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EDITORIAL

Is Patient Education about the Benefits of Physical Activity a Good Adjunct Treatment Strategy in Hypertension?

Dário C. Sobral Filho,[1,2] Maria de Fátima Monteiro[2]

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Editorial referring to the article: Does Hypertension Knowledge Influence Levels of Physical Activity in Hypertensive Patients From a Southern Brazilian Community?

Systemic arterial hypertension (SAH) is a chronic condition that is highly prevalent worldwide. It occurs without symptoms in most individuals and represents the main modifiable risk factor for cardiovascular disease. The adoption of behaviors that do not involve medication, such as changes in lifestyle and regular practice of physical exercise, along with strict adherence to prescribed medication, is a major challenge in the treatment of this disorder.[1,2]

The guidelines of the American Heart Association and the American College of Cardiology[3] on hypertension recommend the implementation of lifestyle changes as the first line of treatment for low- to moderate-risk groups, thereby emphasizing the importance of such measures.

As SAH has multiple causes, it is very difficult to establish the role of each element involved in the development of this condition. Santos and colleagues,[4] in their article published in the current issue, discuss the interrelationship between regular exercise and patient knowledge of the disease and provide important information, especially given the scarcity of studies on this subject.

Burini et al.,[5] evaluated the effect of physical exercise alone (without medication or special diet) in overweight men with hypertension. The authors found benefits in terms of a reduction of blood pressure to normal levels, regardless of normalization of body mass index. However, they also found an inverse effect, of an increase in blood pressure levels and subsequent return to baseline values within four months after cessation of supervised physical activity. These authors also showed better cost-effectiveness of physical exercise over the use of anti-hypertensive drugs.

The effect of an educational program on knowledge and practice of home blood pressure monitoring was evaluated in a study conducted by Fu et al.[6] with individuals with uncontrolled hypertension. Participants were randomly allocated either to a group education or individual counselling to perform home blood pressure monitoring. The practice and knowledge of ambulatory monitoring were evaluated using a questionnaire, applied at the beginning of the program and at six months after conclusion of the intervention. The authors found that individuals who engaged in educational activities as part of a group were eight times more capable of absorbing and retaining information on ambulatory monitoring of blood pressure than the group who received individual counseling. They also found that older, retired individuals and those with adequate knowledge of health issues were more likely to adhere to weekly blood pressure monitoring during the six-month follow-up period. Although these findings strongly suggest that group educational activities are more effective than individual ones, it remains doubtful whether the group strategy could be successfully applied to physical activity and other risk factors.

In a randomized, double-blind, placebo-controlled trial by Fuchs et al.,[7] carried out in Brazil, prehypertensive individuals (systolic blood pressure between 120 and

Keywords

Cardiovascular Diseases; Hypertension; Life Style; Exercise, Blood Pressure; Physical Activity; Antihipertensive Drugs; Risk Factors; Overweight.

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139 mmHg and diastolic pressure between 80 and 89 mmHg) would be allocated to receive either a combination of anti-hypertensive drugs or placebo if they did not reach optimal blood pressure after three months of lifestyle intervention. The authors found that half of these individuals achieved normal levels of blood pressure with lifestyle changes and were excluded from the subsequent phase involving medication.

It is possible that the practice of physical exercise alone, without intervention regarding other risk factors, may produce a beneficial effect regarding hypertension control. Silva et al.,[8] studied obese individuals with hypertension undergoing a twelve-week supervised physical exercise program and found a reduction in blood pressure to normal mean levels. However, no significant changes in anthropometric parameters (body weight, body mass index, or waist-to-hip ratio) were observed, which may be explained by the fact that physical exercise was the only non-pharmacological intervention applied. It is possible that a reduction in calorie intake may also help to reduce these indices.

Ribeiro et al.[9] compared the effectiveness of a physical exercise program, a health education program and a control group on physical activity levels in users of the Brazilian National Unified Health System (SUS). The study covered twelve months of intervention and six months of subsequent follow-up. It was found that both intervention groups increased the time of weekly leisure physical activity and annual scores of physical exercise, recreation and active transport. The physical exercise group obtained a higher mean of the annual score of physical exercise compared to the other groups ($p < 0.001$). In the post-intervention period, however, the physical exercise group experienced a decrease in their annual physical exercise score (mean -0.3; CI 95% -0.5-0.1), while the health education group experienced an increase (mean 0.2; CI 95% 0.1–0.4). These results suggest that education centered on lifestyle changes and healthy habits may produce a longer-lasting effect in terms of the ongoing practice of physical exercise than simply participating in a physical exercise program. It is clear, however, that the adoption of both strategies should produce the best results.

Although it is difficult to pinpoint the precise extent to which each factor (lower body weight, nutritional counseling, or increased physical exercise) contributes to successful non-pharmacological treatment of arterial hypertension, their effectiveness is unquestionable. However, whether this positive effect is sustainable in the long term, is still debatable. Also, some of these factors are influenced by geographic, socioeconomic and cultural factors, and huge differences can thus be found between different populations.[4,10]

The identification of hypertensive patients in the early stages of the disease may provide a good opportunity to strongly advocate the practice of physical activity, prescribed by a multidisciplinary team. The simple prescription of physical exercise, even when accompanied by audiovisual or printed educational material, has been shown to be insufficiently convincing and hence ineffective for most patients.[10]

The research conducted by Santos et al. [3] shows the importance of the patient's knowledge about arterial hypertension and the benefits of physical training. This may help to improve adherence to lifestyle modification measures.

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ORIGINAL ARTICLE

9p21 Locus Polymorphisms: Risk and Severity Factors of Coronary Artery Disease in Venezuelan Patients

Susana Blanco Sobrino,[1] Eva Salazar Alcalá,[2] Asdrúbal Alfonzo Reyes,[1] Jesus Flores-Soler,[1] Romina Leras Mirabal,[1] Yettana Luti,[1] Ingrid Márquez,[3] Mercedes Teresita Fernandez Mestre[2]

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Abstract

Background: The *9p21* region is the most relevant locus associated with coronary heart disease in different populations. However, there are no studies that prove that this region is a risk factor in the Venezuelan population.

Objectives: To analyze whether or not the *9p21* rs1333049 polymorphism is a risk factor for acute myocardial infarction (AMI) in Venezuelan patients, as well as to investigate its correlation with cardiovascular risk factors (CVRF), age of occurrence, type and severity of infarction, and the correlation of the rs10757274 polymorphism with severity of coronary artery disease.

Methods: This was an association study, including 487 unrelated Venezuelan individuals, grouped in 354 patients with AMI and 133 controls. The rs1333049 and rs10757274 polymorphisms were determined using the polymerase chain reaction (PCR) technique with sequence-specific primers. The analysis of association was determined using the SNPStats tool. The continuous variable description and the correlations were performed using the SPSS statistical software. Significance was established at $p<0.05$.

Results: A positive correlation was observed between the rs1333049 polymorphism and the presence of hypertension (*r*: 0.145, *p*: 0.006), and between hypertension and heart infarction (*r*: 0.318, *p*: <0.0001). A positive correlation was found between the rs10757274 polymorphism and the number of coronary vessels that presented obstructive lesions in patients aged ≤ 55 years (*r*: 0.276, *p*: 0.0078).

Conclusion: The rs1333049 polymorphism at the *9p21* locus is correlated with hypertension in Venezuelan patients, while the rs10757274 polymorphism is associated with the progression of coronary atherosclerosis, suggested by the correlation with the number of coronary vessels that presented significant obstructive lesions.

Keywords: Cardiovascular Diseases/complications; Polymorphism/ genetics; Coronary Artery Disease; Myocardial Infarction; Chromosomes (9p21)/ genetics; Epidemiology; Atherosclerosis.

Introduction

Cardiovascular diseases (CVDs) represent the leading cause of death worldwide. An estimated 17.9 million people died from CVDs in 2016, representing 31% of all deaths registered worldwide.[1] Ischemic heart disease was the first specific cause of mortality in Venezuela in 2015, causing 31,338 deaths, representing 18% of the total mortality burden and 59% of cardiovascular mortality.[2]

Epidemiological studies have shown that, in addition to conventional risk factors, environmental factors and lifestyle increase the susceptibility to developing coronary artery disease (CAD). Apart from these factors, studies carried out in twins and nuclear families show that genetic predisposition plays an important role in the pathogenesis of CAD. Although population studies have described multiple genetic variations contributing to the inheritance of CAD risk, the exact identity of candidate

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genes and their effect on disease pathogenesis are not well known.[3] However, epidemiological and family studies, among others, suggest that approximately 50% of the susceptibility to CAD is due to genetic markers.[4]

Genome-wide association studies (GWAS) have shown that the 9p21 locus is associated with CAD.[5-8] In conjunction, the Wellcome Trust Case Control Consortium (WTCCC)[9] and studies carried out in Germany,[8] Japan,[10,11] Korea,[11,12] China,[13] Italy,[14] among others, have considered the *9p21* locus as a risk factor for CAD. This locus has several polymorphisms, but only five of them, rs1333049, rs10757274, rs2383206, rs2383207, and rs10757278, play an important role in the development and prediction of CAD.[15] However, although the *9p21* locus is considered a risk factor for coronary heart disease in Caucasian and Asian populations, it is not a risk factor in African-American populations. Although studies of African Americans have been limited, the *9p21* locus appears to be a risk factor in all ethnic groups that migrated out of Africa. In these groups, it appears that the evolutionary time has not elapsed to break and intermix the haplotype that carries the risk polymorphisms. In contrast, in Africans, who have a longer evolutionary history, the *9p21* risk haplotype has been excised into small haplotypes that produce no or a minimal risk of developing coronary heart disease.[4]

Considering that the *9p21* region is the most relevant locus and has been associated with CAD in different populations, two haplotype-tagging single nucleotide polymorphisms (SNPs) were selected. The SNPs: rs1333049 present in whites and rs10757274 present in both races (whites and blacks), considering the importance of an ancestry-specific allele context.[16.17] The objective of the present study was to analyzed whether the rs1333049 polymorphism in the *9p21* locus represents a risk marker for acute myocardial infarction (AMI) in the Venezuelan mestizo population. Likewise, the possible correlation of an rs1333049 polymorphism with traditional risk factors, age of occurrence, type and severity of AMI, as well as the correlation of the rs10757274 polymorphism in the *9p21* locus, coupled with the severity of CAD, was investigated.

Methods

Design

This was an association (case-control) and correlational study.

Study Population

The study included 487 Venezuelan individuals, unrelated, classified into two groups.

1. Patients (n = 354). Individuals with a diagnosis of AMI, determined by clinical, paraclinical, and electrocardiographic findings, who attended the Coronary Care Unit of Hospital Central del Instituto Venezolano de los Seguros Sociales "Dr. Miguel Pérez Carreño", Coronary Care Unit and Special Studies Unit of the Cardiology Service of the Hospital General del Este "Dr. Domingo Luciani".
2. Controls (n=133). Apparently healthy individuals with or without cardiovascular risk factors (CVRF).

In both groups, those individuals with a history of hepatic, autoimmune, neoplastic diseases, or infarction secondary to other causes were excluded. All participating individuals signed a consent approved by the Bioethics Committee of the participating institutions (DIR-0130/09; official letter No. 00211)

Clinical classification of patients with Myocardial infarction (MI)

Based on the admission electrocardiogram (ECG) and the clinical characteristics of infarcted patients, Myocardial infarction (MI) was classified as:

1. Non-ST-segment elevation (NSTEMI)
2. ST-segment elevation (STEMI).

Types of coronary artery disease

According to the results of the coronary angiography, the patients were classified into two groups:

1. Obstructive CAD. Patients with significant epicardial coronary artery lesions and coronary stenosis ≥50%
2. Non-significant obstructive coronary artery disease (non-CAD). Patients without coronary artery stenosis in any artery related to the infarction. This includes both patients with normal coronary arteries (no stenosis> 30%) or mild coronary atheromatosis (stenosis> 30%, but <50%).

Chromosome *9p21* locus genotyping

To determine the genetic polymorphisms of the *9p21* locus, genomic DNA was extracted from venous white blood cells using the Bunce protocol.[18]

The rs1333049 polymorphism in the *9p21* locus was determined using the primers and the protocol described by Ahmed et al.,[19] For this, two reaction mixtures were prepared, one for the amplification of the ancestral or wild allele [G] and the other for the mutated allele [C]. For genotyping, the amplified products, a 280 bp fragment for the specific alleles (C and G, respectively) and 500 bp for the internal control, were electrophoretically separated on 2% agarose gels and stained with ethidium bromide (0.5µg / ml). The amplified products were viewed through a photo documentation equipment (Chemic Doc, BIORAD).

The rs10757274 polymorphism in the *9p21* locus was determined using the primers and the protocol described by Nawaz et al.,[20] For this, two reaction mixtures were prepared, one for the amplification of the ancestral or wild allele [A] and the other for the mutated allele [G]. For genotyping, the amplified products, a 250 bp fragment for the specific alleles (A and G, respectively), and 419 bp for the internal control, were electrophoretically separated on 2% agarose gels and stained with ethidium bromide (0.5µg/ml). The amplified products were viewed through a photo documentation equipment (Chemic Doc, BIORAD).

Presence and severity of CAD

To determine the presence of CAD, in the Coronary Care Unit of Hospital Central del Instituto Venezolano de los Seguros Sociales "Dr. Miguel Pérez Carreño", diagnostic coronary angiography was performed in 76 patients, using a femoral or radial approach. The technique is determined by the vascular accessibility of the patient and the preference of the operator. All angiographies were filmed at 15 frames / s and Cine, stored at the time of acquisition in DICOM format. For the evaluation of the severity of CAD, the definition established by the American College of Cardiology was used, where the severity of the injury, according to the visual obstruction of the lumen, was classified as Mild: <50%, Moderate: 50-69%, and Severe: ≥70%. Considering significant obstructive CAD when, obstruction was observed of one or more epicardial arteries with at least 70% stenosis. Significant lesions were classified into three types of lesions: A, B, and C. This definition was used for the left (anterior descending artery, circumflex artery) and right (right coronary artery) circuit, with the exception of the left main trunk, for which the disease is present when there is a compromise ≥50% of the vessel diameter.[21]

Statistical analysis

The sample size to achieve 80% statistical power was calculated according to the genetic models and the heterozygous odds ratios (OR) using a single SNP marker in a case-control study under the assumptions of 5% disease prevalence, 5% minor allele frequency (MAF), complete linkage disequilibrium (LD), 1:1 case-to-control ratio, and 5% type I error rate (α).[22] However, in the present study, more data was obtained from affected individuals than from healthy individuals. For this reason, the analysis of association with AMI was adjusted for the selected covariates (cardiovascular risk factors). The Hardy Weinberg equilibrium (HW) and the inheritance models were determined using the SNPStats tool.[23] With this tool, the analysis was also performed to determine the possible susceptibility conferred by the *9p21* polymorphism to develop into a myocardial infarction. To analyze for binary responses, the logistic regression analysis is summarized with genotype frequencies, proportions, OR, and 95% confidence intervals (CI). The statistical significance of genotype frequency differences between patients and controls was estimated by the X2 Mantel-Haenszel test. Probability (p) values<0.05 were considered significant. P-values were adjusted with Bonferroni correction. The continuous quantitative variables were described as mean ± standard deviation (SD), and data normality was tested using the Shapiro-Wilk test. To determine the difference between the means, an unpaired t-test was applied at a 95% CI. The correlations between the variability of the studied polymorphisms, traditional CVRF, occurrence, type and severity of AMI, and the severity of CAD were determined through Pearson's correlation coefficient, using the statistical package SPSS Statistics, version 20.[24]

Results

Demographic, anthropometric, and clinical characteristics of patients with AMI and apparently healthy individuals (controls) are shown in Table 1. When establishing comparisons of the CVRF between both groups, a significantly increased frequency of male individuals was observed (OR: 3; 95% CI: 2.032-4.63; p <0.00001), cases of hypertension (OR: 4.5; 95% CI: 2.908-7.076; p: <0.00001), smoking (OR: 4.9; 95% CI: 2.789-8.905; p: <0.00001), obesity (OR: 2.5; 95% CI: 1.616-3.927; p: <0.000011), and sedentary lifestyle (OR: 1.9; 95% CI: 1.236-3.059; p: 0.001) in the group of patients versus apparently healthy individuals. Likewise, the differences in mean

Table 1 – Demographic, anthropometric, and clinical characteristics of AMI patients and apparently healthy individuals (controls)

Characteristics	AMI Patients (n=354)	Characteristics	Controls (n=133)
Sex		**Sex**	
Female	29.7 (249)	Female	56.4 (75)
Male	70.3 (105)	Male	43.6 (58)
Age Range (years)	24-90	**Age Range (years)**	30-83
Age (years)	57.46 ± 13.22	**Age (years)**	51.79 ± 10.82
Weight (kg)	76.56 ± 15.26	**Weight (kg)**	76,11 ± 15,85
Size (m)	1,64 ± 008	**Size (m)**	1,63 ± 0,09
BMI (kg/m2)	28,38 ± 4,51	**BMI (kg/m2)**	28,69 ± 4,92
Waist circumference (cm)	98,41 ± 10,83	**Waist circumference (cm)**	94,40 ± 11,62
CVRF		**CVRF**	
HT (n=354)	66.4 (235)	HT (n=122)	30.3 (37)
DM (n=345)	23.5 (81)	DM (n=102)	19.6 (20)
Smoking (n=352)	40.9 (144)	Smoking (n=123)	12.2 (15)
Obesity (n=337)	51.3 (173)	Obesity (n=122)	29.5 (36)
Dyslipidemia (n=339)	37.4 (127)	Dyslipidemia (n=120)	27.5 (33)
Sedentary lifestyle (n=351)	42.4 (149)	Sedentary lifestyle (n=120)	27.5 (33)
Clinical presentation			
NSTEMI	42.8 (151)		
STEMI	57.2(202)		

Frequencies are expressed in percentages. The values shown in parentheses represent the number of individuals. Values of continuous variables are expressed as mean ± Standard deviation. AMI: Acute myocardial infarction, BMI: body mass index (kg /m2); CVRF: Cardiovascular risk factors, HT: Hypertension, DM: Diabetes mellitus, NSTEMI: Myocardial infarction without ST segment elevation, STEMI: Myocardial infarction with ST segment elevation.

values of age (p: 0.00001) and waist circumference (p: 0.0005) were significantly higher in patients. Regarding the clinical presentation of the infarction, more than 50% of patients were clinically classified as patients with STEMI.

Using the SNPstats program, the existence of the H-W equilibrium for the genotypic distribution of rs1333049 polymorphism in the *9p21* locus was confirmed in apparently healthy individuals. Jointly, the inheritance model of the homozygous mutated genotype (CC) of the rs1333049 variant was determined, establishing the dominant model as the most adjusted, presenting the lowest probability value. This pattern of inheritance indicates that a single copy of the C allele is enough to modify risk, and being a carrier of two copies modifies it in equal magnitude. The carriers of the GC and CC genotypes have the same risk.

When establishing the comparison of genotypic and allele frequencies of the rs1333049 variant, among patients with AMI and apparently healthy individuals, and among infarcted patients with STEMI and NSTEMI, both adjusted for CVRF and considering the dominant inheritance model, no significant differences were observed (Table 2).

The correlation analysis showed a positive correlation between the rs1333049 polymorphism and the presence of hypertension (r: 0.145, p: 0.006), and between hypertension and acute myocardial infarction (r: 0.318, p: <0.0001). Based on these correlations, the comparison of genotype frequencies between AMI patients with

Table 2 – Association of rs1333049 polymorphism in the *9p21* locus with the development of AMI and type of myocardial infarction

rs1333049 Genotypes	AMI patients (n=314)	Controls (n=94)	*OR* *95% CI*	*P*
GG	31.9 (100)	36.2 (34)	0.8 (0.508-1.336)	0.21
GC	50.6 (159)	48.9 (46)	1.0 (0.675-1.697)	0.38
CC	17.5 (55)	14.9 (14)	1.2 (0.641-2.296)	0.27
Alleles				
G	57.2 (359)	60.6 (114)	0.9 (0.621-1.208)	0.19
C	42.8 (269)	39.4 (74)	1.1 (0.827-1.609)	0.19
rs1333049 Genotypes	**STEMI (n=184)**	**NSTEMI (n=128)**	***OR*** ***95% CI***	***P***
GG	34.2 (63)	28.1 (36)	1.3 (0.814-2.174)	0.12
GC	50.0 (92)	51.6 (66)	0.9 (0.598-1.475)	0.39
CC	15.8 (29)	20.3 (26)	0.7 (0.408-1.317)	0.15
Alleles				
G	59.2 (218)	53.9 (138)	1.2 (0.900-1.714)	0.09
C	40.8 (150)	46.1 (118)	0.8 (0.583-1.110)	0.09

The genotype and allele frequencies are expressed in percentages, followed by the number of individuals or chromosomes in parentheses. AMI: Acute myocardial infarction, NSTEMI: Myocardial infarction without ST segment elevation, STEMI: Myocardial infarction with ST segment elevation. OR: Odds ratio (probability ratio), CI: confidence interval, p: probability value.

and without hypertension (HT) was established, considering the dominant inheritance model, observing a significantly increased frequency of the wild-type homozygous GG genotype in patients with HT when compared to non-hypertensive patients. By contrast, a significantly increased frequency of the heterozygous GC genotype was observed in non-hypertensive patients with respect to hypertensive patients, although this significance is lost when correcting the p-value (Table 3). On the other hand, the comparison of the genotype frequencies between hypertensive and non-hypertensive patients who suffered AMI, aged ≥56 years, showed a significantly increased frequency of the GG genotype in the group of hypertensive AMI patients. Likewise, the comparison of the frequencies of the genotypes and alleles between hypertensive and non-hypertensive patients who suffered AMI, aged ≤55 years, showed a significantly increased frequency of the GG genotype in the group of hypertensive patients (Table 3). Finally, when establishing the comparison of frequencies between hypertensive AMI patients and hypertensive controls, a significantly increased frequency of the GG genotype was observed in hypertensive AMI patients as compared to hypertensive controls.

These results confirm that the GG genotype confers susceptibility to the development of arterial hypertension, which leads the development of AMI regardless of age.

Another observed correlation is the negative correlation between the rs1333049 polymorphism and the age of occurrence of AMI (r: -0.108, p: 0.042). Based on this correlation, the genotype frequencies between patients who suffered AMI, aged ≤55 years, were compared with the group of patients who suffered AMI, aged ≥56 years, considering the dominant inheritance model and adjusted for CVRF. In the group of patients aged ≥56 years, a significantly increased frequency of the CC genotype was observed with respect to the group of patients who suffered AMI, aged ≤55 years (Table 3). These results indicate that individuals with the CC genotype are more likely to suffer AMI at ages ≥56 years.

The severity of CAD was determined in 76 patients with AMI. In this group, more than 50% of

Table 3 – Association of rs1333049 polymorphism in the *9p21* locus with hypertension and age of occurrence of AMI

rs1333049 Genotypes	AMI patients HT (n=202)	AMI patients not HT (n=110)	*OR* *95% CI*	*p*	*Pc*
GG	37.6 (76)	20.9 (23)	2.3 (1.328-3.917)	0.0012	0.0036
GC	47.0 (95)	57.3 (63)	0.7 (0.430-1.046)	0.042	0.126
CC	15.3 (31)	21.8 (24)	0.7 (0.395-1.203)	0.076	0.228
Alelles					
G	61.1 (247)	49.5 (109)	1.6 (1.150-2.231)	0.002	0.004
C	38.9 (157)	50.5 (111)	0.6 (0.448-0.869)	0.002	0.004
rs1333049 Genotypes	**AMI patients HT Age≥ 56 years (n=100)**	**AMI patients not HT Age ≥ 56 years (n=42)**	*OR* *95% CI*	*p*	*Pc*
GG	34.0 (34)	16.7 (7)	2.6 (1.035-6.403)	0.019	0.057
GC	47.0 (47)	52.4 (22)	0.8 (0.391-1.659)	0.27	0.81
CC	19.0 (19)	30.9 (13)	0.5 (0.229-1.191)	0.06	0.18
Alelles					
G	57.5 (115)	42.9 (36)	1.8 (1.077-3.019)	0.012	0.036
C	42.5 (85)	57.1 (48)	0.5 (0.331-0.927)	0.012	0.036
rs1333049 Genotypes	**AMI patients HT Age ≤ 55 years (n=102)**	**AMI patients not HT Age ≤ 55 years (n=68)**	*OR* *95% CI*	*p*	*Pc*
GG	41.2 (42)	23.5 (16)	2.2 (1.146-4.513)	0.008	0.024
GC	47.1 (48)	60.3 (41)	0.6 (0.314-1.090)	0.04	0.12
CC	11.8 (12)	16.2 (11)	0.7 (0.285-1.670)	0.20	0.60
Alelles					
G	64.7 (132)	53.7 (73)	1.6 (1.016-2.463)	0.02	0.04
C	35.3 (72)	46.3 (63)	0.6 (0.405-0.984)	0.02	0.04
rs1333049 Genotypes	**AMI patients Age ≤ 55 years (n=170)**	**AMI patients Age ≥ 56 years (n=142)**	*OR* *95% CI*	*p*	*Pc*
GG	34.1 (58)	28.9 (41)	0.8 (0.484-1.269)	0.16	0.32
GC	52.4 (89)	48.6 (69)	0.9 (0.550-1.343)	0.25	0.75
CC	13.5 (23)	22.5 (32)	1.85 (1.036-3.354)	0.018	0.036
Alelles					
G	60.3 (205)	53.2 (151)	0.7 (0.543-1.028)	0.03	0.09
C	39.7 (135)	46.8 (133)	1.3 (0.972-1.839)	0.03	0.09

The genotype and allele frequencies are expressed in percentages, followed by the number of individuals or chromosomes in parentheses. AMI: Acute myocardial infarction, OR: Odds ratio (probability ratio), CI: confidence interval, p: probability value, pc: probability value corrected.

patients with AMI were clinically classified as patients with STEMI.

In the echocardiographic characteristics of the included patients, the left ventricular systolic function was investigated at the time of admission, estimating a slight decrease (40.59% ± 9.05).

Based on the diagnostic coronary angiography, it was demonstrated that most of the patients had significant obstructive coronary artery disease of the epicardial arteries and only a low percentage had non-significant obstructive coronary artery disease (non-CAD).

CAD severity was defined according to the number of involved coronary arteries. It was observed that more than 60% of the patients had one main affected coronary vessel, and a low percentage of the patients had three main vessels affected. The most frequently affected artery was the anterior descending artery (ADA), followed by the right coronary artery (RCA), the circumflex artery (CxA), and the left coronary artery (LCA) (Table 4).

Table 4 – Angiographic characteristics of patients with AMI under 55 years of age

Angiographic characteristics	Frequency (n= 76)
CAD	96.05 (73)
non-CAD	3.94 (3)
Number of involved coronary arteries	
One	63.2 (48)
Two	32.9 (25)
Three	3.9 (3)
Affected artery	
ADA	68.42 (52)
RCA	40.7 (31)
CxA	30.2 (23)
LCA	6.57 (5)

Frequencies are expressed in percentages. The values shown in parentheses represent the number of individuals. CAD: significant obstructive coronary artery disease, non-CAD: non-significant obstructive coronary artery disease. ADA: anterior descending artery, RCA: right coronary artery (RCA), CxA: circumflex artery, LCA: left coronary artery (LCA).

Using the SNPstats program, the inheritance model of the homozygous mutated genotype (GG) of the rs10757274 polymorphism in the *9p21* locus was determined, establishing the additive model (2 (GG) + GA vs. AA) as the most adjusted, by presenting the lowest probability value. This pattern of inheritance indicates that the risk conferred by the genotype depends on the number of copies of the mutated allele (allele G). Therefore, individuals with the mutated homozygous GG genotype have twice the risk compared to individuals with the heterozygous AG genotype.

The correlation analysis showed a positive correlation between the rs10757274 polymorphism with the severity of CAD (number of involved coronary arteries) in patients aged ≤55 years (r: 0.276, p: 0.0078). Based on the correlation and the additive inheritance model, comparison of genotype frequencies was established between patients with an affected coronary vessel and patients with more than one affected vessel, observing a significantly increased frequency of AG + GG genotypes in patients with two or three affected vessels when compared to patients with only one affected vessel. On the contrary, a significantly increased frequency of the AA genotype was observed in patients with only one affected coronary vessel (Table 5).

Considering that the GG genotype of the rs1333049 polymorphism confers susceptibility to the development of arterial hypertension, the frequency of the haplotypes formed by the polymorphisms rs1333049 and rs10757274 was compared between hypertensive and non-hypertensive AMI patients, observing an increased frequency of the haplotype GG, which is formed by the variant G of the rs1333049 polymorphism, associated with hypertension, and the G variant of the rs10757274 polymorphism, associated with severity (greater number of affected vessels) (0.2605 vs. 0.1111, respectively). By contrast, in non-hypertensive patients a significantly increased frequency of the CG haplotype was observed when compared to hypertensive AMI patients (0.3389 vs. 0.1827, respectively). Confirming the relevance of the GG genotype of rs1333049 in the development of arterial hypertension.

Discussion

Cardiovascular diseases represent the main cause of death in many Latin American countries, with rates similar to those of developed countries. Indeed, in the Venezuelan population, diseases of the heart and blood vessels are the main cause of death and represent a growing health, social, and economic burden for the country. Likewise, Venezuela exhibits one of the highest premature mortality rates from myocardial infarction in the region of the

Table 5 – Association of rs10757274 polymorphism in the 9p21 locus with severity of coronary artery disease

rs10757274 Genotypes	AMI patients Only one affected vessel (n=48)	AMI patients 2 or more affected vessels (n=28)	*OR* *95% CI*	*p*	*pc*
GG +AG	70.8 (34)	89.3 (25)	3.8 (0.994-14.401)	0.02	0.04
AA	29.2 (14)	10.7 (3)	0.3 (0.069-1.005)	0.02	0.04

The frequencies are expressed in percentages, followed by the number of individuals in parentheses. AMI: Acute myocardial infarction, OR: Odds ratio (probability ratio), CI: confidence interval, p: probability value, pc: probability value corrected.

