	0						
PMAQ							
After	-25.64	27.510	-79.56	28.27	0.86	1	0.35
Before	0						
AMI							
Interception	797.77	40.239	718.90	876.63	393.05	1	<0.001
Year	39.98	4.565	31.04	48.93	76.72	1	<0.001
Mais Médicos							
After	55.10	29.150	-2.02	112.24	3.57	1	0.059
Before	0						
Hiperdia							
After	-81.39	37.939	-155.75	-7.03	4.60	1	0.03
Before							
PMAQ							
After	19.50	25.369	-30.22	69.22	0.59	1	0.44
Before	0						

B: Model equation coefficient; CI: Confidence interval; x^2: chi-square; df: degrees of freedom; p: probability; AMI: Acute myocardial infarction.

in hospitalizations and 12.6% for in-hospital mortality.[16] It is important to highlight the limitations of this study regarding the absence of a trend analysis that controls the serial correlation of data and the effect of population size by using absolute data.

The intriguing opposition to the historic trend of stroke and AMI, even with similar risk factors, may have some explanations. One is that SAH is the most important risk factor for stroke,[17] whereas AMI is strongly associated with smoking, central obesity, dyslipidemia and diabetes. Drug approaches for SAH and diabetes have been widely disseminated in PHC services and with well-proven effectiveness; however, the unhealthy lifestyle is increasing the incidence and prevalence of diabetes and obesity in recent years in Brazil.[18] This, possibly, is contributing to raising rates of AMI while cerebrovascular diseases reflect greater effectiveness in controlling blood pressure.[19]

Another factor that helps the decline of stroke are the ten modifiable risk factors that make up about 90% of the population risk attributable to stroke worldwide.[17] The prevention of these risk factors is done with better pressure control, adequate nutrition, reduction in cholesterol levels and the use of tobacco and alcohol and reduced BMI justify being largely responsible for the drop in hospitalizations.[11,14,20]

The worsening of chronic conditions such as AMI and stroke is greatly influenced by social conditions such as income, education, ethnicity and access to health services, for example. In this perspective, the study by Krumholz, Normand and Wang recorded a decline in the rate of hospitalizations for AMI from 914 to 566 patients for every 10^5 people, a reduction of 38.1%. This study addressed an elderly population assisted by Medicare and financed in the form of a fee for service, which reveals possible factors that may influence access to hospitalizations such as having private health insurance, access to better working conditions and income, inherent social conditions quality of health.[21]

Even with similar risk factors, AMI and stroke are conditions that have different paths. However, it is possible to perceive that programs executed at the PHC level, such as Hiperdia and Mais Médicos, and those supported by national policies, such as tobacco control, based on media actions, price taxation, free program to support cessation of smoking, and food and nutrition that aim to improve the food, nutrition and health conditions of the Brazilian population by establishing national goals for reducing the sodium content of processed foods in Brazil.[22-24] These are key points in the decline in the prevalence of several chronic diseases in Brazil, which contrasts with the increase in use in other countries.[22,25]

PHC in Brazil is based on the Family Health Strategy (FHS), a robust approach aimed at defined populations, through comprehensive care to reduce hospitalizations and complications of chronic diseases[26] and improve well-being. Currently, the FHS has a coverage of approximately 137 million people (65.07% of the Brazilian population)[27] and runs national programs mentioned above.

A study pointed out that an investment of US$ 1 to 3 per person in strategies with a wide population reach can control several chronic non-communicable diseases.[20] The FHS allows the adoption of different lines of care, ensuring adequate therapy, bonding between patient and staff and continuity in attendance, with Hiperdia being added to it.[22,26] This program mitigates strong modifiable risk factors for AMI and stroke, such as hypertension and diabetes. These factors are diseases of slow evolution, asymptomatic or oligosymptomatic in most cases, usually noticeable when an acute cardiovascular event occurs.[28] Today, we know that it contributed to a reduction of more than 70% in hospitalizations due to stroke shortly after completion of the program, in 2002.[15,29] Other studies also revealed an effect of the FHS in the management of the conditions surveyed[30,31] associated with health promotion actions focusing on behavior and life habits such as the Academia em Saúde program.

The expansion of the FHS and the shortage of medical professionals in socially vulnerable regions with little supply, the Brazilian government responded with the Mais Médicos program for Brazil, importing 15,000 doctors from other countries.[26] The positive impact in reducing the number of hospitalizations due to stroke and limitation of AMI cases, despite the short time of implementation, reflect the effectiveness of expanding access to general medical care.[32] This greater access helps drug treatment to control blood pressure and dyslipidemia as a cost-effective way to control the CVD[33] and it is also available in a pharmaceutical assistance program,[33,34] with their dispensation in SUS health units.[22]

Despite making the distribution of doctors in Brazil more equitable, the Mais Médicos program, like all PHC, finds itself in a scenario of scarce funding and inefficient planning and management approaches, especially at local level.[35] Another feature of the program is its centrality in the medical professional, without the implementation of other health professionals, minimum FHS team, such as physiotherapists and psychologists, who work mainly in the management of chronic conditions, as well as health professionals for the management of services.[36]

In contrast, the improvements produced by the PMAQ still cannot be felt in the studied outcomes, probably because the organizational effects take longer to reveal impacts or such advances do not result in changes for AMI and CVA. The PMAQ has the characteristic of having the PHC teams adhere to participate and apply the improvement cycles, which also reduces the number of participating services.[37] In addition, the first PMAQ cycle presented a higher proportion of services below the average, which may have delayed the evolution of the quality of access and other dimensions of quality.[37] On the other hand, Hiperdia and Mais Médicos have the characteristic of being programs without bureaucratic and organizational counterparts.

In view of the interesting results, it is necessary to make some limitations explicit. The effect of PHC coverage or the family health strategy was not evaluated purely, but they maintain collinearity with the analyzed programs that interact with the effects of the analyzed programs. Finally, there is the problem of underreporting, which can lead to obtaining distorted information about the mortality profile as it is believed to happen in UF do Amapá.[38,39]

Conclusion

The present study evaluated the trend of hospitalizations for stroke and AMI during the years 1998 to 2018, and it is possible to infer that those resulting from stroke decreased significantly in this period, and that hospitalizations motivated by AMI grew. However, the Hiperdia and Mais Médicos programs considerably mitigated the acute events of these vascular conditions sensitive to primary care. It is also evident that there is a need for collective actions more focused on avoiding AMI.

Author contributions

Conception and design of the research: Lopes JM. Acquisition of data: Martinez ABR, Lopes JM Jesus E, Souza GRS. Analysis and interpretation of the data: Santos JM, Martinez ABR, Jesus E, Souza GRS, Lopes JM. Statistical analysis: Lopes JM. Obtaining financing: Lopes JM. Writing of the manuscript: Santos JM, Martinez ABR, Jesus E, Souza GRS. Critical revision of the manuscript for intellectual content: Santos JM, Lopes JM.

Potential Conflict of Interest

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

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Study Association

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

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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EDITORIAL

Public Health Programs and Cardiovascular Diseases

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Editorial referring to the article: Stroke and Myocardial Infarction: Effects of the "Hiperdia" and "Mais Médicos" Programs on the Hospitalizations Trends in Brazil.

For decades, cardiovascular diseases, mainly coronary artery disease and stroke, have been the main cause of death in Brazil. In 2017, they accounted for 27.3% of all deaths in the country, with an age-standardized mortality rate of 178 per 100,000 inhabitants.[1] In the same year, cerebrovascular diseases had an age-standardized mortality rate of 80 per 100,000 inhabitants.[1] With respect to the burden of cardiovascular diseases, the number are even more concerning, with 1,602.4 disability-adjusted life years (DALYs) per 100,000 inhabitants for coronary disease and 1,145.3 DALYs per 100,000 inhabitants for stroke.[1]

Although these numbers represent a decrease when compared with numbers in the year of 1990, the control of cardiovascular risk factors is clearly important. In this regard, in addition to the traditional risk factors, socioeconomical factors are known to play an important role in the development of these diseases. Investigators of the Prospective Urban Rural Epidemiologic (PURE) study[2] evaluated socioeconomic status and educational attainment in adults aged between 35 and 70 years from 367 urban and 302 rural communities in 20 countries (five low-income countries, 11 middle-income and five low-income countries), with a total of 164,169 participants. The authors concluded that people with a lower level of education had higher mortality rates from cardiovascular events in all the countries.[2] However, the authors discuss that these findings may be explained not only by the higher prevalence of risk factors, but also by the lower access to secondary prevention and medical management of chronic diseases such as hypertension and diabetes mellitus compared with people with higher level of education.[2] This is in line with the study by Schultz et al.,[3] who demonstrated that even in high-income countries, factors like employment status, educational attainment, income level, and neighborhood socioeconomic factors are related to cardiovascular diseases.[3] Thus, the authors consider the access to health services as part of a high-quality health care of low socioeconomic status populations.[3] Therefore, it is possible to infer that, compared with absolute income, inequality levels are more stronger determinants of cardiovascular outcomes.

Several methods have been proposed to measure the degree of inequality, including the Gini coefficient,[4] and indirect indicators of income. One of these is the percentage of health care plan members,[5] considering that individual health care plans are expensive and require regular monthly income, and collective plans require an employment bond.

Today, according to the World Bank, Brazil is classified as an upper-middle-income country,[6] where 24% of population are covered by supplemental health insurance plans. Most of them are from higher income areas like the states of Sao Paulo, Rio de Janeiro and Rio Grande do Sul, and lower percentages of beneficiaries are found in states of the north and northeast Brazil, like Amapa, Tocantis and Maranhao.[7] A previous study showed an inverse relationship between health care coverage and mortality from cerebrovascular and hypertensive diseases.[5]

Evidently, to be a member of a supplemental health plan does not guarantee access to healthcare, but when used as an indirect marker of income, it reflects the huge degree of health inequalities observed in the country. Therefore, nationwide public health programs that include more vulnerable areas are of paramount importance, as reported by Santos et al.,[8]

Keywords

Cardiovascular Diseases; Public Health; Myocardial Infarction; Stroke; Hospitalization; Socioeconomic Factors.

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in the current issue of the International Journal of Cardiovascular Sciences. The authors evaluated the impact of the "Hiperdia" and "Mais Médicos" programs on hospitalizations for acute myocardial infarction and stroke between 1998 and 2018.

Using data from the hospital information system of the Department of Informatics of the Brazilian national unified health system (SIH-DATASUS), Santos et al.,[8] evaluated the time course of the number of hospitalizations by sex and federated states during the mentioned period.[8] Except for Amapa, where hospitalization rates had a stable pattern over time, rates of hospitalization for acute myocardial infarction increased in all federated states. On the other hand, the hospitalizations for stroke decreased in all federated states, except for Amazonas and Roraima.[8]

The authors also showed that the "Mais Médicos" program, and specially the "Hiperdia" program contributed to the reduction in hospitalizations for stroke. However, although the same effect was not observed on the rate of hospitalizations for acute myocardial infarction, these programs attenuated the progression in the number of cases. In addition, the Brazilian National Program for Improving Primary Care Access and Quality (PMAQ) was evaluated for its influence on the trends of hospitalizations for stroke and myocardial infarction. However, this was an organizational flow and capacitation program, which may have limited its ability to demonstrate an impact on the outcomes during the study period.[8]

Finally, the findings reported by Santos et al. should encourage the development and expansion of primary health care programs in the country, mainly in more vulnerable areas. Promoting an equal access to healthcare should be considered an essential condition for cardiovascular risk reduction and occur in parallel with measurements aimed at improving quality of life and reducing social disparities.

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ORIGINAL ARTICLE

Optimal Cutoff of the TG/HDL-c ratio for Cardiovascular Risk in Hypertensive and Diabetic Patients Monitored by Primary Health Care in a city in Minas Gerais

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Abstract

Background: The analysis of the atherogenic potential of the lipid profile for biomarkers, such as the TG/HDL-c ratio, predicts cardiovascular risk better than isolated lipids.

Objective: To identify the TG/HDL-c cutoff points for multiple risks (hypertension, Diabetes Mellitus, obesity) and to evaluate the association between sociodemographic, clinical, laboratory, anthropometric, and life habit variables and the TG/HDL-c ratio in hypertensive and/or diabetic individuals in the context of Primary Health Care.

Methods: This was a cross-sectional study with 833 hypertensive and/or diabetic patients, conducted between August 2017 and April 2018. The cutoff point of the TG/HDL-c were obtained by the ROC curve. Cardiovascular risk was discriminated by TG/HDL-c, categorized by the cutoff and evaluated in relation to multiple risks. The magnitude of the association between TG/HDL-c and independent variables was estimated by logistic regression. The significance level of $p<0.05$ was adopted for all tests.

Results: The cutoff values of TG/HDL-c (3.26 for men and 2.72 for women) were more sensitive and less specific than those in the literature. Women (OR=1.90 and 95% CI 1.13-3.20) and men (OR=4.58 and 95% CI 1.78-11.76) with multiple risks, and white men, alcohol users, with a history of stroke, had a higher chance of altered GT/HDL-c. Increases in glycosylated hemoglobin, glycemia, and phosphorus in women, and cholesterol, glycemia, and microalbuminuria in men increased the chances of altered TG/HDL-c. Being a former smoker and black reduced the chance of altered TG/HDL-c in women.

Conclusions: TG/HDL-c proved to be a good indicator for habitual use in Primary Care.

Keywords: Hypertension, Diabetes Mellitus, Primary Health Care, Dyslipidemias, Biomarkers.

Introduction

Currently, cardiovascular diseases (CVD) are one of the most important public health problems in the world and one of the main causes of prolonged hospitalization and health expenditures in Brazil.[1,2] Among CVD, coronary artery disease (CAD) stands out as the leading cause of death in Brazil[3,4] and worldwide.[3]

Dyslipidemias are related to the development of atherosclerosis and, consequently, CAD.[5] Early detection of individual cardiovascular risk (CVR) is important to prevent CVD,[1,5,6] define therapy[6] and reduce complications[1] and mortality.[5] CVD prevention is a public health priority, especially in high-risk individuals, such as those diagnosed with arterial hypertension (AH) or Diabetes Mellitus (DM). The use of CVR predictors is important in clinical practice,[2,7,8] and the analysis of the atherogenic potential of lipid profile by biomarkers predicts CAD better than the isolated analysis of lipids, as it reflects the interactions between atherogenic and protective lipid fractions.[9]

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CVR indices included the Castelli I Indices (CT/HDL-c ratio) and II (LDL-c/HDL-c ratio),[1] and the Framingham score.[1,6] Among the estimates calculated from routine laboratory parameters, covered by Primary Health Care (PHC), the proportion of triglycerides in relation to HDL cholesterol (TG/HDL-c ratio) is easily obtained from the patient's lipid profile.[5,7–9] The TG/HDL-c ratio, proposed by Gaziano et al.[10] as a strong lipid predictor for acute myocardial infarction, has been used as an indicator of dyslipidemias[8] and cardiometabolic risks (obesity, AH and DM),[5,7–9] being a potent predictor of the development of CAD.[8,9,11]

The TG/HDL-c ratio dispenses with personnel and specialized techniques,[12] it is a safe, economical, fast-to-obtain, practical, and easy-to-use atherogenic marker.[2,7] For these reasons, its use can be especially considered in PHC.[8]

Several studies have suggested cutoff points to indicate CVR, whether equal values for Brazilian elderly men and women[8] or different values for Japanese adult men and women.[5] However, studies whose cutoffs have been calculated specifically for the Brazilian hypertensive and/or diabetic population are unknown. Thus, the present study's objective is to identify the cutoff of the TG/HDL-c ratio for multiple risks (AH, DM and obesity) and to evaluate sociodemographic, clinical, laboratory, anthropometric, and life habit factors associated with the altered TG/HDL-c ratio in individuals diagnosed with AH and/or DM, in the context of PHC.

Methods

Study design, sample size calculation, and participants

This is a cross-sectional study that is part of a larger project,[13] which followed the ethical precepts of Resolution 466/2012 of the National Health Council and was approved by the Ethics Committee of the Federal University of Viçosa (CAAE: 47356115.3.0000.5153). This study's participants included adult and elderly users of the Brazilian Unified Health System (SUS in Portuguese), in a municipality of Minas Gerais, Brazil. The minimum sample (719) was calculated (Statcalc, Epi-Info®) based on the population of 6,624 hypertensive and/or diabetic patients registered according to the Municipal Health Department. The final sample included 833 individuals over 18 years of age, who were hypertensive and/or diabetic and who received followed up by the Family Health Strategy. Excluded from the data collection were those individuals who did not continue their follow-up visits, as well as pregnant women, abusive users of alcohol and/or drugs, individuals with severe clinical conditions, and those with established chronic kidney disease (CKD).

Data collection

Data were collected in the Basic Health Units between August 2017 and April 2018. Sociodemographic data, life habits, and health care were collected through semi-structured questionnaires, previously tested in a pilot study, applied by trained researchers. Blood pressure was measured by trained professionals and classified according to the 7th Brazilian Guidelines on Arterial Hypertension (2016).[14]

The weight, in kilograms (Kg), was obtained on an electronic scale with a capacity of 150 kg and division of 50 grams. Stature, in meters, was measured in a portable anthropometer, with a metal platform for positioning of individuals and dismountable wooden column, with millimeter tape and cursor for reading, according to Jelliffe techniques (1966).[15] The body mass index (BMI), calculated by the Weight/Stature^2 ratio (Kg/m^2), was classified according to World Health Organization (WHO) criteria (2000)[16] for adults, and Lipschitz criteria (1994)[17] for the elderly. The waist and hip perimeters were measured in centimeters (cm) with inextensible measuring tape. The hip perimeter values were obtained at the level of the maximum extension of the buttocks, with the tape positioned transversely to the measured segment, on the skin, without excessive pressure. Waist perimeter values were obtained at the midpoint between the iliac crest and the external face of the last rib and classified as "increased" in relation to the risk for non-communicable chronic diseases when they presented measurements of ≥94cm for men and of ≥80cm for women, according to the WHO (2000).[16] The waist-hip (WHR) and waist-height (WHT) relationships were calculated by dividing the waist perimeter values by hip perimeter and stature, respectively. The reference values for CVR of the WHR for men (≥0.90) and women (≥0.85) were those recommended by the WHO (2000),[16] while the WHT (≥0.5) between genders was recommended by Ashwell and Hsieh (2005).[18]

Biological samples were collected after 12 hours of fasting, and the biological materials were analyzed in an accredited laboratory, using commercial kits and techniques, together with reference criteria. Microalbuminuria (mg/dL) tests were performed, as were tests for serum albumin, phosphorus, calcium, and creatinine (mg/dL); fasting glucose (FG) (mg/dL); glycosylated hemoglobin (HbA1c) (%); triglycerides (TG) (mg/dL); total cholesterol (TC) and fractions - high lipoproteins (HDL-c) and low densities (LDL-c) (mg/dL). The TG/HDL-c ratio (dependent variable) was calculated from plasma lipid dosages, dividing the TG values by cholesterol linked to HDL-c. The results of FG and HbA1c were classified as altered (FG-126mg/dL and HbA1c-6.5%) according to the criteria of the American Diabetes Association, adopted by the Brazilian Diabetes Society (2018).[19]

The Glomerular Filtration Rate (GFR) (mL/min/1.73m^2) was estimated from serum creatinine by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. The criterion for CKD was based on Kidney Disease: Improving global Outcomes (KDIGO 2012),[20] considering the values of GFR < 60 mL/min/1.73m^2.

Statistical analysis

Statistical analyses were performed using computer software programs (SPSS version 20). For descriptive analysis and characterization of the population, absolute and relative frequencies of categorical and mean variables, medians, standard deviations, and interquartile intervals of continuous variables were estimated. Pearson's chi-square test was used to verify associations between categorical variables. The statistically important differences between the continuous variables were verified by the unpaired Student t-tests (parametric) or Mann Whitney U (non-parametric) test, according to the normality of the data. The normality of the distribution was tested by the Shapiro-Wilk test. The significance level of p<0.05 was adopted for all tests.

The cutoff of the TG/HDL-c ratio for CVR discrimination in relation to multiple risk factors (AH, DM, and obesity classified by BMI) were obtained by the Receiver Operating Characteristic (ROC) curve. The ideal cutoff points were selected maximizing the Youden index. The discrimination of the TG/HDL-c ratio was measured by the area under the ROC curve (AUC). The 95% confidence interval (CI) for AUC was estimated by the DeLong method (1988). The sensitivity, specificity, and accuracy of the identified cutoff points, and others already described in the literature,[5,8] were presented.

The magnitude of the association between the TG/HDL-c ratio (categorized by the obtained cutoff points) and the population characteristics were estimated by logistic regression models. The analyses were stratified by sex. Bilateral probability (p) values of less than 0.05 were considered to indicate statistical significance in the multivariate model. To evaluate the magnitude of the associations, the Odds Ratio (OR) and respective 95% CI were used.

Results

Table 1 shows the characteristics of the subjects by gender. The participants were classified as overweight by BMI and presented WHR and WHT in the increased CVR range. The median values of BMI and WHT in women and WHR in men were higher. CVR-related variables were significantly higher in women, and 27 men and 87 women accumulated the three risk factors.

Figure 1 shows the results of the ROC analysis for the relationships between TG/HDL-c and RCV factors. The optimal cutoff values of the TG/HDL-c ratio for multiple risks were 3.26 for men and 2.72 for women (p<0.001), lower than the reference ratio (=3.5) for both genders,[8] as well as for women (=3.75)[5] and for men (=3.0).[5] The new values showed greater accuracy and sensitivity, and lower specificity than conventional ones (Table 2).

Considering the cutoff points established by the ROC curve, the TG/HDL-c ratio was categorized as adequate (<3.26 for men, <2.72 for women) and changed (≥3.26 for men, ≥2.72 for women). Men with altered TG/HDL-c ratio were observed as more obese; more frequently of multiple risks; higher median values of weight, BMI, hip perimeter, WHT, and WHR; higher waist perimeter averages; higher mean levels of TG, FG, HbA1c, creatinine, and albumin; and lower HDL-c. A higher proportion of men with adequate TG/HDL-c used hypoglycemic agents (Table 3). Women with an altered TG/HDL-c ratio were observed as more obese, with a higher frequency of multiple risks; median values of weight, BMI, hip perimeter, WHT, and WHR; higher waist perimeter averages; higher median levels of TG and FG; and lower HDL-c when compared to those with an adequate TG/HDL-c ratio. A higher proportion of women

Table 1 – Characteristics of hypertensive and/or diabetic patients followed by the Family Health Strategy in Viçosa, Minas Gerais, Brazil, 2017-2018

Variables	General (N=833)	Men (n=310)	Women (n=523)	p
Age* (years of age)	62.0(54.0-69.0)	63.0(55.0-69.0)	62.0(53.0-69.0)	0.443
Years of study*	4.0(3.0-7.0)	4.0(3.0-8.0)	4.0(2.0-6.0)	0.062
Formal/informal work with income† (%)	217(26.0)	107(49.3)	110(50.7)	2.000
Marital status with partner† (%)	488(58.6)	216(44.3)	272(55.7)	<0.001
Ethnicity/white color† (%)	261(31.3)	106(40.6)	155(59.4)	0.248
Smokers† (%)	91(11.0)	40(44.0)	51(56.0)	<0.001
Ex-smokers† (%)	227 (27.2)	136(59.9)	91(40.1)	
Alcohol users† (%)	209(25.0)	132(63.2)	77(36.8)	<0.001
Hypertension† (%)	769(92.3)	282(36.7)	487(63.3)	0.260
Diabetes† (%)	413(49.5)	163(39.5)	250(60.5)	0.182
Obesity† (%)	234(28.0)	53(22.6)	181(77.4)	<0.001
Multiple risk factors†‡ (%)	114(13.7)	27(23.7)	87(76.3)	0.001
Weight* (Kg)	71,5(63.0-82.0)	75.0(65.7-85.5)	70.0(62.0-81.0)	<0.001
Stature* (cm)	158 (152-166)	167(161-171)	155(150-159)	<0.001
Body mass index* (Kg/m²)	28.30(25.22-32.05)	27.18(24.31-30.08)	29.21(25.87-33.27)	<0.001
Waist perimeter§ (cm)	93.74±11.31	94.28±10.58	93.42±11.72	0.284
Hip perimeter* (cm)	102.0(96.0-109.0)	100.0(95.0-106.0)	103.0(97.0-111.0)	<0.001
Waist/height ratio*	0.59 (0.54-0.63)	0.56 (0.53-0.60)	0.60 (0.55-0.66)	<0.001
Waist/hip ratio*	0.91(0.85-0.96)	0.94 (0.89-0.98)	0.88 (0.83-0.94)	<0.001
Systolic blood pressure* (mmhg)	130.0(120.0-140.0)	130.0(120.0-141.0)	130.0 (120.0-140.0)	0.585
Diastolic blood pressure* (mmhg)	80.0 (80.0-90.0)	80.0(80.0-90.0)	80.0 (76.0-90.0)	0.044
Total cholesterol§ (mg/dl)	191.4±40.7	188.3±41.1	193.3±40.3	0.082
Triglycerides* (mg/dl)	126.0 (95.0-174.0)	118.5 (86.0-170.0)	129.0 (100.0-175.0)	0.019
LDL-c* (mg/dl)	111.53±34.69	110.89±33.75	111.91±35.26	0.681
HDL-c* (mg/dl)	49.0 (41.0-59.0)	45.5 (39.0-55.0)	51.0 (43.0-61.0)	<0.001
Ratio TG/HDL-c*	2.57 (1.73-3.95)	2.58 (1.73-4.17)	2.50 (1.73-3.85)	0.546
Glucose* (mg/dl)	98.0 (88.0-126.0)	101.0 (88.0-129.0)	97.0 (87.0-125.0)	0.188
Glycosylated hemoglobin* (%)	6.0 (5.6-7.0)	6.0 (5.6-7.1)	6.0 (5.6-6.9)	0.915
Use of medicines* (number)	2.0 (1.0-4.0)	2.0 (1.0-4.0)	3.0 (1.0-4.0)	0.001
Use of hypoglycemic agents† (%)	269 (32.30)	102 (37.9)	167(62.1)	0.772
Use of lipid-lowering† (%)	236 (28.33)	76(32.2)	160(67.8)	0.060
Creatinine* (mg/dl)	0.85(0.71-0.99)	0.98(0.86-1.13)	0.77(0.68-0.88)	<0.001
Albumin* (mg/dl)	4.47(4.30-4.64)	4.56(4.39-4.74)	4.42(4.26-4.59)	<0.001
Phosphorus* (mg/dl)	3.40 (3.00-3.80)	3.20(2.90-3.60)	3.50(3.20-3.90)	<0.001
Calcium* (mg/dl)	9.50(9.20-9.70)	9.50(9.30-9.80)	9.50 (9.20-9.70)	0.258
Glomerular filtration rate* (ml/min/1,73m²)	83.0(71.0-97.0)	82.0(69.0-96.0)	84.5(72.0-100.0)	0.080
Microalbuminuria* (mg/dl)	5.0(3.0-11.0)	5.0(3.0-11.0)	5.0(3.0-11.0)	0.636

Values expressed in absolute numbers (percentages), means ± standard deviations, medians (percentiles 25-75).
**Mann Whitney U test. †Pearson's Chi-square test. ‡Presentation of hypertension, diabetes and obesity. §Student's t-test.*

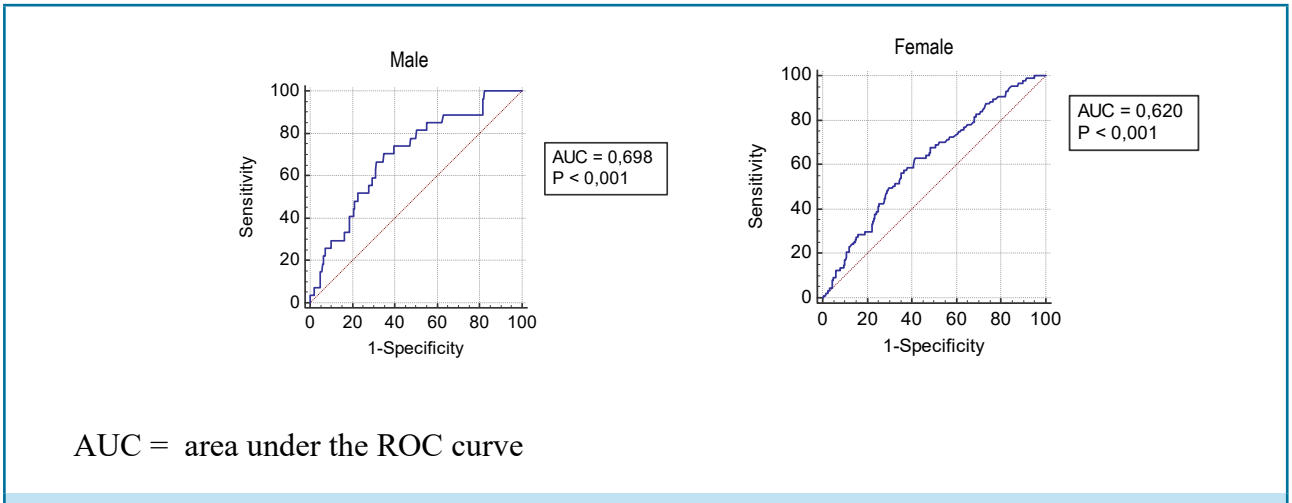

Figure 1 – Receptor operation characteristic (ROC) curves for TG/HDL-c ratio and multiple risk factors for males and females.

Table 2 – Sensitivity and specificity for relationships of multiple risk factors with the TG/HDL-c ratio defined by conventional and new cutoff values for both genders

	Conventional cut-off value[8]: Male and Female = 3.5	Conventional cutoff values[5]: Male = 3.0 and Female = 3.75	Suggested cutoff values: Male = 3.26 and Female = 2.72
Female			
Sensitivity	42.53%	56.32%	63.22%
Specificity	72.48%	64.45%	58.26%
Accuracy	0.575	0.604	0.620
Male			
Sensitivity	66.67%	51.85%	70.37%
Specificity	68.55%	72.08%	65.02%
Accuracy	0.676	0.620	0.698

with an altered TG/HDL-c ratio were diabetic, used hypoglycemic agents and were active smokers, while a higher proportion of former smokers and nonsmokers showed an adequate TG/HDL-c (Table 3).

The reasons for chance (95% CI) for the variables that remained in the final multivariate model were presented by gender (Table 4). Men with multiple risks were 4.58 times more likely to have an altered TG/HDL-c ratio than those without multiple risks, and frequent users of alcoholic beverages were 3.29 times more likely to have an altered TG/HDL-c ratio than non-users. Participants with a previous history of stroke had a 2.90 times higher chance of altered TG/HDL-c ratio than those without this history. A correlation was found between the altered TG/HDL-c ratio and increased TC, FG, and microalbuminuria. White individuals showed a chance of having an altered TG/HDL-c ratio that was 2.40-fold higher than individuals of black ethnicity/color. For women with multiple risks, the chance of altered TG/HDL-c increased by 90%. Smoking cessation (former smokers) represented a protective factor, decreasing the chance of altered TG/HDL-c by 2.86-fold when compared to active smokers. The chance of altered TG/HDL-c increased by 33% for each 1% increase in HbA1c, by 1% in each 1 mg/dL increase of FG, and by 61% in each 1 mg/dL increase of phosphorus. Self-declared brown/yellow/indigenous and white women were twice as likely to have altered TG/HDL-c than black women (Table 4).

Table 3 – Sociodemographic characteristics; lifestyle; and clinical, biochemical, and anthropometric parameters according to the TG/HDL-c ratio by gender

Variables (N=833)	Ratio TG/HDL-c male		p	Ratio TG/HDL-c female		p
	Adequate < 3.26	Changed ≥ 3.26		Adequate < 2.72	Changed ≥ 2.72	
Gender (%)	191(61.6)	119(38.4)		285(54.5)	238(45.5)	
Age* (years of age)	63.0(54.0-71.0)	63.0(55.0-69.0)	0.556	61.0(53,.0-69.0)	62.5(54.0-69.0)	0.347
Years of study*	4.0(2.0-7.0)	4.0(3.0-8.0)	0.194	4.0(2.0-6.0)	4.0(3.0-6.0)	0.446
Marital Status† (%)			0.662			0.164
Single	22(71.0)	9(29.0)		35(64.8)	19(35.2)	
Married/friendly	132(61.1)	84(38.9)		147(54.0)	125(46.0)	
Separated/divorced	18(66.7)	9(33.3)		22(44.0)	28(56.0)	
Widowers	9(56.2)	7(43.8)		68(58.1)	49(41.9)	
Ethnicity/color† (%)			0.064			0.003
Black	43(74.1)	15(25.9)		81(68.6)	37(31.4)	
Brown/yellow/indigenous	77(63.1)	45(36.9)		108(50.2)	107(49.8)	
White	59(55.7)	47(44.3)		80(51.6)	75(48.4)	
Employment situation† (%)			0.952			0.740
Workers with income	64(59.8)	43(40.2)		61(55.5)	49(44.5)	
Housewife	3(60.0)	2(40.0)		78(54.2)	66(45.8)	
Retired	106(63.1)	62(36.9)		129(55.6)	103(44.4)	
Unemployed	18(60.0)	12(40.0)		17(45.9)	20(54.1)	
Smoking† (%)			0.945			0.024
Smokers	24(60.0)	16(40.0)		22(43.1)	29(56.9)	
Former smokers	85(62.5)	51(37.5)		60(65.9)	31(34.1)	
Never smoked	68(63.0)	40(37.0)		184(54.0)	157(46.0)	
Alcohol users† (%)	76(57.6)	56(42.4)	0.122	47(61.0)	30(39.0)	0.235
Hypertensive† (%)	174(61.7)	108(38.3)	0.918	263(54.0)	224(46.0)	0.409
Diabetics† (%)	97(59.5)	66(40.5)	0.423	122(48.8)	128(51.2)	0.012
Obese† (%)	24(45.3)	29(54.7)	0.007	83(45.9)	98(54.1)	0.004
Multiple risk factors†, ‡ (%)	8(29.6)	19(70.4)	<0.001	32(36.8)	55(63.2)	<0.001
Use of medicines (number of)	2.0(1.0-4.0)	2.0(1.0-3.0)	0.793	3.0(1.0-4.0)	3.0(2.0-5.0)	0.080
Use of hypoglycemic agents† (%)	72(70.6)	30(29.4)	0.023	79(47.3)	88(52.7)	0.024
Use of lipid-lowering† (%)	46(60.5)	30(39.5)	0.823	83(51.9)	77(48.1)	0.425
Weight* (Kg)	72.0(63.5-82.0)	79.5(70.0-89.0)	<0.001	67.0(59.1-78.5)	72.0(63.0-82.0)	<0.001
Stature* (cm)	167(160-171)	168(163-172)	0.092	154(149-158)	155(150-160)	0.056

Continuation

Body mass index* (Kg/m²)	26.49(23.45-29.27)	28.17(25.34-31.18)	<0.001	28.39(25.29-32.32)	30.64(26.91-33.73)	0.001
Waist perimeter§ (cm)	92.19±10.34	97.63±10.13	<0.001	90.95±10.97	96.31±11.93	<0.001
Hip perimeter* (cm)	99.5(93.0-104.5)	101.5(96.0-106.0)	0.040	102.0(96.0-110.5)	104.0(97.5-112.0)	0.035
Waist/height ratio*	0.56(0.52-0.59)	0.59(0.55-0.62)	<0.001	0.59(0.54-0.64)	0.62(0.56-0.67)	<0.001
Waist/hip ratio*	0.92(0.88-0.96)	0.96(0.92-1.00)	<0.001	0.87(0.82-0.93)	0.90(0.85-0.96)	<0.001
Systolic blood pressure* (mmHg)	130.0(120.0-140.0)	130.0(120,.0-145.0)	0.691	130.0(120.0-140.0)	130.0(120.0-140.0)	0.484
Diastolic blood pressure* (mmHg)	80.0(80.0-90.0)	80.0(80.0-90.0)	0.903	80.0(77.0-88.0)	80.0(74.0-90.0)	0.608
Total cholesterol§ (mg/dL)	182.87±37.44	196.92±45.24	0.005	190.47±36.95	196.76±43.84	0.080
Triglycerides* (mg/dL)	95.0(77.0-115.0)	195.0(153.0-262.0)	<0.001	102.0(85.0-121.0)	178.0(150.0-223.0)	<0.001
LDL-c* (mg/dL)	107.0(83.8-133.0)	112.2(86.2-138.5)	0.647	105.8(88.6-131.0)	107,8(88.6-136.6)	0.469
HDL-c* (mg/dL)	51.0(44.0-61.0)	39.0(34.0-44.0)	<0.001	59.0(52.0-67.0)	43.0 (38.0-48.0)	<0.001
Glucose (mg/dL)	96.0(87.0-126.0)	108.0(94.0-135.0)	0.001	95.0(86.0-119.0)	101.0(89.0-134.0)	0.005
Glycosylated hemoglobin* (%)	5.9(5.5-7.1)	6.1(5.7-7.3)	0.040	5.9(5.6-6.9)	6.1(5.7-7.0)	0.052
Creatinine* (mg/dL)	0.96(0.84-1.10)	1.00(0.89-1.18)	0.037	0.77(0.68-0.87)	0.77(0.68-0.89)	0.477
Albumin* (mg/dL)	4.54(4.37-4.71)	4.61(4.46-4.78)	0.035	4.40(4.26-4.57)	4.45(4.28-4.61)	0.119
Phosphorus* (mg/dL)	3.20(2.90-3.60)	3.20(2.80-3.50)	0.666	3.50(3.10-3.80)	3.60(3.20-3.90)	0.057
Calcium* (mg/dL)	9.50(9.30-9.70)	9.50(9.30-9.80)	0.442	9.50(9.20-9.70)	9.50(9.30-9.80)	0.003
Glomerular filtration rate* (mL/min/1,73m²)	84.0(72.0-97.0)	79.0(67.0-92.0)	0.085	85.0(73.0-101.0)	83.0(71.0-99.0)	0.319
Microalbuminuria* (mg/dL)	5.0(3.0-10.0)	6.0(3.0-15.0)	0.076	5.0(3.0-10.0)	6.0(4.0-13.0)	0.061

Values expressed in absolute numbers (percentages), averages ± standard deviations, medians (percentiles 25-75).
**Mann Whitney U test. †Pearson's chi-square test. ‡Presentation of hypertension, diabetes, and obesity. §Student t-test.*

Discussion

In the present study, the cutoff points for the TG/HDL-c ratio of 3.26 for men and 2.72 for women, adults, and the elderly, hypertensive and/or diabetic, users of PHC were identified. These results are lower than those used in Brazil in both male and female elderly individuals,[8] those found for Japanese adults,[5] and much lower than conventional cutoff values of 3.75 in men and of 3.00 in women calculated using each of the cutoff values for triglycerides (150 mg/dL in men and women) and HDL cholesterol (40 mg/dL in men and 50 mg/dL in women).