Americas.[2] However, during the decade of 2000–2010, the Americas reported a reduction in the premature mortality rate caused by cardiovascular diseases, coinciding with a period of economic development in most Latin American countries, accompanied by a moderate reduction in poverty and greater emphasis on social services. However, the Pan American Health Organization (PAHO) recognizes that access to health services is still unequal, and the distribution of public health expenditures is poor or insufficient, with a high cost for the population.[25] In Latin American countries, the prevalence of hypertension varies from 8% to 40% in the adult population, but an average of 20% to 23% of this population has high blood pressure. This prevalence is similar to that of developed countries; however, there is considerable variability in each of the countries and their regions. Therefore, studies of prevalence and local factors in the development of hypertension are reasons for research.[26] Considering that CAD is a complex and multifactorial cardiovascular disorder caused by the interaction of risk factors, and genetic and environmental factors, and that Venezuela exhibits one of the highest premature mortality rates due to myocardial infarction in the region, the following main findings were observed in the present study:

1. 49.4% of the patients included in the study suffered AMI at an early age, with an age range between 24-55 years and an average age of 46.56 ± 6.53 years. According to data from PAHO, Venezuela exhibits one of the highest premature mortality rates from myocardial infarction in the region and is one of the most lagging nations in the Americas in meeting global goals to reduce premature mortality due to cardiovascular disease.[27] However, it has been shown that 80% of mortality from ischemic heart disease is preventable. Consequently, it is urgent to apply the Global Strategy and Plan of Action of the World Health Organization (WHO) and PAHO to accelerate the implementation of cost-effective measures to slow down and reduce the epidemic of ischemic heart disease in Venezuela.[2]
2. This is the first study of its kind to demonstrate a positive correlation between the rs1333049 polymorphism in the *9p21* locus and arterial hypertension in Venezuelan patients who suffered AMI. In contrast to other studies, where an association with CAD has been established, it was observed that patients with the GG genotype are more likely to develop HT, which makes them more susceptible to suffering myocardial infarction, since the first factor of risk for this pathology is high blood pressure.
3. Patients with the CC genotype of rs1333049 polymorphism in the *9p21* locus are more likely to suffer AMI at older ages (≥56 years), which runs in line with what has been previously described in the literature.[28]
4. In patients with AMI, the rs10757274 polymorphism in the *9p21* locus is correlated and associated with the severity of CAD (number of involved coronary arteries). Patients aged ≤55 years and the presence of risk G allele (AG + GG) have a greater possibility (~ 4) of suffering CAD in a greater number of vessels. In contrast, the AA genotype would be associated with involvement of a single coronary vessel. Previous studies have established the association of polymorphisms in the *9p21* locus with angiographic severity and clinical prognosis of patients with CAD.[29]

Considerations and Limitations

Some limitations in this study must be considered: First, it is an association study of a candidate locus which hinders the explanation of the full heritability of a complex disease. In fact, to explain the heritability, it is important to detect common variants with very small effects, rare variants with small effects, genes harboring ultra-rare variants, and complex interactions (gene – gene and gene – environment). Furthermore, the present study is restricted due to the investigation of two SNPs. A haplotype-based analysis may better disclose the genetic basis of CAD and hypertension in the population of Venezuela. On the other hand, it is a study of a local population; however, the population of Venezuela consists of several ethnic groups (European, African, and Amerindian groups). Thus, the findings in the study could be explained by the ethnic admixture existing in the Venezuelan population, which is highly admixed due to continuous population migrations from other continents and within the continent. Finally, another of the limitations was to determine the severity of CAD in all patients included in the study due to the lack of resources in the hospitals of the country. Therefore, it is important to increase the sample size to confirm the association of rs1333049 with hypertension, to verify the correlation of rs10757274 with severe CAD, as well as to determine the possible relations between the rs10757274 polymorphism and other risk factors for AMI, including the rs1333049 polymorphism associated with hypertension in Venezuelan patients.

Conclusions

In the studied population, the rs1333049 polymorphism in the *9p21* locus is correlated with arterial hypertension, considered the largest health problem worldwide, and is attributed to approximately 9.4 million deaths per year. Furthermore, HT is the first predisposing factor for the development of AMI, and it is estimated that approximately 30% of the cases are determined by genetic factors. The rs1333049 polymorphism in the *9p21* locus resides within the neighborhood of cell cycle regulatory genes and is in strong linkage disequilibrium with genes that inhibit the cell cycle, including the inhibitors of cyclin-dependent kinase 2A and 2B (CDKN2A and CDKN2B). Consequently, the dysregulation of these proteins can increase the expression of genes that cause cell proliferation, promoting the development of cell hyperplasia, which would lead to an increase in peripheral vascular resistance, causing arterial hypertension and conferring greater susceptibility to suffer AMI. Finally, this study shows that the rs10757274 polymorphism in the *9p21* locus is associated with the progression of coronary atherosclerosis, suggested by the correlation with the number of involved coronary arteries.

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Potential Conflict of Interest

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

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Study Association

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

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Instituto Venezolano de Investigaciones under the protocol number DIR-0130/09; No. 00211. 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: Blanco Sobrino S, Fernández-Mestre M. Acquisition of data: Salazar-Alcalá E, Alfonso Reyes A, Flores Soler J, Leras Mirabal R, Luti Y, Márquez I. Analysis and interpretation of the data: Blanco Sobrino S, Salazar-Alcalá E, Fernández-Mestre M. Statistical analysis: Fernández-Mestre M. Obtaining financing: Fernández-Mestre M. Writing of the manuscript: Blanco Sobrino S, Fernández-Mestre M. Critical revision of the manuscript for intellectual content: Fernández-Mestre M.

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ORIGINAL ARTICLE

Influence of Neuropeptide Y and Neuropeptide Y 2 Receptor Variants in Acute Coronary Syndrome

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Abstract

Background: The neuropeptide Y (NPY) is one of the most abundant neurotransmitters in the nervous system. NPY acts as a potent stimulator of angiogenesis, inflammation, and adipogenesis, through the NPY 2 receptor (NPY2R). Changes in the NPY signaling pathway have been linked to Acute Coronary Syndrome (ACS).

Objectives: The purpose of this study is to determine the association between variants in the NPY and NPY2R genes, as well as the severity of acute coronary syndrome (ACS).

Methods: Approximately 221 ACS patients and 278 healthy controls were selected for this study. Four variants in NPY and two variants in NPY2R genes were genotyped using Taqman allelic discrimination and sequencing. The Chi-square and Fisher's exact tests were used to verify the genotype frequencies. The logistic regression analyses were used for the evaluation of the studied variables. Haplotype analysis was used to evaluate the linkage disequilibrium (LD) between the variants ($p<0.05$).

Results: An association of NPY c.20T>C variant was found with the ACS group when compared to the healthy group. In the analysis between variants and risk factors in the ACS group, NPY c.84G>A was associated with hypertension. The analysis between TIMI risk showed a significance for NPY c.20T>C between the low and intermediate/high TIMI risk groups. In the haplotype analysis, strong linkage disequilibrium (LD) was found between the variants NPY c.150G>A and NPY c.-485T>C.

Conclusion: The NPY c.20T>C variant appears to contribute to the development of ACS. The NPY2R c.-1116A>G variant may contribute to the early development of ACS and the NPY c.84G>A variant appears to contribute to the development of hypertension. In addition, the NPY c.20T>C is associated with a protective effect in ACS severity.

Keywords: Acute Coronary Syndrome; Neuropeptide Y; Receptors Neuropeptide Y; Nucleotide Polymorphism; Epidemiology.

Introduction

The neuropeptide Y (NPY) is a small peptide with 36 amino acids and is one of the most abundant neurotransmitters of the central and peripheral nervous system.[1] It induces proliferation of vascular smooth muscle cells in humans, promoting the formation and development of new blood vessels.[2] As a result, current research is focused on developing a drug delivery mechanism for NPY to prolong the therapy of diabetic cardiomyopathy and ischemic heart disease without significant systemic consequences.[3] In mammals, NPY

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acts through its receptors NPYR1, NPYR2, NPY4R, NPY5R, and NPY6R. The NPY1R, NPY2R, NPY4R, and NPY5R receptors are functional in all mammals, but Y6 is a pseudo-gene in humans and other primates, and is also absent in the mouse genome.[4] The NPY c.20T>C mutation, which results in the substitution of Leucine for Proline (Leu7Pro) in the pre-pro-NPY signal peptide, is associated with an increase in serum lipid levels. NPY c.20T>C increased the risk of accelerated and early progression of atherosclerosis,[5-7] acute myocardial infarction and stroke,[8] coronary artery disease,[9] hypertension,[10,11] and obesity in children.[12] The NPY c.84G>A and c.150G>A variants were investigated for their association with obesity and hypertension,[10-11] while c.150G>A was studied for its association with atherosclerosis.[7]

By contrast, the NPY c.-485T>C (rs16147) variant, which is located in the promoter region,[13] has proven to alter NPY expression in vitro, and is likely to affect mRNA expression levels in vivo.[14-15] Numerous studies have established a link between the c.-485T>C variant and the development of early atherosclerosis[7] and stroke.[16-17] Other studies have established a link between this variant and a reduction of insulin resistance and type 2 diabetes.[18-19] Through the NPY 2 receptor (NPY2R), NPY may also act as a stimulator of angiogenesis, inflammation, and adipogenesis in the abdominal region.[20] NPY2R variants c.-1088C>T and c.-1116A>G are associated with obesity,[21-24] as well as with low HDL-C serum levels.[25] Since the earliest experimental studies with NPY, its association with cardiovascular diseases has been established, with the evidence that cardiac NPY is released from sympathetic nerves during acute myocardial infarction.[26] Plasma levels of NPY were found to be high in human suffering from Acute Coronary Syndromes (ACS), such as acute myocardial infarction and during left ventricular failure.[27-29] NPY and the NPY2R may serve as biomarkers for ACS prognosis, risk stratification for death or cardiovascular events, or even a potential therapeutic target in other types of treatments. This purpose of this study was to evaluate the influence of NPY and NPY2R variants on the severity of ACS.

Methods

Population

The study enrolled patients who were admitted to the Real Heart Hospital (RHH), which is affiliated with the Royal Portuguese Charity Hospital in Pernambuco (RPHCP), located in Recife, Pernambuco, Brazil. Adult ACS patients (n = 221), over 18 years of age, of both sexes, underwent an electrocardiogram, and if necessary, cineangiocardiography was also performed. The myocardial injury markers, creatine kinase-MB (CK-MB) and troponin, were measured. Non-ACS patients admitted to the RHH (n = 95) with atrial fibrillation were also included in this study. The sample size was defined by convenience. A total of 278 healthy blood donors (healthy group), over 18 years of age, of both sexes, were recruited from the Hematology and Hemotherapy Foundation of Pernambuco (Hemope) and participated in interviews on the presence of acute or chronic diseases or significant comorbidities and laboratory tests (HIV, hepatitis C, syphilis, Human T-lymphotropic virus type 1 and 2, and Chagas' disease) to identify infectious parasitic diseases.

Inclusion criteria

This study enrolled patients who were diagnosed with ACS, after having undergone a physical examination, an electrocardiogram, and a measurement of myocardial injury markers. The non-ACS patients were those hospitalized without a diagnosis of coronary disease and typically who presented atrial fibrillation.

Exclusion Criteria

Individuals taking anti-inflammatory drugs, those who had suffered a recent trauma, those with a history of active infectious diseases or neoplasms, and those who refused to participate in the study were excluded from the ACS and non-ACS groups.

Ethical considerations

The Real Heart Hospital/Realcor Research Ethics Committee of the Royal Portuguese Charity Hospital in Pernambuco approved this study (CAAE: 03187512.2.0000.5202). Before sample collection, each subject was informed about the research and signed an informed consent form.

Level of ACS severity in patients

In all patients, the severity level was determined by the left ventricular ejection fraction, which was determined by the echocardiogram. Additionally, the risk score for Thrombolysis in Myocardial Infarction (TIMI) was used. The TIMI Risk Score is used to categorize patients as having an intermediate and high risk of suffering

a cardiovascular event. For the patients without the ST-elevation myocardial infarction, seven risk factors were considered.[30] For the patients with an ST-elevation myocardial infarction (STEMI), eight factors are considered, in accordance with Morrow et al. (2000).[31]

Blood samples and DNA extraction

During the routine of cardiologic exams performed on RPHCP, peripheral blood samples were collected in a 5ml EDTA tube to perform molecular analysis at the Oswaldo Cruz Foundation (Fiocruz-PE). Purification of the DNA was carried out according to manufacturer's instructions, using the Illustra blood genomicPrep Mini Spin Kit (GE Healthcare, Buckinghamshire, UK).

Identification and genotyping of variants

DNA sequencing was used to screen for the NPY gene variants 20T>C (rs16139), c.84G>A (rs5572), and c.150G>A (rs5573). Initial denaturation at 95°C for 5 minutes was followed by 35 cycles of denaturation (95°C for 1 minute), annealing (60°C for 30 seconds), and extension (72°C for 45 seconds), followed by a final extension at 72°C for 7 minutes32. According to manufacturer's recommendations, Platinum® Taq DNA polymerase (Invitrogen Life Technologies) was used. The reagents were used without adding DNA as a negative control. The amplified fragments were viewed on a 1.5% agarose gel. The PCR products were sequenced and analyzed using the Chromas Lite 2.01 program at the Aggeu Magalhes Institute's Technological Platform Centers (NPT/IAM). The NPY variants c.-485T>C (rs16147) (Assay ID C 2267279 10), NPY2R c.-1088C>T (rs6857715) (Assay ID C 29013142 10), and NPY2R c.-1116A>G (rs6857530) (Assay ID C 44837 30) were identified by applying real-time PCR with Genotyping, which was carried out using the 7500 RealTime PCR System (Applied Biosystems, Foster City, CA, USA) under the following conditions: initial denaturation at 95°C for 10 minutes, followed by 40 cycles of denaturation (92°C for 15 seconds), annealing (60°C for 60 seconds), extension (60°C for 60 seconds), and final extension at 60°C for 60 seconds.

Statistical analysis

To determine whether the genotypic frequencies agree with the Hardy-Weinberg proportions, the Chi-square and Fisher's exact tests were used. The clinical variables, inflammatory markers, ischemia, and variants were all evaluated using logistic regression analyses. The data were analyzed using The R Project for Statistical Computing (R Development Core Team), version 2.10. The haplotype analysis and evaluation of linkage disequilibrium (LD) between variants were performed using the HaploView 4.2 software. When the p-value was less than 0.05, the data were considered statistically significant.

Results

Characterization of the study population

A total of 221 patients with ACS were selected, the majority of whom (76.02%) was male. This distribution was also observed for non-ACS patient and health patient groups, comprised of 52.69% (49/93) female individuals and 84.17% (234/278) male individuals, respectively. The median age ACS, non-ACS, and healthy patients was respectively 60, 6,3 and 45 years. No significant differences in age were found between the ACS and non-ACS groups ($p = 0.7775$), but significant differences were observed between the ACS and the healthy groups ($p < 0.001$). According to the TIMI risk, patients with ACS were classified as having a low risk (34.84%), an intermediate risk (46.61%), or a high risk (18.55%). Multiple logistic regression analysis revealed that gender, smoking, diabetes, and dyslipidemia are contributing factors to the increased risk of ACS (Supplementary Table S1).

Analysis of the variants

The groups of patients with ACS and healthy patients showed Hardy-Weinberg equilibrium (HWE) ($p > 0.05$) for all variants in NPY and NPY2R. In the group of non-ACS patients, NPY c.150G>A, NPY2R c.-1088C>T, and c.-1116A>G showed HWE, while NPY c.20T>C and NPY c.84G>A were not in HWE. Therefore, no statistical analyses involved these two populations.

The NPY c.20T>C showed a majority of ancestral homozygous genotype TT (94.57%) in the ACS group, while 5.43% of the patients were heterozygous. In the healthy group, 96.40% of the samples showed the TT genotype, while only 3.60% presented the TC or CC genotypes. When the analysis after adjusting for age and gender was performed, there was an association between this variant and ACS. Previously, it presented $p = 0.3251$ for the TC/CC and $p = 0.3307$ for the C allele, later showing a $p = 0.0256$ for the TC/CC and $p = 0.0892$ for the C allele, with an odds ratio (OR) of approximately three-fold that of the individual having the TC/CC genotype or the C allele to develop ACS, as can be seen in Table 1.

Table 1 – Analysis of the variants of the genes in the ACS and healthy groups

Variants	Healthy		ACS		OR	95% CI		p	$OR_{adjusted}$	95% CI		p
	N*	%	N (221)	%		Inf	Sup			Inf	Sup	
NPY c.20T>C (rs16139)												
Genotype												
TT	268	96.4	209	94.57	1.00				1.00			
TC/CC	10	3.6	12	5.43	1.54	0.65	3.71	0.3251	3.29	1,15	9.52	**0.0256**
Alleles												
T	546	98.2	430	97.29					1.00			
C	10	1.8	12	2.71	1.52	0.65	3.64	0.3307	2.17	0.89	5.40	0.0892
NPY c.84G>A (rs5572)												
Genotype												
GG	264	94.96	207	93.67	1.00				1.00			
GA/AA	14	5.04	14	6.33	1.28	0.59	2.76	0.5320	1.66	0.61	4.46	0.3185
Alleles												
G	542	97.48	427	96.6	1.00				1.00			
A	14	2.52	15	3.4	1.36	0.64	2.87	0.415	1.47	0.66	3.35	0.3506
NPY c.150G>A (rs5573)												
Genotype												
GG	76	27.34	55	24.89	1.00				1.00			
GA/AA	202	72.66	166	75.11	1.14	0.76	1.70	0.5366	1.30	0.75	2.28	0.3568
Alleles												
G	289	51.98	220	49.77	1.00				1.00			
A	267	48.02	222	50.23	1.09	0.85	1.40	0.4889	1.17	0.89	1.54	0.2592

NPY c.-485T>C (rs16147)**												
Genotype												
TT	31	24.22	58	26.61	1.00				1.00			
TC/CC	97	75.78	160	73.39	0.88	0.53	1.45	0.6240	0.75	0.40	1.41	0.3768
Alleles												
T	121	47.27	224	51.38	1.00				1.00			
C	135	52.73	212	48.62	0.85	0.62	1.16	0.2966	0.80	0.58	1.11	0.1790
NPY2R c.-1088T>C (rs6857715)												
Genotype												
TT	44	21.57	39	17.65	1.00				1.00			
TC/CC	160	78.43	182	82.35	1.28	0.79	2.08	0.3089	0.91	0.49	1.73	0.7823
Alleles												
T	201	49.26	188	42.53	1.00				1.00			
C	207	50.74	254	57.47	1.31	1.00	1.72	0.0493	1.31	0.99	1.75	0.0625
NPY2R c.-1116A> G (rs6857530)												
Genotype												
AA	46	21.5	74	33.48	1.00				1.00			
AG/GG	168	78.5	147	66.52	0.54	0.35	0.83	**0.0054**	0.81	0.46	1.44	0.4758
Alleles												
A	212	49.53	257	58.14	1.00				1.00			
G	216	50.47	185	41.86	0.71	0.54	0.92	**0.0109**	0.73	0.55	1.97	0.0286

Note: **The sample N of the variants of the healthy group varies (for NPY c.20T>C, NPY c.84G>A and NPY c.150G>A = 278; NPY c.-485T>C = 128; NPY2R c.-1088C> T = 204; NPY2R c.-1116A G = 214); **The sample N in the ACS group is 218; OR: Odds Ratio; OR-adjusted: Odds Ratio adjusted by age and gender; CI: Confidence Interval; p: p-value, obtained through the logistic regression test.*

Regarding NPY c.84G>A, the results show that 93.67% of ACS patients presented the GG genotype, while 6.33% showed GG or GA genotypes. Results showed that 94.96% of the samples from healthy individuals presented the GG genotype, while only 5.04% showed GA or AA genotypes. No statistical difference was found between the groups and no association between NPY c.84G>A and ACS was identified (Table 1).

Results from the NPY c.150G>A showed 24.89% of the patients with ACS carrying the GG genotype, while 75.11% of the patients showed GA/AA genotypes. Among the non-ACS patients, 32.97% showed the GG genotype, while 67.03% presented the GA/AA genotypes (Supplementary Table S2). The analysis of healthy individuals revealed that the GG genotype was present in 27.34% of the patients, while 49.28% presented the GA genotype and 23.38% the AA genotype (Table 1). No statistical difference was found between the groups and no association between NPY c.150G>A and ACS was identified.

As regards the NPY c.-485T>C variant, 26.61% of the ACS group presented the TT genotype, while 73.39% of these presented the TC/CC genotypes. Among the non-ACS patients, 25.81% presented the TT genotype, while 74.19% presented the TC/CC. No association was found between this variant and the ACS (Supplementary Table S2). In the healthy group, individuals presented 24.22% of the TT genotype, while 75.78% presented the TC/CC genotypes (Table 1). In the two analyses performed with the three populations, no association was found between c.-485T> C and ACS.

Regarding NPY2R c.-1088C>T, the genotypic distribution in the group of patients with ACS showed that 17.65% presented the TT genotype, while 82.35% presented the TC/CC genotypes. In the non-ACS patient group, 24.21% of the individuals showed the TT genotype, while 75.79% presented TC/CC genotypes (Supplementary Table S2). In the healthy group, only 21.57% of the individuals showed the TT genotype, while 78.43% presented the TC/CC genotypes (Table 1). In the two analyses performed with the three populations, no association was found between c.-485T>C and ACS.

The results regarding NPY2R c.-1116A>G showed a genotypic distribution in the ACS group of 33.48% presenting the CC genotype as compared to 66.52% presenting the AG/GG genotypes. In the non-ACS group, 26.32% of the patients showed the AA genotype, while 73.68% presented the AG/GG genotypes (Supplementary Table S2). In the healthy group, 21.50% showed the AA genotype, while 78.50% presented the AG/GG genotypes. When the logistic regression analysis was performed, an association between c.-1116A>G and ACS (p = 0.0054 for the AG/GG genotypes and p = 0.0109 for the G allele) was observed between the healthy and the ACS groups. After adjustment for age and gender, this association continued (p = 0.4619 for the AG/GG genotypes and p = 0.2982 for the G allele), as can be observed in Table 1.

Variants versus TIMI risk

TIMI risk showed an association with the NPY c.20T>C variant. The NPY c.20T>C presented a significant difference (p = 0.0261; OR = 0.25) among the low and intermediate/high TIMI risk groups. In the low TIMI risk group, the genotype distribution was 89.61% TT and 10.39% TC/CC, while in the intermediate/high TIMI risk group, 97.22% showed the TT genotype and 2.78% showed the TC/CC genotypes (Table 2). For the other variants, no association was found with any of the TIMI risk groups.

Relationship between variants and clinical and biological characteristics and habit

The association of the variants with the following variables of ACS was also analyzed: gender/time, smoking, diabetes, hypertension, dyslipidemia, levels of C-reactive protein (CRP), number of arterial lesions, troponin levels, levels of CK-MB mass, and ejection fraction.

The results showed that in the ACS group, the NPY c.84G>A variant was associated with hypertension, indicating a 3.57-fold chance of developing this disease (p = 0.0223) in individuals who do not have GA/AA genotypes (Table 3).

The NPY2R c.-1116A>G variant showed an association with the onset time of ACS (Table 4), indicating that the individual who has this variant has almost twice the chance to developing the early syndrome (p = 0.0253; OR = 1.91). However, no association was found for other variants (Supplementary Tables S3, S4, S5, and S6).

Haplotype analysis

The pairwise LD values (D' and r2) among the studied variants in the NPY gene are provided in the supplements. Strong LD was found between variants NPY c.150G>A and NPY c.-485T>C, which are separated by 41 kb (D'= 0.967; r2 = 0.909). However, a weak LD

Table 2 – Analysis of the variants of the genes in the different degrees of TIMI Risk

Variants (genotype)	TIMI Risk Score						
	Low (n = 77)		Intermediate/High * (n = 144)				
	N	%	n	%	OR	95% CI	p
NPY c.20T> C (rs16139)							
TT	69	89.61	140	97.22	1		
TC/CC	8	10.39	4	2.78	0.25	0.06 – 0.81	**0.0261**
NPY c.84G>A (rs5572)							
GG	71	92.21	136	94.44	1		
AG/AA	6	7.79	8	5.56	0.70	0.23 – 2.19	0.5173
NPY c.150G>A (rs5573)							
GG	22	28.57	33	22.92	1		
GA/AA	55	71.43	111	77.08	1.35	0.71 – 2.51	0.3551
NPY c.-485T>C (rs16147)**							
TT	21	27.63	37	26.06	1		
TC/CC	55	72.37	105	73.94	1.08	0.57 – 2.02	0.8020
NPY2R c.-1088T>C (rs6857715)							
TT	14	18.18	25	17.36	1		
TC/CC	63	81.82	119	82.64	1.06	0.50 – 2.15	0.5300
NPY2R c.-1116A> G (rs6857530)							
AA	20	25.97	54	37.50	1		
AG/GG	57	74.03	90	62.50	0.58	0.31 – 1.07	0.0852

Note: **Reference; **Sample of 77 from the low TIMI group and 144 on the Intermediate/High; OR: Odds Ratio; CI: Confidence Interval; p: p-value, obtained through the logistic regression test.*

was found between the NPY2R c.-1088C>T and NPY2R c.-1116A>G variants (Supplementary Figure S7).

Discussion

Genotyping of NPY and NPY2R polymorphisms in 221 ACS patients and 278 healthy controls indicated that the NPY c.20T>C polymorphism significantly raised the risk of ACS. The NPY2R c.-1116A>G contributes to the development of the early stages of the syndrome. In addition to this, the NPY c.20T>C is associated with a protective effect in ACS severity.

NPY has been linked to hypertension, congestive heart failure, and other cardiovascular diseases due to its high sympathetic nervous system activity.[33] The NPY c.20T>C variant has been linked to cardiovascular pathologies, such as accelerated and early progression of atherosclerosis,[5,6] acute myocardial infarction, and cerebrovascular disease in hypertensive patients.[8] The results of the present study were similar to those reported by Masoudi-Kazemabad et al.,[9] which showed an association between NPY c.20T>C and coronary artery disease in an Iranian population.[9] Wallerstedt et al.,[8] demonstrated the association of this variant with acute myocardial infarction in a Swedish hypertensive population.[8] The NPY c.20T>C variant was initially associated with increased cholesterol and low-density lipoprotein (LDL) levels,[5] in obese and healthy individuals.[6] In a subsequent study in Finnish women with coronary heart disease, the NPY c.20T>C is associated with total cholesterol, but not with LDL.[34] Further, the

Table 3 – Analysis of the variant NPY c.84G>A with habits and biological and clinical features

Variables	NPY c.84G>A (rs5572)				OR	95% CI		p
	GG		GA/AA					
	N	%	N	%		Inf	Sup	
Onset of ACS								
Prospective	95	45.89	4	28.57				
Premature	112	54.11	10	71.43	2.12	0.69	7.93	0.2162
Gender								
Male	156	75.36	12	85.71	1.00			
Female	51	24.64	2	14.29	0.51	0.08	1.95	0.3881
Premature								
Male	102	82.26	9	90				
Female	22	17.74	1	10	0.5152	0.03	2.95	0.539
Prospective								
Male	54	44.26	3	60	1.00			
Female	68	55.74	2	40	0.5294	0.07	3.30	0.4945
Gender/Time								
Male								
Prospective	54	34.62	3	25	1.00			
Premature	102	65.38	9	75	1.5882	0.45	7.38	0.501
Female								
Prospective	41	80.39	1	50	1.00			
Premature	10	19.61	1	50	4.1	0.15	109.92	0.333
Smoking								
No	150	72.46	12	85.71	1.00			
Yes	57	27.54	2	14.29	2.27	0.60	14.29	0.2903
Diabetes								
No	117	56.52	9	64.29	1.00			
Yes	90	43.48	5	35.71	1.38	0.46	4.55	0.5715
Hypertension								
No	45	21.74	7	50.00	1.00			
Yes	162	78.26	7	50.00	3.57	1.18	11.11	**0.0223**
Dyslipidemia								
No	84	40.58	5	35.71	1.00			
Yes	123	59.42	9	64.29	0.81	0.2427	2.4390	0.7198
Change in CRP								
No	65	34.76	6	46.15	1.00			
Yes	122	65.24	7	53.85	0.62	0.20	2.00	0.4100

ALN *								
0	11	5.79	2	14.29	1.00			
≤2	96	50.53	8	57.14	0.46	0.09	2.43	0.3597
>2	83	43.68	4	28.57	0.26	0.04	1.62	0.1503
TROPONIN I > 0.11 ng/ml								
No	30	14.63	1	7.14	1.00			
Yes	175	85.37	13	92.86	2.23	0.42	41.22	0.4481
CK-MB mass >5.6 ng/ml								
No	58	30.85	5	38.46	1.00			
Yes	130	69.15	8	61.54	0.71	0.23	2.45	0.5688
EF								
<50%	66	36.67	5	38.46	1.00			
≥50%	114	63.33	8	61.54	0.93	0.30	3.17	0.8969

Note: *C-reactive protein (CRP); Arteries Lesion Number (ALN); Ejection Fraction (EF); OR: Odds Ratio; CI: Confidence Interval; p: p-value, obtained through the logistic regression test. *Multinomial logistic regression.*

NPY c.20T>C is associated with altered lipid metabolism[18] and increased the susceptibility to type 2 diabetes mellitus (T2DM) and diabetic retinopathy in T2DM.[35] Bhaskar et al.,[11] evaluated the NPY c.20T>C variant with hypertension and found an association.[11] The variations in the associations are due to variations in allele frequencies across populations. The carrier frequency of the C allele of the NPY c.20T>C ranges from 6-15% in Caucasian populations, but it is very low or absent in Eastern populations.[36,3] The highest allele frequencies were found in the Nordic countries. Moreover, the NPY c.20T>C could originate in northern Europe and then spread to neighboring regions.[36] Our results showed no association between NPY variant c.84G>A and ACS, corroborating with Shah et al.,[7] who showed no existence of an association of this variant with the early onset of atherosclerosis in American and European populations. Regarding NPY c.150G>A, it was not associated with hypertension, corroborating Bhaskar et al.,[11] Studies with Korean and Chinese populations have shown that the variant c.-485T>C of NPY can be considered a genetic risk factor or be involved with stroke.[16,17] Likewise, Shah et al.,[7] demonstrated the association of this variant with the risk of developing early atherosclerosis. Our findings indicate that the NPY2R variant c.-1116A>G is associated with ACS. Although no studies corroborate our findings, the NPY2R variant c.-1116A>G has been associated with obesity in Caucasian Danes[23] and with HDL-C in Japanese populations.[25]

In the present study, pairwise LD values between NPY c.20T>C and c.150G>A variants indicated that there is no strong LD between these markers. These findings were corroborated by a few other studies that did not report a significant LD between these markers.[10,11] Further, a weak LD between the NPY c.20T>C and c.-485T>C variants was demonstrated in this study, corroborating with Patel et al.,[18] The possible explanation for the weak LD between these markers is due to the lack of recombination between adjacent markers or low frequency of the alleles.[3]

The study's primary limitation is that the evaluated population was from Brazil, a country well-known for its high genetic heterogeneity. Genetic diversity studies in five Brazilian geopolitical regions revealed that European ancestry contributed the most (77.1%), followed by African (14.3%) and Amerindian (8.5%) contributions.[38] Pena et al.,[39] also showed that the European ancestry was predominant in all regions studied in Brazil, with proportions ranging from 60.6% in the Northeast to 77.7% in the South. Further, Ferreira et al.,[40] demonstrated that 79% of contributions to a population in the state of São Paulo came from Europeans, 14% from Africans, and 7% from indigenous Brazilian Amerindians. Furthermore, the Rio de Janeiro population had a predominantly European genetic influence (from 55.2 to 58.6%), followed by African (from 31.1 to 30.3%) and Amerindian (from 13.7 to 11.0%) contributions.[41] Further, the number of individuals studied may limit the conclusions of our results.

Table 4 – Analysis of the variant NPY2R c.-1116A>G with habits and biological and clinical features

Variables	NPY2R c.-1116A> G (rs6857530)				OR	95% CI		p
	AA		AG/GG					
	N	%	N	%		Inf	Sup	
Onset of ACS								
Prospective	41	55.41	58	39.46	1.00			
Premature	33	44.59	89	60.54	1.91	1.09	3.37	**0.0253**
Gender								
Male	53	71.62	115	78.23	1.00			
Female	21	28.38	32	21.77	0.70	0.37	1.34	0.2787
Premature								
Male	30	78.95	81	82.65	1.00			
Female	8	21.05	17	17.35	0.787	0.3145	2.1008	0.6172
Prospective								
Male	23	48.94	34	41.46	1.00			
Female	24	51.06	48	58.54	1.3529	0.657	2.7931	0.4114
Gender/Time								
Male								
Prospective	23	43.4	34	29.57	1.00			
Premature	30	56.6	81	70.43	1.8265	0.9275	3.5934	0.0802
Female								
Prospective	18	85.71	24	75	1.00			
Premature	3	14.29	8	25	2	0.4983	10.1178	0.3524
Smoking								
No	55	74.32	107	72.79	1.00			
Yes	19	25.68	40	27.21	1.08	0.58	2.07	0.8077
Diabetes								
No	41	55.41	85	57.82	1.00			
Yes	33	44.59	62	42.18	0.91	0.52	1.60	0.7319
Hypertension								
No	16	21.62	36	24.49	1.00			
Yes	58	78.38	111	75.51	0.85	0.43	1.64	0.6354
Dyslipidemia								
No	30	40.54	59	40.14				
Yes	44	59.46	88	59.86	1.02	0.57	1.79	0.9539
Change in CRP								
No	24	34.29	47	36.15	1.00			
Yes	46	65.71	83	63.85	0.92	0.50	1.69	0.7923

ALN *								
0	5	7.35	8	5.88	1.00			
≤2	35	51.47	69	50.74	1.23	0.38	4.05	0.7307
>2	28	41.18	59	43.38	1.32	0.39	4.39	0.6541
TROPONIN I > 0.11 ng/ml								
No	13	58.82	18	56.62	1.00			
Yes	60	41.18	128	43.38	1.54	0.70	3.33	0.2752
CK-MB mass >5.6 ng/ml								
No	20	30.30	43	31.85	1.00			
Yes	46	69.70	92	68.15	0.93	0.49	1.75	0.8241
EF								
<50%	26	40.00	45	35.16	1.00			
≥50%	39	60.00	83	64.84	1.23	0.66	2.27	0.5099

Note: *C-reactive protein (CRP); Arteries Lesion Number (ALN); Ejection Fraction (EF); OR: Odds Ratio; CI: Confidence Interval; p: p-value, obtained through the logistic regression test. *Multinomial logistic regression.*

Conclusions

In summary, the NPY c.20T>C variant appears to contribute to the development of ACS. The NPY2R c.-1116A>G variant may contribute to the early development of ACS, and the NPY c.84G>A variant appears to contribute to the development of hypertension. In addition, the NPY c.20T>C is associated with a protective effect in ACS severity. This information contributes to a better understanding of the effect of NPY and NPY2R variants in the population under study. Further research with a larger sample size is necessary to confirm our results.

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Author contributions

Conception and design of the research: Soares F, Werkhauser RP, Moraes CNL, Martins DBG, Montenegro SML. Acquisition of data: Soares F, Araújo RM, Carvalho VDCV, Amorim EAS, Silva LCA, Montenegro ST, Neco HVPC. Analysis and interpretation of the data: Soares F, Araújo RM, Werkhauser RP, Bhaskar LVKS, Neco HVPC, Moraes CNL, Martins DBG, Montenegro SML. Statistical analysis: Diniz GT, Tashiro T. Obtaining financing: Montenegro SML. Writing of the manuscript: Soares F. Critical revision of the manuscript for intellectual content: Araújo RM, Werkhauser RP, Bhaskar LVKS, Carvalho VDCV, Amorim EAS, Silva LCA, Montenegro ST, Moraes CNL, Martins DBG, Montenegro SML.

Potential Conflict of Interest

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

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Study Association

This article is part of the thesis of master submitted by Fábia Carla Silva Soares, from Aggeu Magalhães Institute (FIOCRUZ/PE).

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Aggeu Magalhães Institute (FIOCRUZ/PE) under the protocol number CAAE: 03187512.2.0000.5202. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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*Supplemental Materials

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EDITORIAL

Neuropeptides Y and Other Promising Biomarkers in Acute Coronary Syndrome

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Editorial referring to the article: Influence of Neuropeptide Y and Neuropeptide Y 2 Receptor Variants in Acute Coronary Syndrome

Neuropeptide Y (NPY) is a very common neurotransmitter with 36 amino acids that acts as a stimulator of angiogenesis, inflammation and adipogenesis through the NPY2 receptor.[1] The description of high plasma concentrations of NPY in acute coronary syndrome (ACS) and left ventricular dysfunction and its close relationship with the sympathetic nervous system reinforces the possibility of a new prognostic biomarker for risk stratification.[2,3]

In recent years, changes in the NPY signalling pathway have been related to ACS. For example, the NPYc.20T>C mutation is associated with increased serum lipid levels and consequent increase in the risk of ACS, stroke, hypertension, and obesity.[2,3] The NPYc.-485T>C variant has been linked to the development of early atherosclerosis and stroke, and possibly to insulin resistance reduction and development of type 2 diabetes mellitus.[4-8]

Soares et al.,[6] gathered genotypic data of four variants (c.20T>C/c.84G>A/c.150G>A/c.-485T>C) in the NPY gene and two variants (c.-1088C>T/c.-1116A>G) in the NPY2R gene of approximately 500 individuals to determine the correlation of these variants with ACS and TIMI risk.[6] Possibly, discrimination of individuals at intermediate from those at high risk and the correlation with clinical outcomes (morbidity and mortality) would allow a more robust inference of a causal link between variants in the NPY and NPY2R genes and cardiovascular events. Finally, further research is also necessary considering the high phenotypic heterogeneity among individuals and populations, and the potential variability in the association between gene variants and outcomes.[5]

The application of large-scale DNA sequencing methods for the analysis of molecular markers has led to an improvement in these techniques, and the development of larger studies have led to the discovery of new cardiovascular disease biomarkers,[9] including myocardial ischemia (Table 1). The clinical application of these biomarkers has been tested in different scenarios, and advances in genomic, proteomic and metabolomic analyses, with the integration of artificial intelligence, would provide better diagnostic and prognostic information.[10]

Keywords

Acute Coronary Syndrome; Neuropeptide Y; Receptors Neuropeptide Y; Nucleotide Polymorphism; Biomarkers; Obesity; Hypertension; Stroke; Mortality.

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Table 1 – Basic information on biomarkers of cardiomyocyte injury

BIOMARKER	DIAGNOSTIC/ PROAGNOSTIC	ORGAN/CELL OF ORIGIN	HALF LIFE
Troponin I, T	Diagnostic and prognostic	Cardiac thin filament	120 min
hFABP	Prognostic	Cardiomyocyte cytoplasmic protein	27 min
NT-proBNP	Diagnostic and prognostic	Cardiac ventricles	120 min
MR-proANP	Diagnostic and prognostic	Cardiac atrial tissue	60-120 min
CMyBP-C	Diagnostic	Cardiac thin filament	unknown
sST2	Diagnostic	Cardiomyocytes, cardiac fibroblasts, and vascular endothelial cells	unknown
GDF-15	Diagnostic	Multiple cells	unknown
Gal-3	Diagnostic	Multiple cells	unknown
Ceramides	Diagnostic and prognostic	Menbrane lipids	24-72 hours

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ORIGINAL ARTICLE

Effects of Hyperthyroidism on Contractility and Na+/Ca2+ Exchanger Activity in the Isolated Papillary Muscle of Rats

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Abstract

Background: Hyperthyroidism (Hy) is an endocrine disorder, in which the thyroid hormones markedly alter the cardiac function. Increased myocardial contractility and cardiac output, improvement in diastolic relaxation, changes in electrical activity, increments in ventricular mass, and arrhythmias have been reported. However, the influences of thyroid hormones upon molecular mechanisms of cardiac functions have not yet been fully understood.

Objectives: To evaluate changes in cardiac contractile parameters and the Na+/Ca2+ exchanger (NCX) function in induced hyperthyroid rats.

Methods: Hy was induced by intraperitoneal injections of T3 (15 μg/100 g) for 10 days. Contractile parameters and NCX function were evaluated in the isolated papillary muscle. Data normality was confirmed by the Shapiro-Wilk test. The comparison between groups was performed through an unpaired Student's t-test. Results are expressed as mean ± SD. The accepted significance level was $p < 0.05$.

Results: Our data revealed, in the Hy group, an increase of 30.98% in the maximum speed of diastolic relaxation (–284.64 ± 70.70 vs. –217.31 ± 40.30 mN/mm2/sec ($p = 0.027$)) and a boost of 149% in the NCX function in late phase of relaxation (20.17 ± 7.90 vs. 50.22 ± 11.94 minutes ($p = 0.002$)), with no changes in the maximum twitch force ($p = 0.605$) or maximum speed of systolic contraction ($p = 0.208$) when compared to the control.

Conclusion: The improvement in relaxation parameters is hypothetically attributed to an increase in Sarco-Endoplasmic Reticulum Ca2+ATPase isoform 2 (SERCA2) expression and an increased calcium flow through L-type channels that boosted the NCX function.

Keywords: Hyperthyroidism; Thyroid Hormones; Papillary Muscles; Rats; Sodium-Calcium Exchanger; Myocardial Contraction.

Introduction

The thyroid hormones (TH) play a role in the entire organism, regulating biological processes, such as metabolic rate, oxygen consumption, gene transcription, and protein synthesis.[1,2] Hyperthyroidism (Hy) is characterized by an increase in the endogenous production of the triiodothyronine (T3) and/or thyroxine (T4) hormones, or by the exogenous administration of these hormones.[3] The heart is the major target organ for TH actions.[4,5]

In the heart, TH has an effect on the membrane ion channels,[6] on the contractile apparatus, and on the sarcoplasmic reticulum (SR),[7] which are linked to the excitation-contraction coupling mechanism[8] and directly alter contractility.[9]

Common changes reported in the hyperthyroid heart are increased myocardial contractility and cardiac output,[2] improvement in diastolic relaxation,[10] changes in electrical activity,[7] increments in ventricular mass,[5] and arrhythmias.[1]

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In short-term Hy, TH is a positive regulator of the cardiac function. By contrast, in the long-term, TH promotes deleterious effects in the heart,[5] causing heart problems, the major cause of death in hyperthyroid patients.[6] However, the influences of TH in molecular mechanisms of the cardiac function have not yet been fully understood. Thus, the present study aimed to evaluate functional changes in contractile parameters and the Na^+/Ca^{2+} exchanger (NCX) function in the isolated papillary muscle 10 days after hyperthyroidism had been induced in rats. This investigation could bring new evidence to explain the actions of TH in the physiology of the heart.

Methods

Animals

Thirty-two male Wistar rats, weighing 250-300 g were provided by the Experimental Animal Center of the Federal University of Paraná. The animals were kept in cages under controlled conditions of temperature and a light-dark cycle of 12 h, with free access to food and water. All experimental protocols used in this study were approved by the Animal Experimentation Ethics Committee of the Biological Sciences at the Federal University of Paraná (license number: AEEC-747) and conducted in accordance with the National Council of Animal Experimentation (CONCEA) guidelines. Rats were randomly divided into the control group (CG, n=16) and the hyperthyroidism group (HG, n=16). Hy was induced by intraperitoneal injections of T3 (15 μg/100 g) for 10 days. The CG received daily injections of saline solution during the same period.[11] The sample size was calculated based on the following statistical criteria: $r=2t\alpha^2s^2/d^2$, where r is the sample size, s^2 is an estimate of the experimental variance from previously performed experiments; $t\alpha$ is the t value with the s^2 degrees of freedom for the α level of probability; d is the desired difference between treatments. The sample size for each group was calculated as follows: $r=s^2q^2F/d^2$, where s and d were defined in the equation above, and F is the F value for the α level of probability with $\gamma1$ and $\gamma2$ degrees of freedom from performed experiments, and q is the studentized range for the experiment to be performed. The q value is the same as that obtained by the Tukey's test table for the α significance level.[12,13] The randomization was performed on the following website: Randomization.com (www.randomization.com).

General Protocol

After the treatment, the animals were weighed, anesthetized with an intraperitoneal injection of ketamine (50 mg kg^{-1}) and xylazine (20 mg kg^{-1}), and euthanized by exsanguination. The chests were opened, the hearts collected and quickly transferred to a Becker containing Ringer's solution (RN) in order to remove the blood from cardiac cavities. This solution had the following composition (in mM): NaCl = 110, KCl = 4, $CaCl_2$ = 2, $MgCl_2$ = 2, TRIZMA = 10 and glucose = 11, pH adjusted to 7.4 with NaOH or HCl. In sequence, the hearts were weighted and fixed in a Petri dish containing RN for papillary muscle dissection, performed as previously described by Szkudlarek et al.[14]

The myocardial portion was fixed to a micromanipulator while the tendinous portion was attached to a force transducer (Fort 10 WPI, Transduction Laboratories Co.), which was calibrated before each experiment using known masses. The muscles were then transferred to a 3 ml chamber containing RN at 30C°, continuously gassed with pure oxygen. This chamber was built in a mobile acrylic block allowing for the transfer of the muscle from one chamber to another, exposing it to the desired composition solutions.

To evaluate the effects of Hy on the heart, papillary contractility was assessed in two protocols. In the first, twitch measurements, such as maximum isometric twitch force (Tmax), maximum speed of force development (+dF/dt), maximum speed of force decrease (–dF/dt), and maximum force (Fmax) in response to increasing caffeine concentration (0.5, 3, 10 and 30 mM), were evaluated. In the second, the NCX contribution to muscle relaxation was evaluated. After each experiment, the muscle length was measured with a graticule positioned at the eyepiece of a microscope. The cross-sectional area (CSA) was calculated using the formula: $A=\pi r^2$. Tmax, +dF/dt, –dF/dt, and Fmax were normalized by the CSA muscle and are expressed in milliNewton per square millimeter (mN/mm^2). The data were collected using an acquisition system PowerLab 4/30, (AD Instrument) and subsequently analyzed using Lab Chart version 7.3.7 software.

Protocol 1

The isolated papillary muscles attached to the force transducer were stimulated (1 Hz) with supra-threshold voltage pulses (15 V) with a duration of 5 milliseconds through a pair of platinum electrodes positioned along the entire length of the muscle. The muscles were stretched

to the length where the maximum active tension (Lmax) was obtained. Under these conditions, the muscles were maintained for a stabilization period of 30 minutes. The twitch measurements (Tmax, +dF/dt, –dF/dt) were then analyzed for 10 minutes of stable contraction.

After the twitch measurements, papillary muscles were quickly transferred to a chamber containing zero sodium and zero calcium Ringer's solution (R0) for 15 minutes to block the NCX[15] In R0 solution, sodium and calcium ions were replaced with lithium chloride (LiCl) to maintain equal levels of osmolarity and ionic strength, as seen in RN. In sequence, the muscles were transferred to a chamber containing R0 + 0.5 mM caffeine. After reaching the maximum force (Fmax) in a plateau, the muscle was transferred back to the R0 chamber until complete relaxation. The process was then repeated with 3, 10, and 30 mM of caffeine.

Protocol 2

As described above, the muscles were electrically stimulated for a stabilization period of 30 minutes. In sequence, the electrical stimulation was stopped, and the papillary muscle was transferred to a chamber containing R0 + 10 μM of cyclopiazonic acid for 15 minutes in order to block SR Ca^{2+} uptake by Sarco-Endoplasmic Reticulum Ca^{2+}ATPase isoform 2 (SERCA2).[16] The muscle was then transferred to a chamber containing R0 + 30 mM of caffeine. After reaching Fmax in a plateau, the muscle was transferred to a chamber containing RN, unblocking the NCX. In this condition, with the SR Ca^{2+} pump blocked, the NCX contribution was evaluated by the muscle relaxation time for early and late phases of muscle relaxation.

Statistical analysis

Results are expressed as mean ± SD. The Shapiro-Wilk test was used to test data normality. For comparisons between groups, an unpaired Student's t-test was used. For data analysis and plotting, Graph Pad Prism 5 (Graph Pad Software, San Diego, California, USA) was used. The accepted significance level was $p < 0.05$.

Results

Body and heart weight of all animals after 10 days of treatment are represented in Table 1. As expected in HG, body weight decreased 7.35%, and heart weight increased by 18.98% when compared to CG.

Twitch measurements

Tmax and +dF/dt did not differ between groups. However, –dF/dt significantly increased 30.98% in HG (Table 2).

Fmax

As represented in Table 3, the maximum force in response to increasing caffeine concentration did not differ between groups.

NCX assessment for relaxation

After reaching the contraction plateau at 30 mM of caffeine, the early and late phases of muscle relaxation were analyzed. The early phase did not differ between groups. The late phase significantly declined (149%) in HG (Table 4).

Discussion

In this study, contractility in isolated papillary muscles from induced hyperthyroid rats was assessed and demonstrated an increase in the speed of diastolic relaxation (–dF/dt) associated with a higher NCX function when compared to the CG. No changes were observed in contractile force (Tmax and Fmax) or in maximum speed of systolic contraction (+dF/dt).

Table 1 – Body and heart weight

	Body weight	Heart weight
CG	297.80 ± 12.75	1.11 ± 0.07
HG	277.44 ± 17.78	1.37 ± 0.17
p-value	0.010	<0.001

Values are expressed in grams. Data is expressed as mean ± SD. Control Group (CG,n=16) and Hyperthyroid Group (HG,n=16).

Table 2 – Twitch measurements

	Tmax	+dF/dt	-dF/dt
CG	27.76 ± 4.53	263.80 ± 47.17	-217.31 ± 40.30
HG	26.64 ± 4.38	297.91 ± 59.66	-284.64 ± 70.70
p-value	0.605	0.208	0.027

Maximum isometric twitch force (Tmax) is expressed in mN/mm². Maximum speed of contraction (+dF/dt) and maximum speed of relaxation (–dF/dt) are expressed in mN/mm²/sec. Data is expressed as mean ± SD. Control Group (CG, n=8) and Hyperthyroid Group (HG, n=8).

Table 3 – Fmax in response to increasing caffeine concentration

	0.5mM	3mM	10mM	30mM
CG	1.25 ± 0.31	2.56 ± 1.63	2.62 ± 1.56	3.05 ± 1.67
HG	0.88 ± 0.44	1.60 ± 1.13	1.55 ± 1.15	1.98 ± 1.03
p-value	0.178	0.251	0.276	0.239

Maximum force (Fmax) is expressed in mN/mm². Data is expressed as mean ± SD. Control Group (CG, n=8) and Hyperthyroid Group (HG, n=8).

Table 4 Na^+/Ca^{2+} exchanger (NCX) contribution for muscle relaxation

	early phase	late phase
CG	39.40 ± 22.17	50.22 ± 11.94
HG	33.80 ± 29.06	20.17 ± 7.90
p-value	0.741	0.002

Early phase is expressed in seconds. Late phase is expressed in minutes. Data is expressed as mean ± SD. Control Group (CG,n=8) and Hyperthyroid Group (HG, n=8).

In animals treated with T3, an increase in the cardiac mass/body mass ratio is commonly reported.[1,5,14,17] This was also observed in this study. Such results are related to a rise in the basal metabolic rate, increased energy expenditure, and oxygen consumption associated with an increment in protein and lipid catabolism.[10,18] In cardiac myocytes, an increase in total protein synthesis[9] and an incremented expression of the alpha myosin heavy chain (α-MHC)[6] were observed, which resulted in an enhanced myocardial function.[2]

The papillary muscles of hyperthyroid rats showed no changes in contractile force when compared with the controls (Tmax, Table 2), which runs in line with results obtained by Szkudlarek et al.[14] and Vieira et al.[11] Fmax in response to caffeine (Table 3) also showed no differences, which demonstrated that the SR Ca^{2+} content has not changed, which is in agreement with previous data published by Alba-Aguayo et al.[1]

Regarding contractility, represented by +dF/dt and –dF/dt, the available information is conflicting, and there is paucity of data. Our data revealed no changes in +dF/dt and a significant increase in diastolic function in HG when compared to the CG (Table 2); similar results were observed by Szkudlarek et al.[14] and Palmieri et al.[19] Vieira et al.[11] reported an increment in + and –dF/dt and a decrease in time to peak contraction. On the contrary, Wolska et al.[8] reported an increase in time to peak contraction, while

Rozanski et al.[5] reported a decrease in +dF/dt and no changes in –dF/dt.

Szkudlarek et al.[14] showed, in vivo, the effects of Hy in rats using echocardiography, and, in HG, demonstrated a decreased end diastolic volume, a total diastolic time and ejection time associated with the increased heart rate, an ejection fraction, and a cardiac output. In a similar experiment, Palmieri et al.[19] observed in hyperthyroid patients that the increased left ventricle performance was sustained by increased preload with enhanced diastolic function.

The changes in cardiac function promoted by Hy are commonly associated with the upregulation of ryanodine receptors isoform 2 (RyR2)[17,20,21] and SERCA2 expression,[7,9,10] as well as the downregulation of phospholamban (PLB).[1,6,7] Moreover, TH stimulates the expression of β-adrenergic receptors in the heart,[6,8,9] which raises the sensitivity to sympathetic stimulation. The activation of the AMPc/PKA/CaMKII pathway leads to increments in RyR2 and PLB phosphorylation with a consequent rise in the Ca^{2+} release to sarcoplasm and the Ca^{2+} uptake to SR.[22]

For the diastole, Ca^{2+} is removed from the cytosol by four mechanisms: SERCA2, NCX, the plasma membrane Ca^{2+}ATPase (PMCA), and the mitochondrial Ca^{2+} uniporter.[22] In rat ventricles, under normal conditions, approximately 92% of cytosolic Ca^{2+} is removed by SERCA2, 7% by NCX, and 1% by PMCA and Ca^{2+} uniporter.[23] The NCX activity assessment, represented in Table 4, revealed no changes in the early phase of relaxation between the groups. However, a significant decline of 149% in the time of late-phase relaxation was observed in the HG when compared to the CG. Although there is a record of increment,[24] most papers report a decline in NCX expression in Hy.[2,25] Cernohorský et al.[26] showed a 50% reduction in rat ventricular NCX expression. According to Davis & Davis,[27] the PMCA appears to be indirectly influenced by TH through increased PKC activation, although its function is unlikely to influence cytosolic Ca^{2+} concentration.

Another mechanism by which T3 alters the cardiac function is by modulating the activity of Ca^{2+} channels in the cell membrane[2]. Gotzsche[28] attributes the changes in myocardial Ca^{2+} homeostasis to an augmented expression of the β-receptor and the activity of AMPc/PKA/CaMKII pathways, while Yu et al.[29] reports an increased activity of these pathways with increased L-type Ca^{2+} channel phosphorylation, raising the density of Ca^{2+} currents through these channels. According to Bers,[22] the Ca^{2+} that enters via ICa is approximately the same as that extruded by the NCX. A consequence of the increased Ca^{2+} entry in the cell is an increased Ca^{2+} extrusion via NCX, which may have boosted the exchanger activity.

In this work, after the contraction of the papillary muscle had been induced by caffeine in the presence of cyclopiazonic acid, simultaneously with the reactivation of NCX, the late phase of relaxation was reduced. Since in this condition the activity of the SR Ca^{2+} pump was blocked, the relaxation of the muscle was mainly due to NCX activity. This suggests that Hy induced an increase in activity and/or expression of NCX.

Conclusion

Much information is missing concerning hyperthyroidism and the cardiac function, especially in isolated muscles. Certainly, the time at which the cardiac muscle is exposed to an increase in circulating thyroid hormones influences the magnitude of the consequences, whose primary changes seem to be related to an increase in the cardiac mass/body mass ratio and increased relaxation kinetics.

Potential Conflict of Interest

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

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Study Association

This article is part of the thesis of master submitted by Angela Mara Rambo, from *Universidade Federal do Paraná*.

Ethics approval and consent to participate

This study was approved by the Ethics Committee on Animal Experiments of the *Universidade Federal do Paraná* under the protocol number CEEA-747.

Author contributions

Conception and design of the research: Fogaça R, Rambo A. Acquisition of data: Rambo A, Silva I. Analysis and interpretation of the data: Rambo A, Peixoto J, Albuquerque R. Statistical analysis: Peixoto J. Writing of the manuscript: Rambo A, Peixoto J. Critical revision of the manuscript: Fogaça R, Silva I, Albuquerque R.

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EDITORIAL

Hyperthyroidism and Cardiac Contractility

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Editorial referring to the article: Effects of Hyperthyroidism on Contractility and Na+/Ca2+ Exchanger Activity in the Isolated Papillary Muscle of Rats

Much information is lacking on hyperthyroidism and cardiac function, especially in isolated muscles. Certainly, the time the heart muscle is exposed to elevated thyroid hormones (TH) influences the magnitude of their effects.[1] The primary changes seem to be related to increases in the heart mass/body mass ratio and in relaxation kinetics.

These cardiac changes may also be related not only to the time of exposure to excess thyroid hormones, but to the level or intensity of hyperthyroidism, as well as the underlying cardiac condition, which may reflect exercise conditioning and overload. In this sense, the cellular mechanisms of muscle adaptation, energy and oxygen consumption, certainly make differences. As well as muscle strength and sarcoplasmic/endoplasmic reticulum calcium (SRCa) activity, they may also have different individual adaptive characteristics.

In any case, prolonged exposure to excess TH can compromise cardiac contractility and function, which are known causes not only of arrhythmia, but also of heart failure.[2]

There is a need for a mechanistic determination of how TH act on myocardial contractility. In this Journal, the authors study, in rat models, the intracellular mechanisms involved in the excess of thyroid hormones (hyperthyroidism) in the contractility and Na+/Ca2+ Exchanger Activity in the heart muscle.[3] However, not all physiological mechanisms can be extrapolated from animals to humans because of their differences and specificities. In clinical practice, we still control heart rate with beta-blockers, and in case of contraindication, with benzothiazepine and calcium channel blocker.

The actions of TH on cardiovascular system involve an increase in heart rate and cardiac contractility, an improvement in systolic and diastolic function of the heart, and a decrease in systemic vascular resistance. Some molecular pathways that mediate the role of TH in the cardiovascular system have been better described in recent years. Genomic and non-genomic molecular pathways underlie the effects of TH on cardiomyocytes. That is, the effects of THs at the cardiac intracellular level are divided into genomic and non-genomic pathways. In the genomic pathway, TH regulate the expression of target genes binding to nuclear receptors on cardiomyocytes, and exert a modulatory and adaptive effect, regulating gene expression. In contrast, the non-genomic pathway includes effects on cardiomyocyte ion channels and effects of THs on peripheral circulation, which regulate hemodynamics and cardiac ejection fraction, and seems be more immediate and permissive to the actions of catecholamines.[2]

A deep understanding of the physiological mechanisms, regulations, and actions of TH on cardiomyocytes are fundamental for the development of new therapeutic targets for control and treatment. Furthermore, it also allows to elucidate the mechanisms of arrhythmia induction, as well as cardiomyocyte remodeling and dysfunction induced by these hormones.

Keywords

Thyroxine; Myocardial Contraction; Arrhythmias, Cardiac; Heart Failure; Rats; Calcium Channels

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ORIGINAL ARTICLE

Epidemiological Profile of Patients with Infective Endocarditis at three Tertiary Centers in Brazil from 2003 to 2017

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Abstract

Background: Infective endocarditis (IE) is a disease with high morbimortality and an increasing incidence. With improved diagnosis and treatment, a number of epidemiological changes have been reported over time.

Objectives: We sought to describe the epidemiological profile, mortality predictors, and analysis of a possible microbiological transition in patients admitted to three tertiary centers in Brazil.

Methods: In this cross-sectional retrospective study, data from 211 patients with definite or probable IE were analyzed according to the modified Duke criteria between 2003 and 2017. The association between categorical variables was assessed using the chi-square or Fisher's exact test, and binary logistic models were built to investigate mortality. We considered $p < 0.05$ statistically significant.

Results: The median age of the sample was 48 (33-59) years old, 70.6% were men, and the most prevalent pathogen was *Staphylococcus spp.* (19%). Mortality was 22.3%, with increasing age being the leading risk factor for death ($p = 0.028$). Regarding the location of the disease, native valves were the most affected site, with the aortic valve being more affected in men than women ($p = 0.017$). The mean number of cases of *Staphylococcus* spp. ($\tau = 0.293$, $p = 0.148$) and *Streptococcus* spp. ($\tau = -0.078$, $p = 0.727$) has remained stable over the years.

Conclusion: No trend towards reduced or increased mortality was evident between 2003 and 2017. Although *Staphylococcus* spp. were the most prevalent pathogen, the expected epidemiological transition could not be observed.

Keywords: Infective Endocarditis; Epidemiology; Mortality; Streptococci; staphylococci; Hospitalization; Comorbidities.

Introduction

With improved resources for the prevention, diagnosis, and treatment of infective endocarditis (IE), significant changes in the characteristics of the disease have been reported over time. If, on the one hand, the prevalence of IE due to rheumatic valve disease has decreased, on the other, there has been an increase in IE related to degenerative valve disease in older adults, valve replacement surgery, the implantation of intracardiac devices, and the use of injectables and hemodialysis. Coincidentally, IE cases due to *Staphylococcus* spp. have surpassed those of *Streptococcus* spp., and cases due to atypical microorganisms have also increased.[1,2] This microbiological change is attributed to medical progress and the resulting increase in invasive procedures.[3,4]

Despite efforts to the contrary, IE is still considered a condition with persistently high morbimortality,

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and its incidence has increased over time.[1] However, most studies that observed this change were conducted in developed countries, and it is unclear whether developing countries are susceptible to this epidemiological transition to the same extent and magnitude, given the possible difference in access to medical resources.[3] Furthermore, it is extremely relevant to understand the risk factors associated with mortality as well as the profile of patients affected by IE.[5,6]

Only 10 epidemiological studies on IE have been published in Brazil, and none of them addressed this possible change, especially since their samples were included over a limited time span. Considering the high regional variability and epidemiological transition in IE, the purpose of this study was to survey the characteristics of a population of patients with IE over 14 years to analyze the behavior of variables over time, determine predictors of mortality, and better understand the profile of affected individuals.

Methods

Sample description and design

This observational, retrospective, cross-sectional study included 211 patients admitted to 3 tertiary health centers in Ipatinga and Belo Horizonte in the state of Minas Gerais, Brazil, between 2003 and 2017. An initial survey of medical records containing International Classification of Diseases related to IE (ICD 10 I33.0) was conducted. These records were analyzed and information on epidemiological, microbiological, valvular, and outcome characteristics were collected in an Excel database.

The inclusion criterion was definite or probable IE according to the modified Duke criteria.[7] Patients whose medical records were incomplete, who were transferred during hospitalization, or who were still hospitalized at the time of analysis were excluded. After selection, data from the medical records were collected, including age, sex, blood culture, and prognosis. The microbiology was determined through blood culture results, and the location of the IE was determined through echocardiographic or perioperative findings.

This study was approved by the ethics committee of the Faculty of Medical Sciences of Minas Gerais (CAAE 60893616.7.0000.5134). Informed consent was not required due to the retrospective nature of the study.

Statistical analysis

Categorical variables are presented as absolute and relative frequencies, and quantitative variables are presented as median (1^{st} – 3^{rd} quartile). The normality of quantitative variables was assessed using the Shapiro-Wilk test, while the Wilcoxon-Mann-Whitney test was used to compare quantitative variables among groups. The association between categorical variables was assessed using the chi-square test and Fisher's exact test. Binary logistic models were constructed to verify the association with mortality, and the results are presented as odds ratios (OR) and 95% confidence intervals. The Mann- Kendall test was used to verify the temporal trend. The analysis was performed in R version 3.5.2, with $p < 0.05$ considered significant.

Results

The sample consisted of 211 patients, whose profile has been described in a previous study:[8] 110 from Belo Horizonte and 101 from Ipatinga. Their median age was 48.0 (33-59) years and 70.6% were men. Bacteria of the genus *Staphylococcus* were the most prevalent pathogens, observed in 19% of cases, with *Staphylococcus aureus* occurring in 10% and *Coagulase-negative Staphylococci* in 9%. Native valves were the site of IE in 70.6% of the cases, and the greatest prevalence was in the mitral valve (41.7%), (Table 1).

Mortality

Overall mortality was 22.3%. It was observed that increasing age is a risk factor for death ($p = 0.028$). However, when the sample was stratified into patients younger and older than 65 years of age, there was no statistical relevance (Table 2). Among patients younger than 65 years who died, the native aortic valve was the most affected site (33.3%) and *Staphylococcus* spp. was the most frequent pathogen, representing 30.6% of the cases. Regarding the 11 deaths in patients older than 65 years, most were due to *Streptococcus* spp., and the most prevalent location was the native mitral valve. Sex, blood culture findings, and lesion location had no statistical relevance on mortality. Mortality from IE remained stable between 2003 and 2017 ($\tau = 0.010$). The highest and lowest death rates occurred in 2004 and 2012, respectively.