High plasma level of LDL-c and TG, and low levels of HDL-c, are important factors of CVR.[3,21] Lipid reasons can be used for early detection of individual CVR.[5] The LDL-c/HDL-c ratio is a classic index for predicting AD, but the TG/HDL-c ratio is the best predictor for acute myocardial infarction, associated with insulin resistance and metabolic syndrome.[5] The TG/HDL-c ratio correlates directly with plasma LDL-c levels, type B,[5,8] reported as an independent CVR factor.[5] To identify cardiac and metabolic threats, it is important to use different TG/HDL-c ratio cutoff points between genders,[5,11] as the HDL-c level is higher in women.[5] Different cutoff values for men and women are, in fact, used in the National Cholesterol Education Program's (NCEP) criteria for metabolic syndrome.[22] Therefore, it is reasonable that there is also a gender difference in the cutoff of the TG/HDL-c ratio: the values were higher in men than in women (Figure 1). Thus, it is preferable to use different cutoff values of the TG/HDL-c ratio for men and women.

Table 4 – Probability of TG/HDL-c ratio changed for gender by adjusted multivariate analysis for each individual component of the participants.

Analyzed variable	Male	Female
	OR (95% CI)	OR (95% CI)
Multiple Risks (Yes)	4.58(1.78-11.76)	1.90(1.13-3.20)
Glucose (mg/dL)	1.006(1.000-1.011)	1.013(1.005-1.021)
Ethnicity (Black)	1	1
Ethnicity (Brown/Yellow/Indigenous)	1.61(0.75-3.46)	2.15(1.31-3.54)
Ethnicity (White)	2.40(1.10-5.22)	2.04(1.20-3.47)
Alcohol Use (Yes)	3.29 (1.13-9.58)	NA
Stroke (Yes)	2.90(1.06-7.92)	NA
Total Cholesterol (mg/dL)	1.01(1.00-1.02)	NA
Microalbuminuria (mg/dL)	1.002(1.000-1.005)	NA
Smoking (Smoker)	NA	1
Smoking (Former Smoker)	NA	0.35(0.16-0.74)
Smoking (Never Smoked)	NA	0.54(0.28-1.02)
Glycosylated Hemoglobin (%)	NA	1.33(1.04-1.70)
Serum Phosphorus (mg/dL)	NA	1.61(1.10-2.35)

NA = Not applicable

It was evidenced that the altered TG/HDL-c ratio, identified from the cutoff points found in this study, was associated with the presence of multiple risks (AH, DM, and obesity), ethnicity, alcohol use, smoking, history of stroke; CT, FG and HbA1c dosages; and high microalbuminuria and high serum phosphorus. Other studies have identified associations between the TG/HDL-c ratio and several cardiometabolic risk factors, such as alcohol use,[7] smoking,[8] metabolic syndrome,[23,24] oxidative[25] and inflammatory profiles,[12,25] adverse events,[10,26] various anthropometric parameters,[5,8,9,24,27] dyslipidemias,[12,24,27] HA.[5,8,11] DM,[5,8,11,24,28] insulin resistance,[11,23,28,29] and renal function.[30] In this sense, the cutoff points found represent the CVR well and are therefore good risk markers for the studied population.

The cutoff values of the TG/HDL-c ratio can be obtained through quartiles;[10] tertiles;[11] for convenience, from values already used by other researchers;[8,9,26,28,30] or even calculated through the ROC curve.[5] Gaziano et al. (1997)[10] calculated the relative risks per quartiles, comparing the TG/HDL-c ratio levels of the second, third, and fourth quartiles with those of the first quartile. Ain et al. (2019)[11] divided the TG/HDL-c ratio into three tercis (0.1-3.59; 3.60-7.18; and 7.19-10.3). Some authors agreed on different TG/HDL-c ratio cutoff values for the sexes (2.5 for women and 3.5 for men,[9] or 3.00 for women and 3.75 for men[5]), while others pre-established the values regardless of gender (2.5[26]; 3.0[28,29]; 3.5[8] and 3.8[30]), or they calculated them by ROC analysis (2.967 for men and 2.237 for women)[5] .

The importance of identifying cutoff values by ROC analysis is due to obtaining more satisfactory values for this population (hypertensive and diabetic), which presents more CVR factors, in the instance where it is attended (PHC). The cutoff for the TG/HDL-c ratio depends on its associated result, and a result that produces greater accuracy in ROC analysis is preferable to determine the cutoff value of the TG/HDL-c ratio. However, because they are obtained for a specific population, the suggested cutoff cannot be extrapolated to the population in general. However, in a study of cardiometabolic risk factors (AH, DM, and visceral obesity) in periodic health examination records of 10,196 Japanese adults, it was concluded that the

power of discrimination of cardiometabolic risk factors of the TG/HDL-c ratio, using conventional cutoff values and obtained by ROC analysis, were similar when applying both methods.[5] The values suggested in the studies mentioned above or presented in the study by Wakabayashi and Daimon (2019)[5] may not fit this population, as they were conducted in other countries and/or with populations with CVRs that were different from those to which hypertensive and/or diabetic patients are subject, or because they were not calculated, but obtained for convenience in the literature. In the present study, the accuracy values for the TG/HDL-c ratio in relation to multiple risks (AH, DM, and obesity) were 0.698 in men and 0.620 in women (Figure 1), which are generally evaluated as low precision (AUC: 0.5 ~ 0.7) but were higher than the accuracy presented by conventional cutoff values (Figure 1). Recent prospective studies conducted in Iran[31] and China[32] showed similar accuracy (0.575 and 0.647).

Considering that the components (TG and HDL-c) are simple, and are already found in routine laboratory tests,[23] the TG/HDL-c ratio can be easily obtained from the patient's lipid profile.[5,7-9] The use of CVR predictors is relevant in clinical practice,[9] and the use of the TG/HDL-c ratio as one of these indices can avoid the indiscriminate use of laboratory tests and related expenses.[23] In addition, the TG/HDL-c ratio has specific characteristics, such as simplicity, low cost, applicability,[27] ease of execution,[5] reliability, practicality, speed in obtaining results, and non-invasive test qualities,[8] making it a useful indicator to predict CVR in routine and screening tests,[5] especially in the context of primary health care.[8]

Strengths and limitations of the study

The present study presents as strengths the achievement of the cutoff values of the TG/HDL-c ratio by ROC analysis with a more satisfactory and effective result to discriminate CVR; having been conducted with adults and the elderly – a population with a tendency to present more CVR-factors, and at the level of PHC – aninstance in which hypertensive and diabetic patients are treated. Limitations of the study include a cross-sectional design, which is insufficient to express a causal association between the TG/HDL-c ratio and the studied variables; the difficulty of comparison with other studies due to the methodological differences of obtaining results and the cutoff values of TG/HDL-c; as well as the non-analysis of food intake and physical activity data. It is suggested that longitudinal, multicenter, and/or prospective additional studies should be conducted to discuss the causative relationships and temporal correlations of CVRs with the TG/HDL-c ratio.

Conclusion

For a population of hypertensive and/or diabetic patients, cutoff values for the TG/HDL-c ratio (3.26 for males and 2.72 for females) were lower than those commonly used in clinical practice. These values showed greater accuracy and sensitivity and less specificity than conventional values. It was also observed that the new cutoff points indicative of altered TG/HDL-c were associated with the presence of multiple risks (AH, DM, and Obesity), ethnicity, alcohol use, smoking, history of stroke, and increased values of TC, FG, HbA1c, microalbuminuria, and serum phosphorus.

These results suggest the use of new cutoff points in the clinical practice of follow-up of patients with AH and DM in PHC, aiming to achieve early screening and the appropriate treatment of risk factors that may indicate an undesirable prognosis in this population.

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Author contributions

Conception and design of the research: Silva EF, Moreira TR. Analysis and interpretation of the data: Silva EF, Moreira TR. Statistical analysis: Moreira TR. Obtaining financing: Cotta RMM. Writing of the manuscript: Silva EF. Critical revision of the manuscript for intellectual content: Mendonça ET, Oliveira DM, Cardoso SA, Colodette RM, Cotta RMM, Moreira TR. Supervision / as the major investigador: Cotta RMM.

Potential Conflict of Interest

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

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Study Association

This article is part of the Master's thesis by Eunice Ferreira da Silva, from the Graduate Program in Health Sciences of the Federal University of Viçosa.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Federal University of Viçosa under the protocol number 1.203.173 - CAAE: 47356115.3.0000.5153. 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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EDITORIAL

TG/HDL-c Ratio as a Predictor of Cardiovascular Risk

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Referent to the article: Optimal Cutoff of the TG/HDL-c ratio for Cardiovascular Risk in Hypertensive and Diabetic Patients Monitored by Primary Health Care in a city in Minas Gerais

Cardiovascular diseases (CVD) continue to be an important public health problem and one of the main causes of morbidity and mortality worldwide, generating economic and social impacts.[1,2] In Brazil, CVD costs have been increasing significantly and are the highest when compared to other causes of hospitalization. Moreover, as the population ages, and with the increase in CVD prevalence, these expenses tend to be even higher.[3] Therefore, early detection and possible changes in cardiovascular risk factors can be important in order to reduce hospitalization and negative outcomes, as well as to improve the population's quality of life.

In an attempt to identify asymptomatic individuals with a greater predisposition for the disease and define therapeutic goals, many evaluation tools have been developed to estimate risks for CVD, such as Framingham's Global Risk Score (GRS), adopted by the Department of Atherosclerosis of the Brazilian Society of Cardiology (SBC-DA, in Portuguese) and which evaluates the risk of cardiovascular events over a 10-year period through the variables of age, sex, high-density lipoprotein cholesterol (HDL-c), total cholesterol, systolic blood pressure, smoking, and diabetes.[4]

Based in this premise, other indexes have been proposed to predict the cardiovascular risk, among which, what stands out are the ratio between triglycerides (TG) and HDL-c (TG/HDL-c), which reflects small and dense particles of low-density lipoprotein (LDL), which are more atherogenic than the larger floating LDL particles.[5,6] The TG/HDL ratio has proven to be a good predictor for myocardial infarction[7,8], and was associated with the incidence of cardiovascular diseases, type 2 diabetes mellitus, and metabolic syndrome.[9] In addition, it was reported that a high TG/HDL-c relationship is significantly associated with an increase in the resistance to insulin in apparently healthy individuals, thus suggesting that this measure can serve as a simple and clinically useful method to identify apparently healthy young individuals who are resistant to insulin and who present an increased cardiometabolic risk.[10]

In the current edition of the *International Journal of Cardiovascular Sciences*, Silva et al.,[11] evaluated 833 individuals, of whom 62.8% were women, with an average age of 62 years, with high blood pressure and/or diabetes, who received medical care at the Family Health Unit in the city of Viçosa, Minas Gerais, Brazil. Exams showed that the cut-off values of the TG/HDL-c ratio that reflect a cardiovascular risk were ≥ 3.26 for men and ≥ 2.72 for women. Moreover, for women with multiple risks, the chance of an alteration in the TG/HDL-c ratio increased by 90%.

The cut-off values considered by Silva et al.,[11] were different from those observed in other populations, such as in Argentina (>3.5 in men; >2.5 in women)[12], Iran (>4.42 for men; 3.76 for women, and 3.68 for both sexes)[13], and Spain (>2.75 for men and > 1.65 for women).[14] Wakabayashi e Daimon[5] compared the discrimination for cardiovascular risk for different cut-off values of the TG/HDL-c relationship and observed that the optimum cut-off value was of 2.967 in men and 2.237 in women. As observed, the values are diverse among the population, which can possibly be explained by genetic factors, the geographic region, race/ethnicity, and the age of the individuals.

Keywords

Cardiovascular Disease, Risk Fators, Dyslipidemias, Hypertension; Diabetes Mellitus

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In Brazil, studies that evaluate the cut-off values of the TG/HDL-c ratio are scarce, which hinders the comparison with the results obtained by Silva et al.,[11] and show the importance of this investigation for scientific literature. However, the results cannot be extrapolated to the Brazilian population in general, since the results were obtained in a specific population in the state of Minas Gerais. Brazil has a high degree of miscegenation and the TG/HDL-c ratio can be influenced by ethnicity; therefore, representative samples of each region should be used so that the results can be more broadly generalized.

In conclusion, the TG/HDL-c ratio is an easy, accessible, and economical measure that can be useful in predicting the cardiovascular risk in routine exams and triage in Primary Health Care. Nevertheless, more studies are warranted in order to establish the optimum cut-off point. Studies should also include confounding factors, such as socioeconomic status, food consumption, and physical activity.

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ORIGINAL ARTICLE

Influence of Factors Affecting Quality of Life on in-Hospital Cardiovascular Events of Patients with Acute Myocardial Infarction with and without ST-segment Elevation

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Abstract

Background: Acute myocardial infarction (AMI), with and without ST-segment elevation (STEMI and NSTEMI, respectively), is the principal cause of cardiovascular morbidity and mortality in Brazil and around the world. Modifiable risk factors (RF) and quality of life (QOL) may correlate with the type of AMI.

Objective: To evaluate the influence of QOL and RF on the type of AMI and in-hospital cardiovascular events in STEMI and NSTEMI patients.

Methods: This was an observational, cross-sectional study. Patients with AMI attending four referral hospitals (three private and one public) for cardiovascular disease treatment were assessed for QOL using the Brazilian version of the 36-item short form survey. A $p < 0.05$ was considered statistically significant.

Results: We evaluated 480 volunteers; 51% were treated in one of the private hospitals. In total, 55.6% presented with STEMI, and 44.4% with NSTEMI. Patients from the public hospital were 8.56 times more likely to have STEMI compared to those from the private hospitals. There was a higher prevalence of smokers in STEMI ($p < 0.028$) patients. QOL was not associated with the type of AMI. A negative patient perception of the physical health and pain domains was observed. Although a significant difference between the physical and the mental health domains was not observed, individual domains were correlated with some in-hospital outcomes.

Conclusion: There was a higher prevalence of smokers among individuals with STEMI. Domains of QOL showed a statistically significant relationship with the occurrence of in-hospital cardiovascular events, with no difference between the types of AMI.

Keywords: Cardiovascular Diseases/epidemiology; Coronary Acute, Syndrome; Myocardial Infarction; Myocardial Infarction; Medication Adherence ; Risk Factors.

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Introduction

The global scenario reveals an increase in the incidence of cardiovascular diseases.[1] According to a report by the Pan American Health Organization (PAHO) published in 2017, 17.7 million people died from cardiovascular disease in 2015, representing 31% of all deaths globally. It directly affects health-related costs, and causes reduction in job productivity and quality of life (QOL).[2,3]

Acute coronary syndromes (ACS), including unstable angina (UA) and acute myocardial infarction (AMI) with and without ST-segment elevation (STEMI and NSTEMI, respectively) are among the main cardiovascular diseases.[4] AMI is one of the leading causes of death and physical disabilities, and modifiable risk factors (RF) and QOL may correlate with the development of this disease.[5-7]

According to the PAHO report, most cardiovascular diseases can be prevented by addressing behavioral RF, such as tobacco use, unhealthy diet, obesity, lack of physical activity, and use of alcohol, by implementing strategies for the general population.[2] Additionally, control of RF and adherence to healthy habits can be associated with better QOL.[8]

QOL is related to the individual's perception of their own life, in connection with their goals and within the value system incorporated in decision-making.[9] It depends on individual's economic status, physical and mental health, social protection, political stability, and the environment.[10]

The measurement of QOL provides valuable information about the individual and helps clinicians to choose the best forms of treatment and rehabilitation. Despite the relationship between RF and the lifestyle of individuals with cardiovascular disease, recommendations to investigate parameters of QOL for estimation of cardiovascular events (CVEs), are not well established, and require further research. Therefore, the present study aimed to assess whether patient QOL affects the type of AMI and in-hospital outcomes.

Methods

Study design

This was a cross-sectional observational study, carried out from October 2013 to September 2015. This study is part of the research entitled "Adherence to drug treatment and lifestyle changes in patients with acute coronary syndrome" conducted in four renowned hospitals for cardiac treatments (three private and one public) in Aracaju, Sergipe, Brazil.[11]

Subjects

Patients who presented with STEMI or NSTEMI were recruited by convenience sampling. We included patients of both genders, aged 18 years or older, diagnosed with AMI, and excluded patients with cardiogenic shock, unstable angina (UA), or Alzheimer's disease.

Variables analyzed

The following variables, collected from medical records were analyzed: educational attainment, marital status, clinical presentation (type of infarction), comorbidities – dyslipidemia, systemic arterial hypertension (SAH), smoking, diabetes mellitus (DM), and family history of coronary artery disease (CAD) – and in-hospital events.

We performed anthropometric measurements – weight, height, waist circumference, and body mass index (BMI). We also analyzed physical activity records using the International Physical Activity Questionnaire (IPAQ, short version),[12,13] and QOL using the Brazilian version of the Medical Outcomes Study Questionnaire 36-Item Short-Form Health Survey (SF-36).[14,15]

Anthropometric measurements

Body weight, height, and BMI[16] of patients were determined. For body weight measurement, patients were dressed in light clothing, barefoot, standing on the platform of a digital scale (Filizola, 150 Kg) to the nearest 0.1 Kg. Height was measured to the nearest 0.1 m using a stadiometer (SECA).

Physical activity

We used the IPAQ – short version to assess physical activity. Habitual physical activity levels were classified based on the consensus proposed by the Physical Fitness Laboratory of São Caetano do Sul, which is the coordinating center of IPAQ in Brazil. Patients were then classified into very active, active, irregularly active, and sedentary.[12,13]

Quality of life

QOL was measured using the validated Portuguese language version[14] of the SF-36 questionnaire.[15]

The SF-36 consists of 36 questions that address eight domains (or dimensions) of two major components: the physical component that involves functional capacity (10 items), pain (two items), general health status (five items), and physical performance (four items), and the mental component that covers mental health (five items), emotional (three items), social (two items), and vitality (four items). There is also one question aimed to compare current health perceived by the patient with that of a year ago.[14,15]

Data analysis

We analyzed the data using the software R, version 3.5.1. Univariate descriptive analysis was performed by calculating the frequencies (absolute and relative) for the categorical variables, and mean and standard deviation for the continuous variables. Continuous variables that were not normally distributed were described as median and interquartile range.

Continuous variables with normal and without normal distribution were compared using the unpaired Student's t-test and the Mann-Whitney, respectively. Distribution normality was assessed using the Shapiro-Wilk test. For categorical variables, the chi-square test or the Fisher's exact test, with 95% confidence interval, was used as appropriate. The odds ratio (OR) was also calculated. Significance level was set at 0.05 ($p<0.05$).

Ethical aspects

The study was approved by the Research Ethics Committee of the Federal University of Sergipe – CEP/UFS on 06/07/2013 under nº 302.544. All procedures were performed following the 2013 update of the Declaration of Helsinki. Informed consent was obtained from all the participants included in the study.

Results

Characteristics of the subjects

A total of 480 patients were included. Out of these patients, 267 (56%) had STEMI, and 213 (44%) had NSTEMI. Among them, 235 (49%) were treated in the public hospital, and 245 (51%) in private ones. The study sample was predominantly elderly and male. Most of them had complete elementary school and were married or lived with a partner. Regarding RF, most patients were overweight and had a sedentary lifestyle, were non-smokers, had SAH, dyslipidemia, and family history of CAD (Table 1).

Considering the type of hospital, 189 patients who were treated in the public hospital were diagnosed with STEMI, compared with 78 patients with STEMI who were treated in private hospitals. Therefore, in the public health system, 80% of the patients with AMI were diagnosed with STEMI, compared to 32% in the private hospitals ($p < 0.001$), indicating a relationship between the type of AMI and the type of hospital. People treated in the public hospital were 8.56 times more likely to have STEMI compared to those treated in the private hospitals (Table 2).

In addition, 183 (60%) of men had STEMI, compared to 84 (48%) of women. Men had a 1.62 times greater chance of having STEMI compared to women ($p = 0.014$). Low educational attainment and age group (between 18 and 49 years) also showed a significant relationship with the severity of infarction (Table 2).

Smoking, DM, SAH, dyslipidemia, obesity/overweight (BMI), and physical inactivity showed a significant relationship with the development STEMI. In the univariate analysis, these variables did not show any statistically significant differences related to the type of infarction (Table 2).

QOL, AMI type, and in-hospital outcome

Considering that the SF-36 score ranges from 0 to 100 (with 0 being the worst state and 100 the best state), the mean scores for all domains ranged from 41 to 69. Only the physical aspects of the domains and pain had a mean value below 50. Social and mental health domains had the highest averages (Table 3)[16]. Comparisons of mean SF-36 scores between STEMI and NSTEMI showed no statistically significant differences (Table 4).[17]

Table 5 [18] shows the mean F-36 scores of AMI patients with and without in-hospital events. Functional capacity showed a statistically significant relationship in the univariate analysis with cardiovascular death ($p < 0.024$). Likewise, a statistically significant relationship between pain and acute and chronic renal failure ($p < 0.041$), and between cardiovascular death and physical performance ($p < 0.040$) was also found.

Table 1 – General characteristics of patients (n=480) with acute myocardial infarction, Aracaju, Sergipe, Brazil, 2019

Variables	Category	Frequency (n°) (%)
ACS type	STEMI	267 (56)
	NSTEMI	213 (44)
Health service	Public	236 (49)
	Private	244 (51)
Sex	Masculine	305 (64)
	Feminine	175 (36)
Color	White	164 (36)
	Black	64 (14)
	Brown	230 (50)
Educational attainment	Elementary School	266 (55)
	High School	142 (30)
	Higher Education	72 (15)
Weight excess	Yes	317 (67)
	No	159 (33)
Tobacco use	Yes	92 (19)
	Ex-smoker	170 (35)
	No	218 (45)
DM	Yes	169 (35)
	No	311 (65)
SAH	Yes	103 (21)
	No	377 (79)
Dyslipidemia	Yes	263 (55)
	No	217 (45)
History of CAD	Yes	276 (58)
	No	204 (43)
IPAQ	Sedentary	254 (53)
	Active	226 (47)
Age group	from18 to 49	63 (13)
	from 50 to 59	117 (24)
	from 60 to 69	158 (33)
	from 70 to 79	93 (19)
	80 or over	49 (10)
Marital status	Married/Stable union	315 (66)
	Divorced/Widow(er)/	101 (21)
	Single	63 (13)

ACS: acute coronary syndrome; AMI: acute myocardial infarction; STEMI: acute myocardial infarction with ST-segment elevation; NSTEMI: acute myocardial infarction without ST-segment elevation; DM: diabetes mellitus; CAD: coronary artery disease; IPAQ: International Physical Activity Questionnaire.

Table 2 – Relationship between types of acute myocardial infarction with qualitative variables, Aracaju, Sergipe, Brazil, 2019

Variable / Category	AMI		OR (CI 95%)	p-value*
	STEMI (%)	NSTEMI (%)		
Health Service				
Public	189 (80)	47 (20)	8.56 (5.64-12.99)	<0.001
Private	78 (32)	166 (68)	1.00	
Sex				
Masculine	183 (60)	122 (40)	1.62 (1.12-2.36)	0.014
Feminine	84 (48)	91 (52)	1.00	
Race (skin color)				
White	79 (48)	85 (52)	0.68 (0.45-1.01)	0.071
Black	40 (63)	24 (38)	1.22 (0.69-2.15)	
Brown	133 (58)	97 (42)	1.00	
Education				
Elementary school	174 (65)	92 (35)	2.97 (1.74-5.08)	<0.001
High school	65 (46)	77 (54)	1.33 (0.74-2.36)	
Higher education	28 (39)	44 (61)	1.00	
Overweight/Obesity				
Yes	171 (54)	146 (46)	0.85 (0.58-1.25)	0.476
No	92 (58)	67 (42)	1.00	
Tobacco use				
Yes	60 (65)	32 (35)	1.91 (1.15-3.16)	0.028
Ex-smoker	99 (58)	71 (42)	1.42 (0.95-2.13)	
No	108 (50)	110 (50)	1.00	
DM				
Yes	90 (53)	79 (47)	0.86 (0.59-1.26)	0.500
No	177 (57)	134 (43)	1.00	
Hypertension				
Yes	56 (54)	47 (46)	0.94 (0.61-1.45)	0.859
No	211 (56)	166 (44)	1.00	
Dyslipidemia				
Yes	136 (52)	127 (48)	0.70 (0.49-1.01)	0.071
No	131 (60)	86 (40)	1.00	
History of CAD				
Yes	151 (55)	125 (45)	0.92 (0.64-1.32)	0.707
No	116 (57)	88 (43)	1.00	
IPAQ				
Sedentary	139 (55)	115 (45)	0.93 (0.65-1.33)	0.742

Active	128 (57)	98 (43)	1.00	
Age group				
from18 to 49	41 (65)	22 (35)	3.51 (1.60-7.68)	0.016
from 50 to 59	71 (61)	46 (40)	2.91 (1.45-5.82)	
from 60 to 69	87 (55)	71 (45)	2.31 (1.18-4.49)	
from 70 to 79	51 (55)	42 (45)	2.29 (1.12-4.68)	
80 or over	17 (35)	32 (65)	1.00	
Marital status				
Married/Stable union	175 (56)	140 (44)	0.62 (0.35-1.10)	0.075
Divorced/Widow(er)/	49 (49)	52 (51)	0.47 (0.25-0.91)	
Single	42 (67)	21 (33)	1.00	

**Chi-square or Fisher's exact test. OR: Odds Ratio, AMI: Acute Myocardial Infarction; STEMI: Acute Myocardial Infarction with ST-segment elevation; NSTEMI: Acute Myocardial Infarction without ST-segment elevation; DM: Diabetes Mellitus; CAD: Coronary artery disease; IPAQ: International Physical Activity Questionnaire.*

Table 3 – Summary of quantitative variables of the SF-36 questionnaire of acute myocardial infarction patients (n=480)[16]

Domains	Average	Median	Standard deviation
FUNCTIONAL CAPACITY	54	55	32
PHYSICAL	41	25	42
PAIN	48	41	30
HEALTH	58	60	22
VITALITY	60	60	24
SOCIAL	68	75	29
EMOTIONAL	60	100	44
MENTAL	69	72	22

Unexpectedly, we did not observe a statistically significant difference between the mean scores of physical and mental health regarding the CVEs that occurred during hospitalization. We observed an association between emotional domain and congestive heart failure (CHF) ($p < 0.004$). Vitality was significantly related to the onset of CHF ($p < 0.045$), cardiovascular death ($p < 0.012$), and reinfarction ($p < 0.007$). The social aspect also showed a statistically significant relationship with CVEs, including angioplasty ($p < 0.049$), myocardial revascularization (MR) ($p < 0.033$), cardiovascular death ($p < 0.047$), and reinfarction ($p < 0.010$).

Discussion

The study sample was predominantly elderly and male, and a family history of CAD was found in 58% of the patients. These three factors (age, sex, and history of CAD) are classified as non-modifiable RF. Among the modifiable RF, the most prevalent were obesity, hypertension, dyslipidemia, and physical inactivity; most patients were non-smokers or ex-smokers.

In a multicenter study carried out in Brazil, most patients were also male, with an average age varying between 61 and 65 years.[19] International studies have also reported

higher incidences of AMI in male elderly populations.[20, 21] This may be related to the high life expectancy and men's health gap, which causes an increased prevalence of these chronic-degenerative diseases.

Regarding the type of infarction, there was a higher prevalence of STEMI (56%) compared to NSTEMI (44%). Marino et al.,[22] described the profile of patients with ACS and found a higher prevalence of STEMI patients (n = 214) compared with NSTEMI patients (n = 73).[22] The literature shows that the incidence of STEMI and NSTEMI varies across the world, and that, in European countries, the incidence of NSTEMI has been increasing.[23,24]

Regarding the type of hospital (public vs. private), the number of patients attending public (49.2%) and private hospitals (50.8%) was similar. Regarding the type of AMI, the number of STEMI cases was higher in the public hospital than in private hospitals. This may be explained by the fact that the public hospital where the study was conducted is a referral center for cardiac surgery in the Brazilian Unified Health System (SUS). In the patient selection process for surgery, higher priority is given to patients with STEMI.

Regarding the relationship between the type of AMI and RF, there was a significant correlation between STEMI and smoking. The nicotine present in tobacco is the most addictive psychoactive drug, and responsible for raising heart rate and blood pressure, in addition to promoting thrombogenicity. Approximately 21% of deaths are associated with tobacco. Smoking also interferes with individuals' QOL.[25,26]

With respect to perception of health-related QOL by all the respondents, the mean scores for the domains of physical component and pain were low when compared with the dimensions of vitality, and social, emotional, and mental health. Studies that evaluated QOL during hospitalization observed a negative perception of QOL in both physical and pain domains, as well as of sleep and emotional reactions. The latter two were related to the type of AMI and the process of hospitalization.[27,28] Angina, together with feelings triggered by hospitalization, can influence pain and physical aspects.

In the last decades, research investigating the QOL of cardiac patients has reported a decline in their physical capacity due to dyspnea and fatigue.[29, 30] The present study corroborates these findings and reinforces that these individuals require proper management not only of pain but also of the decline in physical capacity.

Contrary to expectations, we found no significant difference in QOL between the two types of AMI. Another similar study[23] also found no significant difference between the AMI types, corroborating our results. This study also observed a reduction in patient QOL for all domains, except for the general health domain, following in-hospital CVEs.[23]

Mollon and Bhattacharjee,[31] in a case-control study, identified that individuals who suffered AMI had lower QOL in the domains of general, physical, and mental health compared to individuals without AMI. In the domains of sleep, emotional support, and life satisfaction, there were no differences between AMI survivors and the control group.[31]

When analyzing the relationship between QOL and in-hospital outcomes of our patients, we identified that functional capacity, physical, social, and vitality domains were associated with cardiovascular death. New episodes of AMI were related to the vitality and social domains, and CHF was associated with the emotional and vitality domains. Regarding pain, higher scores were reported by the patients with acute and chronic renal failure.

Furthermore, in the present study, the occurrence of sepsis was related to functional capacity, and angioplasty and myocardial revascularization (MR) were associated with the social domain. Contrary to our expectations mean scores for the physical and the mental health dimensions were not different when the in-hospital events were considered.

Therefore, the social domain was related to a higher risk of in-hospital events. In a similar study, which evaluated the quality of life after MR surgery, we observed that the domain social relationships had the second highest score.[31] According to Souza et al.,[32] social support can act as a protective factor, by relieving stress during crises and facilitating the recovery from the disease.[32]

A major scientific challenge is the improvement in the evaluation of mortality predictors as well as the establishment of appropriate treatment. However, it is common sense to combine the established RF and the factors known to interfere with patient's QOL for the creation of educational programs. One of the relevant achievements of the present study was to identify the differences in the QOL scores according to in-hospital events. These findings can serve as a basis for new scientific projects. Moreover, they prove that psychosocial factors are involved in the development and recovery from the disease.

Table 4 – Comparison of quantitative variables of the SF-36 questionnaire between the types of acute myocardial infarction (n=480)[17]

Domain	STEMI			NSTEMI			p-value*
	Median	P25	P75	Median	P25	P75	
FUNCTIONAL CAPATICY	55	30	80	55	25	85	0.894
PHYSICAL	25	00	100	25	00	75	0.091
PAIN	41	20	72	41	20	62	0.688
HEALTH	62	42	77	57	42	72	0.544
VITALITY	65	45	83	60	40	75	0.065
SOCIAL	75	50	100	63	50	100	0.073
EMOTIONAL	100	00	100	100	00	100	0.564
MENTAL	72	56	88	72	52	84	0.285

**Mann-Whitney test. SD: Standard deviation; FC: Functional capacity; STEMI: Acute myocardial infarction with ST-segment elevation; NSTEMI: Acute Myocardial Infarction without ST-segment elevation*

Some limitations should be considered when interpreting the results. The QOL questionnaire was administered retrospectively, and hence participants' responses relied on their memories. Additionally, since this is a generic tool, it did not focus on characteristics of AMI, and did not include diet as a risk factor.

Conclusion

In the present investigation, we observed that, compared with NSTEMI patients, a higher prevalence of smokers was observed among STEMI patients. The other RF evaluated were associated with both types of AMI equally.

We observed a negative perception in the domains of physical aspects and pain of QOL in STEMI and NSTEMI patients, with no difference in QOL between these two groups. Regarding the association of QOL with in-hospital CVEs, a significant association was found of physical and mental health with the occurrence of events.

Author contributions

Conception and design of the research: Jesus MT, Costa IMNBC, Silva DG, Silva JRS, Buarque MDBM, Sousa ACS. Acquisition of data: Jesus MT, Costa IMNBC, Buarque MDBM, Andrade FA, Sousa ACS. Analysis and interpretation of the data: Jesus MT, Costa IMNBC, Silva DG, Silva JRS, Barreto Filho JAS, Almeida-Santos MA, Oliveira JLM, Sousa ACS. Statistical analysis: Silva JRS. Writing of the manuscript: Jesus MT, Silva DG, Almeida-Santos MA, Oliveira JLM, Sousa ACS. Critical revision of the manuscript for intellectual content: Jesus MT, Silva DG, Almeida-Santos MA, Oliveira JLM, Sousa ACS.

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 Monique Tavares de Jesus, from *Universidade Federal de Sergipe*.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the *Universidade de Sergipe* under the protocol number 302.544. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

Table 5 – Distribution of SF-36 domain scores according to the occurrence of in-hospital events in acute myocardial infarction patients[18]

Variables		Domains							
		FC	Physical	Pain	Mental	Vitality	Social	Emotional	Health
Angioplasty	Y	54±32	42±42	49±31	69±22	61±24	70±29	60±44	59±56
	N	53±32	39±42	47±30	68±22	59±24	64±29	61±44	54±58
Myocardial revascularization	Y	53±32	32±40	42±26	70±23	59±23	60±30	55±47	54±24
	N	54±32	42±42	49±31	69±21	61±24	69±29	61±44	58±22
Overall deaths	Y	31±30	31±47	48±38	54±23	48±24	44±33	83±19	46±11
	N	54±32	41±42	48±30	69±22	60±24	68±29	60±44	58±22
Cardiovascular deaths	Y	38±34	21±36	40±20	61±26	48±24	58±23	60±39	54±17
	N	55±32*	42±43*	49±31	69±21	61±24	69±29	60±45	58±22
Re-AMI	Y	45±34	30±40	44±34	66±19	45±22	52±27	58±44	57±19
	N	54±32	41±42	48±30	69±22	61±24	69±29	60±44	58±22
Post-AMI Angina	Y	40±34	31±42	44±32	60±28	51±25	63±30	44±51	57±22
	N	55±32	41±42	48±30	69±21	61±24	68±29	61±44	58±22
CHF	Y	45±30	23±40	36±32	63±24	46±28	60±29	26±39	61±19
	N	54±32	41±42	49±30	69±22	61±24	68±29	61±44	58±22
CS	Y	50±30	25±43	50±30	66±21	58±18	73±22	60±37	57±20
	N	54±32	41±42	48±30	69±22	61±24	68±29	60±44	58±22
CRA	Y	44±30	21±32	42±18	63±30	53±24	63±29	60±37	57±23
	N	54±32	41±42	48±31	69±21	60±24	68±29	60±44	58±22
CVA	Y	42±42	50±50	48±12	68±10	53±6	58±38	67±33	60±7
	N	54±32	41±42	49±30	69±22	60±24	68±29	60±44	58±22
CRI or ARF	Y	37±21	8±14	17±6	45±23	42±15	38±22	56±19	47±16
	N	54±32	41±42	48±30*	69±22	60±24	68±29	60,17±44	58±22

*FC: Functional Capacity MR: Myocardial Revascularization; AMI: Acute Myocardial Infarction; CS: Cardiogenic Shock; CRA: Cardiorespiratory Arrest; CHF: Congestive Heart Failure; CVA: Cerebrovascular Accident; CRI: Chronic Renal Insufficiency; ARF: Acute Renal Failure; Y: yes; N: no. *: p value < 0,05.*

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ORIGINAL ARTICLE

Prevalence of Frailty in Patients Undergoing Cardiac Valve Surgery: Comparison of Frailty Tools

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Abstract

Background: There is no consensus among tools for assessing frailty.

Objective: To evaluate the prevalence of frailty according to different tools in patients referred for elective valve cardiac surgery.

Methods: This is a cross-sectional study. All patients were ≥ 18 years of age, clinically stable. The following patients were excluded: those unable to perform the tests because of physical, cognitive, or neurological limitations; those requiring non elective/emergency procedures or hemodynamic instability. During the preoperative cardiology visit, frailty was assessed by the Short Physical Performance Battery (SPPB), the Frailty Deficit Index (FDI), handgrip strength, and gait speed 3m. For the entire analysis, the statistical significance was set at 5%.

Results: Our cohort consisted of 258 subjects. From the total cohort, 201 were ≤ 70 years of age (77.9%), the predominant etiology according to rheumatic disease (50.7% *vs* 8.8%; p=0.000) with double mitral lesion (24.9% *vs* 0%; p=0.000). Frailty was present in 32.9% according SPPB, 29.1% with reduced muscular strength. and 8.9% with FDI. Handgrip strength was weaker in elderly patients (26.7 *vs* 23.6; p=0.051) and gait speed was lower in the younger group, in which 36% were considered frail (36% *vs* 14%; p=0.002). Variables associated with frailty were age ≥ 70 years, female gender, aortic stenosis, and regurgitation.

Conclusion: Frailty in adult patients who will have elective heart valve surgery is present even in the younger groups, although the older group with comorbidities are more frail. Frailty was more clearly shown by the SPPB than by the FDI and handgrip tests.

Keywords: Heart Valve Diseases/surgery; Cardiac Surgery; Frailty; Frail Elderly.