Table 1 - Characteristics of 211 patients with infective endocarditis

Characteristic	Total (*n=211*)
Sex	
Male	149 (70.6%)
Female	62 (29.4%)
Age (years) (median [1st – 3rd quartile])	48.00 (33-59)
< 18	15 (7.1%)
18 to 29	25 (11.8%)
30 to 44	55 (26.1%)
45 to 64	78 (37%)
65 or more	38 (18%)
Definite infective endocarditis*	118 (56%)
Possible infective endocarditis*	93 (44%)
Deaths	47 (22.3%)
Blood culture findings	
Staphylococcus spp.	40 (19%)
Staphylococcus aureus	21 (10%)
Coagulase-negative Staphylococci	19 (9%)
Streptococcus spp.	31 (14.7%)
Enterococcus spp.	14 (6.6%)
Other†	10 (4.7%)
Not specified	14 (6.6%)
Negative blood culture	71 (33.6%)
Location	
Native valves‡	149 (70.6%)
Mitral	88 (41.7%)
Aortic	56 (26.5%)
Tricuspid	21 (10%)
Pulmonary	3 (1.4%)
Prosthetic valves	51 (24.2%)
Pacemaker cable	9 (4.3%)
Other§	6 (2.8%)
Unidentified location	3 (1.4%)

** According to the modified Duke criteria for infective endocarditis[7].*
† Candida spp., Proteus mirabilis, Proteus penneri, E. coli, Enterobacter sp., Klebsiella sp., Achromobacter xylosoxidans, Morganella morganii, Stenotrophomonas maltophilia, Facklamia hominis.
‡ Some patients had lesions in more than one place.
§ Right atrium, pulmonary arteries, ostium of the interventricular defect, ostium of the superior vena cava.

Table 2 – Mortality risk analysis in 211 patients with infective endocarditis

Characteristic	Death		OR (CI 95%)	p-value
	No (n=164)	Yes (n=47)		
Sex				
Male	117 (71.3%)	32 (68.1%)	-	-
Female	47 (28.7%)	15 (31.9%)	1.167 (0.568; 2.323)	0.611
Age (years) (median [1st - 3rd quartile])	46.00 (31-59)	52.00 (39-63)	1.020 (1.003; 1.039)	0.028
<65	137 (83.5%)	36 (76.6%)	-	-
65 or more	27 (16.5%)	11 (23.4%)	1.550 (0.263; 3.358)	0.277
Blood culture findings				
Staphylococcus spp.	28 (17.1%)	12 (25.5%)	1.665 (0.750; 3.548)	0.195
Staphylococcus aureus	15 (9.1%)	6 (12.8%)	1.454 (0.493; 3.827)	0.467
Coagulase-negative Staphylococci	13 (7.9%)	6 (12.8%)	1.700 (0.568; 4.590)	0.311
Streptococcus spp.	26 (15.9%)	5 (10.6%)	0.632 (0.204; 1.625)	0.377
Enterococcus spp.	9 (5.5%)	5 (10.6%)	2.050 (0.603; 6.268)	0.219
Other*	10 (6.1%)	-	-	-
Not specified	11 (6.7%)	3 (6.4%)	0.948 (0.208; 3.197)	0.937
Negative blood culture	59 (36%)	12 (25.5%)	0.610 (0.285; 1.237)	0.184
Location				
Native valves†	114 (69.5%)	35 (74.5%)	1.279 (0.627; 2.756)	0.511
Mitral	70 (42.7%)	18 (38.3%)	0.833 (0.423; 1.609)	0.591
Aortic	43 (26.2%)	13 (27.7%)	1.076 (0.506; 2.190)	0.844
Tricuspid	15 (9.1%)	6 (12.8%)	1.454 (0.493; 3.827)	0.467
Pulmonary	2 (1.2%)	1 (2.1%)	1.761 (0.081; 18.779)	0.647
Prosthetic valves	40 (24.4%)	11 (23.4%)	0.947 (0.426; 1.985)	0.889
Pacemaker cable	7 (4.3%)	2 (4.3%)	0.997 (0.145; 4.297)	0.997
Other‡	5 (3%)	1 (2.1%)	0.691 (0.036; 4.428)	0.739
Unidentified location	3 (1.8%)	-	-	-

** Candida spp., Proteus mirabilis, Proteus penneri, E. coli, Enterobacter sp., Klebsiella sp., Achromobacter xylosoxidans, Morganella morganii, Stenotrophomonas maltophilia, Facklamia hominis. OR: odds ratio.*
† Some patients had lesions in more than one place.
‡ Right atrium, pulmonary arteries, ostium of the interventricular defect, ostium of superior vena cava.
P-value refers to the logistic regression model.

Differences between the sexes

Of the 211 patients, 149 were men and 62 were women. A total of 82.3% of the men and 81.9% of the women diagnosed with IE were younger than 65 years of age (no significant difference). Native valves were most affected, especially the mitral valve, regardless of the patient's sex, representing 40.3% of the infections in men and 45.2% in women, while the pulmonary valve was the least affected site. Of note, prosthetic valve endocarditis occurred in 22.8% and 27.4% of the men and women, respectively, at a ratio of approximately

1:3 in relation to native valves. The native aortic valve was significantly more affected in men than women (p = 0.017). There was no association between the other findings (blood culture, age group, and other IE sites) and sex.

Microbiological agent

Table 3 shows the relationship between microbiological findings, age, and affected valve. There was no association between a specific microorganism and age, with individuals younger or older than 65 being equally affected. Infection by atypical microorganisms was more common in patients with prosthetic valve endocarditis (p = 0.014). Individuals without mitral lesions were more prone to infection by *Coagulase-negative Staphylococci* (p = 0.026). Regarding the main pathogens found during the study period (Figure 1), all had a non-significant trend according to the Mann Kendall test: *Staphylococcus* spp. (τ = 0.293, p = 0.148), *Streptococcus* spp. (τ = -0.078, p = 0.727) and negative blood culture (τ = -0.332, p = 0.100), which indicates that the occurrence of these microorganisms was stable over the years.

Discussion

IE is a serious infectious disease, and a multidisciplinary approach involving specialists is necessary to treat and monitor these patients. Although the incidence of IE has been increasing over the years,[9] few studies have been published on IE in developing countries, which makes a general analysis difficult. The overall mortality in our sample was 22.3%, which is consistent with several other observational studies,[10,11] including some conducted in developing countries.[12] The logistic regression model (Table 2), showed that patient age was directly related to mortality [p = 0.028; OR 1.020, 95% CI 1.003; 1.039], which agrees with other studies, eg, Khan et al.,[13] who obtained a similar result with a sample of 523,432 patients in the United States. Moreover, this study reported a trend over the years toward reduced mortality in IE patients, which the authors ascribed to improved medical services in the USA. However, such a trend was not observed in our analysis.

No significant differences were found regarding microbiological profile and mortality, which contrasts

Table 3 – Distribution of microbial agents according to age and location

Microorganism	Age (years)			Mitral valve affected			Aortic valve affected		
	< 65 n=173	≥ 65 n=38	p-value	No n=123	Yes n=88	p-value	No n=155	Yes n=56	p-value
Staphylococcus spp.	32 (18.5%)	8 (21.1%)	0.892†	29 (23.6%)	11 (12.5%)	0.065†	29 (18.7%)	11 (19.6%)	1.000†
Staphylococcus aureus	18 (10.4%)	3 (7.9%)	0.773‡	13 (10.6%)	8 (9.1%)	0.904†	18 (11.6%)	3 (5.4%)	0.296‡
Coagulase-negative Staphylococci	14 (8.1%)	5 (13.2%)	0.348‡	16 (13%)	3 (3.4%)	0.026‡	11 (7.1%)	8 (14.3%)	0.181†
Streptococcus spp.	25 (14.5%)	6 (15.8%)	1.000†	18 (14.6%)	13 (14.8%)	1.000†	22 (14.2%)	9 (16.1%)	0.905†
Enterococcus spp.	10 (5.8%)	4 (10.5%)	0.286‡	7 (5.7%)	7 (8%)	0.581‡	9 (5.8%)	5 (8.9%)	0.531‡
Other*	7 (4%)	3 (7.9%)	0.391‡	8 (6.5%)	2 (2.3%)	0.199‡	8 (5.2%)	2 (3.6%)	1.000‡
Not specified	10 (5.8%)	4 (10.5%)	0.286‡	10 (8.1%)	4 (4.5%)	0.404‡	9 (5.8%)	5 (8.9%)	0.531‡
Negative blood culture	61 (35.3%)	10 (26.3%)	0.386†	35 (28.5%)	36 (40.9%)	0.082†	53 (34.2%)	18 (32.1%)	0.910†

** Candida spp., Proteus mirabilis, Proteus penneri, E. coli, Enterobacter sp., Klebsiella sp., Achromobacter xylosoxidans, Morganella morganii, Stenotrophomonas maltophilia, Facklamia hominis. † Chi-square test. ‡ Fisher's exact test.*

Table 3 (continuation) - Distribution of microbial agents according to age and location

Microorganism	Tricuspid valve affected			Prosthetic valves affected		
	No n=190	Yes n=21	p-value	No n=160	Yes n=51	p-value
Staphylococcus spp.	33 (17.4%)	7 (33.3%)	0.139†	31 (19.4%)	9 (17.6%)	0.945†
Staphylococcus Aureus	17 (8.9%)	4 (19%)	0.140‡	17 (10.6%)	4 (7.8%)	0.789†
Coagulase-negative Staphylococci	16 (8.4%)	3 (14.3%)	0.413‡	14 (8.8%)	5 (9.8%)	0.784‡
Streptococcus spp.	29 (15.3%)	2 (9.5%)	0.746‡	25 (15.6%)	6 (11.8%)	0.652†
Enterococcus spp.	12 (6.3%)	2 (9.5%)	0.636‡	10 (6.2%)	4 (7.8%)	0.748‡
Other*	10 (5.3%)	-	-	4 (2.5%)	6 (11.8%)	0.014‡
Not specified	13 (6.8%)	1 (4.8%)	1.000‡	9 (5.6%)	5 (9.8%)	0.334‡
Negative blood culture	62 (32.6%)	9 (42.9%)	0.485†	56 (35%)	15 (29.4%)	0.572†

** Candida spp., Proteus mirabilis, Proteus penneri, E. coli, Enterobacter sp., Klebsiella sp., Achromobacter xylosoxidans, Morganella morganii, Stenotrophomonas maltophilia, Facklamia hominis.*
† Chi-square test.
‡ Fisher's exact test.

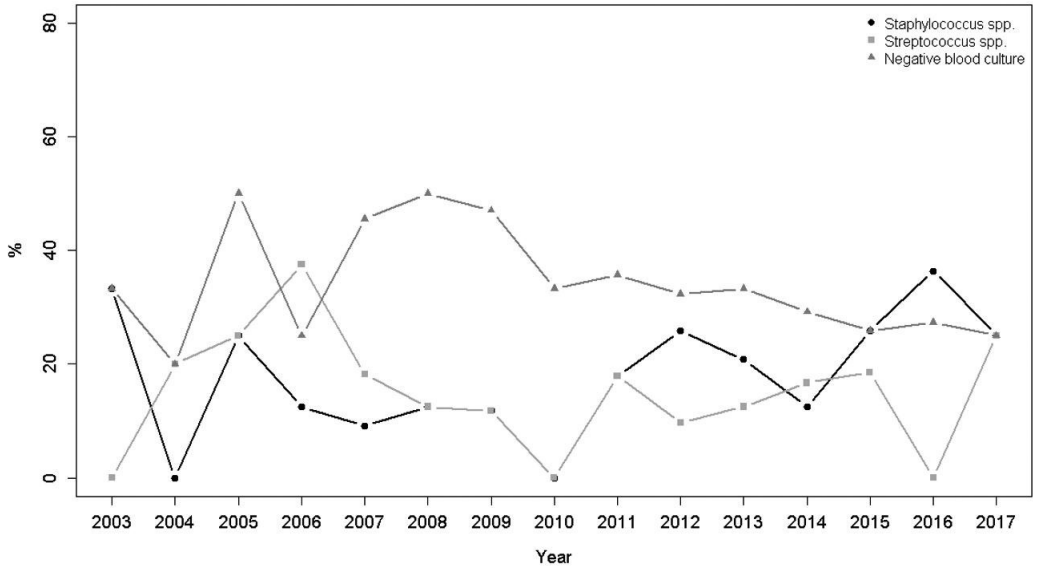

Figure 1 – Main blood culture findings per year. Figure caption: All findings had a non-significant trend according to the Mann-Kendall test (τ = 0.293, p = 0.148, for Staphylococcus spp.; τ = -0.078, p = 0.727, for Streptococcus spp. and τ = -0.332, p = 0.100 for blood culture negative). Source: The authors

with the results of Joffre et al.,[14] who found an association between *Staphylococcus* spp., *Candida* spp. and higher in-hospital mortality, as well as an association between IE due to *Streptococcus* spp. and a more favorable prognosis. It should also be pointed out that these authors found male sex to be a protective factor against death. Other authors have found a direct relationship between mortality and endocarditis location, with the aortic and mitral valves having the worst outcomes.[9,15,16] However, we did not observe this in the present study.

It is possible that comorbidities (e.g. hypertension, heart disease, etc.) and events (e.g. septic shock, need for surgical approach) affect prognosis more than the microbiological or valvular characteristics of the IE. Ren et al.[15] found significant associations between higher mortality and conditions such as hemorrhagic and ischemic stroke, constrictive heart failure, pneumonia, and renal failure. One limitation of our study is the lack of data on these variables.

In general, IE affected men the most (70.6%), at a ratio of 1.7:1. This difference has been found by other authors in Belgium,[17] Saudi Arabia,[18] and Brazil,[9,19] and Bakir et al.,[20] ascribed it to the potential protective role of estrogen against endothelial injury. Other authors have reported a lower prevalence of IE in women, including a lesser likelihood of developing sepsis.[21,22] Nevertheless, none of these mechanisms are fully understood. It is curious that, although IE affects fewer women, it seems to be related to higher in-hospital mortality.[23,24] In fact, prognostic scales such as the EuroSCORE and the results of Martínez-Sellés et al.,[25] indicate a worse outcome among women and a greater likelihood of death.

Furthermore, our analysis showed that native aortic valves are more affected in men than women ($p = 0.017$), which was also described by Sevilla et al.,[26] and Elamragy et al.,[27] who further described that the native mitral valve was more affected in women. Regarding the microbiological profile between the sexes, the most frequent microorganism was *Staphylococcus* spp. (22.6% men vs 17.4% women, $p = 0.501$), a result similar to other authors.[27] The equally high negative blood culture rate in men and women is also of note (32.9% and 35.5% respectively, $p = 0.838$), which may be explained by the indiscriminate use of antibiotics to treat any febrile disease before obtaining cultures, a common practice in Brazil. It should be pointed out that some studies have found a much higher percentage of negative blood cultures than ours, eg, in Egypt (69.5%)[27] and South Africa (55.3%),[28] while others have found lower percentages, eg, in France (9%)[29] and the United Kingdom (12.2%).[30] Thus, it could be cautiously inferred that Brazil is somewhere in the middle of a broad spectrum, which might be associated with improvements to the Brazilian public health system, as well as new and more effective hospital protocols.

The relationship between the affected valve and the blood culture results diverges greatly among studies. What became clear in our study was that a positive blood culture for *coagulase-negative staphylococci* is less related to mitral valve lesion (Table 3), which was also reported by Barrau et al.,[31] These authors also found that *Staphylococcus aureus* affects the aortic valve the least. Another important result of our study was that patients with cardiac prostheses were more likely to be affected by bacteria in the "other" category, which may reflect inadequate laboratory techniques or less strict criteria for diagnosing IE.[32,33]

Finally, we should point out that we found *Staphylococcus* spp. to be the most prevalent pathogen, which agrees with the literature.[1-4,34] However, we did not observe the reported epidemiological transition toward more cases due to *Staphylococcus* spp. and fewer cases due to *Streptococcus* spp. (Figure 1) over the years as consequence of medical progress. Most studies reporting this trend have been conducted in developed countries,[1] and little evidence for such a trend has been found in low/middle income countries, either due to the precariousness of medical systems or the scarcity of new studies.

Limitations

Our study is not without limitations. First, since we performed a retrospective analysis, associations between variables do not necessarily indicate a causal relationship. Second, the sample can be considered small, since we dealt with cases over 15 years at three different centers, as well as the fact that it included many probable IE cases (93 out of 211). However, few studies have been published on the epidemiological profile of Brazilian patients and, to the best of our knowledge, our study involves the largest such sample. It should also be pointed out that most of the probable IE cases involved a negative blood culture, which is related to the use of antibiotics. Third, no data

on comorbidity, heart valve disorder, hemodynamic variables, heart failure, abscess formation, or heart valve surgery were collected. Thus, any discussion of mortality must be extremely limited. Finally, it was not possible to collect blood samples for blood culture in 34 patients, either because they received treatment prior to collection or because they began antibiotic therapy before being transferred to tertiary centers.

Conclusion

In conclusion, among the 211 IE cases included in this study, age had the greatest influence on mortality. However, a trend towards reduced or increased mortality was not evident during the study period. Although more infections occurred in native aortic valves in men than women, no specific bacteria stood out. Additionally, in patients whose IE was due to *coagulase-negative staphylococci*, the mitral valve was less likely to be affected, whereas patients with heart prostheses were more likely to be infected with bacteria in the "other" category. Even though *Staphylococcus* spp. were the most prevalent pathogen in the sample, we did not observe the epidemiological transition described in literature. Finally, further research is needed to better understand the risk factors associated with mortality in developing countries, especially comorbidities, symptoms present at admission, and the effects of surgical interventions.

Author contributions

Conception and design of the research: Bezerra RL, Salgado LS, Silva YM, Figueiredo GGR, Cunha AGJ. Acquisition of data: Bezerra RL, Silva YM. Analysis and interpretation of the data: Bezerra RL, Salgado LS, Silva YM, Figueiredo GGR, Cunha AGJ. Statistical analysis: Gomes IC. Writing of the manuscript: Bezerra RL, Salgado LS, Silva YM, Figueiredo GGR. Supervision: Filho RMB, Machado ELG, Cunha AGJ. Critical revision of the manuscript for intellectual content: Filho RMB, Machado ELG, Cunha AGJ.

Potential Conflict of Interest

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

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Study Association

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Ethics approval and consent to participate

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

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ORIGINAL ARTICLE

Use of Diuretics is Associated with Higher Risk of Sarcopenia in Older Adults with Hypertension

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Abstract

Background: Sarcopenia is a disease that involves skeletal muscle mass loss and is highly prevalent in the older adult population. Moreover, the incidence of sarcopenia is increased in patients with hypertension.

Objective: The study aimed to evaluate the association between the classes of the drugs used for arterial hypertension treatment and the presence or absence of sarcopenia.

Methods: 129 older adults with hypertension were evaluated by the researchers who registered the participants medication for arterial hypertension treatment. Sarcopenia level was measured by anthropometric parameters, muscular strength, and functional capacity. The data were analyzed by one-way ANOVA followed by post-hoc test and Fisher's exact test; statistical significance was set at 0.05.

Results: Age was not different between women with different levels of sarcopenia, but significant differences were observed between men with absent sarcopenia (66.8±4.2 years) and men with probable sarcopenia (77.0±10.2 years). Individuals with absent sarcopenia showed higher handgrip strength (men: 33.8±7.4, women: 23.2±4.6 Kgf) in comparison with those with sarcopenia (men with probable sarcopenia: 9.5±3.3 Kgf, women with probable, confirmed, and severe sarcopenia: 11.7±2.5, 12.2±3.0, 11.8±1.8 Kgf, respectively). The analysis showed an association between the type of medication and degree of sarcopenia; diuretics were significantly associated with probable sarcopenia, and angiotensin II receptor blockers (alone or in combination with diuretics) was associated with absence of sarcopenia.

Conclusions: In conclusion, handgrip strength was a good method to diagnose sarcopenia, and diuretics were associated with increased risk of sarcopenia in older adults with hypertension.

Keywords: Hypertension; Diuretics/therapeutic use; Sarcopenia/complications; Aging; Angiotensin Receptor Blockers.

Introduction

Sarcopenia is defined as a progressive and generalized loss of skeletal muscle mass and function (i.e., muscle power, muscle strength, and physical performance).[1-5] Since 2016, it has been recognized as a disease.[6] People aged 50 years and older lose 1% of skeletal muscle mass, 2% of gait speed, and 1.9 to 5.0% of handgrip strength per year,[7,8] and these variables have been used for the assessment of sarcopenia by renowned organizations.[9] However, the cause and pathogenesis of sarcopenia are not fully understood; the target in sarcopenia treatment is to improve patient survival and quality of life.

Sarcopenia is highly prevalent in older adults,[10] and the incidence of arterial hypertension is over 70% in this population. Data from population studies have shown that the prevalence of hypertension is increased in patients with sarcopenia.[11]

Hypertension pharmacotherapy usually consists of single therapy or a combination of different medications.

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The most used medication classes are angiotensin II receptor blockers (ARBs), angiotensin-converting enzyme inhibitors (ACEIs), diuretics (DIUs), calcium channel blockers, and beta-blockers.[12]

Several researchers have investigated the contribution of different medications to the treatment of sarcopenia, including the role of the renin angiotensin system in skeletal muscle and functional capacity.[13] The renin-angiotensin system modulates muscle function, and ARBs and ACEIs have been shown to remodel the skeletal muscle, protecting against atrophy by transforming growth factor beta.[14] ACEIs have been used to improve skeletal muscle function, as they increase endothelial function, promote angiogenesis, and have anti-inflammatory effects that increase mitochondrial content and insulin-like growth factor values.[15-17]

Meanwhile, the chronic use of loop DIUs, one of the classes of medication used in the treatment of hypertension, has been shown to potentially cause loss of muscle function by suppressing the sodium-potassium pump. In patients with renal failure,[18] heart failure, and hypertension, treatment with DIUs impairs the sodium-potassium pump function. Muscle biopsy specimens of patients have shown decreased intracellular potassium and increased intracellular sodium concentration.[19]

The present study aimed to evaluate the possible associations between drugs used for hypertension and the presence or absence of sarcopenia in the older adult. Handgrip strength, skeletal muscle mass, and physical performance measure were used to determine the level of sarcopenia, following the European Working Group on Sarcopenia in older people criteria.[20]

Material and methods

Study design and participants

This cross-sectional study was conducted from June 2018 to April 2019 in three public geriatric healthcare centers in the cities of Ouro Preto and Mariana, Brazil. The sample was 129 older adults of both sexes, who were recruited by convenience. The sample size was calculated for an 80% confidence interval, using a sample size of 15,000 (prevalence of older adults in the two cities evaluated), anticipated frequency of 70% and test power of 5%.

Inclusion criteria were patients older than 60 years taking anti-hypertensive drugs, capable of walking without assistance, with no history of injury in the lower limbs in the last six months. Patients taking beta-blockers and those with comorbidities other than hypertension were excluded from the study. The study was approved by the ethics committee of the Federal University of Ouro Preto (approval number 82376117.3.0000.5150). All participants signed an informed consent form and received information regarding participation in the study.

Collection of clinical data

For assessment of the drugs used for the treatment of hypertension and other comorbidities, we developed a standard questionnaire with the following information: name of the medication used, and dosage (dose/frequency/time) prescribed. Patients were stratified by classes of antihypertensive drugs.

Anthropometric measurements

The following anthropometric measurements were assessed – body mass (Kg), height (H; in meter), body mass index (body mass [Kg]/height squared [m²], and percentage of body fat and muscle mass. Body fat was estimated using the tetrapolar bioelectrical impedance method (Biodynamics TBW 310); four electrodes were used: two electrodes (with red clips) placed on the posterior surface of the hand (one on middle finger and the other slightly above the wrist joint) and two (with black clips) placed on the posterior surface of the foot (one at the base of the middle finger and the other slightly above the ankle joint line between the malleoli) on the right side of the participant.[21,22] Skeletal muscle mass (SMM) was estimated using the formula proposed by Janssen et al.,[23] using H (in centimeters), bioimpedance resistance (R; in ohm), sex (0 = women; 1 = men), and age parameters: $SMM = [(H^2 / R \times 0.401) + (sex \times 3.825) + (age \times 0.071)] + 5.102$.

Handgrip strength

Handgrip strength was measured using an analog handheld dynamometer (Jamar®) to measure handgrip strength.[22] Each participant was seated on a standard armless chair in an uptight trunk position with a 90° knee angulation, neutrally rotating abduction shoulder, 90° elbow flexion, slight forearm pronation, and neutral wrist. At the evaluator's cue, each participant applied their maximum strength to the device with the dominant hand; motivational verbal commands were used to optimize the test.[22] The test was performed three times with five seconds of duration for each attempt and one minute of rest between attempts to avoid muscle fatigue during the test.

Physical performance

The four-meter walking test was used to assess physical performance. Each participant was asked to walk six meters on a flat straight course at the fastest speed possible, and the time required to walk the central four meters was measured.[24] The highest speed among three measurements was used in the analyses; the cutoff adopted was <0.8 m/s for both sexes, as proposed by the European Consensus.[9]

Diagnosis of sarcopenia

The diagnosis of sarcopenia and analysis of the degree of sarcopenia were made based on the European Working Group on sarcopenia in older people criteria,[20] which requires the measurement of a combination of muscle mass, muscle strength, and physical performance. Diagnosis started with the measurement of muscle strength (handgrip strength test), with a cut-off point of 27 kilogram-force (Kgf) for men and 16 Kgf for women;[9] results lower than these values indicated probable sarcopenia. The second step was the measurement of muscle mass, with cutoffs of 8.5 kg/m^2 for men and 5.75 kg/m^2 for women.[25] Participants with low muscle strength and muscle masses below these values had the diagnosis of sarcopenia confirmed. The third step was the measurement of physical performance through gait speed, values below the cut-off of 0.8 m/s indicated severe sarcopenia. Then patients were classified into four categories: absent, probable sarcopenia, sarcopenia, and severe sarcopenia.

Statistical analysis

Continuous variables were described as mean and standard deviation, and categorical variables as absolute and relative frequencies. Comparisons of continuous variables (age, muscle mass index, handgrip strength, and gait speed), were assessed using GraphPad Prism (Version 6.0). First, data normality was verified by the Kolmogorov–Smirnov test. Subsequently, one-way ANOVA was performed, followed by Tukey's post hoc test. Statistical significance was set at $p<0.05$.

The categorical variables: type of medication and degree of sarcopenia were displayed in a contingency table, and Fisher's exact test [26] was performed to verify whether these variables were associated. Subsequently, the correspondence analysis (a multivariate technique) [27] was used to elucidate the nature of this association, particularly to identify which combinations of variables that contributed most to the association. Correspondence analysis was performed with the "FactoMineR" package[28] of R language.

Results

Table 1 shows characteristics of participants and medications used to treat hypertension. Most patients used ARBs + DIUs (n=119; 70,4%), followed by calcium blockers (n=22; 13.0%), ACEIs (n=14; 8,3%), and beta-blockers (n=13; 7,7%). Table 1 also lists the number of classes of medication used by the patients.

Figure 1 shows the mean number of patients according to the level of sarcopenia (absent; probable; confirmed; and severe) and age (a), handgrip strength (b), muscle mass index (c), and gait speed (d). The results revealed a difference between men's age in the "probable sarcopenia" group compared with "absent" group, and none of the men showed confirmed or severe levels of sarcopenia. Individuals with sarcopenia reported lower handgrip strength, and those with severe sarcopenia had lower muscle mass index and lower gait speed.

Regarding the drugs used to treat hypertension, only seven individuals did not use ARBs or DIUs. In addition, of the 31 individuals who were diagnosed with sarcopenia, 25 used ARBs, DIUs, or a combination thereof. We chose to study the association between sarcopenia and the drugs used for hypertension treatment in the 53 individuals who used only ARBs (n = 17), DIUs (n = 13), or the combination of ARBs + DIUs (n = 23). Distribution of these combinations is illustrated in Figure 2.

The variables "type of medication" and "degree of sarcopenia" were then displayed in a two-way contingency table (Table 2). The Fisher's exact test indicated that these two categorical variables were associated (p-value: 0.0466). As such, correspondence analysis was carried out to investigate the nature of this association. This multivariate technique decomposes the chi-squared statistic associated with a contingency table into orthogonal factors, ordered by degree of variation in the data set. For instance, if the first two factors accounted for most (say, 70%) of the variation, a simple scatter plot of these factors should be sufficient for identifying the categories of variables that most contributed to the association. The scatter plot of the variables "type of medication" and "degree of sarcopenia" is shown in Figure 3a. Two groups of categories contributed most to the association: DIUs associated with probable sarcopenia, and absence of sarcopenia associated with ARBs and ARBs + DIUs. However, as the first two factors accounted for only 52% of the variation in the contingency table, we chose to consider a third factor, to confirm if this trend would continue. The first three factors explained 72% of the variation and were then

Table 1 – Classes of antihypertensive drugs and number of drug classes used by participants

		Classes of medication					Number of drug classes			
		ARB	DIU	calcium blocker	ACEI	β-blocker	1	2	3	4
n	Women	52	53	19	11	11	27	43	18	0
	Men	8	6	3	3	2	8	4	1	1
	Total	60	59	22	14	13	35	47	19	1
Age (years)	Women	69.4±7.0	70.4±7.2	69.3±6.9	68.8±5.8	70.9±7.8	69.3±6.5	69.1±6.6	70.5±7.8	n/a
	Men	66.0±4.5	69.5±3.0	68.7±1.5	69.7±1.5	69.0±1.4	67.3±5.3	67.3±6.3	71	70
	Total	68.9±6.8	70.3±6.9	69.2±6.4	69.0±5.2	70.6±7.1	68.9±6.3	68.9±6.3	70.5±7.6	70
BMI (kg/m²)	Women	28.4±5.2	28.4±4.7	28.0±4.9	26.9±4.5	29.5±6.1	28.4±4.7	28.7±5.2	27.6±5.3	n/a
	Men	26.8±6.0	30.1±4.4	32.8±6.0	31.1±7.2	31.4±10.1	26.1±5.5	28.3±3.9	30.4	38.6
	Total	28.2±5.3	28.2±5.0	28.7±5.2	27.8±5.2	29.8±6.3	27.2±4.8	28.7±4.8	27.8±5.2	38.6
% of users	Women(n=107)	48.60	49.53	17.76	10.28	10.28	25.23	40.19	16.82	0.00
	Men (n=22)	36.36	27.27	13.64	13.64	9.09	36.36	18.18	4.55	4.55
	Total (n=129)	46.51	45.74	17.05	10.85	10.08	27.13	36.43	14.3	0.78

Table 1 – ARB: Angiotensin II receptor blocker; DIU: diuretics; ACEIs: angiotensin-converting enzyme inhibitors; β-blocker: beta-blocker; BMI: body mass index

used to calculate Euclidean distances between categories. Subsequently, the Ward's clustering method[27] was applied to the categories. The resulting dendrogram is shown in Figure 3b. Again, it suggested that DIUs were associated with probable sarcopenia, whereas absent sarcopenia was associated with ARBs or ARBs + DIUs.