Introduction

Associated with an increased life expectancy worldwide is a growing prevalence of valvular heart disease (VHD).[1] The number of cardiovascular procedures in older adults has also increased in recent years and, heart valve disease accounts for a high number of hospitalizations requiring surgery in Brazil.[2] The impact of frailty on cardiovascular disease is striking; it relates to adverse outcomes following surgery, including postoperative morbidity and mortality.[3, 4]

Frailty is defined as a biological syndrome of decreased reserve and resistance to stressors, resulting from cumulative declines across multiple physiological systems, and causing vulnerability to adverse outcomes.[5] Although not routinely estimated in the preoperative setting, prevalence of frailty in community-dwelling older adults can vary in the literature from 10% to nearly 60% depending on comorbidity burden, population, and measurement tool.[6] Even younger patients undergoing cardiac surgery may have a high degree of frailty, and frailty in younger patients (40-64 years) is also related to worse outcomes.[7]

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The rheumatic etiology is the main cause of VHD in Latin America, different from most developed countries, where degenerative etiology is more prevalent.[2] Moreover, patients with rheumatic heart disease have a greater risk of disease progression and often need reoperation 10 or 20 years after the first procedure. Even though the prevalence of rheumatic heart disease worldwide remains alarmingly high, the impact of frailty assessment in this population in unknown.[8]

Heart valve surgery is an inherently relevant iatrogenic stressor for frailty and surgical intervention is the cornerstone of treatment for symptomatic disease – the only definitive approach able to change mortality.[2] Preoperative frailty evaluation would result in better risk assessment for cardiac surgery and could identify patients at a higher risk for adverse clinical outcomes, mortality, and prolonged institutional care.[9]

Operative risk for cardiac surgery is usually measured by the European System of Cardiac Operative Risk Evaluation (EuroSCORE)[10, 11] or the Society of Thoracic Surgeons (STS) score.[12, 13] However, none of these scores have incorporated frailty. Patients who are frail may need rehabilitation because of a decline in functional status after an intervention, with significant loss in quality of life and independence. Higher frailty scores lead to longer mechanical ventilation, prolonged ICU and hospital length of stay, and a higher risk for complications, such as stroke and in-hospital death. The incorporation of frailty into operative risk scores may improve classification with STS and EuroSCORE.[6, 14, 15]

Recent data report that not only do frail patients have higher complications, but there is also an association between pre-frailty and adverse postoperative outcomes following cardiovascular surgery. Rodrigues et al. reported higher rates of stroke and in-hospital deaths in a Brazilian center even in pre-frail subjects.[16]

The clinician often evaluates frailty by the 'eye-ball test, and despite the fact that' – these patients usually have sarcopenia and adverse outcomes,[17] this approach is subjective, unreliable, and prone to bias.[18,19] Objective measurement for frailty is recommended, but many tools are available for assessing frailty, and there is no consensus among them.[4]

The aim of this study was to evaluate the prevalence of frailty according to different tools in patients with VHD referred for elective cardiac surgery in a tertiary reference university hospital.

Methods

This is a cross-sectional study. The present investigation was conducted from March to November 2018, with a convenience sample of 383 patients with symptomatic valve heart disease, who were referred for either elective transcatheter valve therapy or cardiac surgery at our institution. All patients were ≥18 years of age and clinically stable. The following patients were excluded: those unable to perform the tests because of physical, cognitive, or neurological limitations; patients unwilling to perform the tests; patients experiencing symptoms at rest (chest pain, dyspnea); and those requiring non-elective/emergency procedures or presenting hemodynamic instability defined as systolic blood pressure <60 or >150mmHg and heart beats <50 or >130 beats per minute.

Data with baseline characteristics were assessed by reviewing electronic records that included comorbidities, symptoms (e.g. NYHA class assessed by the New York Heart Association functional classification), cardiovascular risk factors, prior cardiovascular events and procedures, medication, height, weight, and ejection fraction.

Age cutoff

The optimal age cutoff to define elderly patients undergoing cardiac surgery is unknown, usually ranging from 65 to 80 years of age. Although the use of 75 years as a cutoff was proposed recently[20] for patients undergoing cardiac surgery, since it marks a steeper increase in mortality, we chose to use the definition of 70 years of age because: 1) our population is different from this cohort regarding multiple aspects of aging (Brazil x USA/Canada); 2) the 70 year cutoff was previously used in other groups;[21,22] 3) we had a representative proportion of patients over 70 years (22%) but not over 75 years (10%).

Frailty assessment

During the preoperative cardiology visit, physical performance (Short Physical Performance Battery [SPPB]), Frailty Deficit Index (FDI), and handgrip strength (dynamometer hydraulic Saehan®) were assessed by a single trained physiotherapist. SPPB is an established tool to assess one's physical performance of the lower limbs and consists of three

timed tasks: standing balance (semi-tandem and tandem), 3-meter gait-speed, and 5-chair sit-to-stand tests. Every task can be given a score between 0 and 4. The score range from 0 to 3 means disability, from 4 to 6 means poor performance, from 7 to 9 moderate performance, and from 10 to 12 good performance. Frailty was considered when SPPB was ≤8, as previously reported in patients undergoing cardiac valvar surgery.[6]

The FDI ranges from 0 to 32 points, and the final score is calculated from the sum of points divided by the number of variables. According to the existing literature, frail patients were defined as those with an FDI index of greater than or equal to 0.25.[23]

Muscular strength was measured using a dominant hand handgrip. The patients were seated with their shoulders adducted, their elbows flexed to 90°, and their forearms in a neutral position. The frailty criteria were based on the highest measure of three tests of grip strength, adjusted for gender and body mass index (BMI).[5]

The Gait Speed was extracted from the SPPB test and calculated with a 3m distance, with the best time out of two assessments. Patients could use their usual walking assistance device. In this study, 0.83m/s was defined as the cutoff for frailty.[24]

Ethical aspects

This study was approved by the Ethics Committee on Human Research of the Hospital das Clínicas at the College of Medicine, University of São Paulo (CAAE 08882019.4.0000.0068). Patients were informed about the purpose of the research, and evaluation procedures and written consents were obtained from all patients. Possible questions were clarified and the patients were informed that they could withdraw from the research whenever they wanted.

Statistical analysis

Statistical analysis was performed using the SPSS software (version 17.0; SPSS Inc.). Continuous data are presented in median and interquartile intervals, and categorical data are expressed in percentages. The Kolmogorov-Smirnov test was used to determine the normality of data distribution; The Mann-Whitney tests were used to assess the differences in data between groups with continuous data as appropriate. The X^2 test was used for categorical data. Spearman's Correlation was conducted to study the association between the tools used to assess frailty, considering the degree of association as weak, r=0.30 to 0.50; moderate, r= 0.50 to 0.70; and strong, r>0.7.[25] For all analyses, statistical significance was set at $p < 0.05$.

Results

During the study, 383 patients were screened for the preoperative visit, of which 125 were excluded mainly due to incomplete data. Our sample, therefore, consisted of 258 subjects (Figure 1). The median age was 59 (48.7-68) years of age, and 57.8% were female patients .

Table 1 shows the baseline characteristics between the groups <70 and ≥70 years of age. From the total cohort, 201 (77.9%) were <70, and the predominant etiology was rheumatic heart disease, with double mitral lesion as the main etiology of heart valve disease. This group also showed a significant prevalence of previous stroke and pulmonary hypertension.

Aortic stenosis was more prevalent in the older group, with more than half of the subjects presenting this condition. A higher number of comorbidities were related to older age, such as diabetes, hypertension, dyslipidemia, anemia, and coronary artery disease. Musculoskeletal limitations were present in both groups but with no statistical difference (21.5% vs. 31.6, p=0.115); the level of physical activity was similar between the groups (9.0% vs.8.8, p=0.966).

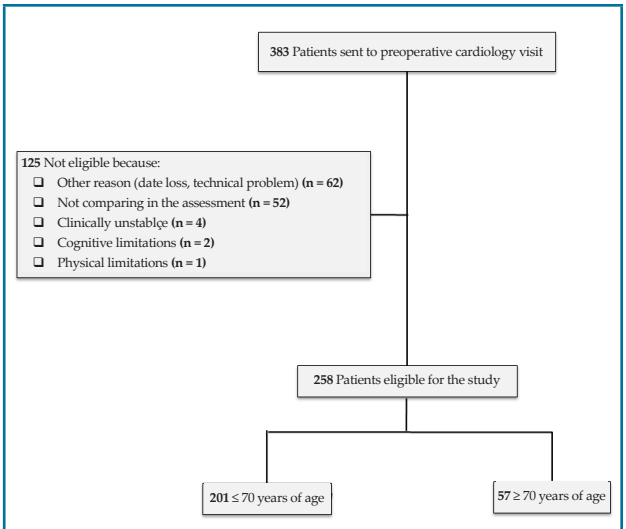

Figure 1 – Flow diagram.

Table 1 – Clinical features of patients evaluated for frailty in the preoperative period for elective heart valve replacement surgery; Heart Institute, March to November, 2018

	< 70 years of age (n=201)	≥ 70years of age (n=57)	Total (n=258)	p-value
Age (years)	54(46-61.5)	74(71.5-79)	59(48.75-68)	**<0.001**
Female, sex (%)	62.2	42.1	57.8	0.007
BMI (kg/m²)	27.1(22.8-30.4)	26.4(24.6-30.6)	26.5(23.4-30.4)	0.319
Valvular Lesion (%)				
Mitral stenosis	9.0	1.8	7.4	0.006
Mitral Regurgitation	22.9	14.0	20.9	0.147
MS/MR	24.9	0.0	19.4	**<0.001**
Aortic stenosis	20.9	56.1	28.7	**<0.001**
Aortic regurgitation	11.9	14.0	12.0	0.944
AS/AR	10.4	56.1	28.7	**<0.001**
Comorbid Conditions (%)				
NYHA functional class	3 (2-3)	2 (2-3)	3(2-3)	0.129
Prior Cardiac Surgery	43.3	31.6	40.7	0.112
Active smoking	8.0	3.5	7.0	0.244
Myocardial infarction	6.5	8.8	7.0	0.966
Diabetes	14.4	40.4	20.2	**<0.001**
PAD	5.0	5.3	5.0	0.930
Stroke	14.9	3.5	12.4	**0.021**
Hemiplegia	5.0	0.0	3.9	0.086
COPD	6.5	1.8	5.4	0.166
Renal impairment	4.0	7.0	4.7	**0.036**
Rheumatic disease	50.7	8.8	41.5	**<0.001**
Hypertension	56.7	87.7	63.6	**<0.001**
Dyslipidemia	28.4	50.9	33.3	**0.001**
Heart failure	35.8	8.6	36.4	0.701
LVEF	62(56-66)	63(55-66)	62(25-75)	0.895
Depression	6.0	1.8	5.0	0.309
Anemia	9.0	21.1	11.6	**0.012**
Pulmonary hypertension	47.7	28.1	43.0	**0.010**
Atrial fibrillation	40.5	28.1	37.7	0.088
CAD	13.9	29.8	17.4	**0.005**

BMI: body mass index; MS/MR: mitral stenosis and mitral regurgitation; AS/AR: aortic stenosis and aortic regurgitation; NYHA: New York heart association; PAD: peripheral artery disease; COPD: chronic obstructive pulmonary disease; LVEF: left ventricular ejection fraction; CAD: coronary artery disease. Used Mann-Whitney test and X^2 test, statistical significance was p<0.05.

Frailty prevalence differed significantly with age and the assessment tool used (Figure 2). Frailty was present in 32.9%, according to SPPB; in 29.1%, according to reduced muscle strength; and in only 8.9% when FDI was applied. No patient used a walking assistance device.

Table 2 shows the groups divided according to age. Handgrip strength was lower in elderly patients, classifying almost half of them as frail. When SPPB was used, 43.9% were considered frail in the oldest group, with moderate performance. Gait speed was lower in the young group, and 36% were considered frail with the SPPB assessment instrument. Only when the FDI was applied, no statistical difference was observed between the groups regarding the degree of frailty.

Frail patients were compared with non-frail patients, according to SPPB. Frail patients were mainly ≥ 70 years

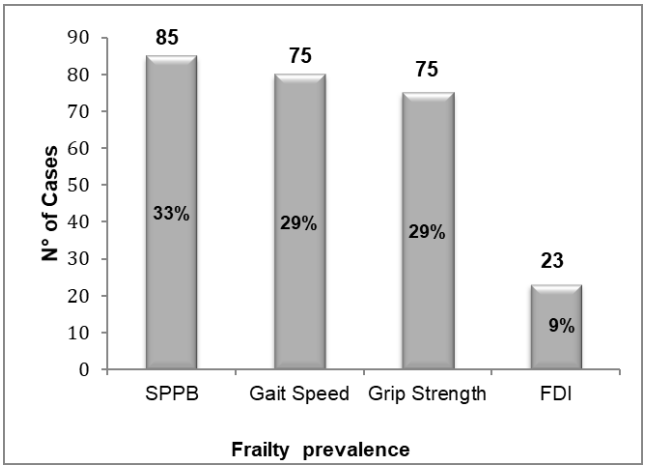

Figure 2 – Prevalence of frailty in the total sample analysis.

Table 2 – Frailty assessment according to age

Frailty Assessment	< 70 years of age (n =201)	≥ 70years of age (n =57)	p-value
SPPB			
Score	0(8-11)	9(7-10)	0.008
(% Frail)	29.9	43.9	0.047
Grip strength			
(Kgf)	26.7(20.8-34.6)	23.6(16.9-33.9)	0.051
(% Frail)	22.9	50.9	**<0.001**
Gait Speed			
(m/s)	1.0(0.75-1.00)	1.0(0.87-1.25)	**0.004**
(% Frail)	36	14	**0.002**
FDI			
Score	0.12(0.07-0.18)	0.12(0.10-0.16)	0.417
(% Frail)	9.0	8.8	0.966

SPPB: Short Physical Performance Battery; Kgf: kilograms force; FDI: Frailty Deficit Index. Used Mann-Whitney test and X2 test, statistical significance was p<0.05.

of age, female, and had aortic stenosis and regurgitation as the main lesion. They also presented a worse NYHA class, and more than half had a previous cardiac surgery. These patients had lower physical activity (2.3% vs. 12.1%, p=0,010) and other comorbidities were more prevalent, such as anemia, atrial fibrillation, musculoskeletal disorders (35.3% vs.18%, p=0.002) and hemiplegia (Table 3).

SPPB score showed a significant and strong correlation with gait speed, which was statistically significant, but a weak association with strength and FDI (Table 4).

Discussion

In this study, despite the fact that the population predominantly consisted of younger adults, frailty was

Table 3 – Comparison between frail and non-frail patients by SPPB; March to November, 2018

	SPPB		
	NON-FRAIL (n= 173)	FRAIL (n= 85)	p-value
≥ 70 years (%)	18.5	29.4	0.047
Female, sex (%)	47	80	**<0.001**
BMI (kg/m²)	26.3(23.4-29.8)	27.4(23.4-31.9)	0.293
Valvular Lesion (%)			
Mitral stenosis	6.9	8.2	0.707
Mitral Regurgitation	23.7	15.3	0.119
MS/MR	17.3	23.5	0.237
Aortic stenosis	28.3	29.4	0.856
Aortic regurgitation	15.0	5.8	**0.034**
AS/AR	8.6	17,6	**0.035**
Comorbid Conditions (%)			
NYHA functional class	2(2-3)	3(2.5-3)	**<0.001**
Prior cardiac surgery	33.0	56.5	**<0.001**
Myocardial infarction	7.5	5.8	0.442
Diabetes	19.6	21.2	0.774
PAD	4.6	5.8	0.436
Stroke	9.8	17.6	0.073
Hemiplegia	1.7	8.2	**0.016**
COPD	5.8	4.7	0.486
Renal impairment	5.2	3.5	0.401
Rheumatic valve disease	38.7	47.0	0.202
Hypertension	60.7	69.4	0.171
Dyslipidemia	34.7	30.6	0.512
Heart failure	35.8	37.6	0.777
Depression	4.6	5.8	0.436
Anemia	8.7	17.6	**0.035**
Pulmonary hypertension	42.4	44.0	0.807
Atrial fribillation	32.4	48.8	**0.011**
CAD	17.9	16.5	0.773

BMI: body mass index; MS/MR: mitral stenosis and mitral regurgitation; AS/AR: aortic stenosis and aortic regurgitation; PAD: peripheral artery disease; COPD: chronic obstructive pulmonary disease; CAD: coronary artery disease. Used Mann-Whitney test and X^2 test, statistical significance was p<0.05.

Table 4 – Spearman's correlation coefficients (r) between the frailty tools

	SPPB	
	r	p-value
Gait speed	-0.805	**<0.001**
Grip strength	0.447	**<0.001**
FDI	-0.417	**<0.001**

SPPB: Short Physical Performance Battery; FDI: Frailty Deficit Index. Spearman test.

present in almost one-third of the total population. In a geriatric population, this prevalence is even higher and frailty evaluation may help to better identify patients at risk for adverse outcomes. Although prior studies have shown that routine risk scores are applied to identify morbidities, they do not assess functional capacity.

A consensus on a validated frailty scoring system that is precise and objective has not yet been established in the literature. Our study applied four different strategies to perform a thorough patient assessment of frailty status, using physical performance, grip strength, gait speed, and deficit measurements. The prevalence of frailty varied considerably according to each tool.

The FDI identified less than 10% of frail subjects, with no significant difference between those over 70 and those under 70. This is probably underestimated according to the current literature, despite a great variation in the prevalence of comorbidities present in each population study. It is possible that FDI did not show a difference between frail and non-frail patients because the questions related to activities of daily living showed low scores and were similar across the sample. Our patients were stable and were referred for elective surgery, which may have contributed to a lower FDI score, although comorbidities were more prevalent in the older group.

The prevalence of frailty, by handgrip strength, however, was more than 2-fold more prevalent in the oldest group (22.9% vs. 50.9%, p =0.000). In this group, the standard deviation was bigger (SD=8.97vs. 0.7), which can be attributed to a large variation in the physical performance that we noted when the test was applied. Bottura et al.[26] evaluated the frailty of 100 individuals in the preoperative period before cardiac surgery, using Fried criteria, handgrip strength, and a gait speed of 5m. Results showed that 70% of the sample were pre-frail and 17% frail, and muscle strength was significantly lower in frail individuals (31±11 vs. 22±8; p=0.007).[26] It was hypothesized that FDI could underestimate the prevalence of frailty, whereas the measure of handgrip strength alone could overestimate it, especially among the elderly.

The FRAILTY-AVR STUDY[27] reported an overall prevalence of frailty that varied from 26% to 68%, with different tools, and SPPB achieved the highest prevalence. Their population was older (median 82 years) than the median from our study group.

In 2010, a study with a 46% prevalence of frailty, according to gait speed, had a 2 to 3-fold increased risk predictive ability beyond the STS-Predicted Risk of Mortality or Major Morbidity and the European System for Cardiac Operative Risk Evaluation (EuroSCORE)[28]. Recently, gait speed has been added to the STS tool.

Interestingly, gait speed was lower in the younger adults probably due to a higher prevalence of pulmonary hypertension which could account for this difference. The pulmonary hypertension in this population results from high left atrial pressure and changes in the pulmonary vasculature, and is considered a marker of disease severity in these patients.[29] Additionally, the prevalence of stroke with hemiplegia may justify the lower walking speed in this population. We believe that these different clinical profiles in younger patients are the result of different etiologies of the valvar disease: more rheumatic heart disease in patients <70 years and more degenerative disease in patients ≥70 years of age. Previous studies showed that rheumatic heart disease is the most common cause of atrial fibrillation in developing countries, affecting mainly young patients, especially women. The uncoordinated contractions of the heart muscle provide an irregular ejection of blood for the ventricle, which can create clots. Atrial fibrillation is

associated with significant morbidity, such as embolic events and stroke.[30,31] This association seems to be present in our sample with a significant number in the younger group.

These data may refine preoperative evaluations and guide future pre-rehabilitation targets that could diminish adverse outcomes of surgery. In 2000, a small randomized trial, conducted in a Canadian tertiary care hospital, randomized 249 patients who had been on a waiting list for elective CABG to receive exercise training, twice per week, education and reinforcement, and monthly nurse-initiated telephone calls. Patients who received the preoperative intervention spent one day less in the hospital overall ($p = 0.002$) and less time in the intensive care unit.[32]. More recently, another study showed a potential benefit of home pre-rehabilitation in frail patients in the 6 weeks before they underwent elective cardiac and valve surgery.[33] The PREQUEL STUDY (Trial Registration number: ChiCTR1800016098) is a randomized controlled trial in progress that will compare a pre-rehabilitation program with standard of care in frail and pre-frail patients undergoing elective coronary artery bypass graft, with or without valve repair or replacement, and define quality recovery as the primary outcome.

The poorer physical performance, strength, and frailty status of female subjects shown in our analysis are in accordance with results from previous studies.[28] Frailty is more prevalent in women, and there are several hypothesis for this finding: higher inflammatory cytokines, higher insulin resistance, as well as lower testosterone and estrogen levels resulting in a progressive decline in muscle mass and physical vulnerability.[34, 35]

Our study has several limitations: 1) The evaluation time consisted of only 10 months, which limited the sample size; furthermore, we lost 114 patients due to incomplete data; 2) The adopted instruments may not be sensitive enough to characterize the functional capacity of this group and predict final outcomes; 3) because not all of the patients have undergone cardiac surgery, we were not able to correlate frailty with mortality and worse outcomes after surgery; 4) we used a shorter walking distance to calculate gait speed.

Conclusion

Frailty is present in elective heart valve surgery even in young patients. The older group, women, those with comorbidities like pulmonary hypertension and previous stroke are likely to be frail. SPPB showed frailty better than did FDI and handgrip. These results can contribute to the implementation of therapeutic intervention, like exercise training in the pre-operative period for patients to reduce postoperative risks.

Author contributions

Conception and design of the research: Harada G, Andrade MC, Feltrim MI. Acquisition of data: Harada G, Andrade MC, Feltrim MI. Analysis and interpretation of the data: Harada G, Andrade MC, Brito JN, Tavares CM, Feltrim MI. Statistical analysis: Brito JN, Tavares CM. Writing of the manuscript: Harada G, Brito JN, Tavares CM, Tarasoutchi F, Pomenrantzeff PM, Bortolotto L, Feltrim MI. Critical revision of the manuscript for intellectual content: Tarasoutchi F, Pomenrantzeff PM, Bortolotto L, Feltrim MI.

Potential Conflict of Interest

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

Sources of Funding

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Study Association

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

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Hospital das *Clínicas da Faculdade de Medicina da Universidade de São Paulo* under the protocol number 08882019.4.0000.0068. 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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ORIGINAL ARTICLE

QTc, Tp-e Interval and Tp-e/QTc Ratio in Patients with Hypocalcemia-case Control Study

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Abstract

Background: To the best of our knowledge, there are studies related to QT and QTc interval in patients with hypocalcemia, but there are no studies evaluating T wave peak and end interval (Tp-e interval), Tp-e/QT and Tp-e/QTc ratios used to evaluate cardiac arrhythmia risk and ventricular repolarization changes rates.

Objectives: Therefore, we aimed to investigate whether there is a change in Tp-e interval, Tp-e/QT and Tp-e/QTc ratios in patients with hypocalcemia.

Methods: Retrospectively, 29 patients with hypocalcemia in the emergency department were included in the study. Twenty-nine patients with similar age and sex distribution were included in the study as the control group. All patients underwent 12-lead electrocardiography (ECG). In addition to routine measurements, Tp-e interval, Tp-e/QT and Tp-e/QTc ratios were measured on ECG. The study data were grouped as patients with and without hypocalcemia.

Results: The mean age of the patients was 66.24 ± 4.95 years. QTc interval, Tp-e interval and Tp-e/QTc values were found to be significantly higher in patients with hypocalcemia ($p < 0.001$ for each). QTc interval, Tp-e interval and Tp-e/QTc ratio showed a significant negative correlation with calcium levels.

Conclusion: Tp-e interval and Tp-e/QTc ratios are significantly increased in patients with hypocalcemia compared to those without hypocalcemia and this can be used more effectively in the follow-up of cardiac fatal arrhythmias.

Keywords: Hypocalcemia; QTc; Tp-e interval; Tp-e/QTc ratio.

Introduction

Hypocalcemia is one of the common electrolyte disorders which can be encountered in the emergency department. It has a wide clinical range from asymptomatic cases to severe life-threatening cases[1]. One of the risk factors leading to prolonged QT interval is hypocalcemia[2]. When cardiac abnormalities related to hypocalcemia are examined, prolongation of QT interval is reported to be the most common[3]. Cases showing that prolonged QT interval associated with hypocalcemia causes fatal ventricular arrhythmias such as Torsades de Pointes are known[4,5].

There are multiple electrocardiography (ECG) measurements associated with ventricular repolarization and are associated with a risk of ventricular arrhythmia. These measurements are QT and QTc interval, QT and QTc dispersion and T wave peak and end interval (Tp-e interval). Among these parameters, QT and QTc are indicative of ventricular depolarization in addition to repolarization. However, Tp-e is more predictive of ventricular repolarization and may be more meaningful especially in the evaluation of repolarization. The obtained Tp-e/QT and Tp-e/QTc ratios are related to ventricular transmural dispersion during repolarization[6]. Increased Tp-e interval shows abnormal spread in ventricular repolarization and is associated with

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increased risk of ventricular arrhythmia[7]. When the literature is reviewed, it is seen that there is no research on Tp-e interval, Tp-e/QT and Tp-e/QTc ratios used in the evaluation of ventricular repolarization in patients with hypocalcemia in the emergency department.

In this study, we aimed to determine whether there was a change in QT, QTc, Tp-e interval, Tp-e/QT and Tp-e/QTc ratios in patients with hypocalcemia in the emergency department compared to patients without hypocalcemia.

Material and Method

The study was planned as a retrospective case control study. Records of patients who applied to Adana City Research and Training Hospital, Department of Emergency Medicine between January 1, 2019 and August 31, 2019, and whose biochemical tests revealed hypocalcemia were retrospectively examined. Electrocardiography (ECG) recordings obtained from the files of these patients were examined. A total of 29 patients were included in the study. These 29 patients included in the study were defined as the patient group. Biochemical parameters of the patients admitted to the emergency department for various reasons and found to be healthy were examined. ECG recordings of these patients with normocalcemia were obtained. 29 outpatients who were found to be healthy were included in the study as the control group.

Exclusion criteria for all patients included in the study and control group were all medical treatments known to extend or shorten QT and QTc distance, known syncope or sudden cardiac arrest history in the patients or their family, presence of acute or chronic systemic or local infection, being in the pediatric age group (<18 years), inability to perform Tp-e and QTc measurements on ECG, presence of known coronary artery disease (CAD) or diabetes mellitus, one of the major risk factors for CAD, medium-advanced valvular disease, systolic heart failure, electrolyte deficiency, and having the diagnosis of chronic liver disease or chronic renal failure. The study was conducted in accordance with the Helsinki Declaration and approved by the Local Ethics Committee Adana City Research and Training Hospital, Ethics Committee, Meeting Number: 45, Decision No: 630, 04/12/2019.

12-lead ECG and laboratory results of all patients were obtained from the files. From the demographic variables of the patients, age, sex, pulse, blood pressure, oxygen saturation values of all patients were recorded from the archived files. From the routine biochemistry parameters, renal function tests, serum electrolytes, liver function tests were recorded.

12 - Lead Electrocardiographic Evaluation

Firstly, 12-lead ECG obtained by MAC 2000 ECG Machine (GE medical systems information technologies, Inc., WI, USA) with a sinus rhythm of 25 mm / sec and 1 mv / 10 mm standard calibration was obtained from the files. All patients were evaluated for the PR interval, from the beginning of the P wave to the beginning of the QRS complex. QRS time was measured from the beginning to the end of the QRS complex. The time from QRS to the point where T wave returns to the isoelectric line was calculated for the QT time. QTc was calculated using the Bazett Formula ($QTc = QT / \sqrt{R - R}$). The Tp-e interval was defined as the time from the peak of the T wave to the point where the T wave interconnected with the isoelectric line. Measurements were made primarily from V5. If V5 was unsuitable for measurement (amplitude <1.5 mm), measurements were taken from V4 or V6[8]. Tp-e/QTc ratio was calculated based on these measurements. All ECG examinations in sinus rhythm were evaluated by two cardiologist with at least 5 years of experience in electrophysiology and ≥2000 arrhythmia patients annually, while unaware of the clinical status of the patient.

Statistical Analysis

All analyzes were performed using SPSS 22.0 (Chicago, IL, USA) statistical software package. Kolmogorov-Smirnov test was used to determine whether the distribution of continuous variables was normal. Continuous variables in the group data were expressed as mean ± standard deviation. Categorical variables were expressed as numbers and percentages. Continuous variables that showed normal distribution was compared using the Student t test, whereas the Mann-Whitney U test is used to compare differences between two independent groups when the dependent variable is either ordinal or continuous, but not normally distributed. Student t test used was paired. Chi-square (χ^2) test was used to compare categorical variables. The kappa coefficient was used to examine the interobserver variability of all ECG measurements. Both Pearson's and Spearman's correlation analysis was used to determine the presence of a relationship between countable parameters. Linear regression analysis of parameters showing statistically significant correlation was done and beta values were obtained. All the assumptions necessary to use the linear regression analysis were verified. Statistical significance level was accepted as $p < 0.001$.

Results

The study data were divided into two groups as patient and control groups. Electrocardiographic measurements were taken successfully from all patients included in the study.

When demographic data were compared according to the study groups, age and sex were found to be similar between the groups. Laboratory parameters were similar between the two groups (Table 1).

When ventricular repolarization parameters were examined according to the study groups, QTc interval, Tp-e interval and Tp-e/QTc values were found to be significantly higher in patients with hypocalcemia (Table 2).

Table 3 shows the correlation of QTc, Tp-e-interval and Tp-e/QTc measurements with the calcium and ionized calcium parameters. All measurements negatively correlated with calcium and ionized calcium levels (Table 3). Linear regression analysis was performed with calcium being significantly related to QTc, Tp-e-interval Tp-e/QTc measurements (Table 4). In linear regression analyses, QTc, Tp-e-interval and Tp-e/QTc ratio were found to be independently associated with calcium level. In Scatterplot analyses of calcium levels with QTc interval, Tp-e interval and Tp-e/QTc ratios, R^2 linear values were 0.656, 0.818 and 0.785, respectively (Figure 1, Figure 2 and Figure 3).

Discussion

The main finding of our study was that the patients with hypocalcemia had significantly higher QTc, Tp-e interval and Tp-e/QTc ratios than those without hypocalcemia. To the best of our knowledge, this finding is the first study in the literature to show an increase in Tp-e interval and Tp-e/QTc ratios among the ventricular repolarization parameters in patients with hypocalcemia. Our study also supported previous studies showing QT and QTc prolongation in patients with hypocalcemia.

Ventricular myocardium depolarization occurs from the endocardial region towards the epicardial region.

Table 1 – Comparison of Demographic and Laboratory Findings between Hypocalcemia and Control Group

	Patients with Hypocalcemia n=29	Patients without Hypocalcemia n=29	p
Age (years)	66.24 ± 4.95	64.07 ± 4.52	0.087
Systolic blood pressure (mmHg)	114.83 ± 12.14	118.28 ± 11.67	0.275
Diastolic blood pressure (mmHg)	70.69± 9.23	72.07 ± 8.19	0.550
Heart rate (pulse/minute)	**118.76 ± 12.40**	**82.76 ± 10.79**	**<0.001**
Urea (mg/dL)	34.38 ± 8.96	37.00 ± 7.02	0.221
Creatinine (mg/dL)	0.75 ± 0.24	0.78 ± 0.21	0.650
Sodium (mEq/L)	139.17 ± 2.67	139.24 ± 3.28	0.930
Potassium (mEq/L)	4.15 ± 0.51	4.23 ± 0.37	0.462
Glucose (mg/dL)	103.76 ± 13.24	108.24 ± 12.03	0.183
ALT (u/L)*	31.21 ± 12.50	18.97 ± 14.56	0.009
AST (u/L)**	24.10 ± 8.26	25.97 ± 12.27	0.501
Albumine (g/L)	40.14 ± 3.01	42.00 ± 4.83	0.085
Calcium (mg/dL)	**6.90 ± 0.65**	**9.47 ± 0.35**	**<0.001**
Ionized Calcium (mmol/L)	**0.98 ± 0.11**	**1.07 ± 0.06**	**<0.001**

**ALT: Alanine aminotransferase, **AST: Aspartate aminotransferase.*

Table 2 – Comparison of Ventricular Repolarization Parameters between Hypocalcemia and Control Group

	Patients with Hypocalcemia n=29	Patients without Hypocalcemia n=29	p
QTc interval time (ms)	476.59± 22.51	432.62 ± 9.28	<0.001
Tp-e interval time (msn)	128.38 ± 15.34	77.38 ± 8.38	<0.001
Tp-e/QTc Ratio	26.91 ± 2.72	17.87 ± 1.81	<0.001

QTc: Corrected QT

Table 3 – Correlation of QTc, Tp-e Interval and Tp-e/QTc Raito with Calcium and Ionized Calcium

	QTc		Tp-e-interval		Tp-e/QTc Ratio	
	r	p	r	p	r	p
Calcium (mg/dL)	-0.810	<0.001	-0.904	<0.001	-0.886	<0.001
Ionized Calcium (mmol/L)	-0.508	<0.001	-0.499	<0.001	-0.459	<0.001

Table 4 – A Linear Regression Analysis for Calcium Significantly Correlated with QTc, Tp-e Interval and Tp-e/QTc Raito

	QTc		Tp-e-Interval		Tp-e/QTc Ratio	
	β	p	β	p	β	p
Calcium	-0.309	<0.001	-0.807	<0.001	-0.647	<0.001

R^2 for QTc, Tp-e interval and Tp-e/QTc Ratio as 0.656, 0.818, 0.785, respectively.

After depolarization, ventricular repolarization occurs. During ventricular repolarization, there is dispersion between the endocardial and epicardial region. The intervals between the T wave peak and the end distance are called the Tp-e interval, which is associated with transmural ventricular repolarization[6,9]. Tp-interval and its ratio to the QT interval have been shown to be associated with an arrhythmic clinical status in many cardiac pathological conditions and also poses a high risk for sudden cardiac death[5,10-12]. Increased Tp-e interval and Tp-e/QTc ratio are associated with arrhythmia and sudden cardiac death, dispersion in the epicardial and endocardial regions of the ventricular myocardium between the epicardial and endocardial regions causes slow conduction in these two anatomic regions and this is thought to create an increase in re-entry, which is the most common cause of arrhythmias.

Hypocalcemia characteristically results in prolongation of the ST segment and a long QTc interval[4,13]. Although there are studies evaluating QT and QTc interval, which are among the ventricular repolarization parameters, in patients with hypocalcemia, there are no studies investigating the Tp-e interval, Tp-e/QT and Tp-e/QTc ratio[2]. Two studies show that prolongation of QTc is an independent risk factor for hypocalcemia[14,15]. In our study, the obtained QTc intervals were increased in accordance with previous literature. In addition, the increase in Tp-e-interval and Tp-e/QTc ratios were markedly more significant in patients with hypocalcemia when compared to the control group. Increased ventricular repolarization parameters such as QT and QTc duration, QTc dispersion, Tp-e interval, Tp-e/QTc have been shown

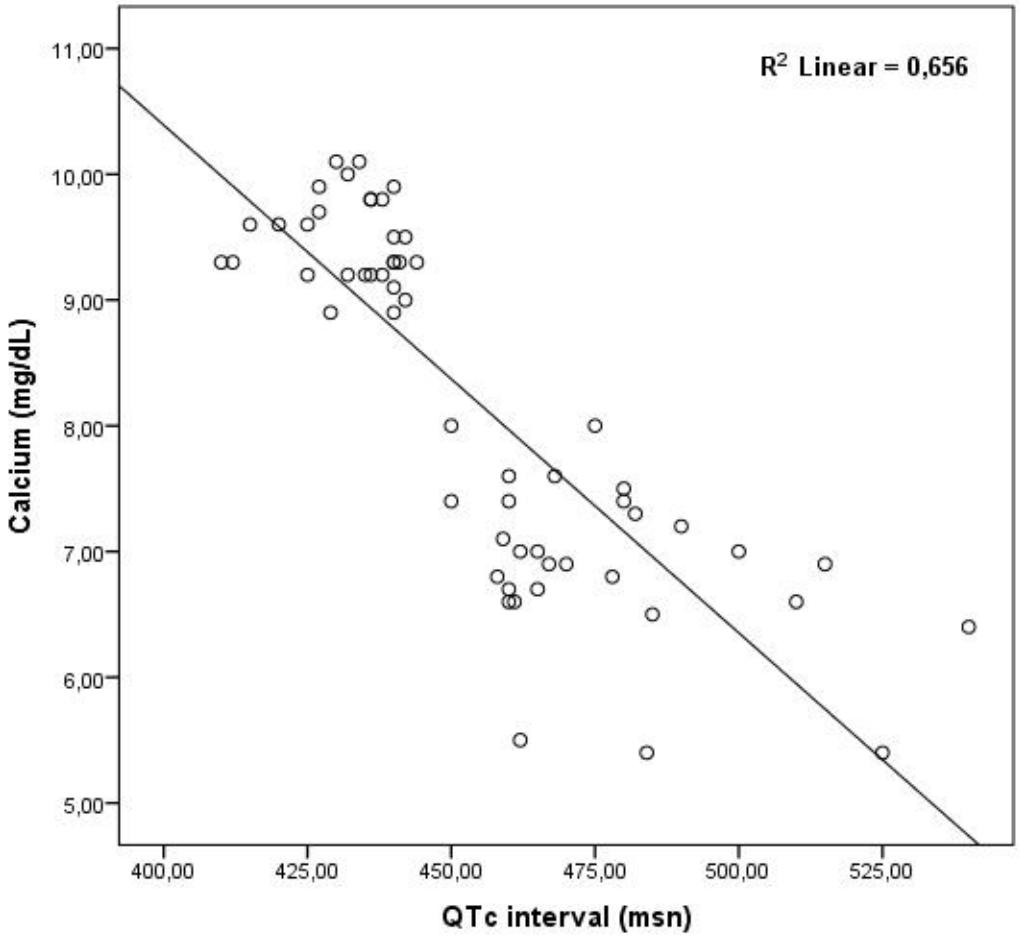

Figure 1 – Analysis of Scatterplot for the relationship between Calcium and QTc interval.

to be risk factors for ventricular arrhythmia and death[6,7]. Increased QTc may cause life-threatening torsades de pointes[16]. In our study, it was shown for the first time that Tp-e interval and Tp-e/QTc increased in hypocalcemia patients. Hypocalcemia may appear as Torsades de pointes due to prolonged QTc interval. This is due to the prolongation of the plateau phase of cardiac action potential depending on the calcium level[17,18]. Tp-e and Tp-e/QTc parameters, as well as prolongation of QTc distance due to hypocalcemia, may be a predictor of ventricular dispersion and repolarization. Therefore, early diagnosis and close monitoring of ventricular repolarization changes in hypocalcemia patients should be performed. According to the data obtained in our study, we think that in addition to QT and QTc intervals, evaluation of Tp-e and Tp-e/QTc ratio may be more useful in the evaluation of ventricular repolarization.

Limitations of Study

There are some important limitations in our study. One of them is the retrospective design of the study, and also the number of patients included in the study. In our study, the number of patients was limited to 29. Prospective studies involving more patients may provide more meaningful information.

Conclusion

Tp-e interval and Tp-e/QTc ratios were significantly increased in patients with hypocalcemia. In addition to QT and QTc evaluation during routine ECG evaluation in patients with hypocalcemia detected in emergency departments, it is important to keep Tp-e-interval and Tp-e/QTc ratios in mind, which are other ventricular repolarization parameters, and that

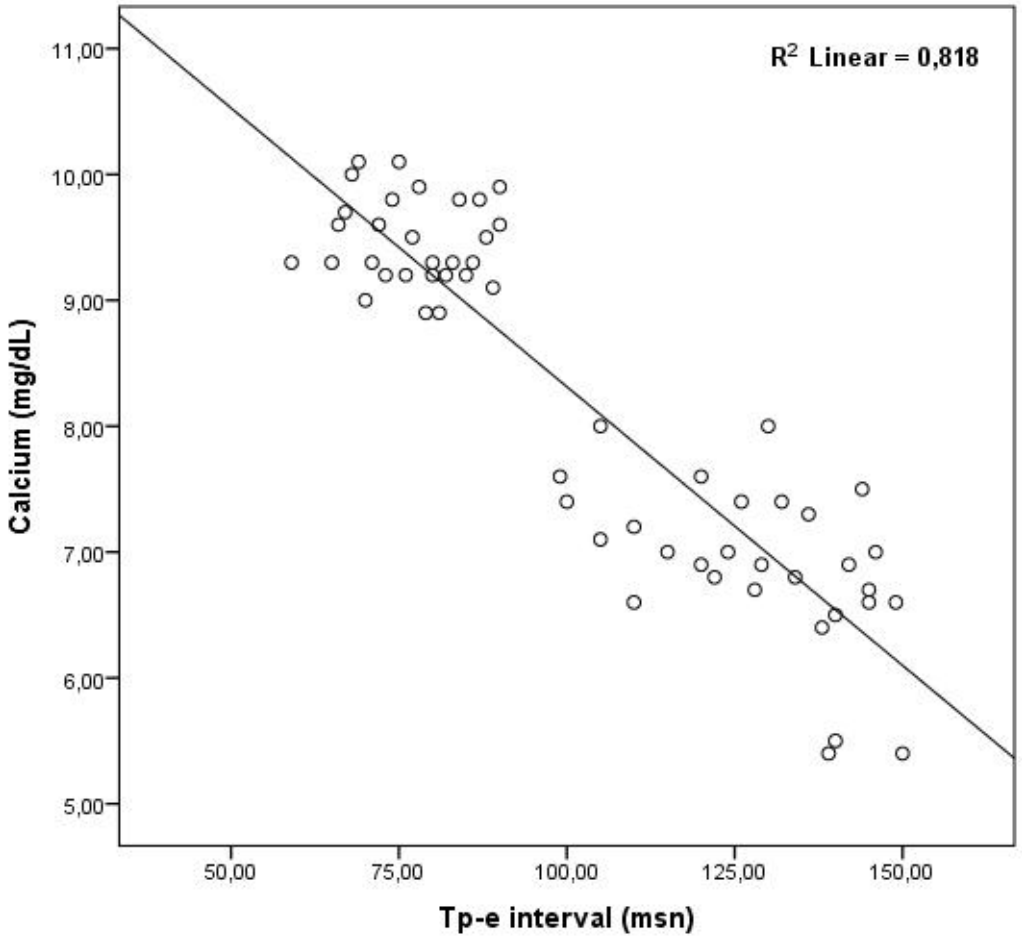

Figure 2 – Analysis of Scatterplot for the relationship between Calcium and Tp-e interval.

cardiac lethal arrhythmias may be seen more frequently in cases where these values are higher. However, as this information is shown for the first time in our study, studies involving new and more patients with hypocalcemia should be performed.

Author Contributions

Conception and design of the research: Avci BS, Avci A. Acquisition of data: Aksu A, Koca H. Statistical analysis: Gulen M, Satar S. Writing of the manuscript: Avci BS. Critical revision of the manuscript for intellectual content: Avci BS, Avci A, Aksu A, Koca H, Gulen M, Satar S.

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 Adana City Research and Training Hospital under the protocol number Meeting Number: 45, Decision No: 630, 04/12/2019. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

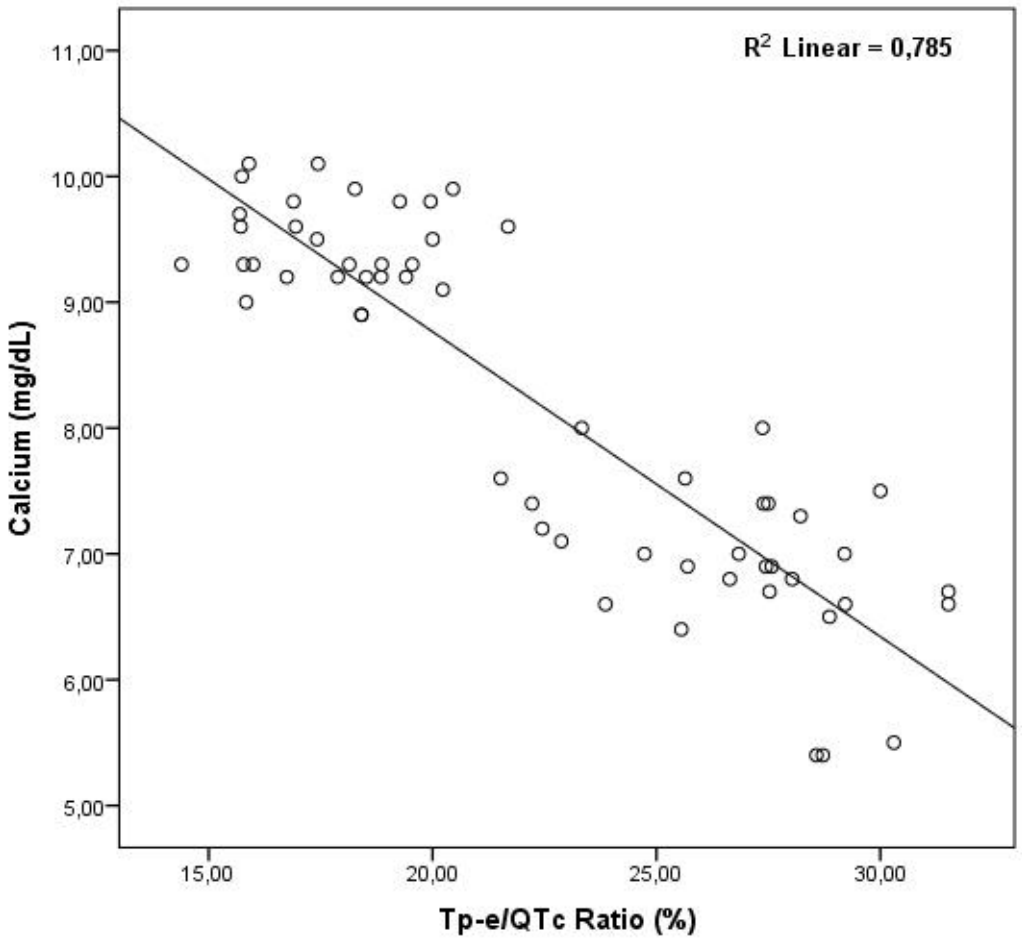

Figure 3 – Analysis of Scatterplot for the relationship between Calcium and Tp-e/QTc ratio.

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ORIGINAL ARTICLE

Spirituality, Religiosity and Quality of Life of Hypertensive and Diabetic Patients in a Referral Hospital in Pernambuco

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Abstract

Background: Religiosity is a system of worship and doctrine that is shared by a group, and spirituality is the individual search for the meaning of life. The relationship between spirituality/religiosity (S/R) and health has a long history, and a positive correlation between spirituality and chronic diseases has been described in scientific literature, showing a decrease in morbidity and mortality in general.

Objective: To evaluate the association between S/R and the quality of life of patients with diabetes and/or systemic arterial hypertension.

Method: An observational, analytical, cross-sectional, quantitative study was conducted with a sample consisting of 40 patients treated at the hypertension and diabetes outpatient clinic of a medical center in Recife. The collection used three assessment instruments (SSRS, Duke-DUREL scale, and WHOQOL-BREF). Data from the questionnaires were analyzed using descriptive (frequency and percentage) and inferential statistics (chi-square test and F test) using the R software, version 3.4.3. The level of significance in all analyses was 5%. The study was approved by CEP/IMIP, according to report no. 2.890.126.

Result: All four domains of the quality-of-life scale (WHOQOL-BREF) showed a positive relationship when correlated with the religiosity scale (DUREL), with statistical significance in the relationship between organizational religiosity and the environmental domain. When correlated with the spirituality scale (SSRS), WHOQOL-BREF also showed a positive relationship, except in the physical domain.

Conclusion: A positive relationship between quality of life and S/R was shown, thus confirming its importance for patients with diabetes and SAH.

Keywords: Spirituality; Quality of Life; Hypertension; Diabetes Mellitus

Introduction

The relationship between spirituality/religiosity (S/R) and health has been longstanding,[1-4] with studies investigating the mechanisms by which faith leads to favorable clinical outcomes and how physicians should address this issue in medical practice.[5] Thus, it is necessary to differentiate the concepts of spirituality and religiosity in order to integrate them into clinical practices. Religiosity is a system of worship and doctrine that is shared by a group,[2,6,7] and it may be organizational (participation in a church or temple) or non-organizational (praying, reading books, watching religious programs).[1] Spirituality, on the other hand, is defined as the individual search for the meaning of life and its relationship with the transcendent, which may or may not include religious activity.[1,2,8,9]

The relationship of S/R with quality of life has been well studied,[10-12] and, although it is difficult to define, the World Health Organization (WHO) has standardized the concept of quality of life as "an individual's perception of their position in life in the context of the culture and

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value system in which they lives and in relation to their goals, expectations, standards, and concerns".[13]

Today, it is known that there are physiological alterations in religious and spiritualized individuals, such as a reduction in the concentration of the adrenocorticotrophic hormone (ACTH) and cortisol, as well as an increase in gamma-aminobutyric acid (GABA), serotonin, and dopamine, which culminates in a more harmonious physiological response to stress. Consequently, there is a release of antalgic substances in these individuals, with an improvement in pain symptoms and a decrease in systolic blood pressure, as well as in heart and respiratory rates.[8,14,15]

Therefore, several benefits from S/R can be seen, such as the positive relationship with physical weakness, heart disease, immune function, neuroendocrine function, and cancer, with decreased overall mortality,[16] lower hospitalization rates, better disease prognosis, and increased adherence to the proposed treatment.[17,18]

From this context, it is noted that there is an influence from S/R on the lives of patients with chronic diseases. Thus, knowing that Diabetes Mellitus (DM) and Systemic Arterial Hypertension (SAH) are prevalent chronic diseases in Brazil,19 the present study aimed to evaluate the association between S/R and the quality of life of patients with diabetes and/or SAH.

Method

This is an observational, analytical, cross-sectional, quantitative study conducted from August 2018 to August 2019 in the hypertension and diabetes outpatient clinics of a medical center in Recife, Pernambuso, Brazil, whcih serves the Unified Health System (SUS, in Portuguese).

The convenience sample was non-probabilistic, consisting of 40 patients treated at the aforementioned health service, diagnosed with SAH and/or DM. Patients who concomitantly had other chronic noncommunicable diseases (NCDs) were excluded from the study.

Collection was performed by the researchers on pre-determined days of the week and, after explanation of the project and signing of the Informed Consent Form (ICF), epidemiological information was collected from the patients (gender, age, education, profession, family income, marital status, and religion). The patients also answered three standardized questionnaires to evaluate their quality of life, religiosity, and spirituality.

The instrument used to evaluate spirituality was the Spirituality Self Rating Scale (SSRS), a scale consisting of six items in Likert-scale format, ranging from 1 (strongly agree) to 5 (strongly disagree). Each item of the instrument was recoded so that the points could then be added, with the total sum ranging from 6 to 30.

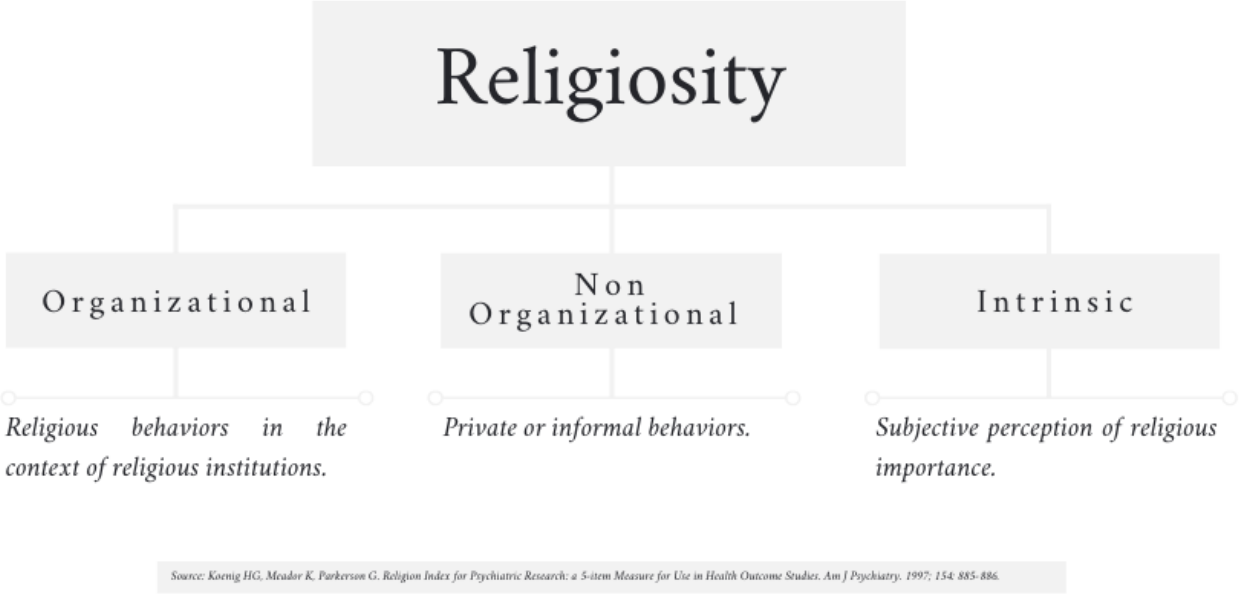

Figure 1 - Religiosity dimensions

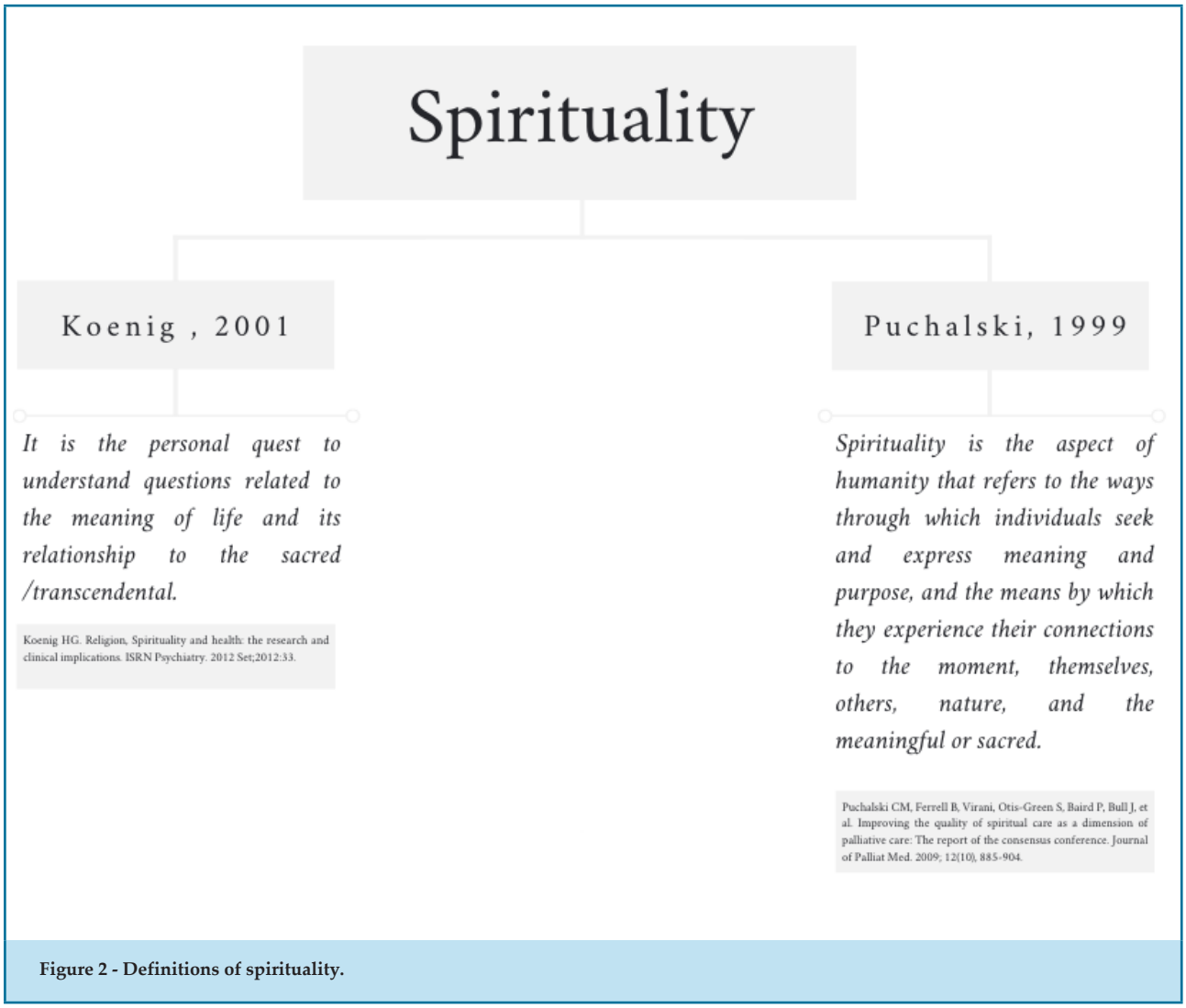

Figure 2 - Definitions of spirituality.

The total score therefore represents the patient's level of spiritual orientation.

The second parameter evaluated in this study was religiosity, in which the Duke-DUREL Scale was used. It has five questions that capture three religiosity dimensions related to health outcomes: organizational (OR), non-organizational (NOR), and intrinsic (IR) religiosity. The two first dimensions refer to the respondent's social support, while the latter relates to religious beliefs and experiences.

The third questionnaire applied was the World Health Organization Quality of Life (WHOQOL-BREF), an abbreviated WHO instrument consisting of 26 questions divided into physical, psychological, social-relation and environmental domains. In this instrument, the result is evaluated by the mean of each of the domains (1 to 5), and then converted to a scale of 0 to 100.[20]

Statistical analysis

The information obtained during the collection period was stored in a Microsoft Excel 2010 database. To summarize categorical variables, absolute and relative values were used. For quantitative variables, mean and standard deviation were applied. The statistical tests used were the chi-square test for categorical variable relationships and the F test for statistical comparison between quantitative variables. Pearson's correlation coefficient was used to evaluate the correlation between quantitative variables. The normality of quantitative variables was examined using the Shapiro-Wilk test. In all analyses, the significance level was 5%, and the R software, version 3.4.3, was used.

All ethical aspects were observed as provided for by Resolutions 466/12 and 510/16 by the National Health

Council. The research project was approved by the Ethics Committee for Research Involving Human Beings at IMIP, according to CAAE no. 94642518.1.0000.5201 and report no. 2.890.126.

Results

Forty patients were included in the study. Their mean age was 59.4 years (30 to 86 years), most of whom were females (60%). Most participants were married or had a common-law partner (55%), and had from one to three children on average (72.5%). A large number of participants were high-school graduates (35%), had housekeeping jobs (37.5%), and a monthly income of one minimum wage (47.5%). Regarding religion, most participants were evangelicals (45%) or Catholics (40%). (Table 1)

Regarding the evaluation of spirituality in this study, SSRS showed that 21 patients (52.5%) strongly agreed with the premise that it is important to spend time with private spiritual thoughts and meditations. As for making an effort to live life according to religious beliefs, most of them (52.5%) strongly agreed that they endeavor to do so. A total of 25 patients (62.5%) fully agreed that individual prayers or spiritual thoughts are just as important as those they would have during religious ceremonies or spiritual meetings. Moreover, 19 patients (47.5%) strongly agreed that they enjoy reading about their spirituality and/or religion, and it was also found that 25 patients (62.5%) strongly agreed with the premise that spirituality helps keep life more stable and balanced (Table 2).

Moreover, regarding the sum of points on the SSRS, the mean score of spiritual orientation was 24.75 (SD=5.24), in which 7 patients (17.5%) had the highest score and none had the lowest.

As regards the DUREL Scale, with respect to OR, it was found that 30% of the interviewees attended religious institutions more than once a week, and the same percentage attended them once a week. When evaluating NOR, it was identified that 50% of the patients dedicated themselves to individual religious activities daily and 32.5% of the interviewees performed them more than once a day. Regarding the questions on IR, most of them stated that it was completely true that they felt the presence of God or the Holy Spirit in their lives (77.5%), that their religious beliefs support their entire way of life (75%), and that they tried very hard to live their religion in all aspects of their lives (52.5%). Moreover, when adding the three questions together to obtain the

Table 1 – Sociodemographic characteristics

Variables	N	%
Sex		
Female	24	60
Male	16	40
Marital Status		
Single	9	22.5
Married/Common-law Partner	22	55
Divorced	5	12.5
Widowed	4	10
Education		
Illiterate	1	2.5
Incomplete Elementary School	13	32.5
Complete Elementary School	6	15
Complete High School	14	35
Higher Education	6	15
Occupation		
Housekeeper	15	37.5
Retired	11	27.5
Unemployed	4	10
Others	10	25
Income		
Less than 1 minimum wage	8	20
1 minimum wage	19	47.5
2-5 minimum wages	13	32.5
>5 minimum wages	0	0
Religion		
Evangelical/Protestant	18	45
Catholic	16	40
No religion	3	7.5
Others	3	7.5

Table 2 – Application of the Spirituality Self Rating Scale (SSRS)

Question: It is important for me to spend time with private spiritual thoughts and meditation.	**N (40)**	**N (%)**
1. Strongly agree	21	52.50
2. Agree	13	32.50
3. Partly agree	2	5
4. Disagree	2	5
5. Fully disagree	2	5
Question: I try very hard to live my life according to my religious beliefs.	**N (40)**	**N (%)**
1. Strongly agree	21	52.50
2. Agree	10	25
3. Partly agree	4	10
4. Disagree	2	5
5. Fully disagree	3	7.50
Question: The prayers or spiritual thoughts that I have when I am alone are just as important to me as those that I would have during religious ceremonies or spiritual meetings.	**N (40)**	**N (%)**
1. Strongly agree	25	62.50
2. Agree	7	17.50
3. Partly agree	2	5
4. Disagree	4	10
5. Fully disagree	2	5
Question: I like to read about my spirituality and/or my religion.	**N (40)**	**N (%)**
1. Strongly agree	19	47.50
2. Agree	8	20
3. Partly agree	6	15
4. Disagree	3	7.50
5. Fully disagree	4	10
Question: Spirituality helps keep my life stable and balanced, just as my citizenship, friends, and society do.	**N (40)**	**N (%)**
1. Strongly agree	25	62.50
2. Agree	9	.22,50
3. Partly agree	4	10
4. Disagree	0	0
5. Fully disagree	2	5
Question: My whole life is based on my spirituality.	**N (40)**	**N (%)**
1. Strongly agree	21	52.50
2. Agree	6	15
3. Partly agree	6	15
4. Disagree	4	10
5. Fully disagree	3	7.50

Table 3 – Application of the Duke-DUREL Scale

Question: How often do you go to a church, temple, or other religious meeting?	N (40)	N (%)
1. More often than once a week	12	30
2. Once a week	12	30
3. Two to three times a month	6	15
4. A few times a year	4	10
5. Once a year or less	1	2.5
6. Never	5	12.5
Question: How often do you dedicate your time to individual religious activities, such as praying, meditating, and reading the Bible or other religious texts?	**N (40)**	**N (%)**
1. More often than once a day	13	32.5
2. Every day	20	50
3. Two to three times a month	2	5
4. Once a week	4	10
5. A few times a month	0	0
6. Rarely or never	1	2.5
Question: In my life, I feel the presence of God (or the Holy Spirit).	**N (40)**	**N (%)**
1. Absolutely true for me	31	77.5
2. It is generally true	5	12.5
3. I am not sure	3	7.5
4. It is not generally true	0	0
5. It is not true	1	2.5
Question: My whole way of living is really based on my religious beliefs.	**N (40)**	**N (%)**
1. Absolutely true for me	30	75
2. It is generally true	4	10
3. I am not sure	3	7.5
4. It is not generally true	1	2.5
5. It is not true	2	5
Question: I try very hard to live my religion in all aspects of life.	**N (40)**	**N (%)**
1. Absolutely true for me	21	52.5
2. It is generally true	11	27.5
3. I am not sure	4	10
4. It is not generally true	1	2.5
5. It is not true	3	7.5

total intrinsic religiosity (TIR) score, which can range from 3 to 15, respondents scored a mean of 13.25 points (SD=2.67) (Table 3).

In measuring the quality of life (WHOQOL-BREF), the highest mean score obtained was in the psychological domain (61.67), followed by the physical (51.16), environmental (49.37), and social (46.25) domains.

When relating the sociodemographic variables to the DUREL Scale, it was observed that women showed a higher level of non-organizational religiosity when compared to men, and the mean scores were 5.375 and 4.375, respectively (p=0.003).

When comparing the WHOQOL-BREF and DUREL Scales, it was found that all quality-of-life domains showed a positive relationship with the religiosity dimensions; however, only the relationship between OR and the environmental domain had a significant value (p=0.0391). A positive relationship was also found when SSRS and WHOQOL-BREF were correlated, except for the physical domain. Nevertheless, no values were statistically significant. When comparing the DUREL Scale and SSRS, a positive correlation was also obtained between SSRS and NOR (p=0.0001), as well as between SSRS and IR (p=0.0005).

Discussion

Regarding the sociodemographic profile, the participants' mean age was 59.4 years, which is in agreement with the literature, where the highest prevalence of SAH and diabetes occurs after 40 years of age,[21,22] especially in the age group from 50 to 59 years.[23]

It was also found that 45% of the participants reported being evangelicals and 40% Catholics, thus corroborating the data from the 2010 Census, which showed these two religions as the most prevalent in Brazil (78.4%).[24] Regarding work activity, housekeeping was predominant (37.5%), and most participants' monthly income was limited to one minimum wage (47.5). This may suggest a lower socioeconomic status of participants, which is compatible with the profile of SUS users.[25,26]

In this study, the spiritual dimension was evaluated by SSRS, and it was found that 21 patients (52.5%) fully agreed that it was important to spend time with private spiritual thoughts or meditation. In the literature, this importance is evidenced by the knowledge that individual spiritual practices can help to focus hope, and that prayer can be understood as one of the main strategies for coping with illness, with relief from suffering.[27]

Furthermore, it was observed that 21 patients strongly agreed that they endeavor to live their lives according to their religious beliefs. This can be justified from studies on patients with chronic illnesses, which revealed that spiritual beliefs give meaning to participants' lives, representing utmost importance for most of them.[27,28]

It was found that beliefs about spirituality were positive when the overall SSRS scores were evaluated, since the spiritual orientation score obtained in the sample showed a mean of 24.75 (SD=5.24). This value is considered high when compared to that obtained in the Brazilian validation study for the scale.[29,30] The data obtained are in agreement with the literature, which showed mean SSRS scores among hypertensive patients, adherent and non-adherent to treatment, of 25.0 and 24.5, respectively.[31]

The religious dimension, in turn, was analyzed by the Duke-DUREL Scale. In this study, it was found that 56.5% of the elderly included in the study attended a church, temple. or other religious meetings more often than once a week or only once a week. Regarding individuals under the age of 60, it was observed that this figure is 64.7%. This is in agreement with the results found in the literature, which suggest that, with age progression, the elderly tend to decrease their participation in formal religious meetings because they face physical limitations resulting from the consequences of chronic diseases and age itself.[32]

On the other hand, to compensate for not attending regular religious meetings, the elderly spend more time on individual activities.[33] In the present study, it was observed that 73.9% dedicate their time to such activities as prayers, meditation, and reading the Bible or other religious texts, which is in agreement with other studies, suggesting that the importance of religion in these people's lives cannot be estimated by how much one attends a religious institution, but by the meaning attributed to individual practices.[32]

Knowing that IR is related to the personal meaning attributed to religion,[34] this study observed that 77.5% of the interviewees feel the presence of God in their lives, 75% act according to their beliefs, and 52.5% strive to live their religion in all aspects of life. These data are in agreement with those from a study on religiosity in renal transplant patients,[35] which showed that the majority of participants reported high levels of intrinsic religiosity.

Regarding the evaluation of the quality of life, measured by the WHOQOL-BREF instrument, the psychological domain obtained the highest mean score

(61.67), followed by the physical domain (51.16) and the environmental domain (49.37). The social domain, however, obtained the lowest mean score (46.25), contributing in a less positive way to the sample's quality of life. Only the psychological and physical domains expressed values above 50, showing positive perceptions about one's quality of life. The obtained result is partially in agreement with that of a study performed on diabetic and hypertensive patients followed by a family health team, which showed positivity in all quality-of-life domains and had the social realm as the domain with the highest mean score (71.38).[36]

Following the same trend, in another study conducted on hypertensive and diabetic patients, the evaluation of the social aspect contributed with the highest mean (69.33), although the psychological domain expressed an approximate mean score value (69.11). The low score for the social domain in this study suggests the lack of support from family members and other people who live with the patients, since diseases require new habits of life that need to be respected and stimulated for their proper control.[37] The divergent results express the subjective character of one's quality of life, which depends on each individual's sociocultural level, age group, and personal aspirations.[38]

Limitations and Strengths

The limitations in this study were the small number of people interviewed, as well as the lack of privacy at the interview site, since it was not always possible to have an isolated room for the interviews. Another limitation was the need for cooperation from patients, since the study required too much time to apply three extensive questionnaires. However, this study is considered innovative for evaluating the association between S/R and the quality of life in patients with SAH and DM, highly prevalent diseases in the Brazilian population, besides serving as a reference source for other studies related to this topic.

Conclusion

All four domains of the quality-of-life scale showed a positive correlation with the religiosity scale, and a significant value was found in the relationship between organizational religiosity and the environmental domain. Furthermore, the correlation between spirituality and quality of life proved to be positive, except when the physical domain was evaluated. However, when analyzing the mean scores in the four quality-of-life domains, the results obtained were low in comparison to those reported in the literature, especially regarding the social aspect.

Thus, the findings in the present study confirm the importance of S/R in the quality of life of patients with chronic non-communicable diseases, especially diabetes and hypertension. However, it is essential to conduct new studies with larger samples to validate the findings described herein in order to provide a better understanding of these individuals' real quality of life.

Author contributions

Conception and design of the research: Brito GPL, Barbosa L, Jordán A, Velloso BAA, Barbosa ME, Bérgamo V, Barreto S. Acquisition of data: Brito GPL, Jordán A, Velloso BAA, Barbosa ME, Bérgamo V, Barreto S. Analysis and interpretation of the data: Brito GPL, Barbosa L, Jordán A, Velloso BAA, Barbosa ME, Bérgamo V, Barreto S. Statistical analysis: Brito GPL, Barbosa L, Jordán A, Velloso BAA, Barbosa ME, Bérgamo V, Barreto S. Writing of the manuscript: Brito GPL, Barbosa L, Jordán A, Velloso BAA, Barbosa ME, Bérgamo V, Barreto S. Critical revision of the manuscript for intellectual content: Brito GPL, Barbosa L, Jordán A, Velloso BAA, Barbosa ME, Bérgamo V.

Potential Conflict of Interest

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

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Study Association

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

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the IMIP under the protocol number 2.890.126. 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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ORIGINAL ARTICLE

Congenital Heart Disease: A Retrospective Analysis from a Tertiary Referral Centre in Portugal

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Abstract

Background: Congenital heart disease is the leading cause of mortality among all congenital malformations.

Objectives: To evaluate the incidence of congenital heart diseases in a central maternity hospital in Portugal from January 2003 to December 2018 and to determine survival in the first year of life.

Methods: Retrospective analysis of newborns diagnosed with congenital heart diseases within 72 hours after birth. Malformations were divided according to pathophysiology. Cumulative survival analysis was performed by the Kaplan-Meier test. Stastical significance was set at $p < 0.05$.

Results: A total of 297 newborns with cardiac malformation was recorded among 47,198 live births (incidence of 6:1000), 16% associated with extra-cardiac disease. The most frequent congenital heart diseases were left-to-right shunt lesions (n = 216), followed by cyanotic (n = 41), acyanotic obstructive (n = 31) and miscellaneous (n = 9). Seventy (24%) patients had prenatal diagnosis, 88% of them cyanotic defects, and a positive association was found between prenatal diagnosis and mortality ($p < 0.001$). Coarctation of the aorta was associated with gestational diabetes ($p = 0.014$). Atrial septal defect was more common in females ($p = 0.02$). Mortality rate due to heart disease was 3.4%. Patients with cyanotic disease, 99%, 97%, 97%, respectively, for patients with left-to-right shunt lesions, and 97%, 97%,97% for those with obstructive lesion cases.

Conclusion: The incidence of congenital heart disease was 6:1000, mostly left-to-right shunt lesions. Heart disease accounted for only half of deaths, and cyanotic diseases have a high nonspecific mortality rate.

Keywords: Congenital Heart Defect; Newborn Infant; Neonatology; Survival.

Introduction

Congenital heart diseases (CHDs) are a group of malformations that are the leading cause of perinatal mortality.[1] Their prevalence is estimated to be six to 10 per 1,000 births.[1-4]

Due to advances in diagnostic techniques, the prevalence of CHDs has increased over the years.[3,5,6] Therapeutic innovations, both medical and surgical, have contributed to reduction in mortality,[7] and most patients with CHD reach adulthood today.[5,6] However, these patients are at a higher risk of developing comorbidities,[8] including higher levels of psychological stress.[7]

CHD was defined by Mitchel[9] in 1971 as a structural anomaly of the heart or large vessels that is could be of functional significance. Although the etiology of CHD is largely unknown, the risk factors known to be related to CHD include maternal infections (e.g., rubella) or conditions (gestational diabetes and obesity, use of vitamin A) and use of teratogenic drugs, tobacco, alcohol and cocaine during pregnancy.[1,4] Medically assisted reproduction[10] and being a child of a mother with heart disease are also associated with CHD.[11] Heart diseases that pose the greatest risk for the development of CHD in the offspring are aortic stenosis, atrioventricular septal

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defect and tetralogy of Fallot. Other diseases may pose a lower risk, such as atrial and ventricular septal defects, coarctation of the aorta, patente ductos arteriosus and pulmonar stenosis.[12]

The aim of this study was to characterize the incidence of CHD in a central maternity hospital and, to assess survival at 28 days, six months and one year of life, in different CHD groups.

Methods

Population

Retrospective study of newborns with CHD, born in a central maternity hospital in Portugal between 01 January 2003 and 31 December 2018.

Congenital heart disease

The diagnosis was made by transthoracic echocardiography by a pediatric cardiologist within 72 hours of life. Congenital heart diseases were classified according to the International Pediatric and Congenital Cardiac Code.[13] All cases of prenatal diagnosis of CHD were confirmed in the postnatal period.

All cases of patent ductus arteriosus were included in this study if present 72 hours of life in term newborns. Cases described as patent foramen ovale and restrictive ostium secundum atrial septal defects were excluded.

In patients with complex cardiac defects, the main (predominant) cardiac defect was chosen as the primary diagnosis. The conditions were divided into three categories, "cyanotic", "obstructive" and "left-to-right shunting" according to the pathophysiological mechanism.[14] Diseases that did not fit into any of the three categories were classified in a fourth category, "miscellaneous".

This study was approved by the ethics and research committe of our hospital.

Statistical analysis

The SPSS® program (IBM®, SPSS® Statistics Inc., Chicago), version 25.0 was used for statistical analysis. Normality of data was tested by the Shapiro-Wilk test. Continuous variables with normal distribution were described as mean and standard deviation (SD) and continuous variables without normal distribution were described as median and interquartile range (IQR). The Fisher's exact test and chi-square test were used to verify associations between categorical variables. Survival curves were based on the Kaplan Meier test. The significance level was set as 5%.

Results

Of a total of 47,198 neonates born during the study period, 297 had CHD, 83 of them complex heart disease (28%). As shown in the Table 1, most of cardiac malformations were left-to-right shunt lesions (73%), followed by cyanotic (14%), acyanotic obstructive (10%) and miscellaneous (3%) lesions. The incidence of CHD was about six per 1,000 births.

Mean maternal age was 32 years (SD ± 5), and median number of both pregnancies and deliveries was one (IQR 1:2).

In 12 women, pregnancies were complicated by gestational diabetes. The only CHD associated with gestational diabetes was coarctation of the aorta ($p = 0.014$). There were 17 cases of prenatal maternal infections, none related to CHD. Previous familial CHD was present in two cases: a newborn with tetralogy of Fallot, whose mother had the same condition, and another with partial anomalous pulmonary venous return and atrial septal defect, whose father had transposition of the great arteries.

Of all the CHD cases, 70 (24%) patients had prenatal diagnosis – 88% of patients with cyanotic lesions, 32% of patietns with obstructive lesions, 11% of those with miscellaneous, and 11% of patients with left-to-right shunting. A positive association was found between prenatal diagnosis and mortality ($p < 0.001$).

Mean gestational age was 38 weeks (IQR 35: 39), 22% of newborns were preterm. The median Apgar score at the fifth minute of life was 10 (IQR 9: 10) and median birth weight was 3,110 grams (IQR 2570: 3505).

Of the 297 newborns with CHD, 149 were male and 47 cases (16%) were associated with extra-cardiac anomalies/malformations. The associations between CHD and gender and CHD and extra-cardiac malformations are summarized in Tables 2 and 3, respectively.