Discussion

Sarcopenia is a disease (ICD-10- M62.84) that affects over 10,000 older adults worldwide, and 43% of those aged 80 or above. Recently, sarcopenia has become the focus of intensive studies, and progress has been made toward a better understanding of its etiology and associated causes. Considering the consequences of sarcopenia and the aging of the world's population, research should continue to refine strategies for diagnosis and prevention of sarcopenia in hypertensive older adults. Falls, functional decline, and fragility are known to cause adverse health effects in the elderly population.[9] Only 5.3% of frail persons are not sarcopenic. Several strategies must be adopted to minimize this problem, and one of them is to identify possible drugs involved in this process.[29]

Taking into account the aging of the Brazilian population[30] – the focus of the present study – researchers should consider building a consensus regarding the diagnosis of sarcopenia in Brazil. There are guidelines on sarcopenia for the Brazilian population; the present study was based on the European Consensus[20] and the SMM index proposed by Janssen et al.[25]

In our study population, although age range was not different between women with different levels of

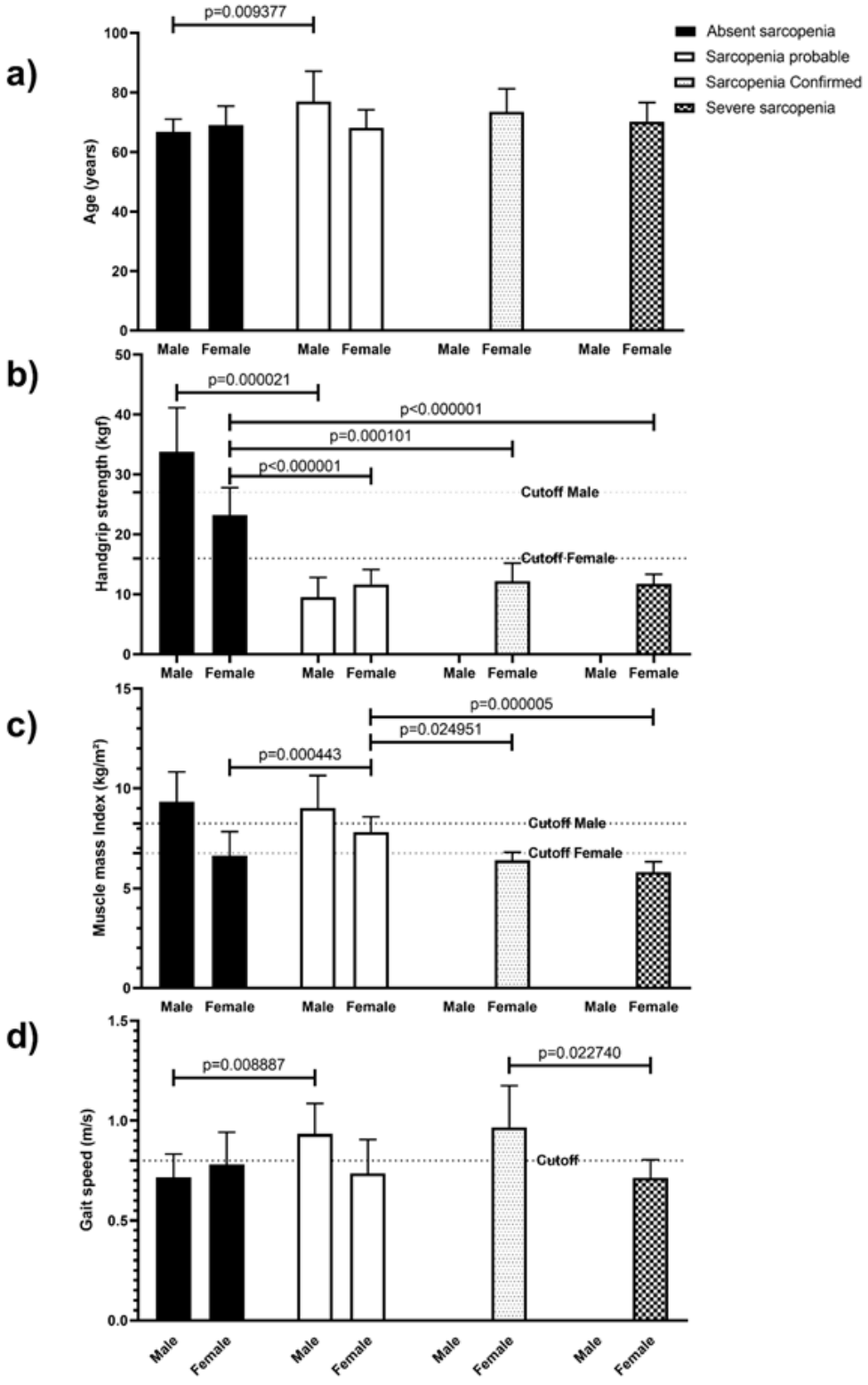


Figure 1 – Distribution of male and female patients according to sarcopenia degree and age (A), handgrip strength (B), muscle mass index (C) and gait speed (D); Multiple t tests; data expressed as mean ± standard deviation. Kgf: kilogram-force; kg/m²: kilogram per square meter; m/s: meter per second

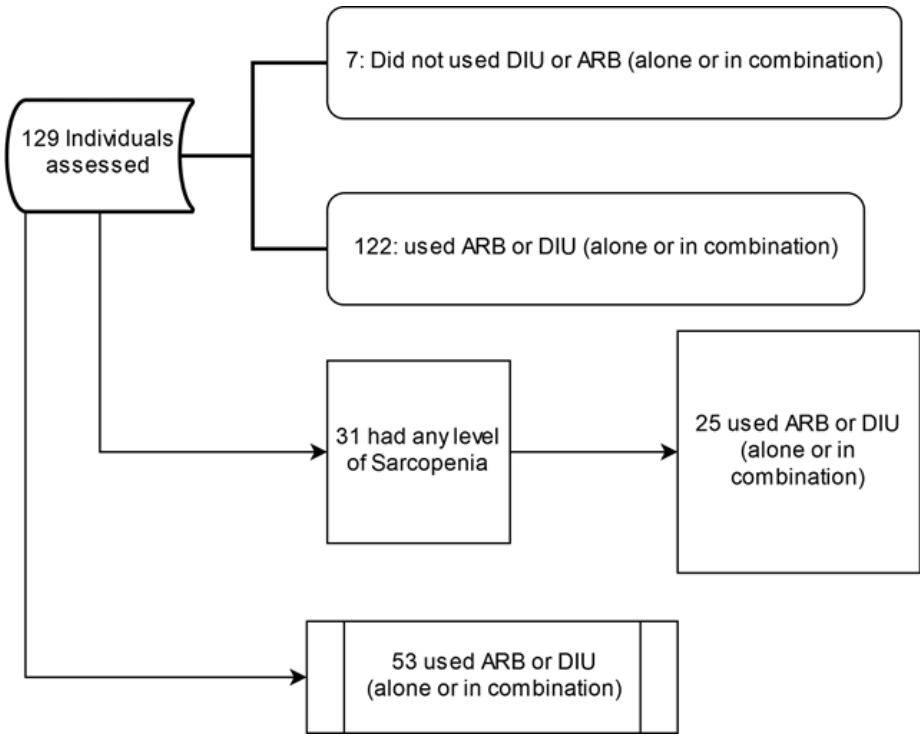


Figure 2 – Study design

Table 2 – Number of individuals distributed by sarcopenia level

	ARB	DIU	ARB+DIU	Total individuals
Absent sarcopenia	11	7	20	38
Probable	5	6	1	12
Sarcopenia confirmed	0	0	2	2
Severe sarcopenia	1	0	0	1

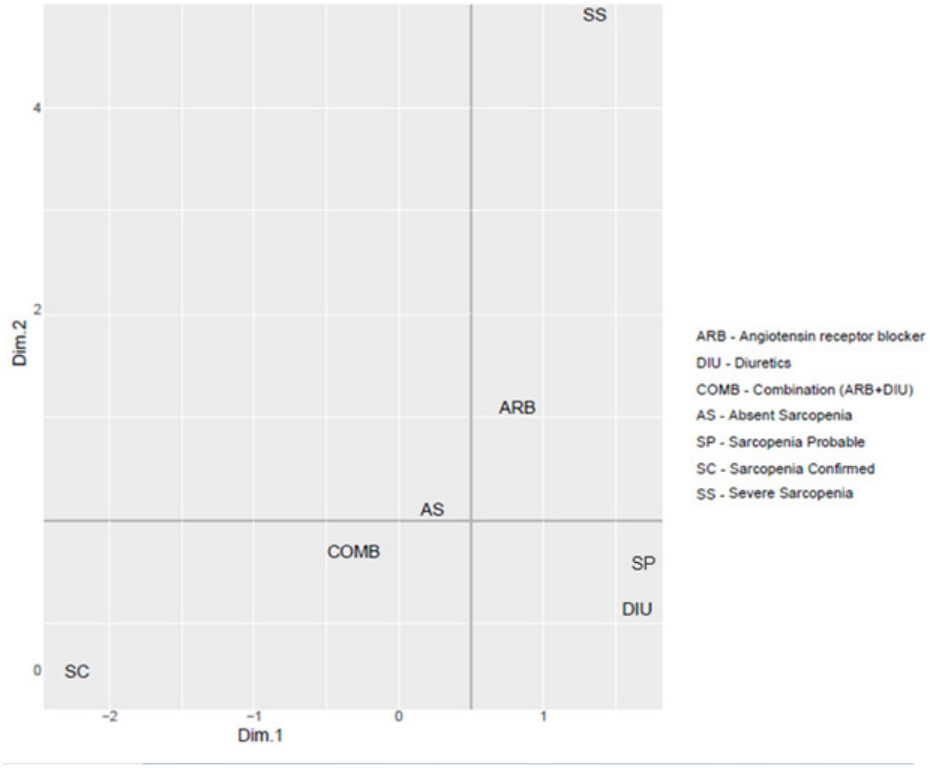
ARB: Angiotensin II receptor blocker; DIU: Diuretics; p-value for Fisher's Exact Test: 0.04662

sarcopenia, mean age was significantly different between men with absent and probable sarcopenia. The prevalence of sarcopenia in older adults aged between 60 and 70 years varies from 5% to 13%, and in those aged 80 years and older, from 11% to 50%, according to SMM.[31]

Meanwhile, mean values of the handgrip test, muscle mass, and gait speed results confirmed that handgrip strength is a good parameter for classifying sarcopenia. Studies have used the handgrip strength test for diagnosing sarcopenia,[2,5,9] and showed it has good intra- and inter-observer reliability and can be used in clinical practice.[32,33] Our data revealed that muscle mass index and gait speed seemed to act as confounding factors, as the absent and probable sarcopenia groups showed different values. Thus, both parameters may be best used after a first screening with handgrip strength.

Coelho-Junior et al.,[34] also reported an increased prevalence of hypertension in individuals with sarcopenia. In our study, most patients (122 out of 129) used ARBs or DIUs. A possible contributing factor to this that these medications are provided for free by the public health services in Brazil.

a)



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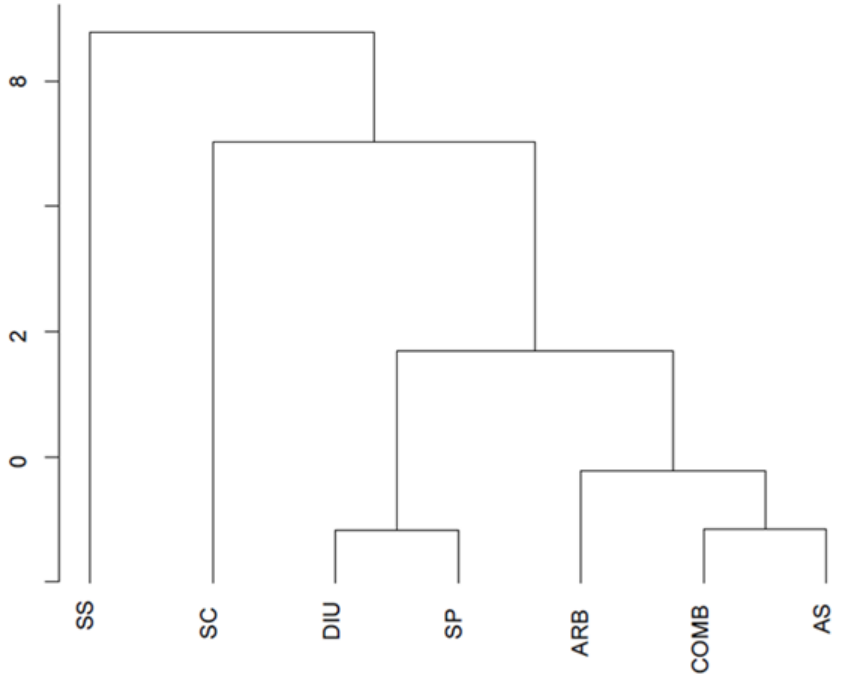

Figure 3 – a: Scatter plot of the first two orthogonal factors of the correspondence analysis of the variables: medications (DIU: diuretics; ARB: angiotensin-receptor blocker; combination: DIU+ARB) and level of sarcopenia (AS: absent sarcopenia; PS: probable sarcopenia; CS: confirmed sarcopenia; SS: severe sarcopenia). b: Dendrogram of cluster analysis with the first three factors of the correspondence analysis of the variables: medications (DIU; ARB; combination: DIU+ARB) and levels of sarcopenia (AS; PS; CS; SS)

The scatter plot showed the association between the type of medication and degree of sarcopenia, and two associations seemed to contribute most to this, the association between DIUs and probable sarcopenia, and the association between absence of sarcopenia and ARBs and ARBs + DIUs. This result was confirmed by the Ward's clustering algorithm.

Treatment with ARBs can have protective effects against muscle loss, since angiotensin II increases superoxide production,[35] reduces the autocrine insulin-like growth factor-1 signaling,[36] decreases mitochondrial function,[35] and increases apoptosis[37] in skeletal muscles, leading to muscle loss. In humans (cardiovascular patients) and in a rat model for heart failure associated with muscle atrophy and with increase in fatigability, ARBs provided protective effects by reversing most of the molecular markers of skeletal muscle loss.[38] Brown et al.,[39] reported that the use of ARBs instead of ACEIs for the treatment of hypertension could prevent mobility disability in older adults, especially in those at risk for decreased mobility and loss of physical independence. Further studies are necessary to investigate if the molecular and biochemical effects are reflected in worse physical performance and reduction in muscle mass.

Regarding the use of DIUs, the present study showed a significant association between DIUs and sarcopenia. A study[40] has shown that in patients with renal failure, heart failure, and hypertension, treatment with DIUs impaired the sodium-potassium pump function. Indeed, muscle biopsy specimens of patients demonstrated a reduction in intracellular potassium concentration and increase in intracellular sodium.[19] *In vitro* studies using skeletal muscle cells have shown that loop DIUs block the Na+-K+-2Cl- cotransporter activity, thereby suppressing skeletal muscle differentiation.[18] Hanai et al.,[41] also reported that the use of a higher dose of loop DIUs was associated with a faster decrease in SMM in patients with liver cirrhosis, independent of the severity of liver disease, suggesting that loop DIUs are one of the risk factors of sarcopenia.

Our study has some limitations that need to be considered. First, there was a small number of individuals that used only DIUs. Second, the frequency and time of use of drugs were not evaluated with respect to sarcopenia level. Third, the diagnosis of sarcopenia was made based on the European Consensus. It is necessary to confirm the reproducibility of this consensus in the Brazilian population.

Conclusion

In conclusion, age of elderly women with sarcopenia was not different from that of elderly women without sarcopenia. The handgrip strength test was a good method for diagnosing sarcopenia. The use of DIUs was associated with increased risk of sarcopenia in hypertensive older adults. Results of the present study is a starting point for health professionals to carefully consider antihypertensive prescription to elderly patients.

Author contributions

Conception and design of the research: Becker L. Acquisition of data: Mateo D. Analysis and interpretation of the data: Martins Júnior F. Statistical analysis: Martins Júnior F; Pinto K; Bearzoti E. Obtaining financing: Becker L; Coelho D. Writing of the manuscript: Martins Júnior F. Critical revision of the manuscript for intellectual content: Oliveira E; Becker L.

Potential Conflict of Interest

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

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Study Association

This article is part of the thesis of master submitted by Lenice Kappes Becker, from *Universidade Federal de Ouro Preto*.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Federal University of Ouro Preto under the protocol number 82376117.3.0000.5150. 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

Correlation of Diuretic use and Sarcopenia in Elderly Patients with Hypertension

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Editorial referring to the article: Use of Diuretics is Associated with Higher Risk of Sarcopenia in Older Adults with Hypertension

Hypertension is a chronic disease with high prevalence in Brazil and worldwide. It is estimated that approximately 31% of the world population has blood pressure levels ≥ 140/90 mmHg or uses antihypertensive medication.[1] Hypertension is also the main risk factor with an independent, linear, and continuous association for cardiovascular diseases.[2] Cardiovascular diseases, in turn, are the leading cause of death, hospitalizations, and outpatient care worldwide, including in developing countries such as Brazil.[3]

With aging, hypertension becomes an even more significant health problem. Around 61% of individuals over 60 years old have hypertension.[1] In Brazil, the epidemiological transition with the increase in the number of elderly people (≥ 60 years) in the next decades will lead to a substantial increase in the prevalence of hypertension and its complications.[2] Aging is still associated with other health disorders, including sarcopenia. As with hypertension, the prevalence of sarcopenia is higher in the elderly. It varies from 5% to 13% in people between 60 and 70 years of age, and from 11% to 50% in people ≥ 80 years of age.[4]

Sarcopenia is a progressive and generalized skeletal muscular disorder that involves accelerated loss of muscle mass and function (such as muscle strength and physical performance). It is associated with an increase in adverse outcomes, including falls, functional decline, frailty, and mortality[5]. For diagnosis of sarcopenia, the European Working Group on Sarcopenia in Older People (EWGSOP) suggests an algorithm based on clinical suspicion with measurement of handgrip strength to define probable sarcopenia, which is confirmed by measuring muscle mass.[5]

Recently, an original article was published that evaluated 129 elderly patients with hypertension, concluding that handgrip strength was a good method for evaluating sarcopenia and that the use of diuretics in the treatment of hypertension in these patients was associated with an increase sarcopenia.[6] This was an unprecedented finding in the literature for this population, and it warrants analysis and reflection.

The association of loop diuretics and sarcopenia has already been reported in patients with heart failure (HF).[7] The mechanism potentially involved would be via the Na^+-K^+-$2Cl^-$ cotransporter (NKCC1), which is highly expressed in mammalian skeletal muscles, where it contributes to the generation of membrane ionic currents and potential. Its elevation when using loop diuretics would worsen the muscular metabolic profile.[8] However, in patients with hypertension, the association of diuretics and sarcopenia had not been previously reported. Differently from what occurs in patients with HF, the main class of diuretics used in the treatment of hypertension are thiazides (hydrochlorothiazide) or thiazide-like diuretics (chlorthalidone and indapamide).

The treatment of hypertension with diuretics in the elderly population has proven benefits in reducing blood pressure and reducing cardiovascular morbidity and mortality.[2] Consistent with this understanding, thiazide diuretics are listed in the hypertension guidelines as one of three equally weighted first-line antihypertensive options alongside calcium channel blockers and renin-angiotensin system blockers.[2] They have electrolytic and metabolic side effects, which are already well known, especially hydrochlorothiazide,

Keywords

Diuretics; Hypertension; Sarcopenia; Aged.

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a medication that is widely used in the public health system in Brazil. Chlorthalidone and indapamide, on the other hand, have a better metabolic profile for adverse effects. The most common metabolic effect is hypokalemia, which is frequently accompanied by hypomagnesemia. Other known effects are glucose intolerance and increased uric acid.[2]

The pathogenesis of sarcopenia is still not fully understood. Aging disturbs skeletal muscle homoeostasis, which requires balance between hypertrophy and regeneration through complex and not yet fully understood mechanisms and pathways.[5] However, chronic inflammation with its relevant catabolic cytokines and even hypomagnesemia continue to be the most widely accepted mechanisms of sarcopenia in hypertension.[9] Accordingly, the adverse effects of thiazide diuretics could, in theory, contribute to sarcopenia in hypertension.

A study published in 2014, however, prospectively evaluated a cohort of 639 elderly patients in the United Kingdom, with a mean age of 65 years, during a follow-up of 4.4 years.[10] In this study, there was no difference in handgrip strength between users and non-users of the evaluated medications, namely, angiotensin-converting enzyme inhibitors, thiazide diuretics, and statins. Furthermore, the analysis of dropout rates by medication use revealed no evidence of selection bias in this study. The authors concluded that the use of these medications was not associated with differences in the decline in handgrip strength in the elderly without previous sarcopenia.[10]

herefore, the article is provocative in its findings, but the association of diuretics and sarcopenia is still unclear, especially thiazide diuretics in patients with hypertension. Larger clinical trials, specifically including this population, stratifying age groups, as well as the types and doses of diuretics, are necessary, since the antihypertensive effect of these medications is not directly linked to the doses used; however, the side effects are related to the dose and potency of diuretic action.[2]

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ORIGINAL ARTICLE

Mortality from Cardiovascular Diseases: A Comparative Analysis between the Medical and Non-Medical Populations in Brazil

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Abstract

Background: Cardiovascular disease (CVD) is the leading cause of death worldwide, including among physicians. Professional peculiarities increase cardiovascular risk in this population, making it relevant to analyze mortality in the medical population (MPop) and non-medical population (NMPop).

Objective: To compare the CVD mortality coefficient (MC) in between MPop and NMPop in Brazil by analyzing the epidemiological profile and the main causes of deaths from CVD.

Methods: Time-series study with data obtained from the Mortality Information System of the Federal Council of Medicine and the Brazilian Institute of Geography and Statistics, from 2014 to 2018. The variables age group, sex, race, occupation, and CVD that caused the death were assessed in MPop and NMPop. MC, relative risk and odds ratio between the populations were calculated. Tests for difference in proportions, with approximation to the normal distribution, and chi-squared tests were performed, assuming $p<0.01$ as statistically significant.

Results: Both MPop and NMPop had a predominance of men (86.7% and 52.3%), senior citizens (85.9% and 79.7%) and white individuals (86.4% and 52.2%). The MCs of the MPop and NMPop was 92.2 and 255.1 deaths/100,000 individuals, respectively. The main cause of death was acute myocardial infarction (AMI) (32.5% and 24.6% in MPop and NMPop, respectively) followed by cerebrovascular accident (CVA) (5.1% and 10.5% in MPop and NMPop, respectively).

Conclusion: In Brazil, mortality from CVD was more prevalent in white elderly males, and mainly caused by AMI and CVA. Being a doctor, man and over 60 years old represents a greater chance of death from CVD in comparison with non-physicians.

Keywords: Cardiovascular Diseases/physiopathology; Mortality; Epidemiology; Physicians/statistics &numerical data; Non-Physicians/statistics & numerical data; Brazil.

Introduction

The morbidity and mortality statistics of a population are of great relevance in helping to understand its demographic profile. Among them, the most important variable is cause of death,[1] as it is the final outcome of life, besides allowing monitoring the health/disease situation, such as early mortality and its main determining factors.[2] This information is important for the development of action plans and proper allocation of resources.[3]

Physicians' health status, like of the general population, can be estimated by analyzing mortality data. This has received considerable attention in the last 50 years; for example, the Federal Council of Medicine (CFM, *Conselho Federal de Medicina*) has conducted studies on physicians' working conditions interfere with their life and health.[1,4]

It is possible that a greater knowledge about health, as well as the occupation of professionals in more privileged situations and at higher socioeconomic levels, represented by the medical population (MPop),

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are factors that contribute to lower mortality compared to the non-medical population (NMPop). On the other hand, high degree of stress, long working hours, the expectation of maintaining a high standard of living, high exposure to ionizing radiation and contaminated biological materials, in addition to a delay to seek treatment when ill, are factors that can increase morbidity and mortality rates among physicians.[1] Associated with this, just as in the general population, the mortality profile is also influenced by the lifestyle of these professionals,[3] such as diet, exercise, sleep habits, tobacco smoking, and alcohol consumption.[5] In this way, it is possible to ascertain whether physicians apply to their own lives health concepts learned in their training[1] that they should pass on to their patients.

Prospective epidemiological studies have shown that the presence of certain behavioral risk factors including tobacco smoking, unhealthy diet, sedentary lifestyle, alcoholism, and psycho-emotional stress[6] increases the probability of clinical cardiovascular disease (CVD)[7]. These factors are associated with increased risk for cardiovascular complications, such as acute myocardial infarction (AMI), cerebrovascular accident (CVA), and heart failure (HF).[8] On the other hand, regular exercise, along with adequate eating habits, weight control, and not smoking, are preventive factors for these CVDs, that can contribute to the monitoring and even controlling of patients with coronary artery disease (CAD).[9]

According to the Pan American Health Organization (PAHO) and the World Health Organization (WHO), the main causes of global death in the last 15 years are CVA and ischemic heart disease, accounting for 15,2 million deaths in 2016.[9,10] Thus, CVD is considered the leading cause of death in the world[3,8,9] and can be avoided prevented through early diagnosis and treatment and health promotion.[9] In Brazil, 29.4% of the deaths reported per year are caused by CVD, such as CVA and AMI. As a result, Brazil is among the 10 countries with the highest rate of death from CVD.[9]

This fact can also be observed in the medical population; a study conducted in the state of São Paulo, Brazil, showed that diseases of the circulatory system were the main cause of death among physicians, with CAD being responsible for 30.1% of deaths in 2001.[3] In the state of Bahia, a study carried out in 2019 showed that the three main causes of death in the medical population were diseases of the circulatory system (28%), neoplasms (27%), and external causes (12%), similarly to other studies conducted in the country.[11]

Thus, due to a lack of data on medical mortality from CVD in Brazil, the present study aimed to evaluate this issue, in addition to describing the epidemiological profile, identifying the main causes of mortality, and estimating the CVD mortality coefficient in the Brazilian MPop and NMPop.

Methods

This is an epidemiological, observational, time-series study with an analytical approach, using secondary data obtained from the Mortality Information System (SIM, *Sistema de Informação de Mortalidade*) of the CFM and the Brazilian Institute of Geography and Statistics (IBGE, *Instituto Brasileiro de Geografia e Estatística*).[12,13]

Data were collected from Death Certificates (DCs) referring to CVD, of physicians living in Brazil and of the general population between 2014 and 2018. Individuals under 20 years of age were excluded so that a factor of comparability between the groups could be maintained, and because younger age groups are characterized by cardiovascular diagnoses that are not the object of this study.

The variables of interest were: age group (categorized every 10 years, as of 20 years old on), sex (stratified as male, female, ignored), race (white, black, yellow, brown, indigenous, ignored),[14,15] year of death (2014 to 2018), occupation (classified as medical and non-medical), and the CVD that caused the death, according to the International Classification of Diseases and Related Health Problems (ICD-10)[14,15] (Table 1).

The cause of death was determined based on the causes reported in the DCs and the ICD-10 codes, and for this reason, similar pathologies can be described separately. For instance, ICD I25.1, which represents atherosclerotic heart disease, refers to a chronic ischemic disease (such as atheroma, atherosclerosis, sclerosis) of the coronary artery, while ICD I21.9, which represents unspecified AMI, relates to an acute event of the heart as cause of death.

Statistical analysis

The populations of interest were grouped into MPop and NMPop. To determine the number of non-physicians, an estimate was calculated by subtracting the total number of physicians registered in the CFM, considering both active (whose registration was regular, inoperative, partially suspended, or those with partial interdiction)

Table 1 - List of the International Classification of Diseases (ICD-10) codes for cardiovascular diseases used for data collection

Alphabetical order	ICD-10
A	A520
B	B332, B570, B376, B572
C	C380, C381, C382, C383, C388, C452
D	D151
F	F011
G	G932
I	I00, I010, I011, I012, I018, I019, I020, I050, I051, I052, I058, I059, I060, I061, I062, I068, I069, I070, I071, I072, I078, I079, I080, I081, I082, I083, I088, I089, I090, I091, I092, I098, I099, I10, I110, I119, I120, I129, I130, I131, I132, I139, I200, I201, I208, I209, I210, I211, I212, I213, I214, I219, I220, I221, I228, I229, I238, I241, I248, I249, I250, I251, I252, I253, I254, I255, I256, I258, I259, I260, I269, I270, I271, I278, I279, I280, I281, I288, I289, I300, I301, I308, I309, I310, I311, I312, I313, 7I318, I319, I330, I339, I340, I341, I342, I348, I349, I350, I351, I352, I358, I359, I360, I361, I362, I368, I369, I370, I371, I372, I378, I379, I38, I400, I401, I408, I409, I420, I421, I422, I423, I424, I425, I426, I427, I428, I429, I440, I441, I442, I443, I444, I445, I446, I447, I450, I451, I452, I453, I454, I455, I456, I458, I459, I461, I469, I470, I471, I472, I479, I48, I490, I491, I492, I493, I494, I495, I498, I499, I500, I501, I509, I510, I511, I512, I513, I514, I515, I516, I517, I518, I519, I600, I601, I602, I603, I604, I605, I606, I607, I608, I609, I610, I611, I612, I613, I614, I615, I616, I618, I619, I620, I621, I629, I630, I631, I632, I633, I634, I635, I636, I638, I639, I64, I670, I671, I672, I673, I674, I675, I676, I677, I678, I679, I690, I691, I692, I693, I694, I698, I700, I701, I702, I708, I709, I710, I711, I712, I713, I714, I715, I716, I718, I719, I720, I721, I722, I723, I724, I728, I729, I730, I731, I738, I739, I740, I741, I742, I743, I744, I745, I748, I749, I770, I771, I772, I773, I774, I775, I776, I778, I779, I780, I781, I788, I789, I800, I801, I802, I803, I808, I809, I81, I820, I821, I822, I823, I828, I829, I830, I831, I832, I839, I840, I841, I842, I843, I844, I845, I846, I847, I848, I849, I850, I859, I860, I861, I862, I863, I864, I868, I870, I871, I872, I878, I879, I880, I881, I888, I889, I890, I891, I898, I899, I950, I951, I952, I958, I959, I99
K	K763, K766
M	M311, M622, M314
N	N280
O	O100, O101, O102, O103, O109, O11, O13, O140, O141, O149, O150, O151, O152, O159, O16, O223, O225, O265, O870, O871, O873, O903
P	P290, P291, P299
Q	Q200, Q201, Q202, Q203, Q204, Q205, Q206, Q208, Q209, Q210, Q211, Q212, Q213, Q214, Q218, Q219, Q220, Q221, Q222, Q223, Q224, Q225, Q226, Q228, Q229, Q230, Q231, Q232, Q233, Q234, Q238, Q239, Q240, Q242, Q243, Q244, Q245, Q246, Q248, Q249, Q250, Q251, Q253, Q254, Q255, Q256, Q257, Q259, Q260, Q261, Q266, Q268, Q269, Q270, Q271, Q273, Q278, Q279, Q280, Q281, Q282, Q283, Q288, Q289
R	R000, R001, R002, R008, R010,R011, R012, R02, R030, R031, R040, R041, R042, R048, R049, R05, R060, R061, R062, R064, R066, R068, R070, R071, R072, R073, R074, R090, R091, R092, R093, R098, R570, R931
Y	Y840, Y520, Y527, Y529, Y522, Y625

Source: SIM/DATASUS, 2020.

and not active professionals (transferred, retired, total interdiction or whose registrations were cancelled, nullified, or suspended) from the Brazilian population in that given year.[12,13]

For data analysis, the R software, version 3.6.3, was used. Categorical variables were expressed as absolute and relative frequencies. The mortality coefficient was estimated considering the total number of deaths per year for every 100,000 individuals and standardized for age to eliminate the effects of age variation on comparisons.

Statistical analysis was made by means of statistical tests, using odds ratios and measures of association

between exposure and outcome. For comparisons between the two groups (MPop and NMPop), a test for comparing proportions with approximation to normal distribution was employed. The inexistence of difference between the proportions was defined as null hypothesis (H0), and the existence of difference, as alternative hypothesis (H1). The odds ratio between the two populations was calculated, and to analyze the relationship between the variables, the contingency coefficients were measured using the chi-squared test. All p values lower than 1% (0.01)[16,17] were considered statistically significant.