About 25% of patients needed pharmacological therapy in the neonatal period. Cardiac catheterization was performed in 35 patients, with Rashkind atrioseptostomy in 13 of them. Sixty-one patients (20%) underwent surgery. Most of patients who underwent surgery had

Table 1 – Prenatal diagnosis and mortality rate of infants with congenital heart disease (n = 297)

Congenital Heart Disease	N	%	PND (n)	Mortality (n)
Cyanotic defects	**41**	**14**	**36**	**8**
Transposition of the great arteries	16	5.4	15	5
Tetralogy of Fallot	15	5.2	14	0
Hypoplastic left heart syndrome	3	1.1	2	2
Double outlet right ventricle	3	1.1	2	0
Ebstein's anomaly	1	0.3	1	1
Pulmonary atresia with ventricular septal defect	1	0.3	1	0
Total anomalous pulmonary venous connection	1	0.3	0	0
Truncus arteriosus	1	0.3	1	0
Acyanotic obstructive	**31**	**10**	**10**	**1**
Coarctation of the aorta	14	4.6	4	0
Valvular aortic stenosis	8	2.5	5	1
Valvular pulmonary stenosis	6	2	0	0
Shone's syndrome	2	0.6	1	0
Left branch pulmonary artery stenosis	1	0.3	0	0
Left-to-right shunt lesion	**216**	**73**	**23**	**7**
Ventricular septal defect	144	48.6	15	2
Atrial septal defect	42	14.1	3	4
Patent ductus arteriosus	24	8.2	-	0
Complete atrioventricular canal defect	5	1.8	4	1
Partial anomalous pulmonary venous connection	1	0.3	1	0
Miscellaneous	**9**	**3**	**1**	**0**
Isolated bicuspid aortic valve	4	1.4	0	0
Left ventricular noncompactation	2	0.6	1	0
Major aortopulmonary collateral arteries	2	0.6	0	0
Criss-cross heart	1	0.3	0	0

PND: prenatal diagnosis

cyanotic CHD (77%), followed by obstructive (48%) and left-to- right shunt lesions (7%).

Mortality rate from heart disease was 3.4% (n = 10; eight cyanotic lesions, one acyanotic obstructive and one left-to-right shunt lesion). The patient with acyanotic obstructive lesion had critical aortic stenosis. Although most deaths occurred in patients with left-to-right shunt lesion, only one death was due to the heart disease, an eight-month-old infant with complete atrioventricular septal defect. Overall mortality rate in the first year of life was 5.4% (n = 16), half of deaths occurred in the neonatal period. The median age of death was 25 days (IQR 5: 225). Of the 16 patients who died, 30% had extra-cardiac disease. Mortality by group and type of CHD is described in Table 1. Overall survival curves at 28 days, six months and one year of life are shown in Figures 1, 2 and 3, respectively.

Table 2 – Associations between congenital heart disease and gender

Congenital heart disease	Male (n)	Female (n)	p - value
Transposition of the great arteries	7	9	0.598
Tetralogy of Fallot	11	4	0.066
Hypoplastic left heart syndrome	1	2	0.622
Double outlet right ventricle	3	0	0.247
Ebstein's anomaly	0	1	1
Pulmonary atresia with ventricular septal defect	1	0	1
Total anomalous pulmonary venous connection	1	0	1
Truncus arteriosus	1	0	1
Coarctation of the aorta	7	7	0.99
Valvular aortic stenosis	3	5	0.501
Valvular pulmonary stenosis	1	5	0.121
Shone's syndrome	0	2	0.247
Left branch pulmonary artery stenosis	1	0	1
Ventricular septal defect	76	68	0.384
Atrial septal defect	14	28	**0.019**
Complete atrioventricular canal defect	2	3	0.371
Patent ductus arteriosus	10	14	0.385
Partial anomalous pulmonary venous connection	0	1	1
Isolated bicuspid aortic valve	4	0	0.122
Left ventricular noncompactation	2	0	0.498
Major aortopulmonary collateral arteries	2	0	0.498
Criss-cross heart	1	0	1

Discussion

The authors of this study set out to describe CHDs in neonates born in a central maternity hospital. First, it is important to higlight the differences between disease prevalence and incidence. Several CHD studies have presented prevalence data over time, due to the fact that many CHDs are only diagnosed during the first year of life, while others heal spontaneously during the same period of time.[7] In this context, some authors have opted to report the number of new cases of CHD at birth, namely the incidence of these diseases. In our study, the incidence of CHD was about six cases per 1,000 births, similar to that described in the literature.[1,3,15-18] Some studies,[5,6,19] however, have estimated an incidence of eight to 10 per 1,000 births. A possible explanation for this difference is the subjectivity in diagnostic criteria for patent foramen ovale and atrial septal defect. The former was excluded from the present study because it is not a CHD, as were patent ductos arteriosus in preterm neonates and neonatal arrhythmias.[1,3,9]

Several studies[3,5,6,16] have shown that both the incidence and prevalence of CHDs have been increasing, which is possibly related to improvements in diagnostic techniques, and advances in health care and CHD management. However, some authors have argued that CHD prevalence has stabilized[4] or even decreased,[17] due to the increase in prenatal diagnosis, and, implicitly, in the number of pregnancy terminations.

Although some authors advocate a classification of CHD based on clinical severity,[18,20,21] in our study, CHDs were classified based on their pathophysiological

Table 3 – Associations between congenital heart disease and extra-cardiac malformations

Congenital heart disease	With extra cardiac malformation	Without extra cardiac malformation	p - value
Transposition of the great arteries	3	13	0.725
Tetralogy of Fallot	3	12	0.714
Hypoplastic left heart syndrome	0	2	1
Double outlet right ventricle	0	3	1
Ebstein's anomaly	0	1	1
Pulmonary atresia with ventricular septal defect	0	1	1
Total anomalous pulmonary venous connection	0	1	1
Truncus arteriosus	0	1	1
Coarctation of the aorta	5	9	0.053
Valvular aortic stenosis	2	6	0.617
Pulmonary valve stenosis	2	4	0.242
Shone's syndrome	0	2	1
Left branch pulmonary artery stenosis	0	1	1
Ventricular septal defect	15	129	**0.013**
Atrial septal defect	11	31	**0.047**
Complete atrioventricular canal defect	4	1	**0.002**
Patent ductus arteriosus	0	24	**0.019**
Partial anomalous pulmonary venous connection	0	1	1
Isolated bicuspid aortic valve	0	4	1
Left ventricular noncompactation	2	0	**0.025**
Major aortopulmonary collateral arteries	0	2	1
Criss-cross heart	0	1	1

mechanism, which allows grouping of diseases with relatively similar mechanisms of action but highlighting their prognostic differences.

CHDs have been linked to several risk factors, including maternal risk factors during pregnancy.[1,4] The most important ones are infections and gestational diabetes. Samánek[7] observed that the highest peak incidence of CHD occurred eight to nine months after a influenza virus epidemic. Øyen et al.,[22] reported that the incidence of CHD, regardless of phenotype, is four times higher in children of women who developed gestational diabetes during pregnancy. In this study, coarctation of the aorta was the only lesion related with gestational diabetes. Another risk factor reported is the increased incidence of CHD in children from parents with CHD,[11,23] and genetic predisposition.[24] In our study, we found a newborn with tetralogy of Fallot, born to a woman with the same disease, and another newborn with partial anomalous pulmonary venous return and atrial septal defect, whose father had transposition of the great arteries.

The presence of prenatal diagnosis was significantly related to mortality. Most patients (88%) with prenatal diagnosis had cyanotic lesions, which carry a worse prognosis. Of the 41 patients with cyanotic CHD, only five had no prenatal diagnosis.

Atrial septal defect occurred more often in females and was the only condition that showed statistically significant gender preference (p = 0.02). These results,

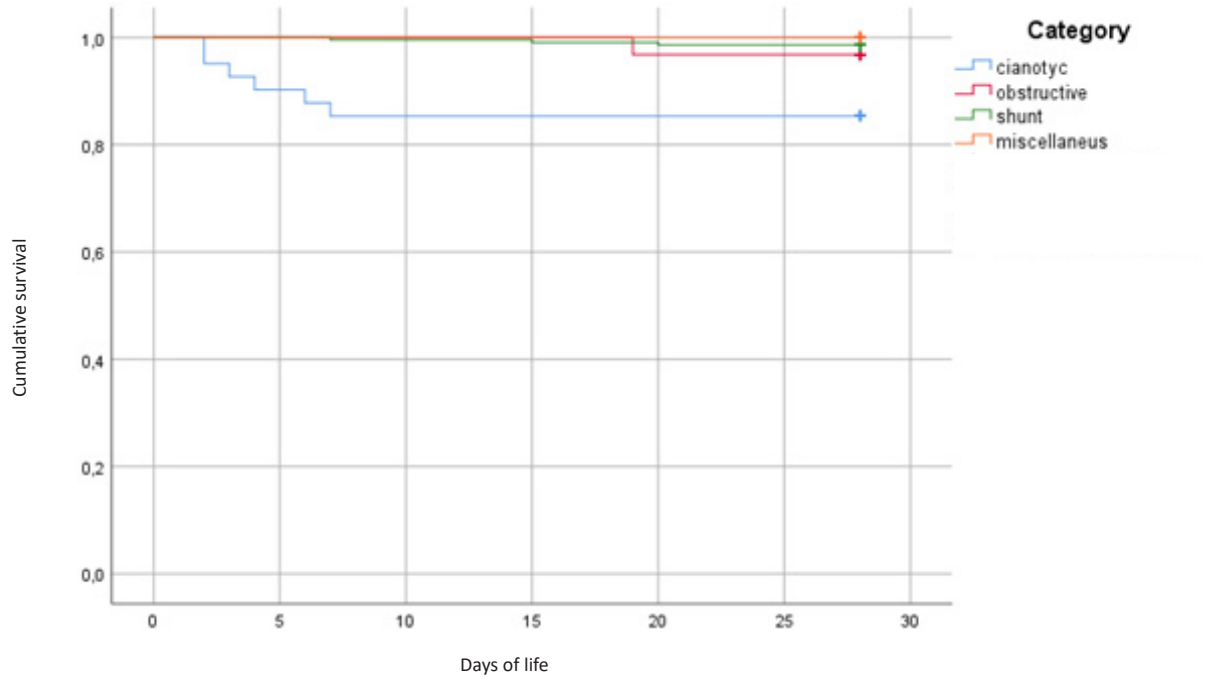

Figure 1 – Overall survival at 28th day of life (97%) by disease category – cyanotic 85%, obstructive acyanotic 97%, left to right shunt lesions 99%, miscellaneus 100%.

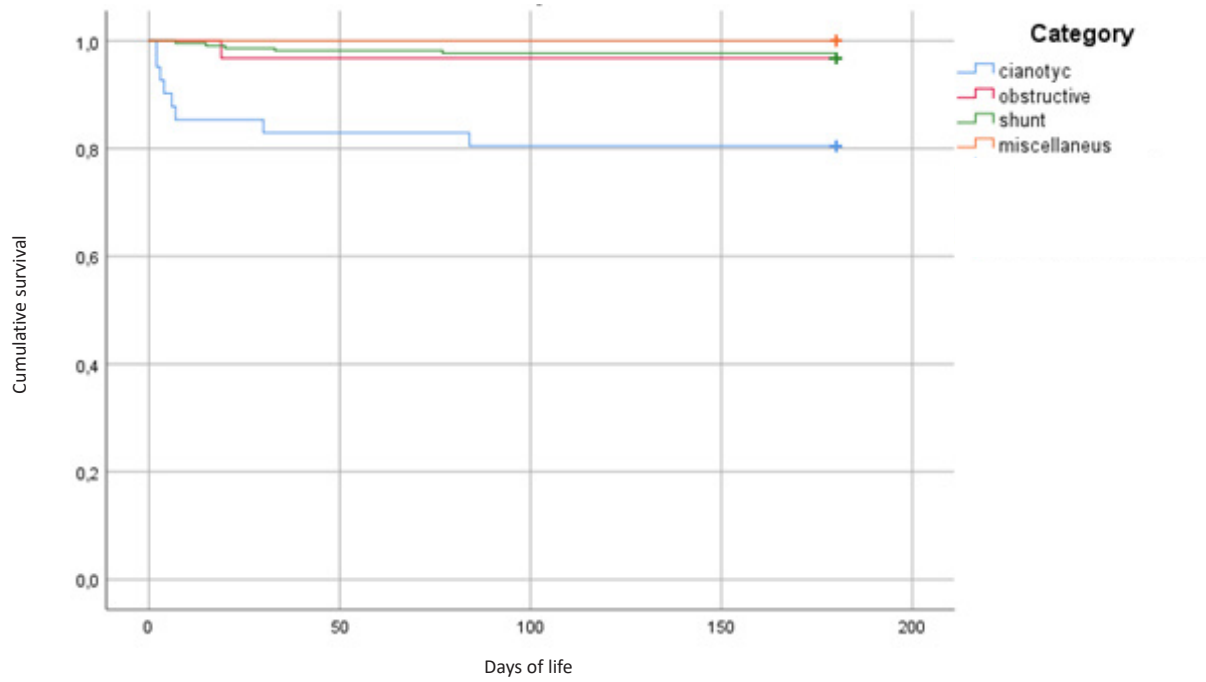

Figure 2 – Overall survival at six months of life (95%) by disease category – cyanotic 81%, obstructive acyanotic 97%, left-to-right shunt lesions 97%, miscellaneus 100%.

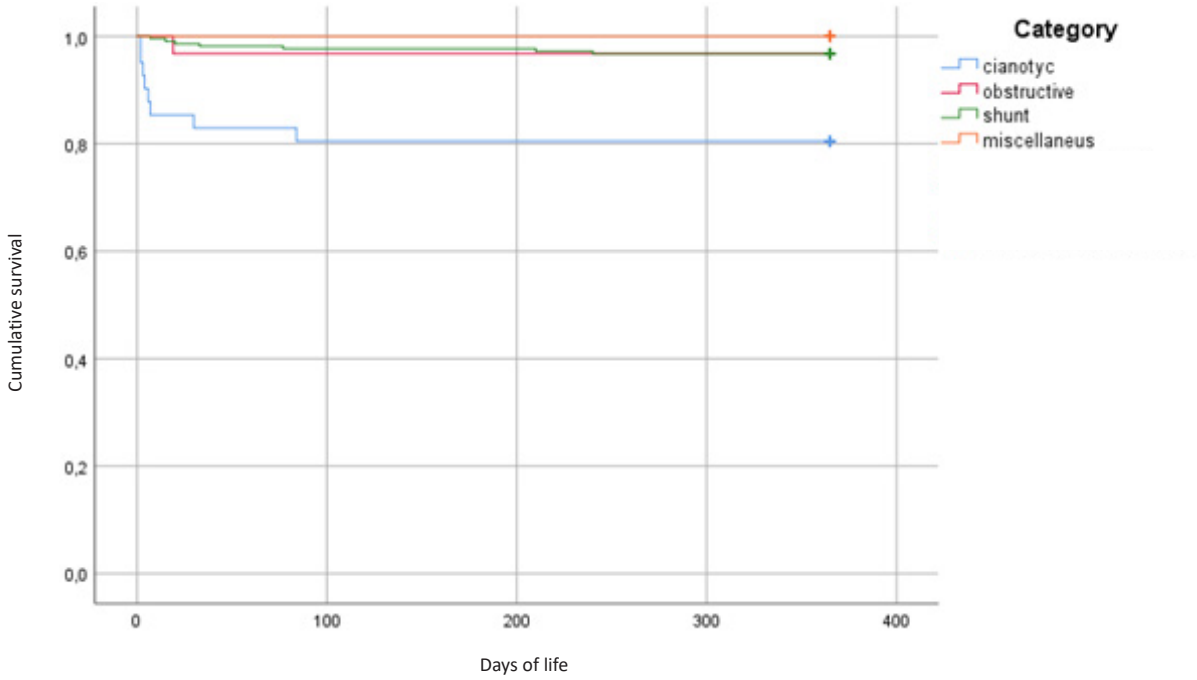

Figure 3 – Overall survival at the first year of life (95%) by disease category – cyanotic 81%, obstructive acyanotic 97%, left-to-right shunt lesions 97%, miscellaneus 100%.

and those for pulmonary valve stenosis reflect the trends published in the literature.[2] As in the study by Mercuro et al.,[25] double outlet right ventricle, tetralogy of Fallot and bicuspid aortic valve were also more frequently found in male than in female neonates.

Overall mortality rate in the first year of life was 5.4%, similar to the results obtained by Khoshnood et al.,[19] who also showed that mortality was highest in the neonatal period. Dolk et al.,[1] reported a perinatal mortality in patients with congenital anomalies of 0.93 per 1,000 births, with 26% of these deaths in patients with CHD. Thus, CHDs are the main group of diseases contributing to perinatal mortality. It should be noted, however, that these patients have a higher incidence of other comorbidities. In our analysis, mortality related to CHD was 3.4% (n = 10), and none of these deaths occurred in the miscellaneous group in the first year of life. In the remaining deaths, the main causes were extreme prematurity, sepsis, intraventricular hemorrahage and Patau and Edwards syndromes. Samánek[7] reported that of all deaths in patients with congenital heart disease, only 48% were related to CHD. Massin et al.,[26] observed noncardiac comorbidities in 15 to 45% of autopsies in patients with CHD. Other authors have documented the association of CHD with diaphragmatic hernia, esophageal atresia, omphalocele[27] and poor neurological outcomes.[2] We observed that 32% of patients with extra-cardiac disease or syndromes had ventricular septal defects (p = 0.013). Complete atrioventricular canal defect, atrial septal defect and left ventricular noncompactation were positively associated with extra-cardiac malformations, such as craniofacial malformations, renal agenesis/hypoplasia, diaphragmatic hernia, cleft lip and cleft palate, esophageal atresia and polymalformative syndromes. Patent ductus arteriosus had a negative association with those.

Survival curves were built to assess overall mortality at 28 days, six months and one year of life according to disease category. Cyanotic diseases have shown the highest mortality in all life periods. As observed in our study, and concordant with others, cyanotic CHDs carry the worst prognosis, whose morbidity and mortality go beyond the neonatal period. Unlike our results, in a study[7] by Samánek published in 2000, the one- year mortality was higher, which probably reflects improvements in health care. More recently, Oster et al.,[21] reported a survival rate of 75% for critical CHDs and 97% for non-critical CHDs at one year of age.

Advances in therapeutic modalities have led to decreasing mortality rates. Marelli et al.,[6] showed that mortality decreased by 40% between 1979 and 1993, and that the prevalence of CHD increased by more than half between 2000 and 2010, mainly due to the surviving adult population. With this increased in survival, CHD is no longer just a pediatric problem, but one that seeps into adulthood. Bracher et al.,[8] reported that the most common comorbidities in adults with congenital heart disease are hypertension, thyroid dysfunction, psychiatric disorders, neurological disorders, chronic lung disease and stroke. Smith et al.,[28] showed that newborns with cyanotic CHDs are at a higher risk for silent ischemic cerebral stroke in the adulthood and that arrhythmias are the leading cause of death in this age group.

As far as we know, our study is the first epidemiological study to infants with CHDs born in a central maternity hospital in the main territory of Portugal. In 2006, Cymbron et al.[15] conducted an identical study on an island in the Azores, Portugal, and found an incidence of 9.16 per 1,000 live births. These results may be due to the existence of several family clusters in a relatively small area.

This study has the inherent limitations of being a retrospective analysis.

Conclusion

The incidence of CHD in our study group was approximately six per 1,000 births, and left-to-right shunt lesions were the most prevalent. Heart disease accounted for 62% of total deaths. Cyanotic CHDs had the highest prenatal diagnosis rate and were associated with increasing mortality rates over the first year of life. There has been an increase in the prevalence of CHD and its survival over time, leading to a shift in paradigm in health care towards comorbidities associated with CHD in adolescence and adulthood.

Potential Conflict of Interest

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

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

Ethics approval and consent to participate

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

Author contributions

Conception and design of the research: Faim D, Tiago J, Castelo R, Francisco A. Acquisition of data: Faim D, Tiago J, Alves R. Analysis and interpretation of the data: Faim D. Statistical analysis: Faim D. Writing of the manuscript: Faim D. Critical revision of the manuscript for intellectual content: Tiago J, Castelo R, Francisco A, Alves R, Pires A.

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ORIGINAL ARTICLE

Accuracy of Self-Reported Arterial Hypertension in Brazil: Systematic Review and Meta-Analysis

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Abstract

Background: Self-reported hypertension is a useful method to estimate prevalence in the population. However, it is necessary to evaluate its accuracy, in relation to the gold-standard diagnostic methods of the disease.

Objectives: To estimate combined measures of sensitivity and specificity for self-reported hypertension, using Brazilian validation studies that included gold standard methods.

Methods: A systematic review and a meta-analysis were developed. Two independent examiners evaluated 1389 and read 113 potentially eligible articles. Since self-reported morbidity is influenced by the cultural and economic characteristics of a population, as well as by its accessibility to medical care, only studies from one country (Brazil) were included. First, a qualitative analysis was performed, evaluating the relationship between self-reported hypertension and its measurement through gold-standard methods. Subsequently, a meta-analysis estimated the combined sensitivity and specificity for the included studies. Due to a high heterogeneity among studies, the meta-analysis used a random effects model. Bias risks were evaluated by the QUADAS-2 protocol and the standard significance level of 10% was used in all modelling.

Results: Five studies were included in the qualitative analysis; and four had the necessary information for inclusion in the meta-analysis. Patient selection and Index Test (the question allowing for self-reporting) were the domains with the highest risk of bias. In the meta-analysis, combined sensitivity and specificity were 77%(95%CI:[74.5-79.0%]) and 88%(95%CI:[86.3-88.6%]), respectively.

Conclusions: The analysed studies allowed for the estimation of more reliable values for combined sensitivity and specificity. These values were higher than those usually found in studies with greater population heterogeneity.

Keywords: Hypertension; Epidemiology; Meta-Analysis; Accuracy; Systematic Review.

Introduction

The estimation of systemic arterial hypertension (SAH) through self-reporting questionnaires in population-based surveys presents advantages, such as low cost, simplicity of measurement, and ease of application. However, as with any diagnostic test, classification errors are expected to occur, with inevitable false-positive and false-negative cases. Thus, a certain proportion of people will report having the disease when in fact they do not have it, and a group of people will report being healthy when they are actually sick.[1, 2]

To quantify the accuracy of this procedure for SAH measurement, it is possible to calculate self-reported SAH sensitivity and specificity indicators, using a reference standard. The most common "gold standards" for this are the use of sphygmomanometers[1, 2] and of automatic measurement devices.[3-5] Results found for sensitivity in these studies varied from 0.45[4] to 0.84[3], and, for specificity, from 0.81[5] to 1[4].

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Concerning the question used for self-assessment, most studies[1-3] question if any doctor or health professional had ever claimed that the subject had arterial hypertension or "high pressure". As objective as this question may seem, there is always a degree of subjectivity within it, making its understanding difficult. For example, it is known that gender, age, schooling, the way the question is asked, and the type of interview (face-to-face or telephone) may influence answers, adding to the uncertainty introduced by the use of different gold standards and cut-off points for diagnosis.

In addition, the validation of self-reported morbidity is influenced by cultural and economic characteristics of a population, as well as by the operating health system. Self-reported morbidity depends on access to health care, and it may be assumed that populations with a similar health system (e.g. a "universal health system") will behave similarly in this respect.

In light of the above, the objective of this study was to estimate combined measures of sensitivity and specificity for self-reported SAH, using only studies performed in Brazil (therefore sharing similar cultural, economic, and access to health characteristics). A systematic review and a meta-analysis were developed for this purpose.

Methods

Study Design

This study is made up of systematic reviews and meta-analyses of diagnostic test accuracy, performed in Brazil, with the aim of estimating combined sensitivity (S) and specificity (E) from studies with validated self-reported hypertension.

Eligibility criteria

Participants: Studies that deal with arterial hypertension, with no restriction of age, gender, place of study, date, or language.

Intervention: Studies that used self-reference methods for SAH tracking, with no restriction as to the question or interview method (for instance, face-to-face or telephone).

Reference: Studies that diagnosed arterial hypertension by any method were considered to be the gold standard.

Outcome: Sensitivity and specificity of self-reported hypertension.

Information sources

The Cochrane Database of Systematic Reviews and other essential databases for primary health studies (WOS, Scopus, EMBASE, MEDLINE and LILACS) were searched until August 2020. Conference proceedings were also searched through the WOS, MEDLINE, and SCOPUS databases, and Theses/Dissertations from Brazil were searched in the CAPES Brazilian Theses and Dissertations Database.[6]

The search strategy included both controlled vocabulary and free terms (see appendix), and was first developed for MEDLINE via its PubMed interface, which was later adapted to the other databases. No language restriction was implemented, and researchers in the area (i.e. with published articles on the subject) were consulted via e-mail to find out if any study, to the best of their knowledge, had been missed by the search.

Data Collection and Analysis

Eligible studies were selected and duplicates were removed by reading the title and summary of the identified articles. Selected studies were then analyzed in their entirety, with the exclusion of those that did not have information necessary for the analysis or that did not use the defined cut-offs (systolic pressure ≥ 140mmHg and/or diastolic pressure ≥ 90mmHg). Studies were also excluded when subjects were restricted to a sub-population, such as "women" "the elderly", "adolescents", or children".

Two independent reviewers assessed the studies and extracted the relevant data using a standardized form. In cases of incomplete data, attempts were made to contact the authors (e-mail). Cases of disagreement among reviewers were resolved by consensus after consultation with a third reviewer.

The self-reporting question used as an index test was: "Did any doctor or health professional ever say that you have hypertension or high blood pressure?". The evaluation of the risk of bias was done through the QUADAS-2 protocol, a Cochrane Collaboration tool for bias evaluation.[7] Four domains of risk of bias were thus assessed: *Patient Selection*, *Index Test*, *Reference Standards*, and *Flow and Time*[7]. Regarding study implementation, three domains were evaluated: *Patient selection*, *Index test*, and *Reference Standards*. Each domain was classified as having a low, high, or unclear risk of bias.[7] No need for blinding was deemed necessary, since self-reported SAH information would not influence SAH gold standard measurements.

In addition, the following bias risk criteria were established:

- Non-random sample or sample based on participants with a pre-defined characteristic: high risk.

- Self-reporting question other than that defined above: unclear risk.

- No information on the reference standard used for SAH validation: unclear risk.

The included studies used the same cutoff point for disease definition (systolic pressure ≥ 140 mmHg and diastolic pressure ≥ 90 mmHg); or indicated the use of antihypertensive medication. Authors whose works were eligible for the present study, but which did not have all the information necessary for the meta-analysis (number of true positives, false positives, true negatives and false negatives), were contacted by e-mail. Assessment of heterogeneity was performed by a visual inspection of forest plots, by the use of χ^2 tests for heterogeneity, and by the Higgins Index I^2 (the proportion of true heterogeneity relative to the total variation of the estimated parameters). A random effects model was used in the presence of heterogeneity, defined as χ^2, with a significance level < 0.10 and $I^2 > 50\%$.[8]

All analyses were performed in the MetaDiSc software, v. 1.4 (Meta-analysis of Diagnostic and Screening Tests, Universidad Complutense, Madrid, Spain).[9] It was defined that a meta-regression would be performed only if at least 10 eligible papers could be identified per covariate.[10, 11]

Results

A total of 2,610 references were found through the database search. After the exclusion of duplicates, 1,388 studies were evaluated by title and abstract, and 113 studies were selected. These 113 studies were completely analyzed, and 24 were further selected. Of these, seven had been conducted in Brazil, one of these used only adolescent subjects and was excluded, and one of these used only elderly subjects and was excluded. Thus, five studies were finally included in the qualitative analysis,

Of the five studies above, four did not have all the necessary statistical information for a metaanalysis. E-mail contacts were successful in retrieving information for three of these, thus resulting in four studies for the meta-analysis.

Figure 1 shows the flow chart for the studies identified, screened, assessed for eligibility, excluded, and finally included in the analyses. No further study could be identified by personal (e-mail) consultation with researchers in the area.

Table 1 presents the characteristics of the studies in the systematic review and meta-analysis. The most common gold standards were sphygmomanometers. Table 2 shows the risk of bias in these studies. The domain with the smallest risk was "Flow and Time", and the domains “Patient Selection” and “Index Test” had the highest occurrence of high/unclear risk.

The forest plots for sensitivity and specificity according to the study are presented in Figure 2. The highest sensitivity was found in Chrestani et al.[3] (S = 84%) and the lowest in Louzada et al.[4] (S = 45%). By contrast, the latter presented a specificity of 100%, with the lowest E found in Selem et al. (E = 81%). The four studies that met the eligibility criteria are presented in Figures 2a and 2b. For both S and E, a high degree of heterogeneity was found, with $I^2 > 98\%$ and a statistically significant χ^2 ($p < 0.0001$). Thus, a random effects model was used to estimate the combined value of S and E, resulting in S = 0.768 (95% CI: 0.745-0.790) and E = 0.875 (95% CI: 0.863-0.886). The small number of studies hindered the development of a meta-regression to assess the influence of study characteristics on sensitivity/specificity or to evaluate publication bias.

Discussion

This study performed a systematic review of and a meta-analysis on self-reported SAH validation studies from Brazil. Five studies were included in the systematic review, four of which were eligible for the meta-analysis. The accuracy of the self-reported hypertension measurement can be considered satisfactory, as it was possible to correctly identify 77% of the people who truly had the disease (sensitivity), together with a specificity close to 88%, showing a high capacity to detect true non-patients. This information, however, should serve as a warning to researchers dealing with population surveys, since it indicates that estimated self-reported hypertension may be quite divergent from real rates. The pooled sensitivity/specificity results were high, and clearly superior to review studies conducted with more heterogeneous populations. For instance, one systematic review aiming to identify the proportion of knowledge of the disease (i.e. whether people with hypertension were aware of their condition) found a combined sensitivity

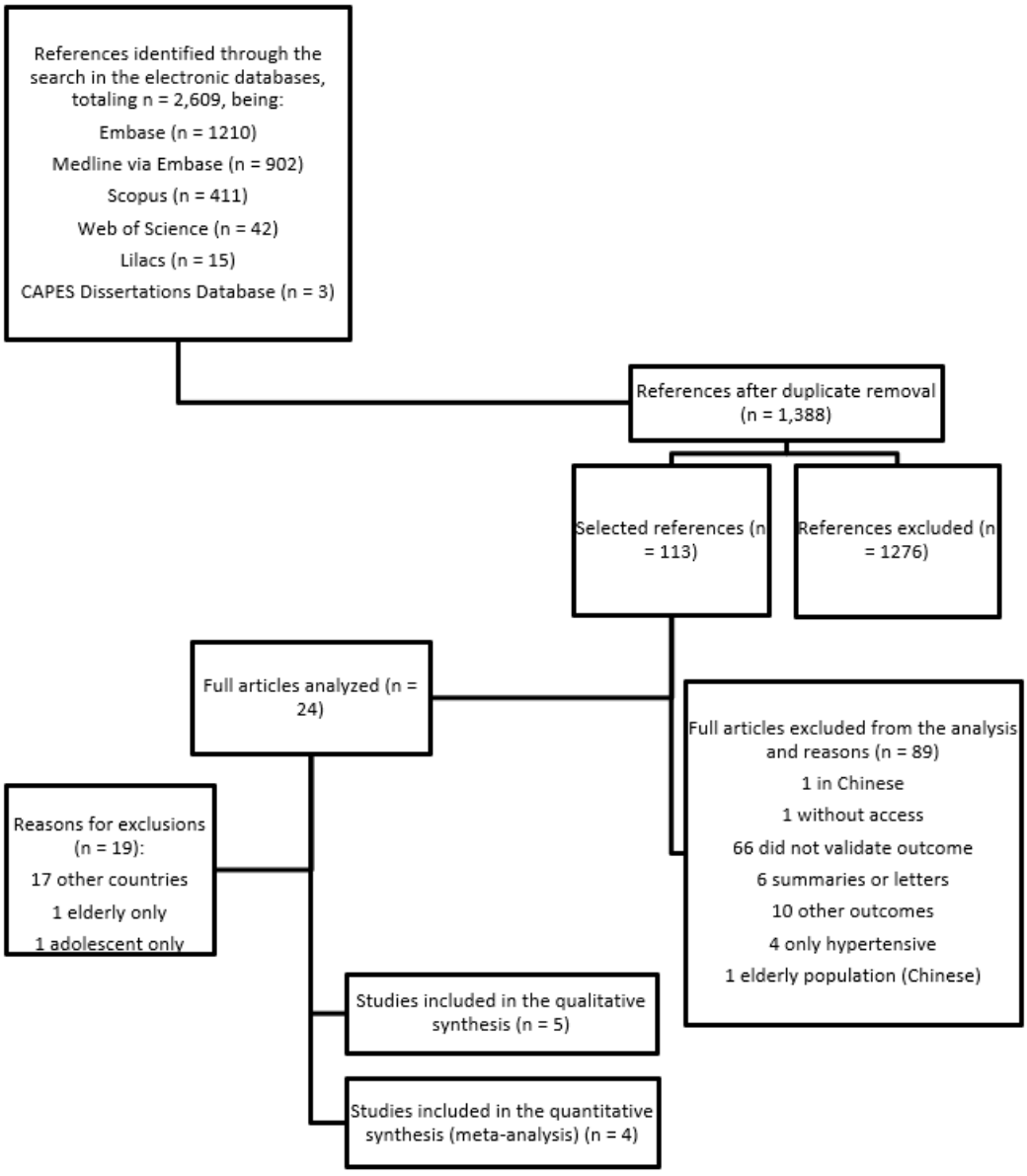

Figure 1 – Systematic review/meta-analysis study selection flow, self-reported SAH studies with reference standard validation.

Table 1 – Characteristics of the studies included in the systematic review and meta-analysis, self-reported SAH studies with reference standards

Study	Use of defined question	Reference standard	Samplesize	Minimum age	Sensitivity	Specificity
Lima-Costa et al, 2004	Yes	Esfigmomanometer	970	18	0.72	0.86
Chrestaniet al, 2007	Yes	Authomatic monitor	2906	20	0.84	0.87
Selem, et al 2013	No	Authomatic monitor	535	20	0.71	0.80
Louzada et al, 2010	Not reported	Esfigmomanometer	349	No treported	0.45	1.00
Campos et al, 2011	Yes	Esfigmomanometer	67	18	0.43	0.89

Table 2 – Bias assessment through the QUADAS-2 protocol

Study	RISK OF BIAS				APPLICABILITY CONCERNS		
	Patient Selection	Index test	Reference standard	Flow and Time	Patient Selection	Index test	Reference standard
Lima-Costa, 2004	☺	☺	☺	☺	☺	☺	☺
Chrestani, 2007	☺	☺	☺	☺	☺	☺	☺
Selem, 2013	?	?	☺	☺	☺	☹	☺
Louzada, 2010	☹	?	☺	☺	?	?	☺
Campos, 2011	☺	☹	☺	☺	☺	☹	☺

☺ *Low risk* ☹ *High risk* ? *Unclear risk*

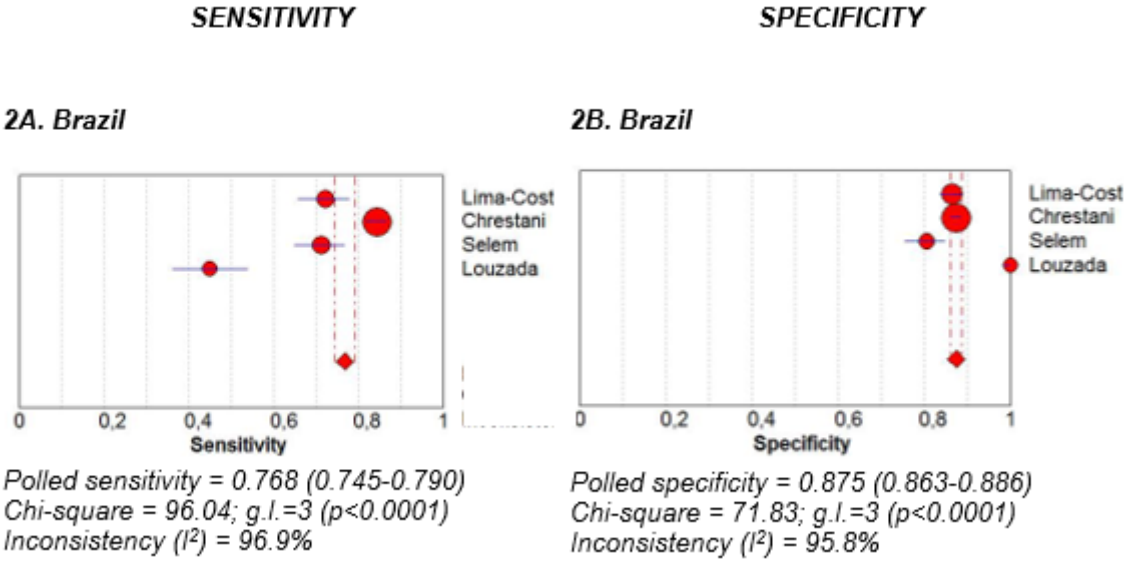

Figure 2 – Forest plots of the self-reported hypertension validity studies using ≥ 140 systolic pressure and/or ≥ 90 diastolic pressure as the reference standard cut-off point, SAH diagnosis.

of 58.4%[12] but included studies from many countries. Another similar study used two of the papers analyzed here, finding a combined sensitivity of 42% and a specificity of 90%,[13] most likely due to the greater heterogeneity of its studies.

As expected, the study of a similar population (country) makes results more comparable, with a higher combined sensitivity. However, it should be noted that this problem does not arise in the validation of exam procedures, such as *resonance versus tomography*, since differences will mainly concern equipment validity and accuracy, and not the social and cultural characteristics of studied populations.

The use of self-reporting questionnaires to estimate the prevalence of hypertension may result in severe bias, and some studies present mathematical methods for dealing with this problem (e.g. [14-16]). However, knowledge on the sensitivity/specificity of measurement procedures in a specific population is a fundamental step in these correction methods.[14-16]

Therefore, the estimates presented here can be useful to obtain better HAS estimates in the analyzed population.

Brazil has a history of population-based health surveys, such as the Health Supplement of the National Household Survey (PNAD), which later gave rise to the National Health Survey (PNS); and VIGITEL – a telephone-based surveillance system for risk factors in chronic diseases,[17] These studies have been conducted throughout the country, allowing, over the years, for a solid basis for epidemiological research and resulting in several self-reported morbidity studies.

Although the separate measures of sensitivity and specificity represented the main objective of this study, Lee et al.[18] point out that analyzing these measures separately (disregarding their correlation) can produce incorrect results and that studies should use the same explicit diagnostic limit.[18, 19]

A limitation of the present study was the small number of studies that fulfilled all the characteristics required for analysis. In addition, despite attempts of direct request, missing information for one of the eligible studies could not be recovered. Furthermore, reference tests, although considered as gold standards, may also have problems in the diagnosis of hypertension. In fact, the best method for SAH diagnosis (greater S and E) is Ambulatory Blood Pressure Monitoring (ABPM). However, the complexity and time needed for ABPM application render its use difficult in population surveys, and apparently no study used this method as a gold standard for the validation of self-reported SAH.