Results

From 2014 to 2018, 2,103 deaths of physicians and 1,819,079 of non-medical individuals due to CVD were recorded in Brazil.

As for deaths by sex, there was a predominance of males in both groups, with 86.7% of men in the MPop and 52.3% in the NMPop, with a statistically significant difference between the sexes (Table 2). Analyzing the odds ratio of deaths from CVD, considering sex and groups, male physicians were found to be more likely to die from CVD [OR 1.72

Table 2 – Frequency of deaths from cardiovascular among physicians and non-physicians in Brazil from 2014 to 2018 by sex, age group and race

Variables	Physicians (n=2,103)	Non-physicians (n=1,819,079)	p-*value**
Sex, n (%)			
Male	1,824 (86.7)	952,271 (52.3)	<0.01
Female	279 (13.3)	866,601 (47.6)	<0.01
Ignored	-	207 (0.1)	-
Age group, n (%)			
20-29	11 (0.5)	15,022 (0.8)	0.16
30-39	37 (1.8)	38,882 (2.1)	0.26
40-49	72 (3.4)	98,958 (5.4)	<0.01
50-59	177 (8.4)	217,006 (11.9)	<0.01
60-69	543 (25.8)	355,555 (19.5)	<0.01
70-79	504 (24.0)	457,615 (25.2)	0.22
>=80	759 (36.1)	636,041 (35.1)	0.29
Race, n (%)			
Yellow	35 (1.7)	10,747 (0.6)	<0.01
White	1,818 (86.4)	950,399 (52.2)	<0.01
Black	29 (1.4)	153,828 (8.5)m	<0.01
Brown	180 (8.6)	638,586 (35.1)	<0.01
Indigenous	-	3,378 (0.2)	-
Ignored	41 (1.9)	62,141 (3.4)	<0.01

**Test for comparing proportions with approximation by normal distribution*
Source: SIM/DATASUS, 2020.

(95%CI 1.49-1.98)] compared to men who were not doctors [OR 0.58 (95%CI 0.50-0.67)] (p<0.01).

With regard to deaths by age group (Figure 1, Table 2), a higher mortality from CVD was observed among elderly people, accounting for 85.9% and 79.7% of all deaths among physicians and non-physicians, respectively. Among the age groups that represent senior citizens, there was a statistically significant difference in the age group from 60 to 69 years, with a higher number of deaths from CVD in the medical population (25.8% vs. 19.5%, p<0.01) (Table 2).

Concerning the other age groups, the proportions of deaths from CVD in the groups 40-49 years, and 50-59 years were statistically higher in the NMPop than in the MPop (3.4% vs. 5.4%, p=0.01; and 8.4% vs. 11.9%, p<0.01; respectively). Analyzing the odds ratio of death from CVD, considering sex and groups, male physicians aged 60 or older were found to be more likely to die from CVD [OR 1.64 (95%CI 1.43-1.89)] compared to men who were not doctors [OR 0.60 (95%CI 0.52-0.70)] (p<0.01).

Considering the deaths from CVD by race, there was a predominance of white people in both MPop and NMPop (86.4% and 52.2%, respectively, p<0.01). In addition, statistically significant differences were observed in the proportion of deaths from CVD between physicians and non-physicians of other races (Table 2). As for the odds ratio of deaths from CVD, considering race and groups, no differences were found between physicians and non-physicians (p=0.6308).

A dependence (albeit weak) was detected between the variables in all crossings, except between race and sex in the MPop (Table 3).

In addition, from 2014 to 2018, the mortality coefficient of the MPop and NMPop was 92.2 deaths/100,000 individuals and 255.1 deaths/100,000 individuals, respectively. The CVD mortality coefficient in the MPop and NMPop, calculated year by year, is shown in Figure 2. No significant variation was found in the mortality coefficients in both populations over the years. However, the MPop had lower CVD mortality rates compared to the NMPop in all years.

A year-by-year analysis revealed that the highest mortality coefficient was observed in the NMPop in 2016 – 261.2 deaths/100,000 individuals. Among physicians the highest mortality rate was observed in 2015, 100.7 deaths/100,000 individuals.

Figure 3 displays the main causes of death from CVD (according to ICD-10) between 2014 and 2018. The main cause of death was AMI (ICD I21.9) in both populations, accounting for 32.5% of deaths among physicians and 24.6% among non-physicians. CVA (ICD I64) ranked second in both populations, with 5.1% of deaths among physicians, and 10.5% among non-physicians. The third main cause of death was Atherosclerotic Heart Disease (ICD I25.1) in the MPop and Essential Hypertension (ICD I10) in the NMPop.

Table 4 presents the mortality rate standardized for age and sex in the MPop and NMPop populations.

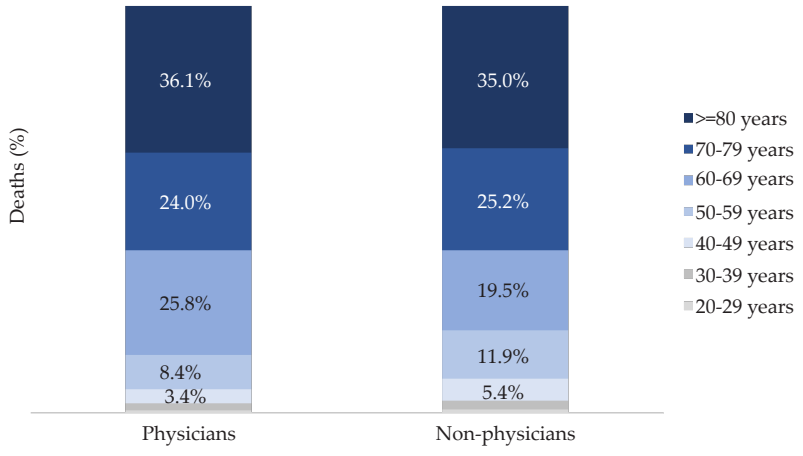

Figure 1 – Deaths from cardiovascular disease among Brazilian physicians and non-physicians between 2014 and 2018 by age groups. Source: SIM/DATASUS, 2020

Table 3 – Contingency coefficients among physicians and non-physicians in Brazil from 2014 to 2018, considering the "Age Group x Sex", "Age Group x Race", and "Race x Sex" crossings

Occupation	Crossing	Contingency Coefficient	p-*value**
Physicians	Group x Sex	0.18	<0.001
	Group x Race	0.17	<0.001
	Race x Sex	0.03	0.67
Non-physicians	Group x Sex	0.17	<0.001
	Group x Race	0.14	<0.001
	Race x Sex	0.06	<0.001

**Chi-squared test for assumption of independence*
Source: SIM/DATASUS, 2020.

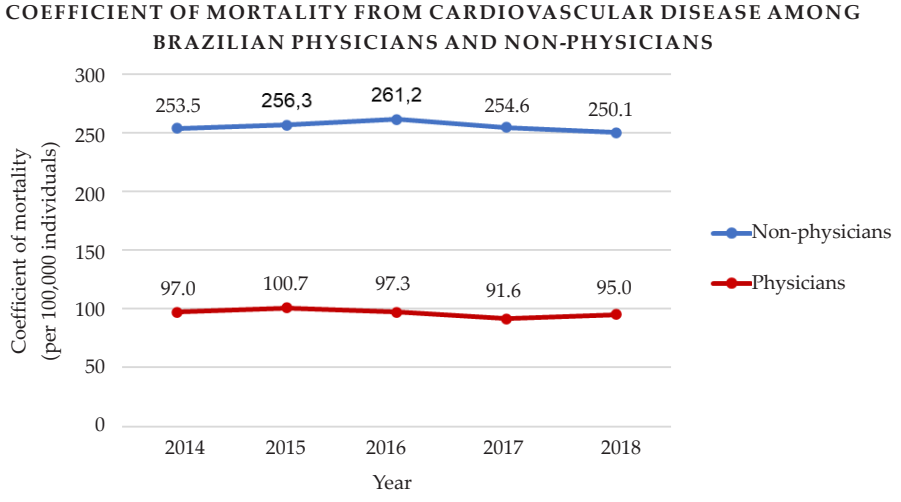

Figure 2 – Coefficient of mortality from cardiovascular disease (per 100,000 individuals) among Brazilian physicians and non-physicians between 2014 and 2018.
Source: SIM/DATASUS, 2020

Discussion

Analyzing the distribution of deaths by sex, mortality from CVD was found to be 6.5 times higher among male physicians than female physicians. The predominance of death in males can be explained by the higher prevalence of men in the medical field, which is associated with a history of greater carelessness on their part with their own health.[11] This finding corroborates other studies on medical mortality in Brazil. Dantas et al.,[11] analyzed the mortality of physicians in the state of Bahia from 2008 to 2017 and showed that 84% of all deaths were of men, with CVD as the most prevalent cause. The Regional Council of Medicine of the state of São Paulo,[3] when investigating trends in the mortality of physicians from 2000 to 2009 in the state, also reported a predominance of men, accounting for 86.7% of deaths. Furthermore, a study in Uruguay reported a mortality rate of 86% in male physicians.[18]

Just as in the MPop, when the NMPop was analyzed, a predominance of males was detected, which corroborates the study by Oliveira et al.,[9] which showed a predominance of deaths from diseases of the circulatory system in males in all Brazilian regions.

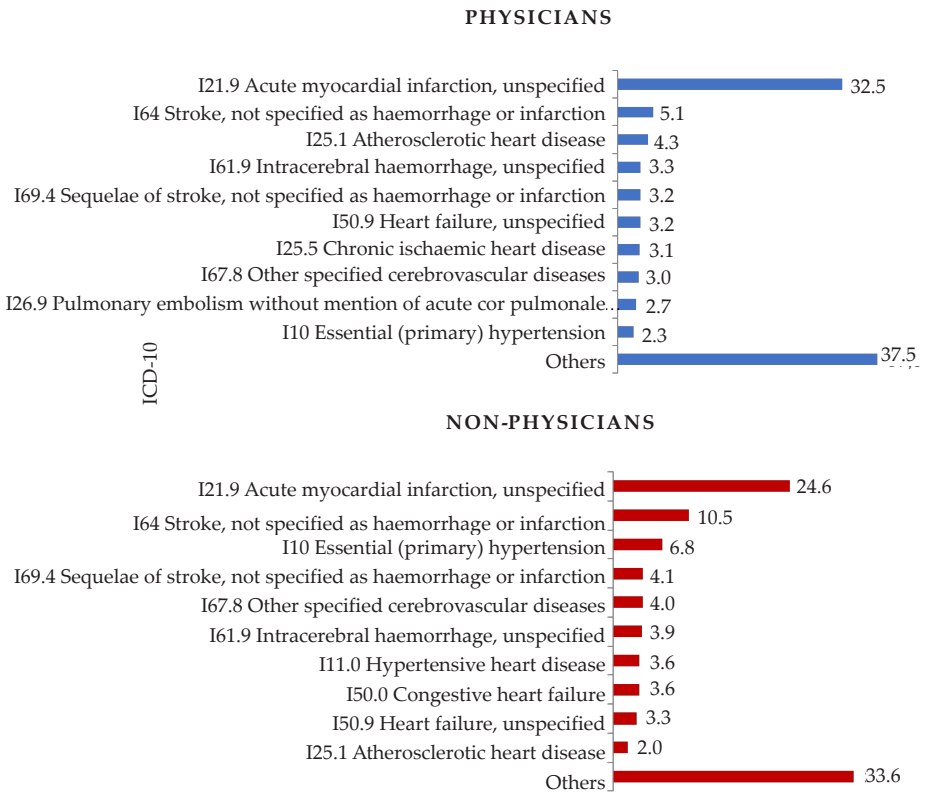

Figure 3 – Relative frequencies of the main causes of deaths from cardiovascular diseases among Brazilian physicians and non-physicians between 2014 and 2018, coded according to the International Classification of Diseases (ICD-10).
Source: SIM/DATASUS, 2020

Table 4 – Age- and sex-standardized mortality rate among physicians and non-physicians in Brazil from 2014 to 2018

Variable	Physicians	Non-physicians	Variation (a/b)%
	Rate (100,000)	Rate (100,000)	
Sex			
Male	872.99	155.42	461.7
Female	147.40	1,309.82	-88.7
Age group			
20-29	191.77	26.82	615.1
30-39	29.63	69.56	-57.4
40-49	91.38	176.88	-48.3
50-59	455.65	38.76	1,075.6
60-69	805.10	63.54	1,167.1
>=70	7,488.88	195.27	3,735.2

Analysis by age group revealed that a greater number of deaths was found among physicians over the age of 80 years, and about three times more deaths occurred in the age group from 60 to 69 years in comparison with 50 to 59 years, which may be a result of the higher prevalence of CVDs in old age.[19] A similar study carried out in the state of São Paulo reported that CVDs were responsible for 29.7% of deaths among physicians from 2000 to 2009; of these, 74.8% occurred after the age of 60, with the peak in the age group from 80 to 89 years,[3] which reinforces the results of this study. On the other hand, analyzing the NMPop, mortality was higher from 50 years of age on.

With regard to race, there was a greater number of deaths from CVD among white individuals, followed by brown and black people. This is probably related to ethnic inequality concerning access to higher education in Brazil, with a markedly smaller number of black doctors in the country. These data corroborate the results of studies conducted in São Paulo[2,3] and Bahia,[11] where a predominance of deaths from CVD among white physicians was shown as well.

Just as among physicians, more white people died from CVD in the NMPop in Brazil, a fact also revealed by Oliveira et al.,[9] These authors also pointed to a higher mortality in the southeast region of the country, which can be explained by the fact that this is the most populous region in Brazil, whose inhabitants are mostly white.[15] It was also evidenced that black people died six times more in the NMPop compared to MPop, which may be influenced by the country's racial historical context, as it limited work and education opportunities for black individuals and caused Medicine to be a mostly white-people profession.

Considering the CVD mortality coefficients described in this study, it was evidenced that, from 2014 to 2018, in Brazil, for every 100,000 physicians, approximately 93 died from CVD, and for every 100,000 non-medical people, approximately 255 died from CVD. This means a CVD mortality coefficient in the MPop of almost 1/3 of the NMPop's coefficient. This disproportion may be linked to the greater access that this population has to health services. Furthermore, no studies assessing CVD mortality coefficients between physicians and non-physicians in Brazil were found. Existing studies have compared the overall mortality coefficient between the two populations and, similarly, found lower levels of mortality in the MPop compared to the general population.[1,11,20]

Over the five years analyzed, no fluctuations were observed in CVD mortality coefficients between physicians and non-physicians. This differs from studies that have analyzed all causes of death between the two populations,[11] or studies that assessed CVD mortality in the general Brazilian population.[21] This discrepancy may be explained by the short period of analysis in our study, in which there were no major changes in the number of inhabitants each year, neither among physicians nor non-physicians.

As the Brazilian population ages, exposure to death from CVD increases, due to a higher risk of diseases affecting the circulatory system. Thus, when assessing the main causes of death from CVD in both populations from 2014 to 2018 AMI ranked first, confirming other studies.[1,19,21,22] However, the present study showed that the MPop was more affected by AMI, despite this group having greater knowledge about the disease and how to prevent it. It is assumed that an exhausting workload leads physicians to neglect their medical needs (e.g., diabetes mellitus, hypertension, and stress) and adopt bad lifestyle habits, such as sedentariness, poor diet, tobacco smoking, and alcohol or drug use, which are risk factors for several CVDs,[1,3] mainly AMI. This hypothesis still needs to be confirmed through studies with primary data and prospective design.

Ranking second among the causes of deaths from CVD, CVA caused twice as many deaths in the NMPop compared to the MPop. Because of this finding, it is suggested that the early diagnosis of CVA favors the survival of physicians, as they are more familiarized with the clinical signs of stroke and have easier and quicker access to cranial computed tomography, differently from the rest of the population. The third most prevalent cause of death from CVD was different between the MPop and the NMPop. Systemic arterial hypertension (SAH) ranked third in the NMPop and only tenth in the MPop, and atherosclerotic heart disease ranked third among physicians, and tenth among non-physicians. This may be explained by the fact that SAH is an asymptomatic disease in its initial stage,[22] and could be diagnosed earlier in physicians due to their greater access to information and diagnostic means in the health system. In contrast, NMPop are likely to suffer a lack of accurate diagnosis of CVD and consequent underreporting. Also, due to factors previously mentioned, the poor quality of life of physicians makes them more prone to develop more severe atherosclerotic heart disease.

Finally, two potential limitations of the study should be addressed. First, since this is a retrospective research based on secondary data, there is a possibility of death underreporting and inaccuracy regarding the cause of death from CVD in the death certificates. Second, selection of the ICD codes was manually made based on the interest of the study, and not restricted to ICD-10 I00 to I99, as proposed by the Brazilian Society of Cardiology.[19]

Conclusion

In Brazil, mortality from CVD among physicians was more prevalent in white elderly males, and mainly caused by AMI and CVA. Additionally, it was shown that being a male doctor, over 60 years of age, represents a greater chance of dying from CVD compared to non-physicians. Nonetheless, the CVD mortality coefficient of the medical population was significantly lower than that of the non-medical population. Given the relevance of the topic, these data point to the need for further prospective studies on medical mortality from CVD in Brazil.

Acknowledgment

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Author contributions

Conception and design of the research: Matos GG, Pacheco RLCB, Magalhães LBNC, Avena KM. Acquisition of data: Matos GG, Pacheco RLCB. Analysis and interpretation of the data: Matos GG, Pacheco RLCB, Magalhães LBNC, Avena KM. Writing of the manuscript: Matos GG, Pacheco RLCB, Magalhães LBNC, Avena KM. Critical revision of the manuscript for intellectual content: Matos GG, Pacheco RLCB, Magalhães LBNC, Avena KM.

Potential Conflict of Interest

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

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Study Association

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Ethics approval and consent to participate

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

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EDITORIAL

And We Doctors, What do We Die of?

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Editorial referring to the article: Mortality from Cardiovascular Diseases: A Comparative Analysis between the Medical and Non-Medical Populations in Brazil

We hardly ask ourselves what we will die from. The certainty of this fact can even pass through our thoughts, but it always seems to us something far away and impossible to predict. We can know the causes of death of our fellow human beings to try to predict our death and perhaps use measures to postpone it, since it is impossible to avoid. Societies need to know their numbers, how many we are, how many are born, how many die, how we die, and how we live. These are questions that gain importance with reports of demographic and epidemiological surveys dating back to 400 BC in some ancient civilizations like Greece, Rome, India, and China. The first modern publication in mortality studies dates from 1662 in England, carried out by a London councilor, John Graunt, who published the work entitled "Natural and Political Observations upon the Bills of Mortality" (Figure 1), using data of burials in London as information. Through this study, it can be known, for example, that one third of London children died before turning sixteen.[1,2]

In the last century, humanity has gone through an epidemiological transition in terms of causes of death. Infectious diseases are no longer the leading cause of death and have given way to chronic non-communicable diseases (NCDs), especially circulatory system diseases (CAD). NCDs are the main cause of death worldwide, and they are responsible for premature deaths, loss of quality of life, and adverse economic and social impacts. NCDs are responsible for about 70% of global deaths, equivalent to more than 38 million deaths per year, significantly exceeding deaths from external causes and infectious diseases. About 45% of all NCD deaths worldwide, more than 17 million, are caused by CAD. A similar distribution is observed in Brazil, where 72% of deaths result from chronic NCDs, with 30% due to CAD and 16% to neoplasms.[3]

Knowing and comparing the occurrences of cardiovascular deaths in a specific professional group, in the case of physicians, with the rest of the population arouses curiosity and can provide important information with the possibility of instituting measures capable of preventing or delaying these deaths. Therefore, analysis of the article in question is very important for our professional group and also for society.[4] Questions that immediately come to mind when we read the title of the article could be answered:

Do we die early? Do we die more ? Do we die worse?

Certainly, one or these three questions was raised at the initial moment of reading.

First fact: the doctors who died during the study period, 2014 to 2018, were mostly White men over 60 years old. This is a reflection of medical training and the organization of society with access to higher education and medical schools in the mid-twentieth century. Few women and few Black people became doctors in Brazil at that time.

Ischemic heart disease was, by far, the leading cause of death for the two populations analyzed in the study. This followed the global trend of the main cause of death in recent decades, for all population types, regardless of the geopolitical level of the analyzed country.[3] However, in the medical population, the risk of dying from this group of diseases was relatively higher than in the non-medical population. One factor can be suggested to explain this fact: the higher socioeconomic level of the medical population, which is a group composed

Keywords

Mortality; Cardiovascular Diseases; Physicians.

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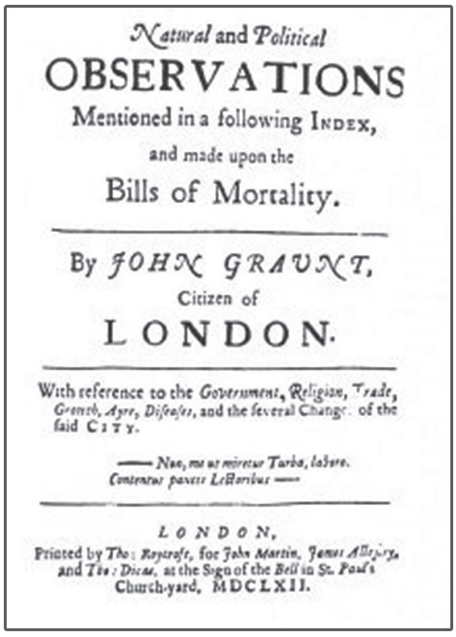

Natural and Political
OBSERVATIONS
Mentioned in a following INDEX,
and made upon the
Bills of Mortality.
By JOHN GRAUNT,
Citizen of
LONDON.
With reference to the *Government*, *Religion*, *Trade*, *Growth*, *Ayre*, *Diseases*, and the several Change of the said CITY.
Nec, me ut miretur Turba, laboro.
Contentus paucis Lectoribus.
LONDON,
Printed by *Tho: Roycroft*, for *John Martin*, *James Allestry*, and *Tho: Dicas*, at the Sign of the *Bell* in St. Paul's Church-yard, MDCLXII.

Figure 1 – Cover of John Graunt's publication – Reproduction of the original by Graunt G. Natural and Political Observations upon the Bills of Mortality.
London 1662.

of people who obviously have higher education, could be a protective factor against deaths from other causes, especially when compared to cerebrovascular disease, where relative mortality was twice as high in the non-medical population.

Two limitations not mentioned in the study's discussion should come to light: the first, the short observation time, 5 years, for a retrospective mortality study. Longer durations could have been included for better evolutionary assessment of deaths, which would generate greater capacity and validity to analyze measures of association between the two groups. The second refers to the following questions: What about retired doctors? Those who died, who were not actively registered in their class councils, were they included in the non-medical population? They certainly died at older ages and could contribute to changes in the outcomes analyzed in the study, especially the mean age of death.

It is very interesting to analyze mortality studies in specific groups. This article provides some answers and also opens space for extension and new research to elucidate and, who knows, propose future measures to prolong life expectancy in the Brazilian medical population.

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ORIGINAL ARTICLE

Effects of Physical Exercise on Lipid and Inflammatory Profile of Women Using Combined Oral Contraceptive: A Cross-Over Study

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Abstract

Background: The use of combined oral contraceptives (COC) is a risk factor for atherosclerotic disease, and physical exercise can minimize this condition.

Objective: To verify if high intensity interval training (HIIT) promotes changes in the lipid and inflammatory profile of women using COC.

Methods: Sequential crossover study with women aged 20-30 years, classified as irregularly active by the international physical activity questionnaire (IPAQ), when using COC. A physical-clinical assessment was performed with anthropometric measurements, VO_{2max}, and analysis of lipid and inflammatory profile. Participants were divided into 2 groups: the initial intervention group (GII), which began practicing HIIT for 2 months, and the posterior intervention group (GIP), which remained inactive for the same period. The GII and GIP would then alternate their conditions. The collected data was divided into: Initial moment (IM), post-exercise moment (PEM) and post-inactivity (PIM). The statistical analyses were performed using the Statistical Package for the Social Sciences, adopting a significance level of $p < 0.05$.

Results: Twelve women were evaluated. After crossing the GII and GIP data, there was a difference in the C-reactive protein values between the IM of 4 (1.6-6.3 mg/dL) vs. PEM 2 (1.5-5 mg/dL); as well as between the PEM vs. the PIM= 4 (1.5-5.8 mg/dL), with a *p*-value = 0.04 in the comparisons. There was no change between the "moments" of the lipid profile, although it was possible to notice a reduction in resting HR and an increase in indirect VO_{2max}.

Conclusion: The HIIT program was able to reduce the inflammatory profile, but it did not alter the lipid profile of irregularly active women using COC.

Keywords: Women; Physical Activity; Contraceptives, Oral, Combined; Atherosclerosis; Risk Factors; Lipids; Inflammation; High Intensity Interval Training.

Introduction

Historical reports state that women started using rudimentary contraceptive methods at least four thousand years ago.[1] Over time, these methods have improved, until between the 1950s and 1960s, the first oral contraceptives appeared in the United States of America.[2,3] Mostly made up of substances known as ethylinestradiol and progestin, oral contraceptives started to be commercialized worldwide in a short time due to their effectiveness, low cost, and feasibility of use.[3]

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Despite their relevance, it is important to note that oral contraceptives are associated with several side effects, since all blood vessels in the human body have receptors for the hormones estrogen and progesterone. The use of ethyl estradiol and progestin, respectively synthesized based on these endogenous substances, promotes local hyperstimulation and the development of a cascade of consequences.[4]

Among the possible responses to the use of oral contraceptives, it is important highlight the increase in endothelin, peroxynitro, angiotensin 2, oxidative stress, and insulin resistance.[5,6] In addition, there may be a reduction in the production of nitric oxide, prostacyclin, and changes in hepatocytes.[5-8] All of these new conditions favor thrombolytic, vasoconstrictive, inflammatory, and lipid changes, which, in combination, promote a series of cardiovascular injuries that are determining factors for atherosclerotic disease.[5,9,10]

It is well-known that the inflammatory and lipid profiles are higher in users of combined oral contraceptives (COC),[11,12] especially in those who have lower levels of physical activity.[11] With this in mind, physical exercise has been used to mitigate, or even reverse, these conditions in some populations.[13] However, in our previous studies, there were no clinical trials that verified the cause-effect relationship of physical exercise in the population of women using COC.[11,12,14-16]

Thus, the present study aimed to test the hypothesis that high intensity interval physical exercise promotes changes in the lipid and inflammatory profile of young normolipid women who are irregularly active and using COCs.

Methods

This is a cross-sectional study, logged in the Brazilian Registry of Clinical Trials (BReCT) under protocol number RBR-4jm343. Participants, aged 20-30 years were evaluated and were nulliparous, with fasting triglycerides ≤ 150 mg/dl and a continuous use of oral contraceptives for at least 6 months. In addition to the criteria mentioned above, the participants should be classified as irregularly active by the international physical activity questionnaire (IPAQ).[17]

Those who did insufficient physical activity, with a minimum of 10 continuous minutes during the week, were classified as irregularly active, in addition to not meeting any of the criteria below:

1. Perform 3 or more days of vigorous activity during the week lasting ≥ 20 minutes a day;
2. Perform 5 or more days of moderate activity during the week or more than 30 minutes of walking per day;
3. Perform 5 days of any combination of moderate, vigorous activities or walks that reach 600 MET-min/week.

Women with osteomyoarticular changes or pain complaints potentiated by physical exercise, liver dysfunction, pre-diabetes or diabetes, hypo or hyperthyroidism, kidney diseases due to use of anabolic steroids, history of alcoholism, smoking, corticosteroids, hypolipidemics, diuretics or beta-blockers, muscle mass (BMI) >30 kg/m^2, and polycystic ovary syndrome were excluded.

Throughout the study, the guidelines on research with human beings in the Declaration of Helsinki and Resolution 466/12 of the National Health Council were observed. This study was submitted to and approved by the Research Ethics Committee of Faculdade Nobre de Feira de Santana, logged under protocol number CAAE: 79549517.3.0000.5654. All participants received detailed information on the study objectives, risks, and benefits involved in the procedures, and signed the free and informed consent form.

The sample calculation was performed based on a pilot study consisting of 3 participants, considering an alpha = 0.05 (bidirectional) and a beta = 0.80 and adopting a significant difference of 20% for the variable triglycerides between the analyzed times. Bearing in mind that the laboratory variation coefficient of triglyceride dosage is 5% and that a difference four times greater than expected cancels the bias of this analytical variation coefficient, 12 participants were needed, with 6 allocated to IIG and 6 others allocated to the PIG. The sample calculation was performed using WinPepi, version 11.65.

Data Collection

To collect general information about the characteristics of the sample, all selected participants underwent a Clinical Physical Assessment (CPA) based on 4 steps, all of which took place at the Fisiocordis Cardiovascular Rehabilitation Clinic, located in the city of Salvador, BA, Brazil, which also provided the space, physical materials, and human resources. The steps were as follows:

1 = **Application of a standard questionnaire:** To screen the sample regarding information relevant to the study protocol at a given time.

2 = **Assessment of vital signs / physical examination:** Composed of measurements of heart rate and systemic blood pressure at rest, total body mass, height, and waist circumference.

To measure the heart rate, a Polar® pulse cardiofrequency meter was used. To measure participants' blood pressure, the recommendations of the Brazilian Society of Hypertension were followed, using a sphygmomanometer and stethoscope from the WelchAllyn® and Littman® brands, respectively.

Height was measured with the help of a professional Sanny® stadiometer with a precision of 0.1 cm, performed with the participants barefoot, with the buttocks and shoulders supported on a vertical back. Total body mass was obtained with a Filizola® digital scale with a maximum capacity of 150 kg, as measured by INMETRO, with its own certificate specifying a margin of error of ± 100 g. The abdominal circumference was obtained with a metallic and inelastic measuring tape, brand Starrett®, with a measurement definition of 0.1 cm. It was measured in the smallest curvature located between the last rib and the iliac crest without compressing the tissues.[18]

The body mass index (BMI) was calculated with the measures of mass and height, according to the Quetelet equation: BMI = mass (kg) / height^2 (m). The cutoff points adopted were those recommended by the IV Brazilian Guideline on Dyslipidemia and Atherosclerosis Prevention of the Department of Atherosclerosis of the Brazilian Society of Cardiology,[19] that is, low weight (BMI <18.5), eutrophy (18.5 <BMI <24.9), overweight (25 <BMI <29.9), and obesity (BMI ≥ 30).

3 = **Graduation test of indirect maximum oxygen consumption (VO_{2max}), by means of the Cooper protocol, performed on the treadmill.**[20] In this test, the participants were initially instructed about all stages of the test and later instructed to perform a warm-up in the form of walking at a speed that represents a self-perceived effort level "easy", regulated by the person evaluated, for 5 minutes on a Movement® treadmill without inclination.

Immediately after the warm-up period, the treadmill was switched off and instantly switched on again. From that moment on, the assessment was actually started, and the participants should walk at their own pace and regulation for the longest possible distance, being allowed to run, march, and walk. After the 12th minute of assessment, the distance covered was viewed on the treadmill odometer and recorded on the participants' record, ending at that moment, with a subsequent cooling down of the treadmill, with a gradual reduction in speed in 2 minutes until the treadmill speed was reset.

If for any possible reason it was necessary to reset the treadmill speed during the 12 minutes of testing, it should be interrupted and canceled that day, with a new performance after 72 hours. However, in our study, there was no need to interrupt any tests.

4 = **Blood collection to check the lipid and inflammatory profile:** On another previously scheduled day, with at least 72 hours after indirect VO_{2max}, the participants were sent to a laboratory to perform lipid and inflammatory profile through blood sample analysis. This examination was carried out in the morning period, with 12h fasting, between the fifth and tenth days of the menstrual cycle, considering the smallest hormonal fluctuations, and/or on the 28th day without medication (inactive phase), as recommended by Casazza et al.,[21] so that the menstrual period did not influence the value of the blood variables analyzed in this test.