Conclusion

Self-reporting has been frequently used for the population screening of SAH, since it is considered to be a valid and relatively cheap procedure. This estimation method may result in bias, but this problem can be reduced with the help of the measurement sensitivity and specificity values. Therefore, the results presented here would allow for health policies based on more reliable data, as government agencies need to know the epidemiological profile of a population, and high-coverage surveys are commonly used for this purpose.

Although the combined values presented here were higher than those that would be used if only one of the analyzed studies were to be considered (sensitivity above 75% and specificity close to 90%), researchers must take into account that the procedure still fails to detect a significant proportion of subjects with the disease.

In summary, the restriction to studies from a similar population allowed for a better characterization of the validity of self-reported hypertension, with combined sensitivity and specificity values higher than those found in studies conducted in several populations. Thus, systematic reviews of self-reported morbidity should consider the use of sub-groups in order to obtain more consistent estimates.

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Author contributions

Conception and design of the research: Luiz RR, Moreira JPL, Almeida RMVR. Acquisition of data: Moreira JPL. Analysis and interpretation of the data: Moreira JPL, Almeida RMVR. Statistical analysis: Moreira JPL. Obtaining financing: Luiz RR. Writing of the manuscript: Luiz RR, Moreira JPL, Almeida RMVR. Critical revision of the manuscript for intellectual content: Luiz RR, Moreira JPL, Almeida RMVR.

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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VIEWPOINT

Association between Periodontitis and Myocardial Infarction: Systematic Review and Meta-Analysis

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Abstract

The association between periodontitis and myocardial infarction remains unclear in the literature. Few studies have addressed periodontitis exposure as a predisposing factor for the development of myocardial infarction. Therefore, the present systematic review aims to analyze the association between periodontitis and myocardial infarction. This meta-analysis systematically searched MEDLINE, EMBASE, The Cochrane Controlled Trials Register, SCIELO, LILACS, CINAHL, Scopus, Web of Science and grey literature for studies estimating the association between periodontitis and myocardial infarction. Quality of evidence was assessed for all studies. The meta-analysis was conducted using random-effects models. Four of the six studies selected were included in the meta-analysis, including 1,035,703 subjects. The association between periodontitis and myocardial infarction was: RR: 5.99 (95% CI: 1.17-30.68), but with high heterogeneity (I^2 = 100%; p <0.01). The results including only the highest quality articles, was lower: RR: 2.62 (95% CI: 1.47-4.70 3.83), but with lower heterogeneity (I^2 = 85.5%; p < 0.01). The present systematic review with meta-analysis showed an association between periodontitis and acute myocardial infarction, but with a high level of heterogeneity.

Keywords

Cardiovascular Diseases/mortality; Periodontitis/complications; Pulpitis, Myocardial Infarction/complications; Atherosclerosis/complications. Lipoproteins/analysis; Inflammation; Meta-Analysis.

Introduction

Cardiovascular diseases (CVDs) are the leading causes of death in the world, with an annual mortality of 17.9 million people.[1] Atherosclerotic disease is the most prevalent CVD, characterized by chronic inflammation mediated by the accumulation of lipoproteins in the arteries, which can cause chronic coronary disease and myocardial infarction (MI).[2] Several risk factors predispose to this condition, notably the genetic determinism, smoking habit, physical inactivity, high body mass index, hypertension, dyslipidemia and diabetes.[3] Poor oral health status, especially periodontal conditions, such as periodontitis, has also been reported as a potential aggravating factor for CVD.[4]

The latest consensus of the American Academy of Periodontology (AAP) and the European Federation of Periodontology (EFP) states that periodontitis is characterized by an "inflammation mediated by the host associated with microorganisms that results in loss of periodontal insertion".[5] It is a chronic, non-curable disease associated with many strains of bacteria, especially gram-negative ones.[5] There is evidence that oral pathogenic bacteria can cause bacteremia, increased expression of pro-inflammatory proteins (e.g. IL-1, IL-6, IL-8, TNF and of C-reactive protein), leading to vascular infection and development of CVD.[6,7]

As with CVD, periodontitis is more prevalent in adults. A Brazilian epidemiological survey[8] showed that about 19.4% of adults between the ages of 35 and 44 years, and approximately 3.3% of elderly between 65-74 years old have some degree of periodontal disease. The lower prevalence in the elderly is justified

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by the greater number of missing teeth for long exposure to oral diseases. Although there is sufficient evidence to support the relationship between CVD and periodontitis,[9] the association between periodontitis and MI remains unclear in the literature. Most studies have shown the increase of the prevalence of periodontitis in infarcted patients, suggesting a strong association between this condition and the acute ischemic event[10-12]. However, few of these studies have addressed periodontitis as a predisposing factor for the development of MI. Thus, the present systematic review aimed to analyze the association between periodontitis and MI.

Methods

This systematic review and meta-analysis were performed following the PRISMA guidelines, and its protocol was registered in the PROSPERO database (CRD42016052902).

Eligibility criteria

The inclusion criteria for studies were the following: (i) use of periodontitis as exposure factor and MI as outcome; (ii) observational studies (of all types). There was no language restriction. Case studies, review studies, case series, experimental models, response letters, editorials and duplicated publications were excluded. Duplicate studies were those published by the same study group, with the same inclusion date and population characteristics. In case of duplicate studies, the study with the larger sample size was considered for analysis.

Information sources

The following databases were used in the literature search, from inception to October 2018: MEDLINE (via PUBMED), EMBASE, Cochrane The Cochrane Controlled Trials Register (CCTR), Latin American Caribbean Health Sciences Literature (LILACS via BIREME), Cumulative Index to Nursing and Allied Health Literature (via EBSCOhost), Scopus and Web of Science (Thomson Reuters). The MEDLINE search strategy was adapted to the other databases.

Study selection and data extraction

Two authors independently screened the abstracts and titles of the studies retrieved. Full texts of all potentially relevant articles were then analyzed. In both phases, in case of disagreement between the researchers, a third independent researcher was involved to achieve final consensus. For studies that fulfilled the inclusion criteria, three authors worked in the data extraction process. The agreement between the authors, estimated by the Kappa coefficient, was considered good (k = 0.735).

The following data were extracted from the articles selected: identification (authors and year of publication), general characteristics of participants (including age and gender), sample size, time of observation, definition of MI and periodontitis, magnitude of exposure and effect size.

Risk of bias

The association between exposure and outcome was synthesized from a meta-analysis using estimated risk calculations.

Risk of bias was analyzed using the NIH Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies.[13] This tool allows the assessment of the risk of bias and the quality of the study, and classified them as "good", "fair" or "bad". "Good" quality was attributed to studies that adopted at least eight of the established criteria. The biases were assessed by two evaluators and, in case of disagreement, a third evaluator was involved.

Statistical analysis

The association between periodontitis and MI was analyzed using meta-analysis with random-effects models. The heterogeneity among studies was assessed using the Q-Cochran test and I^2 statistics. We planned to explore heterogeneity using race as a factor, but the studies did not provide sufficient data. For longitudinal and clinical trials that assessed phase angle in more than one moment, the baseline values were considered for analysis. The authors of the present review were aware that some of issues suitable for sensitivity analysis were only identified during the review process, when the characteristics of each study were identified. At this phase of our review, we performed a sensitivity analysis to assess the robustness of our analyses by including only good-quality studies with good quality. The meta-analysis was performed using the Meta R package (https://CRAN.R-project.org/package=meta).

Results

A total of 3,384 articles were retrieved from the selected databases. Of these, 1,272 duplicate articles were excluded. After reading the titles and abstracts, 2,013 articles were excluded according to the exclusion criteria. Of the 99 articles selected for full reading, 93 were excluded, of which 75 did not utilize periodontitis as exposure and/or MI as outcome, 12 articles were not available, one analyzed periodontitis treatment, three were letters to editor, and two were *in vitro* studies (Figure 1).

Characteristics of the included studies

Of the six articles included in qualitative analysis, the studies of Noguchi et al.,[14], Lee et al.,[15] Hansen et al.[16] and Holmlund et al.[17] were cohort studies, one retrospective[15] and three prospective studies[14,16,17] and the studies by Arbes et al.,[10] and Holmlund et al.[18] were cross-sectional studies. The shortest observation period was 5 years[14] and the largest was 34 years.[17] The sample size of the studies ranged from 3,081[14] to 1,025,340 participants,[15] and their ages ranged from 1[15] to 85[17] years, with two studies without maximum age restriction.[10,16] Except for the study by Noguchi et al.,[14] who included only men in their sample, the other studies did not show gender restriction. No study used 'previous diseases' as inclusion criteria. Data extracted from the selected studies are described in Table 1. Data regarding the number of outcomes and estimated risks of the six studies included in the qualitative analysis are available in Table 2.

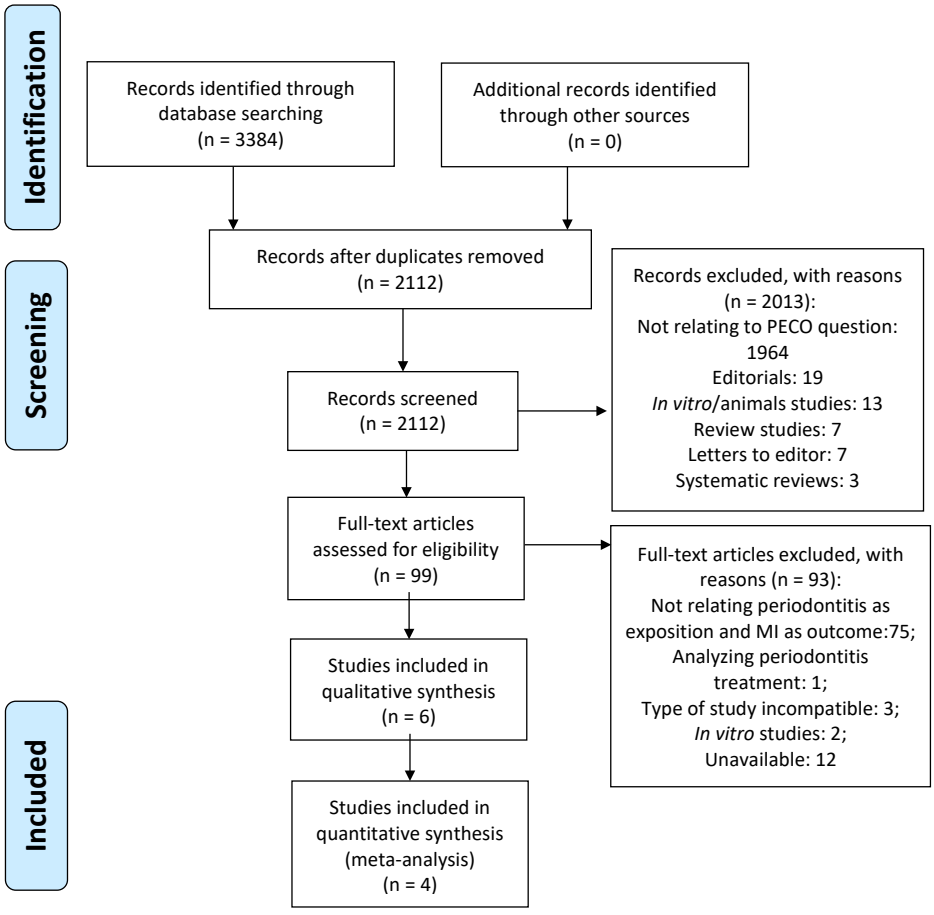

Figure 1 – Flowchart of the study selection process MI: myocardial infarction
From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097
For more information, visit www.prisma-statement.org.

Table 1 – General characteristics of the studies

Author, year	population	n	Age (Years)	Gender	Design and observation time	Definition of mi	Definition of periodontitis
Arbes et al., (1999) [10]	NHANES III* data of United States population sample	5564	≥40	2,757 men 2,807 women	Cross-sectional study	Self-reported heart attack	Clinical attachment loss ≥ 3mm
HOLMLUNet al., (2006) [17-18]	Patients from the Department of Periodontology, Gävle County Hospital	4.254	20 – 70	1,866 men 2,388 women	Cross-sectional study	Self-reported heart attack	Bone loss >2mm
NOGUCHI ET AL., (2014) [14]	Employees of a financial company in Japan	3081	36 – 59	Only men	Prospective cohort between 2004 - 2009	Patients report that they were undergoing myocardial infarction treatment	Self-administered questionnaire produced by the authors.
LEE et al., (2015) [15]	Random sample (2% of total) of South Korean population covered by National Health Insurance	1.025.340	1-79	513,258 men 512,082 women	Retrospective cohort between 2002 a 2013	Records of the 6th ed. Korean Classification of Diseases (KCD-6): Code not specified	Records of the 6th ed. Korean Classification of Diseases (KCD-6): K052 – K056
HANSEN et al., (2016) [16]	Sample of the Danish population from the National Patient Registry	100.694	≥18	57,421 men 43,273 women	Prospective cohort between 1997- 2011	International Classification of Diseases (ICD-10) Records: Codes I21-I22	International Classification of Diseases (ICD-08) Records: Code 523.49 and 523.49 International Classification of Diseases (ICD-10) Records: Code K05.2 - 05.3.
HOLMLUNet al. (2017) [17-18]	Patients from the Department of Periodontology, Gävle County Hospital	8.999	20-85	3,870 men 5,129 women	Prospective cohort between 1979 - 2013	International Classification of Disease Records: 421 (ICD-8 and ICD-9) and I21 (ICD-10)	Probing depth ≥ 4mm

**NHANES III, Third National Health and Nutrition Examination Survey*

Meta-analysis

The association of MI in patients with periodontitis was calculated using data retrieved from four studies[10,14,15,18] including 1,035,703 subjects. The result of this analysis was – RR: 5.99 (95% CI: 1.17-30.68), but with a high heterogeneity (I^2 = 100%; p <0.01). Result of the analysis including only the highest-quality articles was lower – RR: 2.62 (95% CI: 1.47-4.70 3.83), with a lower heterogeneity also (I^2 = 85.5%; p < 0.01) (Figure 2).

Table 2 – Results of risk analysis between periodontitis and AMI found in the studies

Author, year	Severity		Control	Outcome (N. cases/N. controls)	HR, ODDS, RR, OR (IC 95%)	Variable
ARBES S.J, (1999)	Percent of sites with periodontal attachment loss of ≥3 mm:	>0-33	No periodontitis	88/5.564	ODDS 1,38 (0,75-2,54)	Percent of sites with periodontal attachment loss ≥3; age; sex; race; smoking status; history of diabetes; history of high blood pressure; body mass indices; poverty index; serum cholesterol.
		>33-67		73/5.564	ODDS 2,28 (1,18-4,39)	
		>67-100		55/5.564	ODDS 2,28 (1,18-4,39)	
HOLMLUND A, (2006)	Periodontal bone loss		No periodontal bone loss (<2mm)	Not informed	ODDS 2,69 (1,12-6,46)	Age, gender and smoking.
NOGUCHI S, (2014)	With periodontist or without periodontitis		No periodontitis	9/3081	OR 2,26 (0,84-6,02)	Age; BMI; current smoking; hypertension; diabetes; dyslipidemia; family history of heart disease.
LEE J.H, (2015)	With periodontist or without periodontitis		No periodontal disease	8.179/1.025.340	ODDS 0,98 (0,86-1,12)	Sociodemographic/ economic status and comorbidities.
HANSEN G.M, (2016)	With periodontist or without periodontitis		No periodontitis	Not informed	IRR 1,16 (1,04- 1,30)	Age; sex; smoking; comorbidities; medication and socioeconomic status.
HOLMLUND A, (2017)	Numbers of surfaces with pocket depth > 4mm		No periodontal disease	570/8.999	IRR 1,13 (0,98-1,30)	Age; sex; education level and smoking.

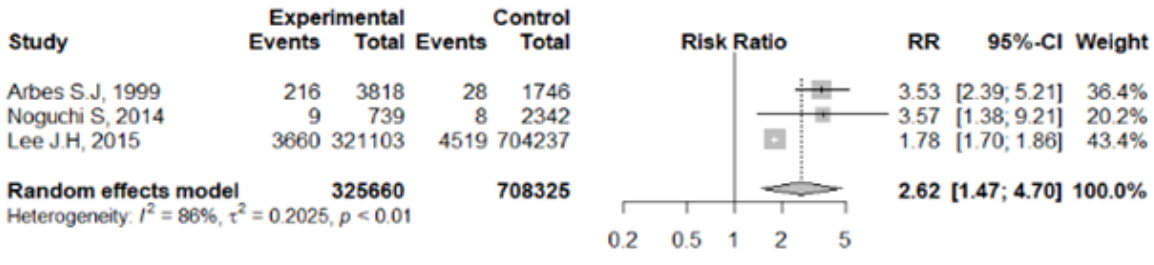

Figure 2 – Meta-analysis of high-quality studies on the association of acute myocardial infarction with periodontitis

Risk of bias

The quality of the included studies was considered reasonable. All of them described adequately the purposes and the population of the study, and evaluated periodontitis prior to the development of MI. Only in one study (16.67%)[18] the participation rate was less than 50% of the population. No study described the sample calculation in detail, blinded the periodontitis assessment

or performed periodontitis measurement more than once over time. The follow-up time described was considered good in four (66.7%) of the studies.[14-17] In only three[10,14,18] (50.0%) studies patients were classified according to the degree of periodontitis. Misdiagnosis and/or validation of the diagnosis of acute MI were found in all studies; in contrast, only three[10,17,18] (50.0%) studies were considered adequate satisfactory in the definition and validation of the diagnosis of periodontitis. Only one study[18] (16.67%) did not perform statistical adjustment for losses to follow-up, and three (50.0%) studies[10,15,17] reported losses to follow-up of less than 20% of the participants.

Publication bias was not evaluated due to the limited number of studies.

Discussion

The present systematic review with meta-analysis showed an association between periodontitis and MI, but with high heterogeneity.

The results obtained in this study corroborate the hypothesis that chronic inflammation is involved in the pathogenesis of the atherosclerotic process and in triggering acute ischemic events.[19] Previous studies have demonstrated that infectious agents are capable of inducing local and systemic inflammatory mechanisms. In response to pathogens, reactive oxygen and lipoprotein species are released, leading to the recruitment and proliferation of inflammatory cells such as T lymphocytes and macrophages.[20] Infection stimulates the release of cytokines (Il-1 beta and TNF-alpha) by the periodontal vascular complex or coronary endothelial cells, promoting platelet aggregation and thrombus formation.[20,21]

The present study has several limitations. Most of the included studies classified the outcome and exposure according to medical records or self-reports. Only three[10,17,18] studies used standardized diagnostic methods for periodontitis, and none used standardized methods to define MI. This variability in the definition criteria of periodontitis and MI may be one of the causes of the great heterogeneity identified in the studies. Another factor is the reduced number of well-structured studies, and the long period between the studies, which compromises the reliability of this meta-analysis. Despite that, the search strategy was broad and included the most relevant evidence available.

The results of this systematic review and meta-analysis suggest an association between periodontitis and an increased risk of MI. The heterogeneity identified between the studies suggests the need for more studies that include the assessment of these factors in a more standardized manner and longer follow-up period to support a causal relationship.

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.

Author contributions

Conception and design of the research: Baptista AH, Bodanese L, Salum FG, Mattiello R. Acquisition of data: Louzeiro GC, Magnus GA. Analysis and interpretation of the data: Louzeiro GC, Magnus GA, Bodanese L, Salum FG, Mattiello R. Statistical analysis: Mattiello R. Writing of the manuscript: Louzeiro GC, Magnus GA. Critical revision of the manuscript for intellectual content: Bodanese L, Baptista AH, Salum FG, Mattiello R.

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*Supplemental Materials

For additional information, please click here.

VIEWPOINT

Mentoring in cardiology: A New Teaching Tool in a Rapidly Transforming World

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Abstract

This is an article aimed at showing the mentoring role in a fast-changing society, particularly during and after the COVID-19 pandemic. The intense flow of information feelings and new knowledge makes it necessary for medical education to be updated to keep up with social and professional dynamics, according to health requirements and new knowledge demands.

The mentoring program is a development process in which the mentor promotes the mentee professional and personal growth, by the exchange of visions and experiences. It allows an increase in the repertoire of solutions, particularly important in such an unstable context imposed by the pandemic. The mentor and mentee are challenged to move from a traditional to a virtual environment, characterized by physical distancing, development of digital medicine and distance learning.

Article Motivation

This article was motivated by the experience with the project implemented by the Cardiology Society of Rio de Janeiro (SOCERJ). The project, launched at the 2018 SOCERJ Congress, aims to promote experienced medical professionals and teachers as mentors of medical students and young doctors. In addition, the COVID-19 pandemic was another important motivating factor for this study, since at this crucial moment for healthcare in Brazil and worldwide, the development of leadership and the use of digital technologies make a difference in this scenario of uncertainties.

Keywords

Mentors; Mentoring; Cardiology.

Historical context / Historical background

The concept of mentoring originated from the Homer's famous "The Odyssey". In the epic poem, Odysseus, the king of Ithaca, entrusted Mentor with the great challenge of preparing his son, Telemachus, to replace his father after he leaves for the Trojan War. Telemachus was not only under the tutelage of the Mentor, but also under his supervision and guidance to become prepared for future responsibilities. In 1750, the word "mentor" was incorporated into the English and French dictionaries, with the words: advisor, friend, tutor, teacher, and wise man as synonymous.[1]

"Mentoring" in Brazilian medical schools

In Brazil, the mentoring process is known as "mentoria". Although the latter has been more restricted and limited to technical knowledge, both processes fall within the movement of changing medical teaching. Changes are being made to the curriculum guidelines and are being established with the intention of forming mentoring and, to a lesser extent, mentoring programs (2).

In order to provide a more active training, some medical schools in Brazil have adopted methods that help in this process, which, although not based on the mentoring format, makes the teaching-learning process more dynamic. The Marília Medical School one of the first in the active methodology of problem-based teaching (PBL) in Brazil, Problem Based Learning program in the medical course in 1997.[5] The Rio Grande do Norte Medical School implemented a mentoring program in 2015, with integrative activities between students and teachers of the university. The objective of the program was to promote the development of mental, professional and academic health of students.[3] The São Paulo State University has incorporated mentoring into the support and development program format, where students have

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the opportunity to meet monthly with experienced doctors who encourage them to evaluate the profession and support them during their undergraduate studies.[4]

Importance of mentoring

Medical academics and young doctors have faced increasing challenges in terms of the volume of information, concepts, professional opportunities and the speed of technology development. In this context, mentoring becomes a valuable tool for career development and preservation of physical and mental health.[6] According to Agarwal et al.,[7] a good mentor makes you not only a more qualified professional, but a better human being. In addition, it has been demonstrated that mentoring has allowed an increase in career satisfaction and stimulated the presence of more professionals involved in mentoring projects.[8]

In recent years, medical societies, in Brazil and abroad, have created mentoring programs to develop technical and personal skills, and consequently better academic performance. Young students are in contact with senior professionals, who, during discussions of cases and technical medical procedures, allow students to acquire important skills for the profession.

The new national curriculum guidelines of the undergraduate medical course point out that, among doctor skills and competences, there are four pillars on which the mentoring process can have great impact – 1) continuing education, 2) communication, 3) management and 4) medical leadership, all present in the mentor-mentee binomial process.[9] Another concern of mentoring programs is the increasing number of "burnout syndrome" cases among medical students. This condition has been recently made official by the World Health Organization (WHO) as a chronic syndrome and will be included in the new International Classification of Diseases (ICD-11). The number of "Burnout" cases have increased among physicians, secondary to technological changes in the work environment, increased bureaucracy, and imbalance between personal and professional life, leading to an increase in chemical abuse, depression, and suicide rates.[10]

The mentoring

Regarding the current physician training, it is known that there is a great priority for the development of technical skills to the detriment of other formations also important for the apprentice, including knowledge of cognitive skills and postures in professional training. In this sense, the mentor plays a fundamental role in the process of mentoring by developing resourcefulness skills in the professional environment and promoting psycho-emotional control.[10]

The mentor

There are no strict rules to finding a mentor. Often the mentor-apprentice relationship begins as a boss and subordinate or as a teacher-student connection, which evolves over time into a mentoring relationship. It may be difficult to choose the ideal mentor due to the dynamic nature of the mentor and apprentice relationship, which depends on personality, aptitude, and attitude of both parties.[7]

Types of mentor

Currently, some authors believe that throughout a person's life there must be more than one mentor, or the same one may have more than one characteristic, as exemplified in Table 1. Such a situation is based on rapid changes in technology, organizational structure, and global health market dynamics.[7] According to Janasz et al.,[11] as more information is available, it is difficult for an individual mentor to process all the knowledge required by the mentee, making it necessary to form and maintain a network.

Given this scenario, we can infer that it would be of great importance that medical schools and medical societies, aiming at a more holistic development of students and professionals, analyze the possibility of progressively offering greater means of training for the mentoring process. In addition to providing a more complete development of students and professionals, the process also allow measuring the results of mentoring process in the development of the medical professional.

Mentoring in practice

Medicine practice requires excellence in performance, satisfaction, quality of care and good safety practices for the patient. It may become deficient in light of the increasing complexity of the training of new doctors, imposed by the health environment changes.12 Thus, to fill the training gaps, the mentor plays a determinant role in an encompassing professional training12 (Table 2).

Table 1 - The main types of mentors

Level	Types of Mentors	Mentee's benefits
I.	Educator	Promotes the advancement of apprenticeship education, including medical knowledge, technical proficiency, and procedural and digital skills.
II.	Defiant	Encourages the mentee to contribute to the dedicated work and achieve high levels of excellence.
III.	Moderate	Makes questions that encourage the mentee examine his/her actions to generate continuous learning and change of values.
IV.	Planner	Stimulates career planning and time management, considering the mentee's skills and the mentor's experience.
V.	Connecter	The mentor uses his influence and his network of contacts for the mentee to participate in projects or enter the labor-market.
VI.	Hybrid model	Creates a model that combines the five profiles mentioned, throughout the development of the mentoring process.

Source: *Adaptad from JANASZ et al.*[11]

Reverse mentoring and intergenerational aspects

The medical work environment goes through a process of transformation never seen before, having in the increase of life expectancy an important pillar for the changes. This transition can be observed in the work environment, where 80-90-year-old professionals share space with younger generations, which highlights challenges of coexistence, adjustments, disruption, and respect to the characteristics of each time.[13]

In view of the traits of each generation, technological advances have striking importance among them and founded the idea of the "Generation Theory", represented by Figure 1. This theory shows that individuals exhibit similar behaviors as a function of the period in which they were born.[13]

Definition of generations

Traditionals (T): This is the generation of individuals born between 1925 and 1945.[13]

Baby boomers **(BB):** People over 50 years old. They value a steady and stable job, taking into account the experience.[13]

Generation X: in professional life, this generation values positions, salaries, and functions. They remain long periods in the same company.[13-15]

Generation Y: in a short time of life, this generation witnessed the greatest advances in technology and electronic communication. It does not value the hierarchy so much and believes that working together offers great results.[14,15]

Generation Z: in the Internet era, they are known as "digital natives" with high levels of creativity, expressiveness, and individuality. Connected to mobile devices and other technological features, they are "native speakers" of digital language.[16]

Given all these diversities, the intergenerational aspects must be considered, so that the work environment becomes productive and harmonious. In this regard, a new concept called "Reverse Mentoring" has been created, in which the mentee is not the only one to learn and benefit from this relationship, since the new generations are connected, technological, creative and are open to the logic of the health transition observed over the last few years.[17]

In this process, the relationships established in the mentoring process can create a favorable environment for the mentor-mentee mutual growth. For the mentor, it can be a challenging and rewarding experience, that offers new perspectives, ideas, feedback in professional life, chance to develop in areas such as information technology, and mainly, opportunity for self-assessment on their technical and personal conduct in face of diverse situations. Building a synergistic relationship generates an environment of respect and friendship, making the two-way flow of learning and growth for both parties.[17]

Table 2 – Mentor's duties

AREAS	DUTIES	DESCRIPTION
Professional	Support	The mentor helps the mentee to obtain opportunities in the area of operation.
	Development	The mentor creates opportunity for the mentee to demonstrate competence and improve their performance.
	Coaching	The mentor teaches the mentee through sharing ideas and feedback, suggests work strategies and tactics, and guides on career aspects.
	Challenges	The mentor supports the development of specific mentoring skills by providing challenges and jobs that encourage learning, such as digital mentoring and entrepreneurship.
Personal	Role modeling	The mentor serves as an example, admiration and respect for the mentee. It helps mentors to manage groups and tensions in the work environment and family.
	Acceptance and confirmation	The mentor provides support and encouragement to the mentee. It makes it possible to experiment with new behaviors.
	Counselling	The mentor listens to the mentee and supports him on personal concerns, anxieties and fears that can affect his performance.
	Friendship	The mentor enables social interaction inside and outside the organization, resulting in the exchange of information in a more informal environment and with a mutual understanding. It promotes the sharing of personal experiences.

Source: *Adapted from Kram (1983; 1985).*

Figure 1 - Generation Theory

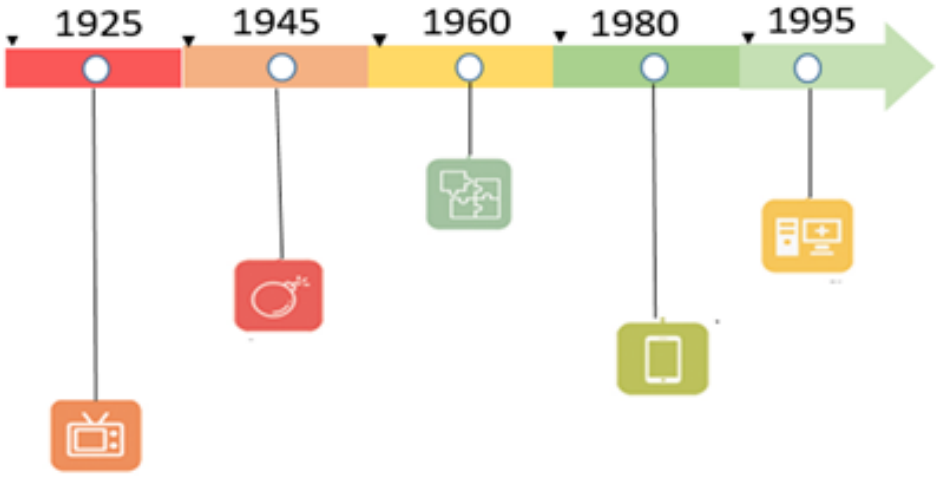

Figure 1 – Generation theory - each icon represents one of the described generations. In order, from left to right: Traditional, Baby Boomers, Generation X, Generation Y and Generation Z. Source: Authorial image.

Mentoring and digital medicine

Digital medicine has been increasingly incorporated by health workers. As an example, Dr. Eric Topol, one of the most influential cardiologists in the world, developed a training matrix aiming at training English healthcare professionals. This tool showed that digital mindset was an important feature of the mentor for the development of young leaders. Extending to a post-COVID-19 pandemic world, these skills and mindset become relevant to patient care, since the pandemic has introduced an environment marked by electronic medical records, robotic tools, teleconsultation and telemonitoring.[16,18,19]

Under this new perspective, the development of digital medicine-related skills will enable the incorporation of a new health care model, different from the pre-pandemic setting. Therefore, there will be another chapter in the history of humanity, in which the outbreak of a certain disease alters the dynamics of health, functioning as a path for the humanistic development of professionals in the area.[20]

Mentoring in Cardiology training

The American Heart Association (AHA) and the American College of Cardiology (ACC) have used the mentoring process to train physicians, researchers, and cardiovascular scientists, aiming to accelerate the teaching and learning process of young professionals. The ACC pioneered the development of a structured mentoring process for cardiovascular professionals and scientists and edited an important publication: the "Mentoring Handbook", which is in the third publication.[20] This manual aims to promote the mentoring relationship between clinicians and senior researchers. Written for physicians and basic science researchers in a wide range of disciplines, this popular handbook is a practical guide to promote successful mentoring relationships between clinicians and senior and early-career scientists. In addition, it includes updated lists of mentoring resources and funding opportunities for young researchers.[20]

The Brazilian Society of Cardiology (SBC), in conjunction with the University of Duke, implemented in 2008-2009 an institutional program, to create a partnership in clinical research.[5] The collaboration between the SBC and the Duke University resulted in increased productivity in cardiovascular research centers.[21]

In 2018, during its 35th conference, the SOCERJ started a mentoring project, which is in the third edition. Over the years, there has been substantial growth in demand for the program. The objective is to enable, during a one-year partnership, that medical mentors and professors of excellence in the field of cardiology help medical academics and young doctors to manage their careers assertively, develop scientific initiation projects, guide on postgraduate programs, and develop personal skills.[21]

SOCERJ 2019-2020 mentoring program experience

The SOCERJ mentoring program had a great impact on the career of some participants in the first edition. Some of the mentees got into the master's degree program, managed to organize the curriculum to try residency in the United States, wrote and submitted the scientific papers and, mainly, got feedback on the skills that needed to be improved to achieve their goals. The opportunity to be in contact with successful doctors and teachers allowed mentees to raise improve their standard level of performance and become professionals of excellence.

The SOCERJ mentoring meetings take place according to the availability of the mentor and the demand of their projects. Face-to-face meetings are carried out weekly between academics and mentors for preparation of their first scientific papers. During the COVID-19 pandemic, these meetings were held online, keeping the same objectives, constancy, and deadlines.

A mentor's opinion in the context of new medical skills in the chronic cardiovascular diseases context

Advances in the diagnosis and treatment of cardiovascular diseases have allowed a marked increase in survival and quality of life of patients. In this new context, the doctor maintains a long-term routine follow-up of the patients. Diseases such as heart failure, atherosclerotic arterial disease, atrial fibrillation, systemic arterial hypertension and cardiometabolic conditions have become chronic diseases in an increasingly elderly population with multiple comorbidities and different levels of frailty.

The training of young doctors and cardiologists of the 20th century has followed a teaching model in which they should act in isolation, maintain a certain distance, deciding alone the direction of care and treatment of the patient. In recent decades, however, the multidisciplinary work and the formation of a cardiological team at care institutions have favored the complex health system, which increasingly requires professionals to develop teamwork skills, interdependence management, leadership attributes and active clinical governance.

This new perspective will increasingly count on the support of different specialists such as family doctors, hospitalists, palliative care physicians, intensivists, rehabilitation professionals and multidisciplinary teams. Models of health care and clinical management have become fundamental in the competence matrix of the cardiologist of the 21st century, as well as the mastery of new areas such as telemedicine, nanomedicine and genetics/genomics as important tools for diagnosis and treatment.

Thus, a new relationship based on the doctor-patient-family triad has been established, with a strengthening of the bonds of trust and shared decision-making. Also, a space is opened for patients to become participative in treatment choices and procedures, and to assume their self-care. In this way, choices are aligned with their preferences, values, and beliefs.

In this dynamics, heart disease patient becomes an active individual in the acquisition of information about his/her disease and is no longer satisfied with consuming prescriptions and guidelines. The physician is a professional who can adapt the therapeutic approaches and respects patient complexity as a biopsychosocial spiritual being.[22]

Conclusion

The mentoring process in cardiology begins to be developed as a tool of broad and fundamental use in the formation of human capital. Young and senior cardiologists will face a growing challenge throughout their professional life, working in an environment of uncertainty, regulatory, health and epidemiological changes, and mainly with the new format of well informed and participatory patients with regard to their care. Therefore, multiple mentoring model and digital mindset are imperative in the training process and should be led by educational organizations and cardiology societies.

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Author contributions

Conception and design of the research: Mesquita ET. Acquisition of data: Soares AC, Matos RC. Analysis and interpretation of the data: Mesquita ET. Writing of the manuscript: Soares AC. Critical revision of the manuscript for intellectual content: Soares AC, Mesquita ET, Matos RC.

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CASE REPORT

Kounis Syndrome: Case Report in Goiânia/BR

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Abstract

22-year-old male patient with no heart disease, who was given an ambulatory medication with analgesics due to an acute renal crisis. After the drug administration, the patient presented dyspnea, cyanosis, and hemoptysis. There was suspicion of anaphylactic shock, which was treated, but there was no improvement in the clinical condition. The patient was referred to the Intensive Care Unit, where tests were performed showing elevated cardiac enzymes and Immunoglobulin E and Computed Tomography of Thoracic revealed alveolar hemorrhage. He developed clinical worsening and died after sepsis. The final diagnosis was of kounis syndrome due to the hypersensitivity reaction to the analgesics introduced in the patient, generating an acute coronary syndrome (ACS). The purpose of this case report was to highlight a syndrome that is little reported because it is not part of the differential diagnosis routines of ACS, but it generates important complications.

Introduction

Kounis syndrome (referred here as SK) is consisted of an acute coronary syndrome but despite the usual atherosclerosis etiology has its origin in anaphylactic or anaphylactoid allergic reactions. It was described in 1991, also having as variants vasospastic angina of allergic etiology, allergic myocardial infarction, and stent thrombosis – if occlusive thrombus infiltrated by eosinophils and/or mastocytes .[1-3]

Keywords

Heart/drug effects; Biomarkers; Immunoglobulins; Kounis Syndrome; Acute Coronary Syndrome; Sepsis; Hemorrhage; Diagnostic Imaging; Tramadol.

The syndrome is caused by inflammatory mediators such as histamine, platelet activating factor, arachidonic acid products, neutral proteases, cytokines, and chemokines that trigger a cascade that results in the activation of inflammatory cells. This set of mediators, in turn, feed a vicious cycle with the release of more mediators. All of this leads to coronary vasospasm justifying its clinic of an acute coronary syndrome.[3]

To date, several triggering factors of such a hypersensitivity reaction have been described and their number continues to grow. In addition, factors like medicines and food can be highlighted.[3] Among the drugs, several classes frequently used in clinical practice are triggers of SK, such dipyrone, etomidate, beta-lactam antibiotics, trimetafan, non-steroidal anti-inflammatories, antineoplastics, contrasts, corticosteroids, antiseptics, muscle relaxants, proton pump inhibitors, thrombolytics and anticoagulants, among others.[4]

Apparently, SK is not a rare syndrome, but there is little medical knowledge in general due to lost cases and undiagnosed and/or reported cases. Although there are no large prospective studies evaluating its exact incidence and prevalence, it is distributed in all age groups, races and geographic locations.[3]

Given the shortage of literature on SK, this report contributes to the dissemination of knowledge about such pathology. Thus, its recognition by the medical community may be more effective causing an increase in the number of reported cases, its description in the literature and most important, the management of patients presenting such condition.