The tests were carried out at the Clinical Pathology Laboratory (CPL) of the Barra unit in the city of Salvador, BA, Brazil, which provided the space, physical materials, and human resources needed for collections and laboratory analysis. Total cholesterol (TC) values, including Triglycerides, Low density lipoproteins (LDL) cholesterol, High density lipoproteins (HDL) cholesterol, Very low density lipoprotein (VLDL) cholesterol, and high sensitivity C-reactive protein (CRP) were observed so that, according to these values, the lipid and inflammatory profiles of the sample could be traced. The participants were instructed not to change their diet in the week of the test and not to practice any physical effort other than the normal routine, as well as not to drink alcoholic beverages in the 24 hours preceding the test.

The assessment of total cholesterol with HDL cholesterol and triglycerides was carried out by applying the enzymatic method. LDL cholesterol was calculated by the Friedwald equation (LDL = TC – HDL – (Triglycerids/5)),[22] and non-HDL-C cholesterol was calculated by the difference between TC and HDL

cholesterol. High-sensitivity CRP was measured using the turbidimetry method.

Monitoring Period

Immediately after blood collection, the first six participants were allocated to the initial intervention group (IIG) and the last six to the posterior intervention group (PIG).

At first, only the participants of the IIG entered the high-intensity interval exercise program, which was also performed at the Fisiocordis Cardiovascular Rehabilitation Clinic. Participants of the PIG remained with the same level of physical activities as before the beginning of the study, with a follow-up period of 2 months for each group. A second CPA was then performed after this period, followed by alternating groups in relation to physical exercise and physical inactivity in another 2 months. Finally, a third and last CPA was performed, reaching a total follow-up time of 4 months, as shown in Figure 1.

It is important to clarify that there was no type of intervention or guidance regarding any variable other than physical exercise for both groups. Thus, the participants were managers of their own diet, both during the two months of physical exercise and during the two months of inactivity.

Intervention Protocol

In the physical exercise session, both at the beginning and at the end, the blood pressure and heart rate data of the participants were collected. If the expected standards for age and level of effort were checked, activities were continued. The protocol consisted of a high intensity interval training done by means of sprints, performed on a treadmill without inclination, with a frequency of 2 times a week and a total period of 2 months, as previously described.

During the exercise sessions, the warm-up phase lasted 5 minutes with an intensity of 60% of the predicted reserve heart rate (PRHR), calculated according to the following equation: {[(220 - age) - resting HR] x 0,6] + resting HR}.[23] For the conditioning phase, the treadmill speed was then increased until 90% of the CRP was reached {[(220 - age) - resting HR] x 0.9] + resting HR}, maintaining this speed for 1 minute, with a subsequent reduction to the heating speed for the next 2 minutes, configuring the active rest. The sprints were alternated with the moments of active rest 10 times, with respective durations of 1 and 2 minutes, with the last 9 speeds of the sprints and active rests being maintained according to the speeds achieved in the first phase of each of these moments. The cool-down phase at the end of the session maintained a speed identical to the warm-up speed,

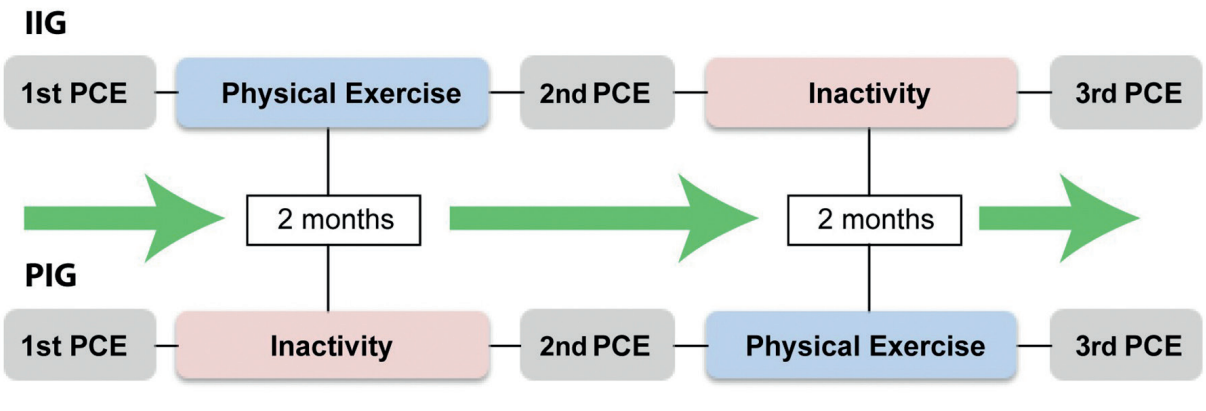

Figure 1 – Study design: Sequential crossover study, where both groups underwent 3 physical-clinical evaluations (PCE), performed at the beginning of the study, after 2 and 4 months of follow-up. The initial intervention group (IIG) performed the high intensity interval exercise protocol directly after the 1st PCE; after the 2nd PCE, the period of inactivity began, followed by the 3rd PCE. The posterior intervention group (PIG) after the 1st PCE maintained its routine (inactive); after 2 months, it underwent a new PCE and started a period of 2 months of high intensity interval physical exercise; at the end of that period, it performed the final PCE.

lasting 2 minutes, until the treadmill was turned off. A summary of this protocol can be seen in Figure 2.

The participants were monitored by the same pulse cardiofrequency meter used during the protocol. Which measured the caloric expenditure of the session, based on BMI, age, maximum expected HR, and average HR during exercise. Each session performed by the same pulse cardiofrequency meter consumed approximately 250kcal, causing a weekly caloric expenditure with the exercise of approximately 500kcal. The interventions had an average duration of 37 minutes.

Data Analysis

Initially, to verify the data distribution, the symmetry, kurtosis, and Shapiro-Wilk tests were applied, in addition to the visual inspection of the histograms. CRP, which was the only variable with an abnormal distribution, was used as a measure of central tendency and dispersion for the median and interquartile range, respectively, applying the Kruskal Wallis test to measure the comparison between period of activity and inactivity. If the null hypothesis was rejected, the post-hoc DUNN test was used.

For all other variables, the mean and standard deviation was used for data presentation, the Anova test was applied with repeated measures, and Tukey's post-test was used to verify the existence of statistical differences between the moments of exercise and inactivity. All analyses were performed using the SPSS statistical package (Statistical Package for the Social Sciences), version 21.0, adopting a significance level of $p<0.05$.

The results collected from the IIG and PIG groups were distributed in 3 different moments: 1st: initial moment (IM); 2nd: post-exercise moment (PEM), and 3rd: post-inactivity moment (PIM). To assess the data of the "initial moment", the IIG and PIG groups were combined, obtaining the values of central tendency and dispersion resulting from 12 collections.

A cross was made between the data from the PEM and PIM of the IIG and PIG, with the difference that, in the IIG, the data of the PEM were collected 2 months after the beginning of the study, whereas in the PIG these same data could only be collected after four months.

After all data had been collected for crossings, comparisons of the investigated variables were made between the three distinct moments, as follows: IM vs. PEM; PEM vs. PIM, and IM vs. PIM. This crossing

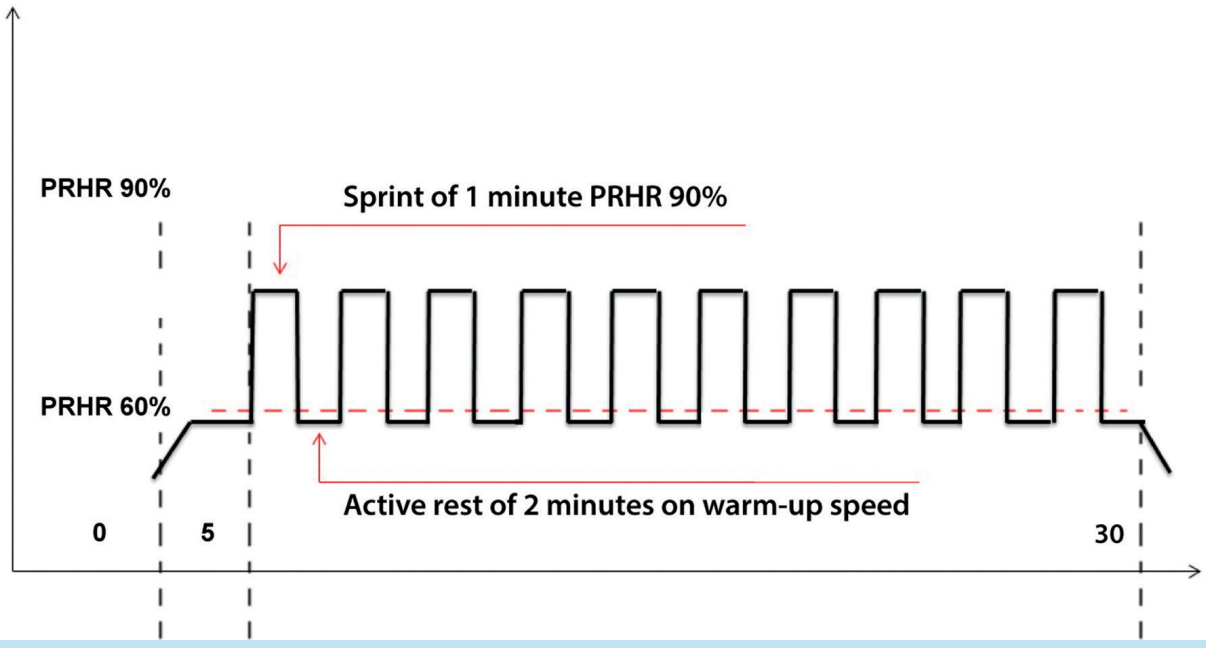

Figure 2 – Representation of high intensity interval training: Training based on predicted reserve heart rate (PRHR). The sprints had a duration of 1 minute and speeds identical to the value reached in the first sprint. Periods of active rest had a duration of 2 minutes and speeds identical to that achieved in the warm-up.

intended for the participants to become their own controls, minimizing bias.

In this study, the predictor variable was high-intensity interval exercise and the outcome variables were triglycerides, HDL, LDL, and CRP. Food and other lifestyle habits, which were not fully controlled, were considered confounding variables.

Results

Fourteen women were evaluated, one of whom was excluded due to pain complaints in the knee region and the other gave up on continuing the study, withdrawing her informed consent form. Twelve women participated in the research and were divided equally between IIG and the PIG, with 6 in each group, all of whom participated in the exercise and inactivity moments, lasting 2 months each. Table 1 presents the age of the sample and a summary of the oral contraceptives used by the participants. All contraceptives were combined between at least two substances, and 100% of them contained the synthetic estrogen - Ethinyl estradiol in their formulation.

Table 2 shows the comparison of CPE variables in the three moments, with the data already crossed between IIG and PIG. The changes in resting heart rate and VO_{2max} are highlighted, indirectly obtained through the distance covered in the Cooper protocol.

Figures 3A and 3B show the graphic representation of resting HR and VO_{2max} in CPE.

As for the inflammatory profile, after crossing the data from IIG and PIG, it was verified that the CRP values changed after the exercise. The CRP had a median and interquartile range of 4 (1.6 - 6.3 mg/dL), respectively, at the initial moment; 2 (1.5 - 5 mg/dL) in the post-exercise

Table 1 – Age and combined oral contraceptive use for the sample (n = 12).

Variable	Mean ± Standard Deviation
Age (years)	**24 ± 2.5**
COC	**Percentage of sample in use**
Selene Ethinylestradiol 0.035 mg / Cyproterone acetate 2.0 mg	27%
Adoless Ethinylestradiol 0.015 mg / Gestodene 0.060 mg	18%
Tamisa 020 Ethinylestradiol 0.020mg / Gestodene 0.075mg	18%
Tamisa 020 Ethinylestradiol 0.020mg / Gestodene 0.075mg	18%
Tamisa 030 Ethinylestradiol 0.030mg / Gestodene 0.075mg	9%
Level Ethinylestradiol 0.020mg / Levonorgestrel 0.100 mg	9%
Tamisa 030 Ethinylestradiol 0.030mg / Gestodene 0.075mg	9%
Active principle	**Frequency of the substance in COC**
Ethinylestradiol	100%
Gestodene	55%
Cyproterone acetate	27%
Levonorgestrel	18%

COC - Combined Oral Contraceptives.

Table 2 – Physical-clinical evaluation and lipid profile of young women using combined oral contraceptives submitted to high-intensity interval exercise on the treadmill (n = 12)

Variable	IM	PEM	PIM	P-value
BMI (kg/m2)	21 ± 2.6	21 ± 3	21 ± 2.7	0.97
SBP (mmHg)	108 ± 10.8	109 ± 8.7	108 ± 10	0.96
DBP (mmHg)	70 ± 8.0	66 ± 8.5	71 ± 6.1	0.19
Waist (cm)	71 ± 7	72 ± 8	74 ± 6	0.66
Cooper Test (mt)	1337 ± 119	1712 ± 188	1362 ± 199	< 0.01*
TC (mg/dl)	189 ± 19.9	181 ± 26.9	176 ± 19.5	0.37
HDL (mg/dl)	57 ± 11.3	57 ± 12.1	54 ± 9.7	0.67
TG (mg/dl)	100 ± 33.5	107 ± 30.8	111 ± 43.3	0.75
VLDL (mg/dl)	21 ± 4.59	19 ± 3.35	19 ± 3.40	0.60
LDL (mg/dl)	111 ± 22.1	103 ± 25.7	101 ± 17.2	0.53

Values obtained from data from the initial intervention group (IIG) and from the posterior intervention group (PIG), being crossed and expressed as means and standard deviations from the initial moment (IM); post-exercise moment (PEM) and post-inactivity moment (PIM). BMI: body mass index; SBP: systolic blood pressure; DBP: Diastolic blood pressure. TC: Total Cholesterol; HDL: high density lipoprotein; TG: Triglycerides; LDL: low density lipoprotein; VLDL: Very low density lipoprotein. The ANOVA test of repeated measures was used in the comparison between MI vs. PEM, PEM vs. PIM, and IM vs. PIM.
**** Statistical significance found.***

moment (2 months of intervention), and 4 (1.5 - 5.8 mg/dL) in the post-inactivity moment (2 months of inactivity). Comparisons were made between CRP of IM vs. PEM ; PEM vs. PIM; and IM vs. PIM, with a p-value of 0.04. Figure 3C presents the median values at the three moments of collection.

In table 2, it was possible to see that, after crossing the data from IIG and PIG, none of the variables of the lipid profile was modified by the high intensity interval exercise protocol. Values did not change between IM vs. PEM, between PEM vs. PIM, nor between the IM vs. PIM.

Discussion

In the present study, young women using COC, after the period of high-intensity interval exercise, showed a reduction in resting HR and an increase in indirect VO_{2max}, demonstrating the effectiveness of the program in improving the functional capacity of the participants. However, despite the improvement in indirect VO_{2max}, no change in the lipid profile was observed, but CRP optimization was detected.

Through previous studies carried out by our group, we were able to verify that women using COC have a higher lipid (↑ LDL, ↑ CT, ↑ TG)[12] and inflammatory (↑ CRP and ↑ oxidized LDL) profiles,[11] especially in those who declared themselves to be irregularly active. Therefore, it is possible to conclude that the implementation of physical exercises in the weekly routine of COC users can modify this.

Some factors may explain the findings of this study, including the fact that the participants are normolipidic. It is well-known that, in the general population, the reduction in triglyceride levels mediated by physical exercise occurs in a sensitive manner in inactive people and with fasting hypertriglyceridemia.[24,25] Regarding total cholesterol and HDL, it was observed that the reduction of its levels occurs when physical exercise is associated with a diet that culminates in a reduction in BMI.[25] Therefore, as the participants in our study were normolipidic and did not undergo any type of dietary restriction during the study period, perhaps because of this, the values of triglycerides and cholesterol-rich lipoproteins were not modified.

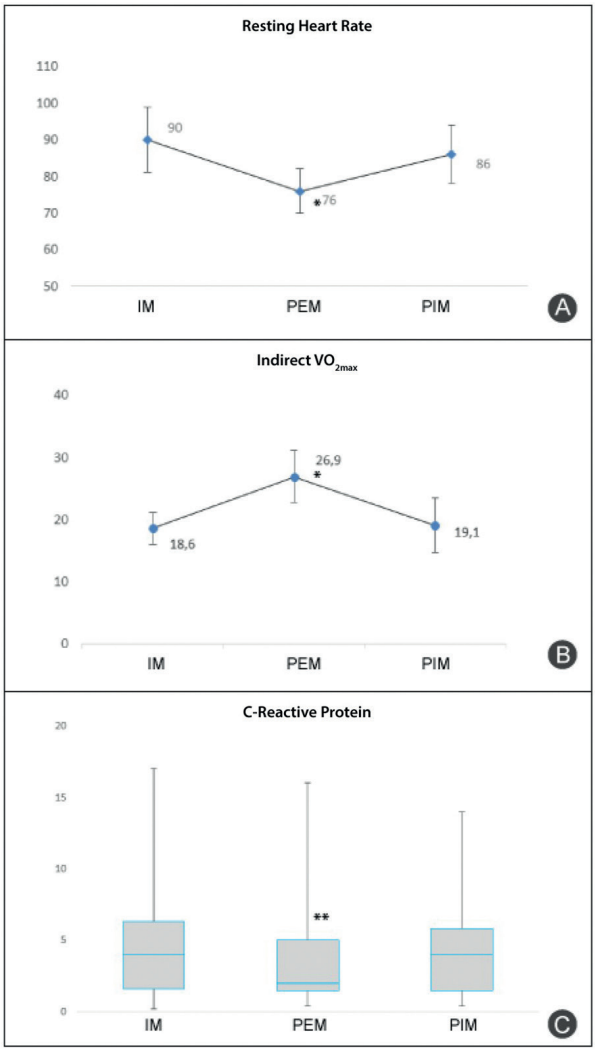

Figure 3 – A: Mean values and standard deviation of resting heart rate (RHR) in beats per minute (bpm) with cross data between initial intervention group (IIG) and posterior intervention group (PIG), respectively in the initial moment (IM), post-exercise moment (PEM), and post-inactivity moment (PIM). * p <0.01 in the ANOVA test of repeated measures with difference between IM vs PEM and PEM vs PIM. B: Indirect values of mean and standard deviation of maximum oxygen consumption (VO2 max.) In ml O2/Kg/min with crossed data from IIG and PIG in the IM, PEM, and PIM. * p <0.01 in the ANOVA test of repeated measures between IM vs. PEM and PEM vs. PIM). C: Values for median and interquartile range of C-Reactive Protein (CRP): Data in mg / l, crossed from the IIG and PIG, in the IM, between the PEM and between PIM. ** p =0.04 (Kruskal-Wallis test) in the comparison between IM vs. PEM and between PEM vs. PIM.

In addition, when thinking about physical exercise as a means to obtain gains, it is necessary to consider other issues associated with it, which are fundamental to achieving the proposed objective or not. Such variables as frequency, intensity, modality, and duration of the session are only a few of the factors that can also influence the final result.[26]

For the participants in this study, a specifically designed training included high-intensity, low-volume physical exercise, with a twice-a-week frequency. This type of training was chosen because it fit the participants' life routine and met the basic prerequisites of physical training. In addition, this protocol minimizes the monotony of training and increases adherence, as it is performed only two days a week.[27]

Thus, training was effective in indirectly improving VO_{2max}, but it was not enough to induce changes in the lipid profile. It is necessary to consider the hypothesis that another type of protocol that was carried out by manipulating the variables in another way could induce changes in the lipid profile. An example of this is the work that analyzed the effect of physical exercise on postprandial lipemia (PPL). In two studies carried out by our research group, different results (without modification and with reduction of the PPL) due to the modification of the exercise protocol were observed.[15,16]

Another important point to be discussed to explain the results of the present study is the caloric expenditure between exercise sessions. According to Kim et al.,[28] for changes in the lipid profile to occur, it is necessary not only to implement physical exercise sessions, but also to increase caloric expenditure between exercise sessions. In their study, it was found that the participants who reduced the PPL were those who received instructions to stay active on a daily basis. With this purpose in mind, participants were included in the routine of avoiding the use of elevators, prioritizing walking as the main means of transport, among other actions that increased daily caloric expenditure and contributed to improving the lipid profile, especially the PPL.

To further reinforce the importance of lifestyle for the lipid profile in COC users, we highlight the observational study that we conducted in 2015. This study identified that physically active women had a fasting lipid profile, PPL, and CRP that were less than irregularly active women.[16] The explanation for these findings may be based on the fact that these women, in addition to exercising regularly, also had an active life, that is, they

developed activities of daily living that promoted greater caloric expenditure.

In addition, people who frequently engage in physical exercise programs usually take greater care with eating habits. The present study did not encourage changes in the participants' lifestyles (higher levels of physical activity between sessions and changes in diet). On the contrary, the participants were asked to maintain their daily routine and eating habits throughout the study.

As for the inflammatory profile, corroborating the findings of our article, a retrospective study published in 2017 demonstrated a directly proportional relationship between heart rate and subclinical inflammation.[29,30] In fact, in our study it was possible to notice both the reduction in resting HR and CRP, which reinforces the thesis that physical exercise was effective in decreasing the inflammatory profile and sympathetic discharge simultaneously. This finding may have other implications, since in the genesis of atherosclerotic disease, sympathetic imbalance, and subclinical inflammation are important.[30]

The improvement of the inflammatory profile results in significant benefits, such as the reduction of oxidized LDL, a lipoprotein that participates in the genesis of atherosclerotic plaque.[31] The failure to measure this variable in our study was a limitation that prevented a deeper analysis of the effect of the exercise program on the reduction of CRP. It is important to highlight, however, that in the Women's Health Study, conducted with postmenopausal women, the increase in the inflammatory profile represented the main risk factor for cardiovascular diseases when compared to other variables, such as the elevated lipid profile and the levels of homocysteine.[32]

Regarding the last study mentioned, in the analysis of subgroups, it was found that even those participants who presented low levels of LDL-cholesterol showed greater risks of developing acute cardiovascular events when they had CRP levels > 3 mg/L.[32] Continuing with this study, it was found that the inflammatory profile remained more sensitive to unwanted cardiovascular outcomes when compared to the lipid profile, represented by LDL-cholesterol.[33]

Therefore, it is possible to hypothesize that the reduction in CRP with the exercise protocol proposed in this study may be crucial in controlling the onset of cardiovascular diseases in the long term, regardless of the reduction in the lipid profile.

Finally, the increase in indirect VO_{2max} caused by exercise can have other significant benefits. Although a reduction in the lipid profile was not observed, an inverse correlation between VO_{2max} and cardiovascular diseases and mortality from all causes was observed.[34] In this sense, the increase in VO_{2max} promoted by the physical exercise program in this population may well represent a long-term reduction in the risk of morbidity and mortality from cardiovascular diseases. We therefore recommend that healthcare professionals encourage the practice of physical exercise in this population as a way to minimize the cardiovascular risk promoted by the use of COC.

Such variables as total caloric expenditure, food intake, and other lifestyle habits also contribute to the improvement of the lipid and inflammatory profile, and should therefore be observed in conjunction with any physical exercise program. Thus, future studies with women using COCs should be conducted, taking into account parameters other than physical training. Furthermore, maximum tests should be used to determine the VO_{2max} and HR in order to make the exercise prescription more individualized.

This study is noteworthy as it is the first clinical trial with the application of HIIT in women who use COC. The evaluations carried out in this research open discussions on the real effectiveness of exercise on one's lipid profile, which remains within normal limits. In addition, the improvement in inflammatory activity allows us to emphatically recommend physical exercise for this group, as it acts upon a cardiovascular risk factor and reduces the risk for the development of type II diabetes (with insulin resistance), the latter of which has already been demonstrated in women using COC.[35]

Conclusion

The high intensity interval exercise protocol performed on the treadmill and applied in this study was not able to modify the participants' lipid profile; however, it was able to optimize the inflammatory profile of irregularly active women using COCs.

Author contributions

Conception and design of the research: Gomes AF, Petto J. Acquisition of data: Sacramento MS, Santa Cecilia LM, Almeida FOB, Jesus DS, Barbosa JS. Analysis and

interpretation of the data: Gomes AF, Petto J. Statistical analysis: Gomes AF, Petto J.

Writing of the manuscript: Gomes AF, Oliveira ECO, Petto J. Critical revision of the manuscript for intellectual content: Petto J.

Potential Conflict of Interest

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

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Study Association

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Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Faculdade Nobre de Feira de Santana under the protocol number 79549517.3.0000.5654. 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

Oral Contraception: Beyond What Meets the Eye. Sorry, the Ovaries!

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Editorial referring to the article: Effects of Physical Exercise on Lipid and Inflammatory Profile of Women Using Combined Oral Contraceptive: A Cross-Over Study

The concept of oral contraception, historically, was supposed to enable control of unwanted pregnancies and facilitate family planning for women of reproductive age in an elegant fashion for everyone needing it. However, the influence of different prescriptions on women's health during active use, as well as later on in life – *beyond the quintessential fear of thromboses lay women worldwide have* – has not been studied extensively or meticulously, despite the widespread use. Also, with some countries recently starting to embrace the over-the-counter concept for oral contraceptives in addition to the mechanical ones, a mandatory visit to a physician to get a personalized prescription will become a growing phenomenon and its public health consequences are unforeseeable, evidently.

In the current issue of *IJCS*, we had the pleasure of reading a paper by Gomes *et al*,[1] who presented their original article with results of a cross-over study of the influence of high-intensity interval training (HIIT) on the lipid and inflammatory profile of women using combined oral contraceptives (COC) that showed a beneficial effect to the latter, but not the former.

For the purpose of this Editorial, the Authors conducted an extensive systematic review of the currently available evidence hoping to identify gaps in the current knowledge globally.

Besides, dedicated societies – such as the American College of Obstetricians and Gynecologist[2-5] and the European Board and College of Obstetrics and Gynecology[6] – an occasional comment on importance of contraception can be found in cardiovascular societies' guidelines or position papers offering advice on long-term management of women with heart disease, but with no particular detailed, yet comprehensive, "Dos" and "Don'ts" being currently available. Therefore, aiming to facilitate further choices for all facing one , we have tried to summarize contraindications and cautious use in Figure 1. As pictured, the two prescription options – *combined estrogen-progestin oral contraceptives in monophasic and biphasic version and progestin-only oral contraceptives* – are globally available; however, how a woman and her physician(s) choose the best one considering the indication (contraception or other) remains in the domain of personalized medicine.

The pro-inflammatory, endothelial-dysfunction promoting and pro-thrombotic effects cause a myriad of pro-atherothrombotic states that facilitate cerebrovascular and cardiovascular events accompanied by diabetes and dyslipidemia, especially in the presence of pre-existing smoking.

Pasvol et *al*[7] have observed an increase in the risk of inflammatory bowel disease in women using combined, instead of progestogen-only, pills in a UK cohort of patients, consistent with Quinn et *al*[8] that reported that women using oral contraceptives to have higher oxidative stress and CRP.

Jimoh et *al*,[9] in the African population, have shown lipid profile alterations for COC, it is quite the opposite for progestin-only oral contraceptives in a Spanish cohort[10] that left glucose, insulin, and hemostasis intact. Short-term cardiovascular risk gets aggravated with COC;[9] however, the WISE cohort[11] unadjusted prior oral contraceptives' use was associated with lower longer-term all-cause and cardiovascular disease mortality, except for women with very elevated menopausal

Keywords

Contraception; Oral contraceptives; Cardiovascular risk.

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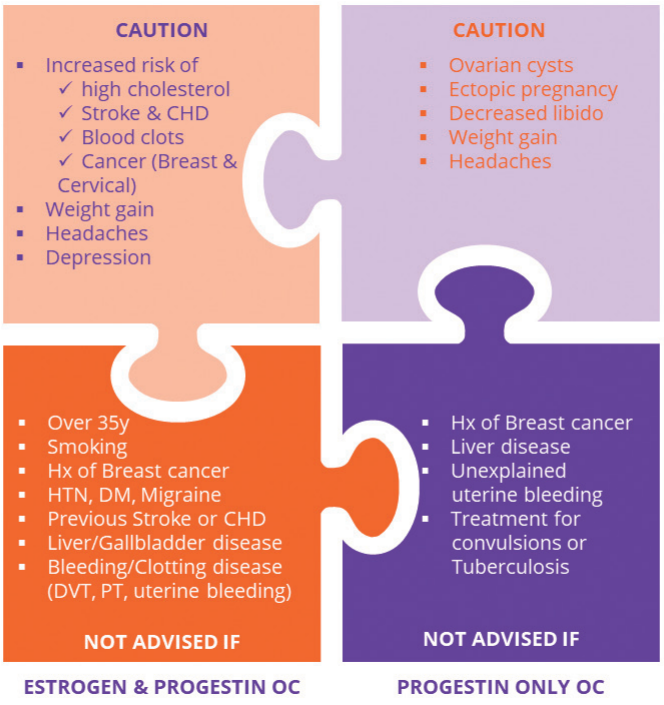

Figure 1 – Oral contraceptives' formulations.
Abbreviations: CHD: coronary heart disease; Hx: history; HTN: hypertension; DM: Diabetes mellitus; DVT: Deep Venous Thrombosis; PT: Pulmonary Thromboembolism

systolic blood pressure. Still, none of these cohorts reported the percentage of women with family hypercholesterolemia, whose issue of oral contraceptive choice remains a debate.[12]

Lamenting on the regrettable outcomes will surely not improve healthcare for women worldwide who need it despite their respective countries' economies and social determinants of health,[13,14] yet region- and country-specific solutions[15] must be implemented if we aim to improve cardiovascular and reproductive care of women on a global scale.

However, when the Venn diagram of "the pill" as an over-the-counter medication[4] overlaps with a rising hostility to abortion rights for women worldwide – *although it risks opening the dangerous doors of clandestine abortions we had hoped to have closed forever in the previous century* – we find ourselves in the area of the only viable and sustainable solution for both our patients and ourselves and that is a more comprehensive, global, and ethnically diverse research agenda that mimics the population we see in our hospital corridors and clinics' waiting rooms to mitigate the side effects of existing therapies and progress to new ones.

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ORIGINAL ARTICLE

The Medical Burden of Heart Failure: A Comparative Delineation with Cancer in Brazil

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Abstract

Background: Due to its poor prognosis and mortality rates, heart failure (HF) has been recognized as a malignant condition, comparable to some cancers in developed countries.

Objectives: To compare mortality from HF and prevalent cancers using data from a nationwide database in Brazil.

Methods: This was a descriptive, cross-sectional study using secondary data obtained from Brazilian administrative databases of death records and hospitalization claims maintained by the Ministry of Health. Data were analyzed according to main diagnosis, year of occurrence (2005-2015), sex and age group. Descriptive analyses of absolute number of events, hospitalization rate, mortality rate, and in-hospital mortality rate were performed.

Results: The selected cancers accounted for higher mortality, lower hospitalization and higher in-hospital mortality rates than HF. In a group analysis, HF showed mortality rates of 100-150 per 100,000 inhabitants over the period, lower than the selected cancers. However, HF had a higher mortality rate than each type of cancer, even when compared to the most prevalent and deadly ones. Regarding hospitalization rates, HF was associated with a higher risk of hospitalization when compared to cancer-related conditions as a group.

Conclusions: Our findings indicate that HF has an important impact on mortality, hospitalization and in-hospital mortality, comparable to or even worse than some types of cancer, representing a potential burden to the healthcare system.

Keywords: Cardiovascular Diseases/mortality; Heart Failure; Neoplasms/mortality; Brazil; Epidemiology; Mortality; Hospitalization; Answering Services/statistics & numerical data.