Case Report

A 22-year-old male patient was admitted to the Santa Maria Hospital in Goiânia-GO on 10/19/2017,

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complaining of severe low back pain on the right associated with nausea and vomiting. He reported being under treatment for epilepsy. During physical examination, he was in good general condition, eupneic, pale (++/4+), sweaty, acyanotic and afebrile. Tramadol hydrochloride 100mg was prescribed, without clinical improvement, then he was medicated with 1 ampoule of scopolamine + butylbromide + dipyrone and 40 mg of tenoxicam intravenously (IV). After administration, the patient presented dyspnea, profuse sweating, cold skin, cyanotic extremities, and an episode of hemoptysis, being administered intravenously hydrocortisone 500mg, promethazine and adrenaline. The patient denied fever, cough or previous respiratory distress, as well as the use of anabolic/steroids or narcotics.

The patient evolved to respiratory failure and was transferred to the Intensive Care Unit. Upon admission to the ICU, the patient presented chest pain, tachypnea, tachycardia, hypotension, diffusely decreased vesicular murmur in pulmonary auscultation, O2 saturation of 81% coupled to the oxygen mask. Volume replacement, adrenaline (1amp), dimenhydrinate (1 amp) and promethazine (1 amp) were initiated.

Laboratory tests for admission showed leukocytosis (26,300 leukocytes/mm^3), neutrophilia (13% of neutrophils), C Reactive protein 4.2 mg/L , DHL 242 U/L, Troponin T 0.138 ng/ml, CPK 120 U/L, CKMB 38 U/L, D-dimer 2.6 mg/mL, Immunoglobulin E 177 IU/mL. Among the requested imaging tests, the electrocardiogram and echocardiogram showed no alteration, chest CT scan showed alveolar hemorrhage.

The patient evolved with worsening of respiratory mechanics and orotracheal intubation was performed while clinical support was maintained. On the second day of hospitalization, the patient presented CPK 708 U/L, CKMB 34.5 U/L, lactate of 3.2 mmol/L and CRP 143.3 mg/L. On the third day, myocardial injury biomarkers began to decrease until they normalized.

The patient had a clinic follow up with several specialties in the ICU due to pauci-immune pulmonary capillaritis, pneumonia and the Acute Respiratory Distress Syndrome. Treatment included pulse therapy with solumedrol, immunosuppressive and plasmapheresis, in addition to antibiotic therapy and intensive care. Due to hemodynamic instability, the patient evolved into sepsis and cardiorespiratory arrest and did not answer to any resuscitation maneuvers. He died after 19 days of hospitalization.

Discussion

Kounis syndrome, also known as allergic angina, can be defined as an acute coronary syndrome caused by vasospasm, secondary to a hypersensitivity reaction. As it is little known, it is not part of most differential diagnostic routines for acute coronary syndromes and for this reason, it is often underdiagnosed. The risk factors involve previous history of atopy, hypertension, smoking, diabetes and dyslipidemia, and the main triggers are medications and insect bites. (Table 1)[5,6]

The hypersensitivity reaction culminates in mast cell degranulation, releasing proteases and vasoactive mediators. Among these substances, the main one is histamine, which is a potent

Table 1 – Drugs with the possibility of causing Kounis Syndrome

Painkillers	Dipyrone
Anesthetics	Etomidate
Antibiotics	Ampicillin, ampi/sulbactam, amoxicillin, amicacin, cefazoline, cefoxitin, cefuroxim, penicillin, vancomycin, ciprofloxacin
Anticholinergics	Trimetafan
NSAIDs	Diclofenac, naproxen, ibuprofen
Antineoplastic	Cisplatin, cyclophosphamide, interferon
Contrasts	Indigotindisulfonate, lohexol, loxaglato
Corticosteroids	Betamethasone, hydrocortisone
Skin Disinfectants	Chlorhexidine, povidone iodine
Muscle relaxants	Cisatracurium, rocuronium
Proton pump-inhibitors	Lansoprazole, omeprazole
Thrombolytics and anticoagulants	Heparin, streptokinase, urokinase, lepirudine, hirudine, bivalirudine
Others	Alopurinol, enalapril, smolol, insulin, protamine, iodine, part of nicotine, mesalamine, bupropion, tetanus toxoid

Source: Ceped, Herrejon, Aguirregabiria [4]

vasoconstrictor. The vasospasm provided by histamine justifies the symptomatology of this syndrome. In addition, histamine lowers diastolic blood pressure, increases intimal thickening and platelet activation. Furthermore, studies suggest the possibility that mastocytes present near thrombi may destabilize and cause thrombus maturation due to the anticoagulant effect of fibrinogen degradation. [7]

There are three types of presentation already described: type I, the more frequent one, is found in patients without predisposition to coronary artery disease whose arteries are normal as the patient reported in the case: young and without risk factors. In type II, patients have quiescent atheroma, which, added to the sudden allergic condition, leads to angina and acute myocardial infarction. Type III, on the other hand, is related to drug-eluting stent thrombosis, late to stent placement by hypersensitivity reaction to nickel alloys, drugs and polymers present in the device. [7]

The clinical condition is characterized by chest pain - the most common manifestation - palpitations and shortness of breath, followed several times by hives, wheezing and skin reactions. Such allergic signs, however, are not mandatory and dyspnea was observed in the reported patient, accompanied by nausea and vomiting. Common evolution is an acute pulmonary edema, which may explain hemoptysis presented by the patient, and severe anaphylactic reaction, which lead to hypotension and shock. Differential diagnosis is made with other acute coronary syndromes, such as stable angina, unstable angina, acute myocardial infarction, Takotsubo, stress-induced cardiomyopathy, hypersensitivity myocarditis, and coronary vasculopathy. [6-8]

The diagnosis is clinical but laboratory, echo, and electrocardiographic tests can complement it. As histamine has a short half-life, its low rates do not exclude diagnosis, as well as low IgE. Cardiac troponins I or T and myocardial injury biomarkers (CK and CK-MB) are important in the diagnosis of myocardial injury with the patient elevated Troponin T by 4.6 times the normal combined with an increase in CK and CK-MB. The electrocardiogram may present characteristic changes of ischemia and the ST segment elevation is the most common. However, the electrocardiogram will only be altered in the presence of vasospasm associated with pain. Therefore, it is possible that such a finding would not appear on the exam, as occurred in the case presented. [5,9]

The therapeutic approach should prioritize the resolution of anaphylaxis using corticosteroids, antihistamines, and calcium channel blockers. Despite being an acute coronary syndrome, medications such as aspirin, nitroglycerin, beta-blockers, and epinephrine should not be used due to the risks of clinical deterioration being greater than the benefits. The prognosis of Kounis syndrome is good although it can lead to serious complications.[8,10]

Conclusion

After analyzing the case report, we identified that the patient presented Kounis Syndrome, a rare condition that is difficult to diagnose and justifies the need to report and discuss the topic. Such a syndrome is probably underdiagnosed in the medical practice and its suspicion should be raised in patients with a history of allergy, in patients with acute drug allergy on suspicion of acute ischemic syndrome, or the ones who have allergies to implanted devices. If suspected, medications such as nitroglycerin, beta-blockers and epinephrine should be avoided.

Author Contributions

Acquisition of data: Hunkar KGO. Analysis and interpretation of the data: Freitas AIH. Writing of the manuscript: Pereira M. Critical revision of the manuscript for intellectual content: Vieitas GL.

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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 Estadual Geral de Goiânia Dr. Alberto Rassi* - HGGI under the protocol number 15449119.7.0000.0035. 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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CASE REPORT

Renal Sympathetic Denervation Using a Novel Device: A Clinical Case Discussion and Literature Update

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Introduction

Resistant hypertension (RH) is directly related to increased mortality, severe renal changes, and cardiac and cerebrovascular diseases, due to lack of adequate drug treatment.[1] Cardiovascular disease mortality increases progressively and linearly as BP increases, whereas BP lowering is associated with significantly reduced risks.[2-5] Increased sympathetic tone in renal arteries is one of the major components of RH, and catheters have been developed using several technologies which allow for radiofrequency ablation (RA) and blood pressure (BP) reduction. The discussions and controversies about the effectiveness of this treatment are quite broad, especially when associated with the use of new devices. In this clinical case study, with an 18-month follow-up, we describe the development of knowledge regarding this technique and its evidence basis.

Clinical Case

Male patient, 48 years old, with uncontrolled RH, under treatment with seven antihypertensive drugs at maximum tolerated daily doses (Atenolol 100 mg, Furosemide 80 mg, Hydrochlorothiazide 25 mg, Spironolactone 25 mg, Hydralazine Hydrochloride 200 mg, Methyldopa 1000 mg and Telmisartan 160 mg). Office blood pressure remained above 185/105 mmHg and mean arterial pressures measured by Ambulatory Blood Pressure Monitoring (ABPM) were 186/120 mmHg over the total period, 193/127 mmHg while awake, and 174/107 mmHg during sleep. All major causes of secondary hypertension (primary hyperaldosteronism, pheochromocytoma, aortic coarctation, Cushing syndrome, hyperthyroidism, renal parenchymal disease, renal artery stenosis, obstructive sleep apnea syndrome) were excluded by biochemical, graphic and imaging exams. In late November 2017, the patient was admitted due to failure to obtain adequate BP control. In that occasion, complementary exams, such as electrocardiogram, echocardiogram and renal function, did not reveal abnormal findings.

Renal Sympathetic Denervation (RSD) was indicated due to the ineffectiveness of medical treatment and the change of habits to which he was submitted. The procedure was performed on November 17, 2018.

The Symplicity Spyral® catheter (Medtronic, Galway, Ireland) (Figure 1) was used, which allows for multiple simultaneous radiofrequency (RF) ablations in the renal artery.

We opted for conscious sedation with benzodiazepine and venous opioid, to avoid intense visceral pain, caused by RF ablation, and possible patient mobilization. The angiographic image showed anatomy favorable for RSD, with adequate-caliber major arteries and bilateral branches, and absence of accessory branches (Figure 2).

Access to the renal arteries was facilitated by an angioplasty guidewire, which allowed for the placement of the Symplicity Spyral catheter, whose helical pattern conforms to the lumen, taking the shape of these branches, and delivering RF energy simultaneously to

Keywords

Hypertension; Antihypertensive Agents, Renal Artery; Aortic Coarctation; Cushing Syndrome; Comorbidity; Sympathectomy; Vascular Access Devices/trends.

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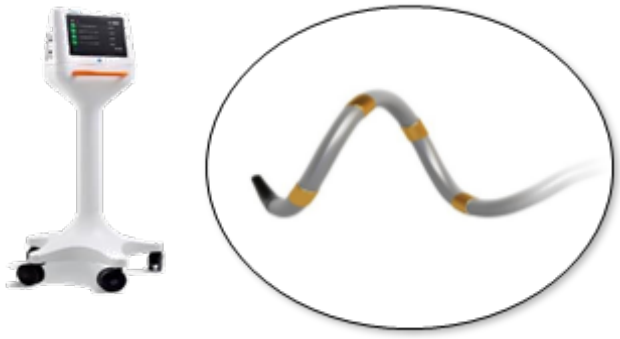

Figure 1 – The Symplicity G3 generator (Medtronic)

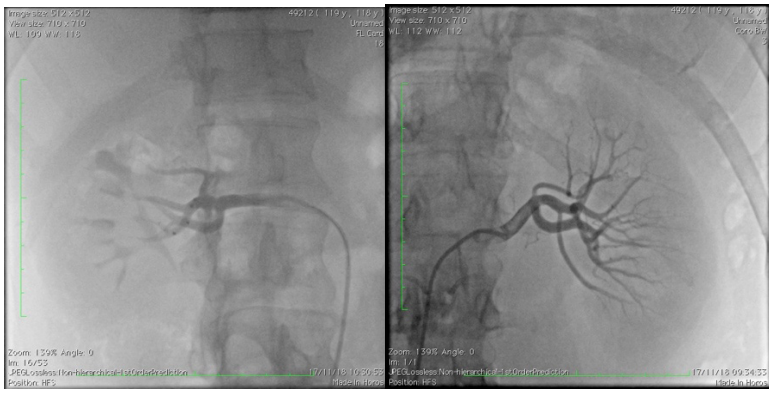

Figure 2 – Selective arteriography of renal arteries.

all 4 quadrants for 60 seconds. After that, ablations were performed in the main renal arteries of both kidneys (Figure 3). We performed 27 RF ablations in all segments of the renal arteries, with effective treatment of 59 sites, with 11 ablations being applied to the left renal artery, with 25 sites effectively treated, and 16 ablations to the right renal artery, with 34 sites effectively treated. Control arteriography did not reveal angiographic complications. There were no hemorrhagic complications at the puncture site. The contrast volume of the procedure was 200 ml and the procedure time was 88 minutes.

During hospitalization, the patient remained asymptomatic and was discharged after 24 hours, with no complications and BP at stable normal levels. For 18 months, he evolved well, with a decrease in office and ABPM BP. The mean ABPM values over the total period were 125/79 mmHg in the 2-month follow-up, 149/97 mmHg in the 8-month follow-up, and 147/196 mmHg in the 18-month follow-up (Figure 4). The laboratory tests, the antihypertensive therapy and the labor activity profile, without physical activities, remained unchanged.

Discussion

Systemic Arterial Hypertension (SAH) is the most prevalent disease worldwide, affecting between 30 to 40% of the population in developing countries, with serious consequences in the long term.[1,2] Even a small reduction in BP levels results in significant gains regarding cerebrovascular complications.[3] Uncontrolled RH is defined as BP ≥ 140/90 mmHg in individuals under treatment with at least three antihypertensive medications at maximum tolerated daily doses, when secondary causes are excluded.[4] It is estimated that 2-16% of people with hypertension are resistant. According to data from the Ministry of Health, the prevalence of hypertension in

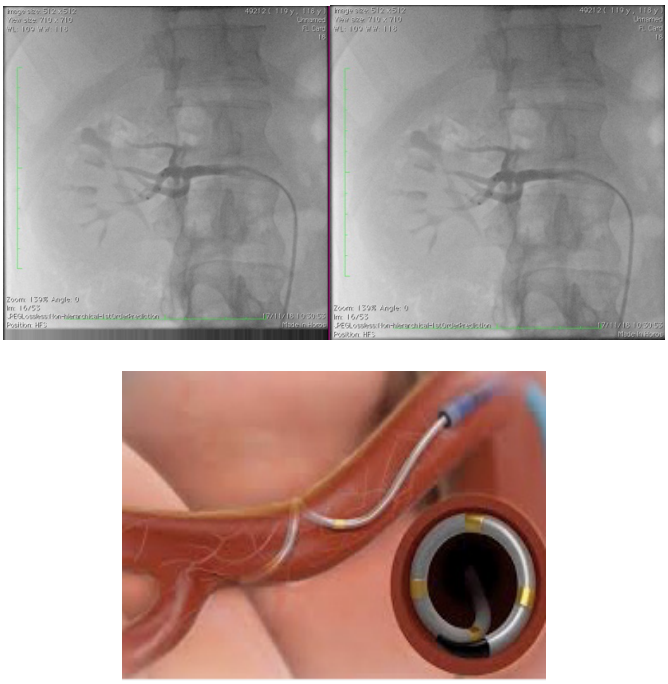

Figure 3 – Symplicity Spyral (Medtronic) Catheter with a helical configuration in the renal artery.

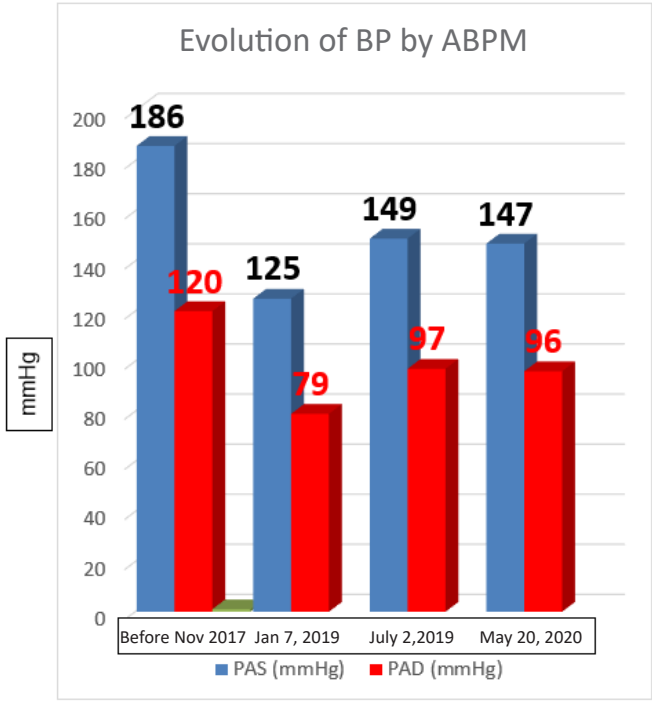

Figure 4 – Evolution of BP by ABPM 1 year before RSD, and within 2, 8 e 18 months after the procedure.
BP (Blood Pressure); ABMP (Ambulatory Blood Pressure Monitoring); RSD (Renal Sympathetic Denervation); SBP (Systolic Blood Pressure); DPB (Diastolic Blood Pressure)

the Brazilian population is 24.7%. With an estimated adult population of 86 million inhabitants, Brazil has at least 400,000 patients with RH.[5]

In general, resistance is multifactorial, and it is the main cause of medication non-adherence.[6] Factors associated with health habits, such as sedentary lifestyles, increased sodium and alcohol intake, as well as the use of medication like non-steroidal anti-inflammatory drugs, also contribute to treatment resistance. Even after correction of all these factors, BP levels remain elevated in a subgroup of patients. The sympathetic nervous system has a major role in this condition, and increased sympathetic tone is one of the main components of RH. The efferent innervation of the central nervous system arises from the second sympathetic ganglion and reaches the kidney through a network of fibers that spread across the renal artery adventitia. These fibers stimulate the the Renin-Angiotensin-Aldosterone System (RAAS), eventually resulting in sodium and water retention. The final product of this system, angiotensin II, is a potent vasoconstrictor that decreases renal blood flow and contributes to increased systemic blood pressure. Afferent innervation carries feedback from the kidney to the hypothalamus, completing and perpetuating the cycle.[7,8] In the 1950's, surgical sympathectomy, with the removal of abdominal and lumbar nerve plexuses, presented significant results in decreasing blood pressure, but with high morbidity and mortality rates.[9] Recently, the extension of renal artery sympathetic innervation has been demonstrated, with a predominance of sympathetic nerve fibers closer to the lumen in the distal part of the arteries.[10]

Initial Studies

Studies on the safety of the ablation of sympathetic innervation using intra-arterial devices with several types of action mechanisms, i.e., RF RSD, began in 2009, and it was the most widely used technology. The Symplicity HTN 1[11] trial was the first human study to confirm the safety of the method, followed by the randomized Symplicity HTN 2 trial.[12] Both studies showed a significant and sustained reduction in SBP (about 25 mmHg) and few complications, which led to expectations about the long-term benefits of the method for reducing cardiovascular complications.[1,2] The Symplicity HTN-3 trial, conducted in the United States, randomly assigned 535 patients with RH (ratio 2:1), comparing RSD with the control procedure group (CPG). The latter consisted of patients submitted to renal arteriography only, with no therapeutic intervention, in order to eliminate the placebo effect. The result of the primary endpoint (a decrease of 5 mmHg in systolic BP within six months) was negative, although there was a significant reduction in systolic BP in both groups.[13] Basically, four factors account for the lack of success of the SYMPLICITY HTN-3 trial, and the main one refers to the inadequate technique used, in which only 6% of the patients received a four-quadrant ablation in both arteries. The study was perfomed using the Symplicity Flex® catheter (Medtronic, Galway, Ireland), with a monopolar distal electrode. The device was difficult to manipulate, and required the use of more radiation and contrast to perform RF ablations in several points. For this reason, most investigators performed only one or two procedures. Other factors associated with failure were: medication changes (up to 40%) in the post-procedure period in both groups, the inclusion of patients with isolated systolic SAH, and the African American group, in which the drop in BP was more evident in the sham group compared to the RSD group.[14] Simultaneously, the Global SYMPLICITY Registry (GSR), a multicenter registry which assessed 1,199 patients during 3 years, showed an important reduction in SBP (ABPM – 8.0 mmHg and Office -16.5 mmHg), without impairing renal function.[15] The French randomized study DENERHTN, which compared RSD with optimized antihypertensive therapy, presented expressive results, with a reduction in SBP of −5.9 mm Hg (−11.3 to −0.5; p=0.0329).[16] These studies did not compare RSD with the CPG, which limits the validation of their findings. The identification and correction of the fators that resulted in the failure of SYMPLICITY HTN-3, combined with the sucess of RSD in other studies, and the development of a novel quadripolar Symplicity Spyral catheter (Medtronic, Galway, Ireland), which allows for simultaneous circumferential ablation with access the branches fostered this evolution of Symplicity Spiral. This easier-to-use device allows for more ablation, because it reaches the four quadrants of the artery, simultaneously and safely. RF energy delivery is also predictable, with a shorter ablation time compared to the previous device. At first, a limitating factor would be less penetration of RF (an average of 4 mm). However, since the nerves are located closer to the lumen in the arteries, most of them are accessed by

the device. Another limitation of this device is related with the anatomy of the arteries. The distal segment of the catheter, where the electrodes are located, adapts to lumen diameters ranging from 3 to 8 mm. Accessory arteries and branches with smaller lumen diameter cannot be acessed and, therefore, represent a possible cause of treatment failure, since they are also innervated.

Post Symplicity HTN-3 Studies

Based on these observations, other studies were conducted. The Spyral-HTN OFF-MED trial, performed with this new device, was conceived as proof of concept to assess the biological viability of RSD. A total of 80 patients with mild-to-moderate SAH (BP <180 mmHg), in the absence of antihypertensive medication evaluated by laboratory testing, were randomly assigned (1:1) to either RSD or CPG. The results within 3 months showed a positive effect of RSD, with a decrease in ABMP SBP and diastolic blood pressure (DBP) of -5.0 (p=0.0414) and – 4.4 (p=0.0024) mmHg, and a reduction in office BP of -7.7 (p=0.0155) and – 4.9 (p=0.0077) mmHg, respectively, corresponding to the difference of what was obtained in the CPG.[17] Later, the Spyral ON-MED trial, using the same device, included patients with the same epidemiological characteristics, but who were taking up to three antihypertensive agents. The result within six months was positive for RSD versus CPG, with a sustained drop in 24-hour ABPM SBP and DBP of –7.0 mmHg (p=0.0059) and – 4.3mmHg (p=0.0174), and a reduction in office SBP and DBP of – 6.6 mm Hg (p=0.0250) and – 4.2 mm Hg (p=0.0190).[18]

Simultaneously with these studies, the RADIANCE-HTN SOLO Trial of Ultrasound Renal Denervation (Paradise® system) (ReCor Medical, Palo Alto, CA, USA) was performed. A total of 176 patients with mild-to-moderate SAH off antihypertensive medication were randomly assigned (1:1) to RSD versus CPG. Daytime ABPM SBP ranged from – 8.5 mm Hg to – 2.2 mm Hg within 2 months (the adjusted difference between the groups was – 6.3 mm Hg p=0.0001).[19] After this phase, optimized antihypertensive treatment was initiated in patients with BP greater than 135/80 mmHg. After six months, the initial result was maintained, with reduced BP values and less antihypertensive medication in the RSD group. During six months, 65.2% of patients in the RSD group were treated with the optimized antihypertensive therapy versus 84.5% in the CPG (p=0.008) and mean antihypertensive drug use was lower in the RSD group compared to the CG (0.9 ± 0.9 x 1.3 ± 0.9 (p=0.010)). Even with a smaller amount of medication, RSD was associated with larger reductions in ABMP SBP when compared with the CG group (-18.1 ± 12.2 x -15.6 ± 13.2 mmHg, respectively). The adjusted difference in BP and the number of drugs was -4.3 mmHg, CI-95%, -7.9 to -0.6 (p=0.024).[20]

The RADIOSOUND-HTN trial compared both technologies by randomly assigning 120 patients in a 1:1:1 manner to 3 groups: 1) RSD of the main renal artery only, using the Symplicity Spyral catheter; 2) RSD of the main renal artery and accessory branches using the Symplicity Spyral catheter, and 3) RSD of the the main renal artery using the Paradise catheter. The group that received the ultrasound catheter-based therapy showed greater BP reduction compared with the two groups that received RF catheter therapy (−13.2 x 6.5 mmHg within 3 months, P = 0.042). No difference was observed regarding BP reductions between the groups treated with RF. Multicenter studies with more participants, follow-up and time are needed to establish a more definitive comparison between these technologies.[21]

In a meta-analysis comparing the results of six first- and second generation randomized trials for RSD versus GPC, with 977 participants, Sardar et al.,[22] observed ignificant SBP and DBP reductions, in both ABPM and Office BP, in RSD versus GPC, as well as low complication rates. The results were more expressive in the second-generation trials, in which the confounding factors previously described had been excluded.[14,22]

The proof-of-concept trials validated RSD from the biological point of view, and were not designed to obtain statistical power for positivity responses as their primary efficacy endpoint.

The SPYRAL HTN-OFF MED Pivotal multicentre, randomized trial assigned 331 moderate hypertensive patients off antihypertensive medication to either RSD (n=166) and CPG (n=165). With a Bayesian design, this trial used evidence from the SPYRAL HTN-OFF MED pilot trial. The primary efficacy endpoint was baseline-adjusted change in 24-h systolic blood pressure and the secondary efficacy endpoint was baseline-adjusted change in office systolic blood pressure from baseline within 3 months. The primary and secondary efficacy endpoints were met, with posterior probability of

superiority more than 99% for both. The treatment difference between the two groups for 24-h systolic blood pressure was -3·9 mm Hg (Bayesian 95% credible interval -6.2 to -1.6) and for office systolic blood pressure the difference was -6.5 mm Hg (-9.6 to -3.5). The study showed the superiority of RSD compared with a sham procedure, which ultimately corresponds to the clinical treatment group.[23]

In a meta-analysis of 5,769 subjects submitted to RSD, Townsend et al.,[24] describe renal artery dissection requiring stenting in 24 patients (0.41%). Most events (79%) occurred in the in-hospital phase or within the first year of follow-up. Thus, the need for post-treatment intervention is not common and the procedure is considered very safe.[24]

The Brazilian Position Statement on Resistant Hypertension – 2020 describes that: "based on this evidence, RSD is currently an alternative only for patients with UC-RHTN with optimized pharmacological treatment and proven therapeutic adherence or with important drug-related adverse effects, to be always performed at referral centers trained for the procedure".[25]

We managed to demonstrate that, using the same techniques prescribed in the studies, similar positive results were obtained. This young patient with RH, treated with RSD, presented excellent results within eighteen months. After a significant initial drop in BP (- 61 / - 41 mmHg) within 2 months, there was BP stabilization at higher levels, but still with a very significant reduction (- 39 / - 24 mmHg) in relation to baseline after 18 months, and clear benefits regarding cardiovascular complications.[3] The significant reduction in BP may be related with the placebo effect or with the increased baseline BP prior to procedure.[26]

The changes in patient seletion and technique, and the results of recent randomized trials bring new perspectives into the treatment of RH, whose pressure control is inadequate, despite all the available drug armamentarium. The most robust randomized trials have already shown the biological validity and clinical utility of RSD. Real-world registries indicate that the ideal patients for receiving this technique are those at high cardiovascular risk, mainly young, and with very high SBP and DBP levels.[15]

In addition, it is important to highlight some encouraging studies that have applied RSD in patients with heart failure with reduced ejection fraction[27], Chagas Disease[28], atrial[29] and ventricular malignant arrhythmias[30], sleep apnea[31] and changes in glucose metabolism[32], i.e., pathologies that include increased sympathetic tonus in their genesis.[33]

Conclusion

We present the case of a young, uncontrolled hypertension resistant patient submitted to sympathetic renal denervation using the Symplicity Spyral RF system with sustained results in 24-hour ABPM BP within 18 months. We approached RH and the several available interventionist treatment techniques. We opted for the use of the the aforementioned device especially due to the excellent results presented in clinical trials, in addition to the low complication rates registered in all the studies presented.

Author contributions

Conception and design of the research: Ferreira E, Fuks V, Esporcatte R. Acquisition of data: Ferreira E. Writing of the manuscript: Ferreira E, Fuks V, Staico R, Brandão AA. Critical revision of the manuscript for intellectual content: Ferreira E, Esporcatte R, Brandão AA, Albuquerque DC.

Potential Conflict of Interest

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

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Study Association

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

Ethics approval and consent to participate

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

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CASE REPORT

Oral Antibiotic Therapy for Infective Endocarditis Due to Enterococcus Spp. After Hemorrhagic Stroke and Heart Surgery

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Introduction

Infectious endocarditis (IE) is a severe infectious disease with an annual incidence of 3 - 7 cases per 100 000 people, and is considered the 3rd most life-threatening infection after pneumonia and intra-abdominal abscess.[1] Intra-hospital mortality ranges from 15 to 30%[2] and patients affected today are older and have more comorbidities than in the past. [3]

In IE the treatment is traditionally performed in hospitalized patients, due to the need for intravenous antibiotics. Patients with IE on the left side of the heart are typically treated for 2 - 6 weeks, according to the American and European Guidelines. [1-2] *Enterococcus* spp. is the third cause of IE, representing 10% of cases in non-users of intravenous drugs, and is considered to be a bacterium that is difficult to eradicate, requiring 6 weeks and the combination of antibiotics.[2]

The possibility of home or outpatient treatment is attractive from both a social and an economic point of view,[4] but it still finds resistance in clinical practice. We will present a case of infective endocarditis by *Enterococcus* spp. complicated with hemorrhagic stroke and need for cardiac surgery that used oral antibiotics after initial intravenous course.

Case Report

A 75-year-old white male, smoker, hypertensive, previous myocardial infarction with coronary stent in 2013, using 100mg of ASA, sought care for night sweats for 1 month, fever, loss of 8 kg, left flank pain and dyspnea on moderate efforts. He had tachycardia and tachypnea, cardiac auscultation with ++ / 4 diastolic murmur and + / 4 systolic murmur in the aortic area, and crackles on the right lung base. Cultures were collected and piperacillin-tazobactam associated with Furosemide was started. Examinations showed hemoglobin 11.3, Leukocyte count 5500, cells with a predominance of neutrophils and without deviation, Platelets 125 000, C-Reactive Protein 70 mg / dL (VR < 1mg / dL), Creatinine 1.25 mg / dL, HIV negative, and normal pancreatic enzymes and transaminases. Electrocardiogram showed sinus tachycardia, 1st degree atrioventricular block (AVB), and lower inactive zone. Contrast tomography of the abdomen reported abdominal lymph nodes of 1.2 cm and normal spleen. A transthoracic echocardiogram was performed with an ejection fraction of 55%, slight aortic regurgitation and left ventricle with hypokinesia of the basal segment of the inferolateral wall. There were 2 positive blood cultures for *Enterococcus* spp. sensitive to ampicillin and gentamicin**.** Transesophageal echocardiogram with aortic vegetation up to 7mm, confirming definite infectious endocarditis from 2 Major Criteria of Duke's Modified Criteria. Antibiotic replaced by ampicillin and ceftriaxone due to the renal dysfunction presented by the patient and his age. Negative control blood cultures after 48 hours, and improved inflammatory signs and dyspnea. Seven days after the start of the antibiotic, the patient presented motor incoordination in the L hand, performed magnetic resonance imaging (MRI) with the presence of a 27 mm lobar hematoma (Figure 1A) in the right post-central gyrus, without deviation from the midline. One week later he had paresthesia in the right upper limb and focal convulsion,

Keywords

Antibiotic Prophylaxis; Endocarditis, Bacterial; Enterococcus; Stroke, Cardiac, Surgery.

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MRI with subarachnoid hemorrhage (Figure 1B) between grooves of the frontal lobe on the left, opting for conservative treatment and carbamazepine. Hypothesis of hemorrhagic events secondary to septic emboli, transesophageal echocardiogram with vegetation of the same size and mild regurgitation was raised, as well as negative blood cultures. A few days later he developed acute kidney failure and acute lung edema, a new echocardiogram with severe aortic regurgitation, with increased dose of furosemide and vasodilators, besides an evaluation by a cardiac surgeon. He underwent emergency surgery with a Biological Aortic Valve. The excised valve was not sent for histopathology. In the surgical report there was a description of perivalvar abscess. After surgery, he had control of heart failure and recovery of renal function to baseline. The patient evolved with symptomatic 2:1 AVB and had definitive PM implantation. While a CBC showed lymphocytosis, a bone marrow biopsy confirmed chronic lymphocytic leukemia (CLL). Due to presenting RAI stage 0 for CLL, it was defined a conservative treatment by Hematology, without the need for specific therapy. Due to the worsening of valve dysfunction with adequate antibiotics, the day of surgery was considered the day 0 of treatment. After 16 days of intravenous ampicillin and ceftriaxone, there was migration to isolated ampicillin orally. Discharge occurred on the 18th day after surgery and the remainder of the treatment was completed at home, totaling 42 days after surgery. A review visit was performed at 2 weeks, and 2, 6, and 12 months after the end of the antibiotics, without clinical manifestations of congestion or infection, without murmurs, and with negative blood cultures. Repeated echocardiogram at 12 months showed biological aortic valve in normal operation and without vegetations. The patient underwent cerebral angiotomography at admission, as well as 2 months after discharge. The images were not compatible with mycotic aneurysm. He was accompanied by Neurosurgery and Neurology, requiring no neurosurgical intervention.

Discussion

Compared to patients with other types of IE, patients with IE due to Enterococcus tend to be older, have a higher prevalence of cancer, vegetation in the aortic valve, relapse, and a previous history of urinary and abdominal infection. Older patients with various comorbidities, including kidney failure as a limiter for the use of aminoglycosides, and the need for combined therapy to eradicate enterococcal infection makes the antibiotic treatment of IE by Enterococcus a challenge.[5] The atypical presentation is common in older adults or immunocompromised individuals. Our patient presented these two characteristics, being diagnosed with chronic lymphocytic leukemia on admission. In a Danish cohort of patients with IE, 11.8% of cases were

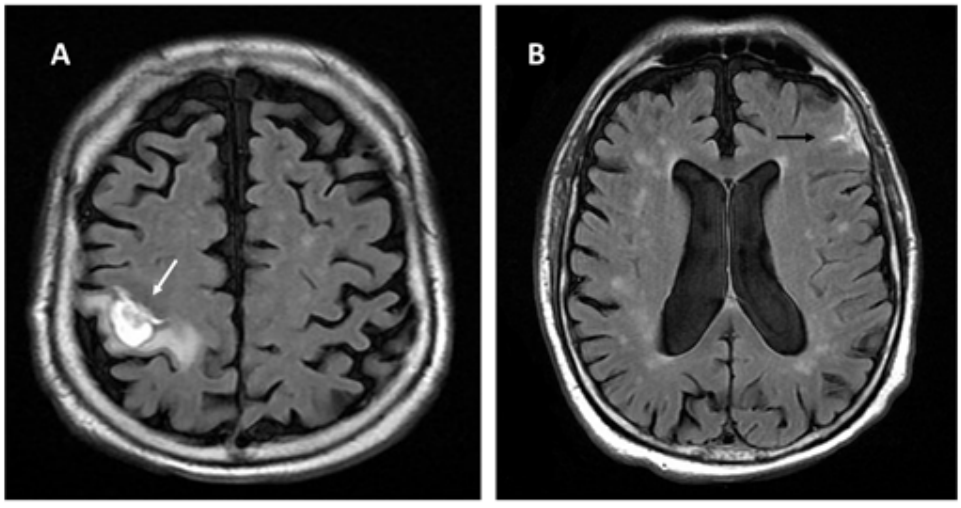

Figure 1 –Magnetic resonance imaging of the brain in the T2Flair sequence. Lobar hematoma (white arrow) in the right post-central gyrus (A) and subarachnoid hemorrhage (black arrow) to the left (B).

diagnosed with cancer in a 3.5-year follow-up, and the risk of a hematological neoplasm was 24 times higher in the first 3 months after the infectious diagnosis.[6]

Systemic embolization due to vegetations complicates from 22% to 50% of cases. Of these events, 65% involve the central nervous system (CNS), with ischemic stroke (CVA) being the most diagnosed.[2] In general, mitral vegetations are associated with a higher risk of embolization (25%) compared to those in the aortic valve (10%). [7] The size (> 10mm) and mobility of vegetations are independent predictors of an embolic event.[3] In a study including patients with IE in the mitral and or aortic valves, [8] the incidence CNS embolism after antibiotic initiation was of 12.9%, and 65% of these events occurred in the first 2 weeks of treatment. Our patient had hemorrhagic events, probably related to embolization, with 14 and 31 days of treatment.

After an IE-related hemorrhagic stroke, there is a tendency to postpone valve surgery, if indicated, for at least one month. [2] Garcia Cabrera et al.,[9] in a study of patients with IE in the left valves and hemorrhagic stroke, observed a mortality rate of 75% when the surgery was performed in less than 4 weeks after the hemorrhagic event compared to 40% after 4 weeks. The patient evolved with refractory heart failure, considered the main indication for surgery today,[1] and the decision was made to proceed with valve replacement surgery on the 6th day after the last hemorrhagic event, given the impossibility of postponing. Regarding the use of oral antibiotics, in a cohort of 426 cases with IE, 214 patients after initial intravenous treatment migrated to use of oral antibiotics, occurring on average 21 days after diagnosis of IE, and average of 28 days for *Enterococcus*, with amoxicillin being the medication chosen in 91% of these patients. The rate of relapse and reinfection in the oral treatment group was similar to that observed in intravenous treatment.[10]

In a multicenter randomized clinical trial of stable patients with aortic and/or mitral valve IE who used at least 7-10 days of intravenous antibiotics, participants were randomized for maintenance of intravenous treatment or migration to oral antibiotics. Approximately 38% performed heart surgery before randomization. The primary composite outcome of 6 months (all-cause mortality, unplanned heart surgery, embolic phenomena, or relapse) occurred in 12.1% in intravenous treatment and 9% in oral treatment (p=0.4), with the conclusion that migration to oral antibiotics was no less than the exclusive IV antibiotic. Enterococcus spp. corresponded to 25.4% of the cases that received oral treatment.[11]

Exclusive intravenous treatment imposes problems such as impaired venous network, risk of catheter-related infection and prolonged hospital stay.[10] In this reported case where the patient had a controlled infection, with negative control blood cultures, and where there was removal of site of infection by valve replacement surgery, it was possible to migrate to an oral antibiotic after an initial intravenous course, although Enterococcus is a difficult bacterium to eradicate. However, infectious endocarditis is a serious infection, and caution in antimicrobial treatment should be employed. Oral treatment has not yet been recommended by the American or European guidelines for endocarditis. [1,2]

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 *Sociedade Porvir Científico* under the protocol number 21406519.7.0000.5307. 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.

Author contributions

Conception and design of the research: Pereira GAR. Acquisition of data: Pereira GAR; Kist GR; Machado TS; Barcellos CS. Analysis and interpretation of the data: Pereira GAR; Kist GR; Machado TS; Barcellos CS. Writing of the manuscript: Pereira GAR. Critical revision of the manuscript for intellectual content: Pereira GAR; Kist GR; Machado TS; Barcellos CS.

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CASE REPORT

Acute Coronary Disease in very Young Patient: A Reality!

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Introduction

Acute cardiovascular events such as acute myocardial infarction (AMI) are uncommon in young individuals.[1] Additionally, it is known that different factors may be involved in the occurrence of AMI.[1] Here, we report a case of acute myocardial infarction due to severe coronary lesion in a very young patient.

The Case

P.A.G.T., 22-year-old male, was brought to the hospital with a Δt of 60 minutes experiencing typical chest pain that started during a soccer match and did not radiate. On admission, the patient had high blood pressure (160x80mmHg) and was diaphoretic. Electrocardiogram (ECG) was done within eight minutes of his arrival and showed elevation of segment ST in leads DII, DIII, AVF and V3 to V5. (Figure 1). Due to clinical findings and ECG tracing, thrombolytic therapy with alteplase was started. He also received double antiplatelet therapy, statin, angiotensin converting enzyme inhibitor and enoxaparin. The patient showed pain relief and serial electrocardiograms showed a reduction of the ST segment elevation greater than 50%, which is criterion for reperfusion. At the end of thrombolysis, the patient experienced sinus bradycardia and blood pressure of 114x61mmHg. Laboratory exams at admission revealed negative qualitative troponin I (<0,5 ng/mL), creatine kinase (CK) of 448/L and CKMB of 28 U/L. Fourteen hours after admission, laboratory results showed positive qualitative troponin, total CK of 1171 U/L and CKMB of 121 U/L. After 24 hours of the initial event, the patient was transferred to a catheterization lab for invasive test . The coronary angiography revealed descending anterior coronary artery with severe segmental lesion (90%) with an intracoronary thrombus in its proximal third (Figure 2). Angioplasty was performed, with successful implantation of two conventional stents and final TIMI flow III.

When asked about his family history of cardiovascular diseases, the patient denied family history of premature cardiovascular disease, or use of cocaine, tobacco, or other drugs. Alcohol consumption was of 18 doses per week. The screening for diabetes revealed fasting glucose of 81mg/dL and HbA1c of 5%. The patient also denied any condition that required long term treatment such as immunodeficiency or inflammatory disorders. After five days, the patient was discharged with stable vital signs and no symptoms. Subsequent exams showed total cholesterol 101mg/dL, low-density lipoprotein 44mg/dL (LDL), high-density lipoprotein (HDL) 37mg/dL, very low-density lipoprotein (VLDL) 20mg/dL, non-high-density lipoprotein 64mg/dL and triglycerides 121mg/dL. Normal coagulation tests. Biomarkers for coagulopathies were requested. Echocardiogram did not show segmental alterations after hospital discharge.

Discussion

The risk factors associated with ST-segment elevation myocardial infarction (STEMI) in young adults can be different as compared with elderly population.[1,2] A study conducted in Switzerland with 27 patients younger than 30 years old with previous STEMI revealed that history of smoking, dyslipidemia and

Keywords

Young; Artery Coronary Diseases; Hyperlipidemias; Atherosclerosis; Myocardial Infarction; Hereditity; Street Drugs; Statins; Enoxaparin; Platelets/treatment.

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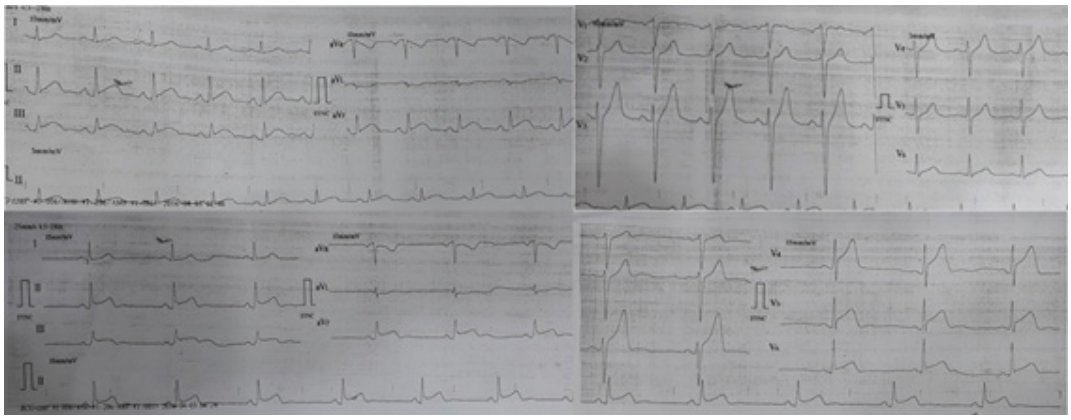

Figure 1 – Electrocardiogram showing inferior and anteroseptal wall ST segment elevation

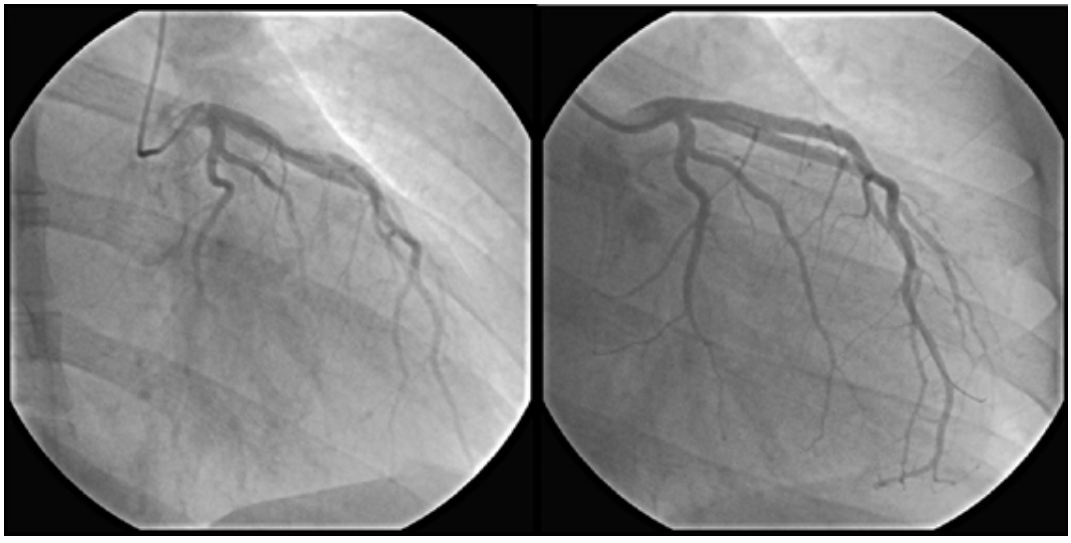

Figure 2 – Coronary angiography images showing severe lesion of anterior descending artery before angioplasty (on the left) and after angioplasty (on the right)

family history of premature cardiovascular diseases (< 55 years old for men and < 65 years old for women) were the most common factors in this group.[1]

A cohort study called AFIJI (Appraisal of risk Factors in young Ischemic patients Justifying aggressive Intervention) investigated 880 patients under 45 years old (average age of 40 years) that experienced an acute coronary syndrome associated with obstructive causes.[3] Most of the patients were male (87%). Different from the findings in this report, the prevalent risk factors identified in the AFIJI study were smoking, family history of coronary artery disease (CAD) and hyperlipidemia.[3]

As for the etiology, there are many causes of acute STEMI.[1] When young patients are analyzed, a great proportion is free from significant atherosclerotic lesions which indicates that different mechanisms can lead to coronary obstruction.[2] Nonatherosclerotic coronary disease, hypercoagulable states and chemical substance abuse could also trigger an ischemic event.[2] Also, the diagnosis of coronary dissection is more common in

young women than men,[4] and the artery most affected by dissection is the anterior descending artery.[5]

Findings in the literature correlated with this case reveal that the most common type of AMI is a single vessel disease, affecting mainly the left coronary artery in its anterior descending branch.[6] The AFIJI cohort also demonstrated that a new ischemic event was caused more frequently by a new coronary lesion.[3]

Invasive and non-invasive imaging tests can be used to identify atherosclerosis.[7] According to the 2019 ACC/AHA guidelines, coronary artery calcium (CAC) assessment is useful to estimate the risk.[7] Also, coronary computed tomography has a potential role to guide prevention recommendations in younger adults.[8] Advances in coronary computed tomography angiography has enabled the description of remodeling and necrotic aspects of plaques along with the association with the risk of coronary events.[9]

Regarding the prognosis of very young patients with STEMI, in-hospital mortality and survival rate are better compared with older patients.[1,2] Recent findings have shown no difference in all-cause in-hospital mortality between young men and women.[10] Although early mortality rate is low, additional ischemic events may occur in the future.[3] In the 20-year cohort study,[3] AMI was the most frequent new major acute cardiovascular event (MACE) (2.6 per 100 patient-years). All-cause death and stroke were less frequent in this group (1.60 per 100 patient-years, 0.70 per 100 patient-years, respectively).[3]

Although some risk factors for STEMI cannot be avoided, such as the family history, other risk factors can be modified.[2] Discontinuance of cigarette smoking, for example, is the lifestyle change most likely to reduce the risk of a new ischemic event.[3] In addition, hypertension and diabetes are well-known risk factors for CAD and should be treated in the young patient with previous STEMI to prevent recurrence.[3] The AFIJI study also stated that LDL levels in these young patients was particularly higher when compared to the population that is most affected with STEMI.[3] These results differ from the ones shown in this case report.

Conclusion

AMI in young adults remains a challenge in the emergency department. In this clinical case, although major risk factors for AMI were not evident, it is possible that other underlying mechanisms may have participated in this episode. More research is needed to evaluate chronic inflammatory profile in patients with premature coronary disease.

Potential Conflict of Interest

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

Sources of Funding

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Study Association

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Ethics Approval and Consent to Participate

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

Author Contributions

Conception and design of the research: Nascimento, EA. Acquisition of data: Mello, ALFP; Cunha, LS e Villela, MF. Analysis and interpretation of the data: Writing of the manuscript: Nascimento, EA; Mello, ALFP e Cunha, LS. Critical revision of the manuscript for intellectual content: Nascimento, EA.

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CASE REPORT

Cardiac Arrest Due to Hypocalcemia

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Fifty-nine-year-old male patient had a sudden cardiac arrest (CA) while waiting for his appointment at the urology outpatient clinic. The local staff and the rapid response team (RRT) promptly started cardiopulmonary resuscitation maneuvers. Initial CA rhythm was ventricular fibrillation (VF) and the collapse-shock interval was five minutes. Return of spontaneous circulation (ROSC) occurred on the following cycle, comprising six minutes of arrest. There was not enough time to administer epinephrine or any other drugs. After ROSC, a definitive airway was placed as the patient remained in a coma. The post-arrest electrocardiogram (ECG) (Figure 1B) did not show signs of acute ischemia, but revealed a prolonged QT interval (corrected QT (cQT), using the Bazett's formula: 558 ms) and, for that reason, amiodarone was not administered.

After initial management, it was possible to check patient's history and exams. He had previous diagnosis of Graves' disease, systemic arterial hypertension and polycystic kidney disease, which led to chronic renal insufficiency and hemodialysis. The patient then developed tertiary hyperparathyroidism and, in 2008, was submitted to surgical removal of the parathyroid glands, followed by unsuccessful autotransplantation in the let upper limb, leading to hypoparathyroidism post-parathyroidectomy. For this condition, the patient was given calcitriol and calcium carbonate, both orally and parenterally during hemodialysis sessions. Calcium serum levels were periodically monitored. In May 2019, he underwent kidney transplantation but had urinary tract infection that caused acute dysfunction of the graft. The patient was discharged from the hospital 35 days after the procedure, with serum creatinine level of 7.3 mg/dL (reference value [RV]: 0.7 to 1.2 mg/dL). The ECG during hospitalization had already revealed a prolonged QT interval (cQT 485 ms) (Figure 1A). Three days after hospital discharge, the patient was seen at the medical clinic and had blood samples tested: creatinine level 9.74 mg/dL; total serum calcium 4.0 mg/dL (RV: 8.4 to 10.2 mg/dL); normal serum potassium level (3.7 mEq/L; RV: 3.5 to 5.0 mEq/L). The patient was immediately referred to the Emergency Department for parenteral calcium supplementation and monitoring of kidney function, but left the hospital before medical evaluation. Two weeks after this episode, he returned to the hospital for a previously scheduled appointment in the urology department for follow-up of kidney transplant, reporting progressive weakness, stiffness and cramps, and experienced CA shortly after.

Immediate post-arrest laboratory tests showed serum level of ionized calcium of 1.8 (RV: 4.6 to 5.3 mg/dL) and potassium of 3.4 mEq/L. Initial high-sensitive troponin T was 0.187 ng/mL (RV< 0.014 ng/mL), with a peak of 0.242 ng/mL (in a patient with previous chronic kidney disease). However, transthoracic echocardiogram, showing no wall motion abnormalities, and ECG were not suggestive of myocardial ischemia. Besides, the patient had been submitted to a myocardial perfusion scintigraphy in the year before and there were no signs of stress-induced ischemia. So, given the pre-CA symptoms, the prolonged QT interval and the

Keywords

Heart Arrest; Cardiopulmonary Resuscitation; Hypocalcemia; Hypertension; Renal Insufficiency; Tachycardia Ventricular; Renal Dialysis; Kidney Transplantation.

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Table 1 – Serum levels of different electrolytes and its correlation with QT interval in electrocardiograms

Event	ECG (Fig. 1)	cQT (ms) (RV:340- 450 ms)	Ionized calcium (RV: 4.6- 5.3 mg/dL)	Total calcium (RV:8.4 - 10.2 mg/dL)	Potassium (RV:3.5- 5.0 mEq/L)	Creatinine (RV: 0.7- 1.2 mg/dL)
Hospitalization for kidney transplant	Fig. 1A	485	2.42	-	3.8	10.51
Post-arrest	Fig. 1B	588	1.8	5.2	3.4	7.14
Discharge for cardiac arrest	Fig. 1C	436	5.84	10.4	5.1	7.16

ECG: electrocardiogram; cQT: corrected QT interval using Bazett's formula.

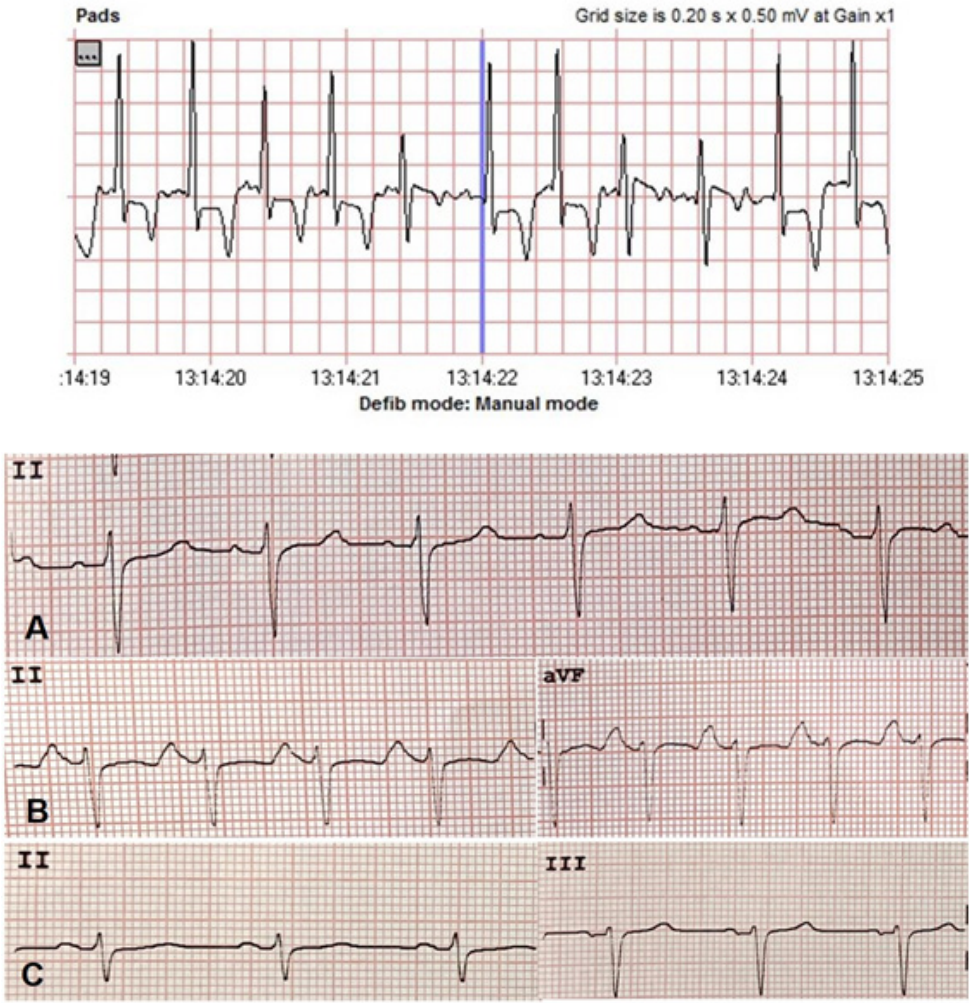

Figure 1 – Segments of electrocardiograms (ECG) showing the progression of the QT interval.
A – ECG during hospitalization for kidney transplant revealing a long QT interval (corrected QT (cQT) using Bazett's formula, of 485 ms); B – post-arrest ECG, with cQT of 588 ms; C – ECG after hospital discharge for cardiac arrest, with normal QT interval after calcium supplementation (cQT of 436 ms)

reduced serum ionized calcium level, hypocalcemia was considered the cause of CA, and intravenous calcium gluconate was administered. After restoration of consciousness, the patient informed that he had discontinued the supplementation of oral calcium by his own - parenteral supplementation had been suspended after the transplant, since no more hemodialysis sessions would be performed. During hospitalization, the patient showed favorable neurological recovery, but due to complicated urinary tract infection with unsatisfactory response to antibiotic therapy, the transplanted kidney had to be removed. The ECG at that time exhibited normal QT interval (cQT 436ms) (Figure 1C), with normal calcium serum levels after supplementation (ionized calcium of 5.84 mg/dL and total calcium of 9.5mg/dL).

Discussion

Long QT syndrome (LQTS) can be congenital or acquired. The causes of acquired LQTS include hypocalcemia, due to prolongation of the phase 2 of the action potential (AP),[1] medications (amiodarone, antidepressants and neuroleptics), hypokalemia, hypomagnesemia and severe bradycardia.[2-4] LQTS is associated with a specific polymorphic ventricular tachycardia (VT), named as *torsades de pointes* (TdP), because of the characteristic shift in the QRS axis that gives the impression of a "torsion".

The QT interval is a marker of the AP duration. In LQTS patients, the AP is prolonged unevenly across the myocardium, so as to cause high dispersion of repolarization. The AP prolongation favors the formation of early afterdepolarization (EAD), which are deformities in the plateau and rapid repolarization phases (2 and 3) capable of inducing ventricular extrasystoles. EADs in the unevenly repolarized myocardium are the cause of TdP. Tachycardia is sustained due to focal electric activity and/or a reentrant mechanism. It may either cease spontaneously or degenerate into ventricular fibrillation and cardiac arrest [3,5].

In this report, the CA initial rhythm described – not documented by ECG – was VF. It is possible, however, that the patient experienced a TdP that degenerated to VF, due hypocalcemia-induced LQTS. Amiodarone, which is the first choice of treatment for refractory VF and VT, prolongs QT interval and should be avoided in TdP; lidocaine, on the other hand, has an unclear role in TdP, but could be an alternative in VF/VT due to its effect in reducing the duration of the AP.[6] The American Heart Association suggests the use of magnesium for treating TdP, but is against its routine use.[6,7] Calcium gluconate or calcium chloride is indicated for the treatment of hyperkalemia with electrocardiographic manifestations[8] and for hypocalcemia, with initial bolus followed by continuous infusion, until adequate serum levels are achieved.[9] In this case, the administration of calcium gluconate probably contributed positively to the favorable outcome.

Cardiac arrest due to hypocalcemia is a rare event that lacks specific recommendations in current literature and guidelines. Hypocalcemia is not part of the differential diagnosis for the causes of CA, known as the "5Hs and 5Ts" – "5Hs" refers to hypothermia, hypo/hyperkalemia, hydrogen ion excess (acidosis), hypovolemia and hypoxia; and "5Ts" refers to cardiac tamponade, coronary thrombosis, tension pneumothorax, pulmonary thromboembolism and toxins.[7] The aim of this report was to suggest that cardiac arrests may have other causes than the ones described in current guidelines, and that it is important to evaluate each patient individually to determine the best possible adjunct treatment. The definite treatment for any CA, however, is the same: early defibrillation when indicated and high-quality chest compressions.

Conclusion

Although hypocalcemia is not among the most common causes of CA, it should be considered for patients with a suggestive history. Guidelines are important to establish standards for the management of patients following CA, but sometimes it is crucial to go beyond standards and individualize strategies for each patient.

Potential Conflict of Interest

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

Sources of Funding

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Study Association

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Ethics Approval and Consent to Participate

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

Author Contributions

Conception and design of the research: Salvadori FA. Acquisition of data: Salvadori FA, Moreira EM, Dias MB. Analysis and interpretation of the data: Salvadori FA, Moreira EM, Dias MB. Visualization: Duarte-Neto AN. Writing of the manuscript: Salvadori FA, Moreira EM. Critical revision of the manuscript for intellectual content: Duarte-Neto AN, Paiva EF.

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CASE REPORT

High-Grade Pleomorphic Sarcoma of the Left Atrium after Incomplete Resection and Adjuvant Chemotherapy

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Introduction

Primary cardiac tumors are extremely rare, found in only 0.02% of all autopsies.[1] These tumors are malignant in only 25% of the cases, 75% of which are sarcomas, frequently affecting young people with no risk factors.[2] The median overall survival is less than 1 year,[3] ranging from 9 to 16 months,[4,5] with rapid proliferation and deaths caused by arrhythmias, thrombosis, pulmonary embolism,[6] and, most importantly, heart failure.[7] Due to its rarity, reports in the literature about the best treatment are scarce, especially in malignant tumors.[1] The aim of the present work is to report a case of an undifferentiated pleomorphic sarcoma (UPS) in the left atrium in which surgical treatment was associated with chemotherapy, with an overall and progression-free survival of neoplastic disease higher than the median described in previous manuscripts.

Case Report

A 32-year-old woman was admitted to the institution in May 2019, complaining of dyspnea upon exertion, which had lasted for 6 months and had progressively worsened, associated with sinus tachycardia, coughing, and vomiting. The patient underwent a Doppler echocardiogram, which showed a mass in the left atrium, with irregular contours, attached to the interatrial septum and involvement of the mitral valve, with an ejection fraction (Simpson) of 62%; a double mitral lesion, with significant stenosis and moderate insufficiency; as well as tricuspid valve insufficiency and moderate pulmonary hypertension. It is important to note that the mass was not an artifact, since it was viewed in more than one slice.

Symptoms were attributed mainly to pulmonary congestion, caused by the predominance of stenosis, as compared to mitral regurgitation. Right (RA) and left (LA) atria presented a slight volumetric increase, the right ventricle (RV) with a moderate increase in diameter and the left ventricle (LV) with a normal diameter. Slightly impaired biventricular function decreased to a slight degree only in the RV. The mitral valve apparatus contained a thickened anterior leaflet with reduced mobility and cupola due to the presence of tumor mass infiltration in the leaflet body, measuring approximately 18 x 21 mm in diameter, coupled with a reduced valve opening, once again justifying the diagnosis of stenosis. The Doppler images showed a moderate, eccentric reflux to the LA lateral wall and a valve area of 0.7 m^2. Tricuspid valve apparatus with slightly thickened leaflets was also observed, pulled by ventricular remodeling and presenting reduced mobility. Aortic and pulmonary valves showed no major changes, and the presence of diffuse pericardial effusion showed no major hemodynamic repercussions. The patient did not undergo a transesophageal echocardiogram, nor was the pericardial fluid evaluated .

The patient underwent surgery, conducting an incomplete resection of the mass in the interatrial septum and reconstruction with bovine pericardium, leaving a residual infiltrative lesion in the mitral valve, which was considered inoperable. Thus, this surgery was considered to be palliative to relieve the symptoms and to aid in the final diagnosis. Upon macroscopy, the surgical specimen revealed fragments of solid, infiltrative,

Keywords

Cardiovascular Diseases; Neoplasms; Sarcoma/complications; Sarcoma/surgery; Heart Atria/surgery; Atrial Function; Drug Therapy

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yellowish-brown, and elastic tissue neoformation, with areas of non-encapsulated hemorrhaging. Histological sections showed fragments of poorly differentiated mesenchymal tissue neoformation, with high cellularity, comprised of spindle and epithelioid cells, with nuclear pleomorphism and moderate anaplasia, dispersed in a fibrillar or myxoid stroma, with up to 12 mitoses / 10 high-magnification fields (occasional atypical mitoses) and a tumor necrosis area (less than 50% of the neoplasia volume). Upon immunohistochemistry, histopathological analysis allowed us to conclude that it was a high-grade undifferentiated pleomorphic sarcoma. Staging exams showed disease restricted to the heart, and chest computed tomography (CT) showed a mass with soft tissue density and a lobulated contour located in the left atrium, measuring 6.0 x 5.3 cm (Figure 1).

After incomplete tumor resection (R2 surgery), the multidisciplinary team decided to start cytoreductive chemotherapy in an attempt to target the maximum response rate with subsequent reassessment for the second surgical procedure, if feasible, regarding the residual infiltrative lesions in pulmonary vessels. In this sense, the patient received three cycles of chemotherapy with ifosfamide and doxorubicin, followed by three cycles of ifosfamide alone. Doxorubicin was suspended at the end of the third cycle due to a drop in the left ventricular ejection fraction (LVEF) to 48%. The patient is currently asymptomatic, using Carvedilol, Furosemide, and Enalapril, having been prophylactically anticoagulated only during the immediate postoperative period, as advised by the assistant cardiology team. She has a regular heartbeat with two sounds and a systolic murmur in the mitral focus 3 + / 6 +. Moreover, she is normotensive (blood pressure: 110/70 mmHg), eupneic (respiratory rate: 18 breaths per minute), with a heart rate of 62 beats per minute.

The revaluation tomography (Figure 2) showed a partial reduction in mass, but the echocardiogram quantified the lesions as stable after six cycles of chemotherapy, configuring a stable cancer disease, rendering the infiltration in the mitral ring inoperable. Therefore, it was decided to maintain chemotherapy with ifosfamide to control the underlying disease. A second line of treatment has not been proposed so far due to an episode of febrile neutropenia with sepsis. Heart transplantation, in turn, was not indicated due to active neoplastic disease.

Despite the failure to convert the residual disease into operable, the patient has been evolving in good general condition, is asymptomatic, and is maintaining a good quality of life, with 7 months of current survival. For the follow-up, although the magnetic resonance imaging exam (MRI) had been recommended, the fact that the service in question did not perform the referred exam led to the consideration of only the transthoracic echocardiogram to monitor the case. A new surgical approach is still under discussion, especially if a reduction in tumor size from second-line drugs is considered.

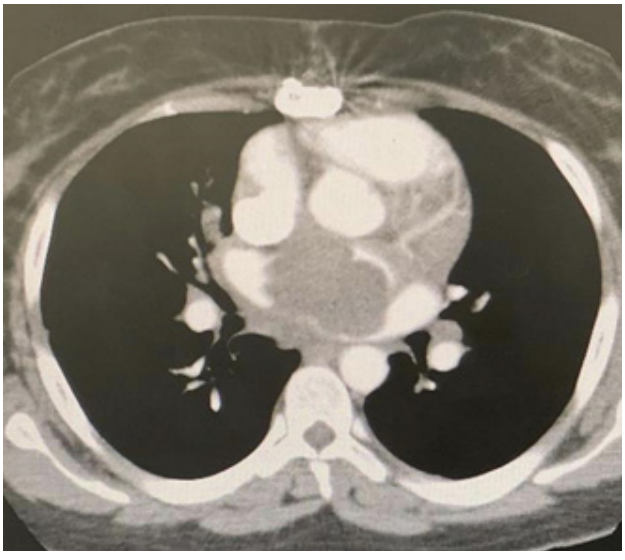

Figure 1 – Computed Tomography Exam showing heart region before chemotherapy

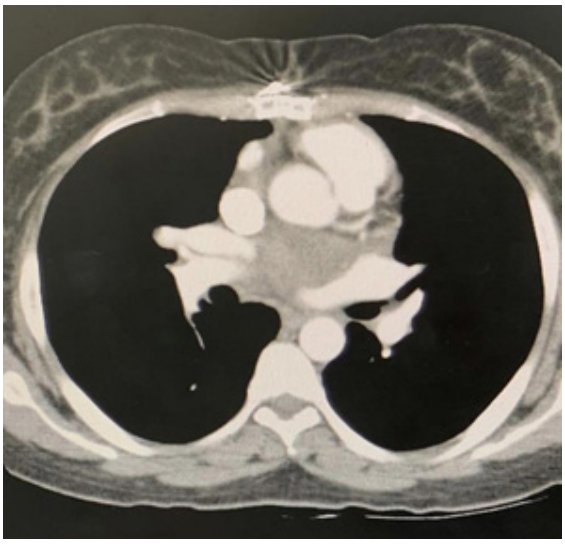

Figure 2 – Computed Tomography Exam after third cycle of chemotherapy

Discussion

Tumors of the heart and pericardial sac can be divided into primary and secondary tumors. The main histological types of primary heart tumors are myxomas, fibromyxomas, and sarcomas, which are differentiated into benign or malignant, as shown in Table 1. The main secondary tumor, in turn, comes from metastases of melanomas.[8]

The most common type of benign primary heart tumor is myxoma. This prevails among women of 40 and 50 years of age, and is usually located in the left atrium, close to the mitral valve leaflets.[8]

In its morphology, the myxoma is mostly pedicled. It is able to suffer prolapse through the mitral valve and prevent the filling of the ventricle during the diastole phase.[9] In microscopic histopathological analysis, myxomas may present stellate, fusiform or elongated, polygonal cells, wrapped in a myxoid stroma.[10] In addition, it has characteristics of mesenchymal cells with intermediate filaments and narrow intracellular junctions, there are no desmosomes, and some cells may have characteristics of myofibroblasts.[10] Macroscopically, these can reach up to 15 cm and be of different colors and consistencies, in addition to being able to present a myxoid or gelatinous structure.[9]

The most frequent primary malignant tumor of the heart is the sarcoma type[11] of the heart muscle, with a higher frequency between the third and fifth decade of life and with a predominant location in the right atrium.[12] The angiosarcoma type is the most common, with a higher incidence in men, originating from mesenchymal tissue, with a broad multilobulated base, measuring between 2 and 10 cm, dark brown or blackish in color, close to the inferior vena cava, and with early metastases to the pleura, mediastinum, and lungs.[12] The patient usually shows a clinical picture of heart failure and pericardial effusion.[12]

Histologically, angiosarcoma can present different aspects, depending on its degree of differentiation. They may contain atypical pleomorphic endothelial cells, which form papillary structures and vascular channels in well-differentiated areas, and in areas with little differentiation have fusiform anaplastic cells.[13] An angiosarcoma can, therefore, have both well-differentiated and undifferentiated regions.[13]

The UPS, or malignant fibrous histiocytoma,[14] in turn, makes up to one third of all cardiac sarcomas,[15] and its etiology and pathogenesis are uncertain.[16] The age of onset varies from 14 to 80 years of age,[17] 47 years of age on average.[18] The incidence is higher (67%) in women.[17] Symptoms are variable and dependent on the location and size of the tumor, but dyspnea was reported in 70% of all cases; palpitations in 45%;[17] chest pain in 20%;[11,19] and cough, bilateral edema of the lower limbs, and hemoptysis in 8%,[19] with nausea and vomiting also reported.[20] Pericardial effusion is a complication present mainly in metastatic tumors to

Table 1 – Differences between benign and malignant primary tumors of the heart

	Benign tumors	Malignant tumors
	Myxoma	Rhabdomyosarcoma
	Rhabdomyoma	Mesenchymoma
Types	Fibroma	Angiosarcoma
	Lipoma	Spindle cell tumor
	Angioma	Lymphosarcoma
	Papillary tumors of the heart	Malignant hemangioma of the heart
Most common type	Myxoma	Angiosarcoma
Population with higher incidence	Women between 40 and 50 years of age	Men between 30 and 50 years of age
Most common location	Left atrium	Right atrium
Microscopicallly	Starred cells, fusiform or elongated, polygonal cell, wrapped in a myxoid stroma; absence of desmosome	Atypical pleomorphic endothelial cells in well-differentiated areas and fusiform anaplastic cells in poorly differentiated areas
Macroscopically	Reach up to 15 cm, varying colors and consistency; present a myxoid or gelatinous structure	Measure between 2 and 10 cm, colored black or dark brown, wide and multilobulated base
Most affected structures	Mitral valve leaflets	Inferior vena cava, metastases to the pleura, mediastinum, and lungs
Clinical findings	Heart failure, dyspnea, palpitations	Heart failure, pericardial effusion
Both can manifest with disorders in the electrical conduction of the heart, atrial fibrillation and flutter, ventricular extrasystoles, right bundle branch block, and, primarily, arrhythmias.		

Source: *Authors themselves, 2020.*

the heart, which occur mainly in the pericardium, due to lymphatic dissemination, and in the right cavities, caused by hematogenous dissemination. Thus, patients with metastasis to the pericardium may present massive pericardial effusions and cardiac tamponade.[8]

Physiologically, patients who have benign or malignant primary tumors or secondary tumors due to metastasis from another tumor, may manifest disturbances in the electrical conduction of the heart, atrial fibrillation and flutter, ventricular extrasystoles, right branch block, and, primarily, arrhythmias.[12] In addition, they may show signs and symptoms of heart failure, requiring tests to make a differential diagnosis with other pathologies.[12]

The best exam for an initial assessment in clinical investigation is transthoracic echocardiography.[21] MRI and CT demonstrate the extent of the tumor in the myocardium and the presence of metastases.[22] The diagnosis of sarcoma is only made after histological analysis, but there are characteristics of radiological tests to differentiate it from the myxoma, such as the non-septal connection of the mass, multiple masses, extensive connection to the left atrial wall, extension

to the pulmonary vein, and semi-solid consistency.[23] Moreover, gastrointestinal symptoms appear more in UPS than in myxomas.[14]

In general, the prognosis of tumors in the right atrium is worse, with significantly reduced survival.[17,24] However, this occurs in only 7% to 10% of the UPS,[11,17] which have a preference for the left atrium[20] in 65.5% of cases, usually in the posterior wall,[18] with an invasion of the mitral valve in up to 10%.[17] When a malignant tumor is found in the left atrium, the UPS and leiomyosarcoma are more likely, making up 44% and 22% of the cases, respectively.[11]

Surgery, the best treatment for local sarcomas,[11] can relieve symptoms,[25] but it is not usually curative, unlike that which happens with benign neoplasias.[3] The prognosis is better when the tumor is completely removed, with an average survival of 4 years more than that of incomplete resection[26] Although complete resection with negative microscopic margins does not prevent recurrence in 2/3 of the patients, it does increase survival by 30 months, when compared to those with positive margins.[26] However, the rate of complete resection is only 13%,[19] partly attributed to the difficulty in diagnosis.[27] When complete resection is not practicable, more than 90% of the patients die within a year, regardless of post-surgical therapy[15]

The recommendation for adjuvant treatment is not well established in the literature, and there is no consensus on the ideal time for onset or duration.[27] There are reports of good evolution without it, even with positive margins on microscopy after resection.[27] However, there are studies that demonstrate the advantage of multimodal treatment,[28,29] although the use is limited in those cases with incomplete resection.[28]

In one cohort, patients who received chemotherapy alone, or in combination with surgery, presented better survival rates than did those who did not receive it. However, those who received chemotherapy showed better physical performance.[11] Local disease control, associated with imp17,roved cardiac function, most likely leads to greater tolerance for aggressive therapies.[11]

Several studies show better disease-free survival with doxorubicin without impacting overall survival.[30] The usual administration is six cycles of ifosfamide and doxorubicin,[17,20,31] and a better survival rate with taxanes has recently been reported.[19] Sarcomas are resistant to radiotherapy.[32] However, it can be used to prevent or delay local recurrence.[26,14] Proton beam irradiation has been successfully used.[28] Furthermore, neoadjuvant chemotherapy can increase the chance of a complete resection of the tumor, which would translate into better patient survival.[33]

Heart transplantation has been reported with variable results. However, this practice is hampered by the scarcity of donors, the possibility of tumor recurrence by post-transplant immunomodulation, and the exclusion of many patients for other chronic and psychosocial diseases.[27]A promising alternative pointed out in the literature would be the genetic identification of the tumor for individualized therapeutic options, including tyrosine kinase inhibitors, monoclonal antibodies, and CKD-4 inhibitors.[33]

Conclusion

Cardiac UPS is rare and aggressive, and presents a poor prognosis, with an average survival of less than one year. It presents variable symptoms that depend on the location and can cause multiple complications. The most effective treatment for localized tumors is surgical resection, and adjuvant therapies are not well established in the literature. However, there is a consensus on the administration of six cycles of ifosfamide and doxorubicin, a protocol followed by our patient, who remained stable, with a short follow-up of only seven months.

Author Contributions

Conception and design of the research: Razera R, Bernardes V, Moisés F, Araújo A, Araújo R. Acquisition of data: Razera R, Bernardes V, Moisés F, Araújo A. Analysis and interpretation of the data: Razera R, Bernardes V, Moisés F, Araújo A, Mundim L. Writing of the manuscript: Razera R, Bernardes V, Moisés F, Araújo. Critical revision of the manuscript for intellectual content: Razera R, Bernardes V, Moisés F, Araújo A, Mundim L, Araújo R.

Potential Conflict of Interest

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

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Study Association

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

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of the *Universidade Federal de Uberlândia* under the protocol number 4.041.793. 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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