Introduction

More than 64 million people live with heart failure (HF) in the world.[1] Due to its progressive nature, HF is characterized by high mortality in the advanced phase, and its prognosis varies widely according to the population studied.[1] According to population-based studies, after the diagnosis of HF, survival estimates at 5 and 10 years are 50% and 10% respectively.[2-6] The risk of mortality for HF patients is twice of people without the disease.[7-9] A recent cohort study of patients diagnosed with HF from 2000-2017 in the United Kingdom reported only a modest improvement in survival in the 21st century.[10-12]

In a review published in 2002, McMurray and Stewart[11] conducted a comparison of HF mortality with different types of cancer. The authors showed that HF killed more patients than breast, prostate, bladder, bowel, and ovarian cancer. Only lung cancer was more malignant than HF.[11] Mamas et al.,[12] in a more recent review, showed that the statement presented by McMurray and Stewart remains valid until today, allowing us to conclude that HF is a more malignant disease than many types of cancer.[12] However, although the international literature is abundant in articles addressing HF mortality, there are no data to support that HF mortality is higher than cancer mortality in Brazil.

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The primary objective of this study was to compare the number of in-hospital deaths due to HF and selected cancer diseases in Brazil between 2005 and 2015. Secondary objectives were to compare the number of hospital admissions due to HF and selected cancer diseases in Brazil between 2005 and 2015; and to compare in-hospital mortality rates from HF and selected cancer diseases in Brazil between 2005 and 2015.

Study design

This was a descriptive, cross-sectional study using secondary data obtained from the SIM (Mortality Information System)[13] and the SIH (Hospital Information System) of the Information Technology Department of the Brazilian Ministry of Health.[13] The SIH is an administrative database of data from hospitals of the Brazilian unified Health System (SUS), including admission data – authorization forms, demographics, hospitalization cause – length of stay and in-hospital mortality, which are used for health service and system planning and knowledge production in the field of public health.[14] The SIM provides nationwide population-based data about mortality – main cause and secondary causes of death, and demographics, obtained from death certificates. As for SIH, these data help in planning of health services and programs.[15]

Both SIM and SIH are publicly available databases created and maintained by DATASUS.[16] The analysis comprised a period of eleven years, of registries between 2005 and 2015 of individuals aged ≥ 45 years, age when cardiovascular disease is most diagnosed. Files containing anonymized data were downloaded directly from the DATASUS website in their original format. Data on hospitalization and death were retrieved from the SIH and SIM databases, respectively, of the 26 states and the Federal District in Brazil. Data cleaning and validation was conducted by the investigators to identify completeness and integrity of available data.

We considered the 10th International Classification of Disease (ICD-10) code for Heart Failure I50, and the most prevalent cancers: C16 stomach cancer, C18 colon cancer – grouped with C19 malignant neoplasm of recto sigmoid junction and C20 rectum cancer, C34 trachea, bronchi and lung cancer, C50 breast cancer (except for male cases of breast cancer for both death events and in-patient admissions), C53 cervix cancer and C61 prostate cancer.

Brazilian population projections were obtained from DATASUS website.[16] These projections are obtained from the Brazilian Institute of Geography and Statistics (IBGE) using methods described in the Brazilian National Population Projections by age and sex: 2000-2060.[17] Estimates are calculated using data from the Brazilian 2010 Demographic Census and information of births and deaths obtained from official records.

Statistical analysis

The data were aggregated for calculations of mortality and hospitalization, in absolute numbers and rates, by disease and year of occurrence. Each event (hospitalization, death and in-hospital death) was coded according to the ICD-10 classification (after accounting for ill-defined or undefined causes of death) and the aggregated groups of causes were analyzed considering the year of occurrence (2005 to 2015).

For death events, a redistribution method of ill-defined causes of death (Chapter XVIII of the ICD-10 - Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified) was used as described by Soares et al.[15] Undefined causes of death were redistributed using the proportion of each defined cause except for external causes (which were assumed to contribute to a small proportion of in death records). These reclassified death records were summed to the absolute number of deaths initially coded with eligible ICD-10 codes for the study.

Data were then descriptively compared year by year between selected diseases using graphs.

As a descriptive study, all data on death and hospitalization that met the eligibility criteria were organized and stored in a Microsoft Excel spreadsheet. Thus, sample size calculation was not applicable.

Results

Due to the nature of the study – a retrospective database study without patient-level data – information about participants is not disclosed.

Table 1 presents the absolute number of hospitalizations for different types of cancer and HF from 2005 to 2015. The frequency of hospitalization for HF was higher compared with various types of cancer.

Table 2 shows the number of patients who died during hospitalization for cancer or HF treatment.

We observed a higher number of in-hospital mortality for HF compared with selected types of cancer over the study period. Undefined causes of death contributed to an average of 8.13% of deaths in the period.

Table 1 - Absolute number of hospitalizations for different types of cancer and heart failure from 2005 to 2015

Selected diagnoses	Year										
	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
C16 Stomach cancer	14,550	14,861	14,440	13,154	14,119	15,395	16,552	17,604	18,770	19,983	20,673
C18-C20 Colorectal cancer	16,471	18,295	19,313	22,864	25,662	30,574	37,050	41,244	46,871	49,760	52,734
C34 Trachea, bronchi and lung cancer	11,558	12,481	12,996	12,408	13,725	14,982	15,515	16,916	18,075	19,366	20,113
C50 Breast cancer	25,111	25,804	27,208	27,833	29,405	31,742	33,375	37,450	41,607	43,395	45,565
C53 Cervix cancer	15,406	15,305	13,969	14,126	13,564	13,347	12,992	12,859	12,578	11,754	11,523
C61 Prostate cancer	14,224	13,388	13,938	17,659	19,850	21,985	23,852	25,669	26,685	27,593	29,549
I50 Heart Failure	277,168	265,628	248,010	242,094	241,536	236,827	232,277	216,834	210,346	198,370	192,181

Table 2 - Absolute numbers of in-hospital mortality from the selected diseases in each calendar year from 2005 to 2015

Selected diagnoses	Year										
	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
C16 Stomach cancer	3,038	3,220	3,330	3,140	3,594	3,695	3,768	4,060	4,276	4,455	4,308
C18-C20 Colorectal cancer	2,297	2,556	2,731	3,004	3,336	3,852	4,223	4,659	5,084	5,365	5,373
C34 Trachea, bronchi and lung cancer	3,275	3,567	4,185	4,027	4,617	5,034	5,230	5,671	6,141	6,500	6,541
C50 Breast cancer	1,968	2,163	2,467	2,709	2,940	3,270	3,494	3,822	4,160	4,292	4,438
C53 Cervix cancer	1,041	1,069	1,231	1,274	1,510	1,622	1,684	1,739	1,756	1,744	1,788
C61 Prostate cancer	1,196	1,273	1,501	1,734	2,060	2,322	2,553	2,654	2,932	3,135	3,161
I50 Heart Failure	22,517	24,238	24,440	24,682	25,616	26,457	27,422	26,264	26,713	26,059	25,004

Table 3 shows the percentage of in-hospital mortality of patients with HF and with different types of cancer. HF mortality has increased progressively in these eleven years. Patients with HF hospitalized for compensation had an average mortality in of 11.08%, higher than breast cancer (9.60%) and prostate cancer (10.32%) and lower than other types of cancer.

Discussion

Several authors have called attention to the fact that the mortality of HF patients is high and more pronounced than of patients with some types of cancer.[13,14] In Brazil, the mortality of patients with HF is also high, particularly when compared with mortality rates described in developed countries, but there are no data comparing mortality from HF with cancer in our country. In this article, we made this comparison using data from DataSUS.[15-17]

The comparative analysis of hospital admissions for HF with admissions for the most prevalent types of cancer revealed significantly higher numbers of patients hospitalized due to HF than cancer (Table 1). Besides, the number of patients who died from HF was significantly higher than those who died from different types of cancer (Table 2). In addition, considering in-hospital mortality,

Table 3 – Percentage of in-hospital mortality of patients with HF and with different types of cancer

Selected diagnoses	Year										
	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
C16 Stomach cancer	20.88	21.67	23.06	23.87	25.46	24.00	22.76	23.06	22.78	22.29	20.84
C18-C20 Colorectal cancer	13.95	13.97	14.14	13.14	13.00	12.60	11.40	11.30	10.85	10.78	10.19
C34 Trachea, bronchi and lung cancer	28.34	28.58	32.20	32.45	33.64	33.60	33.71	33.52	33.98	33.56	32.52
C50 Breast cancer	7.83	8.38	9.07	9.73	10.00	10.30	10.47	10.21	10.00	9.89	9.74
C53 Cervix cancer	6.76	6.98	8.81	9.02	11.13	12.15	12.96	13.52	13.96	14.84	15.52
C61 Prostate cancer	8.41	9.51	10.77	9.82	10.38	10.56	10.70	10.34	10.99	11.36	10.70
I50 Heart Failure	8.12	9.12	9.85	10.20	10.61	11.17	11.81	12.11	12.70	13.14	13.01

we may say that HF was more malignant than breast cancer and prostate cancers (Table 3), as mean mortality rate of patients hospitalized due to acute HF (11.08%) was higher than breast (9.60%) and prostate cancers (10.32%).

In Latin America, HF is the leading cause of hospitalization, with rehospitalization rates of 33%, 28%, 31%, and 35% at 3, 6, 12, and 24 to 60 months of follow-up, respectively.[18,19] Despite treatment advances, HF still has a poor prognosis, with high mortality rates. Five-year mortality rate for HF was estimated at approximately 50%.[20] In Latin America, it is estimated a one-year mortality rate of 24.5%, and in-hospital mortality rate of 11.7%.[19] Brazilian registry data indicate an in-hospital mortality rate of 12.6%.[21]

As shown in previous studies in developed countries,[14,20,22] HF can be associated with worse outcomes than some types of cancer. Askoxylakis et al.,[20] conducted a systematic review of the literature and noted a five-year survival of approximately 43% for all cancer types and 26-52% for HF, showing that HF in some settings is as deadly as some cancers, and even worse as compared with cancers like breast cancer (73-89%), prostate cancer (50-99%) and colorectal cancer (43-63%).[20] Using a retrospective approach, Stewart et al.,[22] identified that the annual incidence of first-ever hospitalization for HF was higher than for cancer in Sweden: 484 versus 373 (lung, colorectal, prostate, and bladder cancer combined) per 100,000 men and 470 versus 350 (lung, colorectal, bladder, breast, and ovarian cancer combined) per 100,000 among women aged > 20 years. The authors also observed that the 30-day and five-year mortality rates were comparable between HF and cancer, and that during the 10-year follow-up period, HF was associated with more premature life-years lost than all common forms of cancer in men but not in women.[22] Mamas et al.,[12] conducted an analysis of survival rate comparing HF with some forms of cancer. The authors' findings indicated that HF had significantly worse five-year survival rate (55.8%) than prostate cancer (68.3%) and bladder cancer (57.3%), but significantly better than lung cancer (8.4%) and colorectal cancer (48.9%). In women, HF mortality outcome was worse (49.5%) than breast cancer (77.7%), but better than colorectal cancer (51.5%), lung cancer (10.4%), and ovarian cancer (38.2%).[14]

Our data confirm the described in Latin America and in the world[14,20,22] regarding high rates of mortality from HF as compared with some cancers These data reinforce the need to recognize HF as a priority condition in Brazil, mainly by health system managers and policy makers, but also by the general population. Besides the magnitude of the disease burden in terms of deaths and hospitalizations, the decreasing rates observed in temporal series highlight that HF potentially responds to improvement in care with better outcomes that are relevant for both patients and the health care system, once hospitalization is the main cost driver in HF.[22,23]

Since the data used in this analysis were representative of all the death certificates and hospitalization claims from the Brazilian public health care system during the 2005-2015 period, it is possible to assume that the findings are applicable to the national setting for mortality data and for the public health care system for hospital admission data.

It is important that physicians become aware of these data, to try to make an earlier diagnosis of HF and provide earlier treatment using the best evidence, and thereby modify the natural history of the disease.

It is worth remembering that the CONSENSUS study showed that, although it was possible to modify the course of HF, the mortality remained high (44%) in the control group in the first six months and in the first year (52%). The prescription of enalapril reduced mortality to 26% in the first six months and to 36% at the end of the first year.[23] With the introduction of beta-blockers, mineralocorticoid receptor antagonists, angiotensin receptor antagonists and, more recently an angiotensin receptor neprilysin inhibitor (ARNI), it is possible to substantially reduce the mortality of patients with insufficiently treated HF.[24-26]

An interesting point often discussed in Brazilian scientific meetings is the interpretation of the recent reduction in the number of hospitalizations for HF per year, as indicated by the SUS data. Some presentations interpret such decrease as a result of better management of the cases, without taking into account, however, the significant reduction in the number of SUS beds (Table 4) in recent years. With a smaller number of beds, physicians are pressured to admit only the most serious patient who will have the highest mortality, even with the best treatment available.

We can conclude that HF alone promotes more hospitalizations and deaths than some types of cancer. The mortality of patients with HF was higher than the one observed in patients with breast or prostate cancer, a result similar to other studies around the world. This concept of HF malignancy should be better disseminated so that more attention would be paid to patients with the syndrome, as its prognosis varies with treatment (e.g. timing and dosage, use of neurohormonal blockers), according to national guidelines.

Limitations

The results of hospitalization and in-hospital mortality of the present study are probably not applicable to the private health care system, since the access to health care services, treatment patterns and epidemiological profile of patients are markedly different between both settings. The main limitation of this study is its retrospective approach based on administrative databases that were not specifically designed for the purposes of the study. For this reason, detailed clinical data about diagnosis and treatment were not available, limiting our ability to adjust for the comorbidity burden of HF, for example. Also, it was not possible to differentiate between HF with reduced and preserved ejection fraction. Another limitation was that it was not possible to use record linkage to combine HF- and cancer-related hospitalization and mortality data to identify unique patients. Another limitation of this study was the absence of patient-level longitudinal data that could allow further analysis including survival analysis, as previously performed by other researchers.[14,20] Despite these limitations, both SIM and SIH databases have been widely used for epidemiological research in Brazil with valid and well-accepted results.[15,16] These aspects can be further explored in futures studies conducted in Brazil, including HF cost studies, to provide greater knowledge about the clinical and economic burden of HF in the country.

Table 4 – Number of public hospital beds by geographic region in Brazil

Regions	2009	2020	Δ (difference)
North	29,984	30,357	373
Northeast	121,864	114,215	-7,449
Southeast	197,809	171,967	-25,842
South	74,277	72,947	-1330
Midwest	37,194	36,902	-292
Total	**460,928**	**426,388**	**-34,540**

Source: Estado de São Paulo, March 25th 2020

Conclusion

The results of this analysis indicate that HF causes a significant burden to the health care system and the society, in terms of mortality and hospitalization. This burden is comparable or even worse than that caused by some types of cancer. It is urgent that health managers, policy makers and the society need to prioritize the early diagnosis, prevention and treatment of HF, when deciding about resource allocation in the health care system

Author contributions

Conception and design of the research; Analysis and interpretation of the data; Writing of the manuscript; Critical revision of the manuscript for intellectual content: Almeida DR, Pereira-Barretto AC, Forestiero FJ, Nakamuta JS, Bichels A. Obtaining financing: Bichels A.

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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

The Medical Burden of Heart Failure and Cancer in Brazil. Fact or Fiction?

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Editorial referring to the article: The Medical Burden of Heart Failure: A Comparative Delineation with Cancer in Brazil

Cardiovascular disease and cancer are the leading causes of mortality in most high-income countries around the globe.[1] It is estimated by the Brazilian Ministry of Health that circulatory diseases and cancer are the leading causes of mortality in patients over 50 years of age,[2] which makes them the main public health concerns in absolute numbers. This is not only true in treatment-related costs, but also in terms of social harm imposed on an economically productive population and the health system this population subsidizes.

Recently, Almeida et al. have published a comparative analysis on mortality rates for patients with heart failure.[3] The paper performed a retrospective comparative analysis with data retrieved from DataSUS, an administrative database from brazilian's public health system and was able to reach the conclusion that heart failure has a prognosis that is worse than many types of cancer. As the author himself says, the paper is limited by the administrative characteristics of the database itself, and, as already mentioned in the BREATHE registry, this kind of data has inherent limitations.[4]

Although both populations face dismal prognostic rates, Santos et al. have shown that the relative mortality rate for heart failure (per 100,000 inhabitants) has dropped during the last 40 years.[5] These findings, according to the authors, can be attributed to increased access to and optimization of health care.On the other hand, the prognosis for cancer patients has remained unchanged over the last 20 years.[5] It is possible that an organized public health program, combined with a strong cardiology society, could provide uniformization of guideline-directed therapies, resulting in more efficient implementation and improved mortality rates.

Of course, the desire for lower mortality rates in prevalent diseases such as heart failure and cancer is uncontroversial. However, the immediate concern is the high prevalence of both diseases, which are responsible for frequent hospitalizations. More than 1 million hospitalizations occurred due to acute heart failure in 2012.[4] The economic burden is also quite impressive: 2.1% of all health care expenditures in 2017 were for the treatment of patients with acute heart failure.[6] In parallel, over 700,000 hospitalizations were attributable to cancer of any kind in 2018, at an estimated cost of over BRL 1.8 billion.[4,7]

It should also be recognized that newer and better treatment options are a huge factor in the lower mortality rate of heart failure patients. The recent approval of sacubitril/valsartan and dapagliflozin for heart failure patients in the Brazilian public health system will entail a considerable increase in treatment costs. The annual cost increase per patient, according to Brazil's technical committee for incorporating technology, will be BRL 806,65 for dapagliflozin and BRL 2460,10 for sacubitril/valsartan.[8,9] While heart failure patients face challenges to medication access, cancer patients face abysmal differences in treatment options depending on region, social class, and access to private health infrastructure. Inequality certainly plays a key role in the unchanged mortality curve.[7]

The answer for both groups could be obtained in part by effective universal preventive interventions. This is especially true since both cancer and heart failure patients share common risk factors for the development and worsening of their diseases. For example, Corrêa Ferreira da Silva et al. reported that

Keywords

Heart failure; Cancer; Epidemiology.

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body weight-associated cancers were responsible for 1.76% of all cancer-related costs in Brazil in 2018.[10] Therefore, it is plausible that public health policies focusing on minimizing tobacco exposure, promoting body weight awareness, and increasing healthier food consumption patterns could result in remarkable outcomes in terms of reduced prevalence and improved quality of life in both patient groups, not to mention the resulting economic savings.

Cancer and heart failure patients have not only common prognostic rates, risk factors, and clinical attributes, but also an intertwined correlation between their diseases. This fact is of such relevance that a new cardiologic subspecialty has arisen: cardioncology. Cancer patients have a substantial risk of developing cardiovascular complications, such as cardiotoxicity, accelerated coronary artery disease, and pericardial pathologies. In contrast, heart failure is an obstacle to cancer treatment regimens.

The situation for cancer and heart failure patients seems to have improved over the years in Brazil. Mortality rates have dropped, treatment options have expanded, and public policy favors preventive measures. Nevertheless, minimizing the social and regional discrepancies in access to diagnostic tools and time to treatment is an ongoing challenge. The answer for the growing economic burden of cancer and heart failure seems to be universal public effort toward prevention of their common risk factors.

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ORIGINAL ARTICLE

Impact of Air Pollutant on Heart Rate Variability in Healthy Young Adults

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Abstract

Background: Air pollution and sex independently affect cardiac autonomic control, which can be assessed by heart rate variability (HRV). The research hypothesis is that individuals exposed to low concentrations of pollution have higher cardiac autonomic modulation compared to those exposed to high concentrations and that women have better cardiac autonomic control than men.

Objective: To analyze the impact of exposure to air pollutants, specifically smoke, and sex on HRV in healthy young people exposed to different concentrations of pollution over an average period of 22 years.

Methods: From April to September 2011, 36 participants of both sexes (20-30 years old) were selected, grouped by levels of air pollution exposure according to indices provided by the Environmental Company of São Paulo State. The R-R intervals (R-Ri) of the electrocardiogram were captured using a heart rate monitor during supine rest. HRV was analyzed by spectral analysis and conditional entropy. The Queen´s College step test was used to characterize functional capacity. A between-group comparison was performed using the two-way ANOVA statistical test (post hoc Tukey) and $p<0.05$.

Results: Significant differences were found in mean R-Ri ($p<0.01$) and cardiac parasympathetic modulation between sexes in the same city ($p=0.02$) and between groups exposed to different air pollution concentrations ($p<0.01$).

Conclusion: Our results suggest that long-term exposure to air pollutants, specifically smoke, has an unfavorable impact on HRV, with reduced cardiac vagal autonomic modulation in healthy young adults, especially females.

Keywords: Air pollution; sex; autonomic nervous system; heart rate.

Introduction

Air pollution is defined as the presence of substances in the atmosphere resulting from human activity or natural processes. When these materials surpass pre-established concentrations, they can be harmful to health, as well as to normal community activities, such as activities of daily living and social participation.[1,2]

Impacts of air pollution on cardiovascular morbidity and mortality have been described,[3] and can be explained by: 1) an increase in fibrinogen and circulating inflammatory factors that lead to an increase in blood viscosity and coagulation disorders; and 2) changes in autonomic nervous system (ANS) modulation to the heart,[4–9] which can be evaluated through heart rate variability (HRV).

Studies have shown that some factors like sex and functional capacity can influence ANS modulation.[10-12] Women have a higher resting HRV than men of the same age group, indicating a parasympathetic predominance in females and a sympathetic predominance in males.[10,12-14]

Assessment of HRV is a non-invasive, simple and inexpensive method, widely used in the quantification of cardiac sympathetic and parasympathetic modulation using linear and non-linear measures.[11,15-19] An individual who exhibits efficient cardiac autonomic control

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mechanisms has a high resting HRV, characterized by a parasympathetic predominance.[8,19,20] However, some cardiac conditions (e.g., conduction disturbances and atrial fibrillation) can also induce a high HRV.[19]

Thus, the research hypothesis is that individuals exposed to low concentrations of air pollution have better cardiac autonomic modulation compared to those exposed to high concentrations, and that women have better cardiac autonomic control than men. Thus, this study aimed to analyze the long-term impact of exposure to pollutants, specifically to smoke, and the influence of sex on cardiac autonomic modulation in healthy young people exposed to two different levels of air pollution.

Methods

Study design

This was an observational, cross-sectional, prospective study.

Sample

Thirty-six participants (20 men and 16 women) between 20 and 30 years old were selected by convenience, and divided into two groups according to the place of residence: a) group 1 – 10 men and 8 women living in a city with a high concentration of air pollution (São Paulo, São Paulo State) and; b) group 2 – 10 men and 8 women living in a city with a low concentration of air pollution (São Carlos, São Paulo State).

All volunteers were considered healthy according to the anamnesis: they did not have any disease of the respiratory, cardiovascular, or skeletal muscle systems. They lived in the same city for at least 15 years, without staying more than six months in other cities that had a concentration of air pollution different from the place of origin. It is known that short-term exposure to pollutants, depending on the concentration and type of pollutant, can acutely increase the risk of respiratory and cardiovascular mortality,[3,21] while exposure to air pollutants for a period between 15 and 30 years can cause medium and long-term impacts on human health.[22] Individuals using medications that can alter cardiac autonomic modulation, individuals who consumed alcohol, smokers, hypertensive subjects, those with diabetes mellitus, respiratory or cardiovascular diseases, sedentary lifestyle and/or a body mass index ≥ 30 kg/m^2 were excluded.

Classification of locations regarding air quality

The indices for estimating air quality and classifying the cities as "highly polluted" and "low polluted" were consulted on the website of the Environmental Company of São Paulo State (CETESB).[23] Primary standards for high pollutant concentrations were those that, when exceeded, can affect the health of the population, that is, the maximum tolerable levels. Secondary standards were defined as concentrations below which have the least impact on the population's well-being, that is, the desired levels of pollutant concentrations. In this study, we adopted 150μg/m^3 and 100μg/m^3 per day for primary and secondary standards, respectively.[24]

To obtain the annual averages of 2011, the averages of the indices from the seven air quality monitoring stations in the metropolitan region of São Paulo and from the single monitoring station in São Carlos in that same year, provided by CETESB, were calculated.[23] These data are shown in Table 1.

However, for the purposes of this research, only smoke concentrations were considered for estimation of air pollution of the two cities mentioned above (São Paulo and São Carlos), which represent only a fraction of the particulate matter that influences this type of pollution. This decision was made based on the information available on the website of CETESB,[23] which provides only smoke indices as measurements in the city of São Carlos.

Procedures

Volunteer recruitment and data collection were carried out from April to September 2011 at the Physical Education and Sport School of the University of São Paulo and the Cardiovascular Physiotherapy Laboratory of the Federal University of São Carlos.

Initially, volunteers were informed about the purposes of the study and experimental procedures and signed an informed consent form. The study was approved by the Research Ethics Committee (EEFE-USP 2011/36) and complied with the 466/12 Resolution of the National Health Council 12/12/2012.

The subjects were instructed to abstain from caffeine and alcoholic beverage intake, and from strenuous physical exercise for at least 24 hours before the HRV measurement, and to have a good night's sleep the night before the tests. The experimental procedure was carried out in the morning period (between 7 am and 12 pm), considering circadian variations.[18,25]

Table 1 – Primary and secondary smoke index standards of the cities of São Paulo and São Carlos, Brazil, in 2011

	Reference value	São Paulo, SP	São Carlos, SP
Primary standard (μg/m³)	150	158,85	46
Secondary standard (μg/m³)	100	109,71	38

NB: μg/m³ = micrograms/cubic meter. Source: CETESB.[23]

On the day of the experiment, the volunteers were asked whether they had followed the instructions correctly and if they were in good health. Then, the heart rate monitor (Polar Electro, Finland, S810®) was placed on the volunteer's chest, according to the manufacturer's specifications.[18] Afterwards, the RR intervals (R-Ri) of each participant at supine rest were recorded (in ms), for 15 minutes, in a silent and climate-controlled environment, at a temperature of around 22 °C and relative humidity between 40 and 60%.

Next, the submaximal exercise test was performed with a 40.9 cm step, following the Queen´s College protocol[26] for people between 18 and 30 years old. The protocol consisted of stepping up and down on the step for three minutes, in cadence with a metronome set at 96 beats per minute (bpm). This test aimed to indirectly estimate the maximum oxygen consumption (VO_2max) reached by the volunteer, considering heart rate recovery (from the 5th to the 20th second heartbeat after the test), and the following equations proposed by the protocol:

Men → VO_2max (mL/Kg/min) = 111.33 – (0.42 x heart rate recovery)

Women → VO_2max (mL/Kg/min) = 65.81 – (0.1847 x heart rate recovery)

The estimated VO_2max values were used considering the indices established by the American Heart Association (AHA)[27] to characterize the sample and ensure that the studied groups had similar aerobic functional classification, as this is also a factor that can affect HRV values.[10,18,25]

Data processing

R-Ri analysis

For HRV analyses, the R-Ri sequence with the highest stability, with a length of 256 points, was selected for each volunteer, excluding the initial and final stretches.[18,19]

Linear analysis of HRV

The spectral analysis of the HRV was performed by the autoregressive method[28,29] in two bands: low frequency (LF) and high frequency (HF).[13,18,25] Their values were expressed in normalized units – LFnu for cardiac sympathetic modulation and HFnu for parasympathetic modulation – [6,7] calculated as follows: LFnu = LF power/TP – VLF power × 100; HFnu = HF power/TP – VLF power × 100.[28,29] Mean R-Ri and variance were also calculated.

Nonlinear HRV analysis (conditional entropy)

The study of entropy qualifies and quantifies HRV complexity.[30] Conditional entropy based on symbolic dynamics[17] shows information about the regularity of HRV, that is, it is able to clarify whether the amount of information provided from a new sample can be determined by analyzing previous values.[15,16] This analysis provides the complexity index (CI), which was normalized by Shannon entropy, resulting in the normalized complexity index (NCI).[17] According to Porta et al.,[17] the NCI can range from 0 (null information) to 1 (maximum information). This means that the higher the NCI, the lower the regularity of the series and the greater the complexity.

Statistical analysis

The Shapiro-Wilk test was used to verify data normality. The impact of exposure to pollutants and of sex on HRV were analyzed by the two-way ANOVA statistical test, taking sex (male and female) and pollution (most polluted location – São Paulo and least polluted location – São Carlos) as factors, and analyzing the interaction between them using the post hoc Tukey's Test. Data were expressed as mean ± standard deviation. A significance level of 5% ($p<0.05$) was considered. For this purpose, the Sigma Plot 11.0 for Windows software was used.

Results

Anthropometric characteristics and age of participants are described in Table 2. There were statistical differences in body mass, height and estimated VO_2max between the sexes, where women showed lower values compared to men (as expected), regardless of the city in which they lived (Table 2). Group 1 volunteers lived in São Paulo for 21.94 ± 1.43 years and group 2 volunteers in São Carlos for 22.55 ± 4.40 years.

Table 3 shows the results of linear (time and frequency domain) and non-linear (conditional entropy) HRV analysis in supine rest of the evaluated groups. Mean R-Ri showed the impact of sex and its interaction with air pollution exposure, which was higher in men compared to women in the city of São Paulo. Likely, HFnu (cardiac parasympathetic

Table 2 – Age, anthropometric characteristics, and functional capacity of residents of São Paulo and São Carlos, included in the study

	Group 1 (São Paulo, SP)		Group 2 (São Carlos, SP)		P values		
	Men (n = 10)	Women (n = 8)	Men (n = 10)	Women (n = 8)	Impact of air pollution exposure	Impact of sex	Interaction between the impacts
Age (years)	22.2 ± 1.7	21.6 ± 1,1	22.8 ± 3.2	23.8 ± 3.2	0.109	0.822	0.363
Body mass (Kg)	74.1 ± 7.9	61.6 ± 5.8	76.4 ± 11.5	64.7 ± 16.4	0.473	0.003 *	0.918
Height (m)	1.8 ± 0.1	1.6 ± 0.1	1.8 ± 0.1	1.6 ± 0.1	0.395	< 0.001 *	0.938
BMI (Kg/m²)	23.4 ± 1.5	22.7 ± 1.9	24.7 ± 2.9	24.3 ± 6.2	0.228	0.640	0.886
Estimated VO_2max	50.5 ± 3.8	36.2 ± 3.1	50.8 ± 5.5	34.4 ± 2.7	0.559	< 0.001 *	0.443

*NB: values expressed as mean ± standard deviation; BMI: body mass index; VO_2max = maximum oxygen consumption; * significant difference according to the two-way ANOVA statistical test, with post hoc Tukey test. Source: research data.*

Table 3 – Heart rate variability assessed in the time, frequency and conditional entropy domains

	Group 1 (São Paulo, SP)		Group 2 (São Carlos, SP)		P values		
	Men (n = 10)	Women (n = 8)	Men (n = 10)	Women (n = 8)	Impact of air pollution exposure	Impact of sex	Interaction between the impacts
Mean R-Ri (ms)	1078.6 ± 138.7	816.6 ± 89.8	1005.1 ± 135.5	909.9 ± 57.4	0.798	< 0.001 *	0.0037 *
R-Ri Variance (ms²)	6373.5 ± 7263.5	2921.8 ± 2425.1	3998.4 ± 2626.7	3876.9 ± 2128.8	0.631	0.231	0.264
Spectral analysis							
LFnu (nu)	42.0 ± 20.5	46.1 ± 11.9	48.2 ± 18.3	30.2 ± 18.9	0.424	0.254	0.075
HFnu (nu)	55.8 ± 18.1	49.3 ± 12.2	47.5 ± 17.3	68.4 ± 19.1	0.351	0.217	0.022 *
Conditional Entropy							
NCI	0.8 ± 0.1	0.8 ± 0.0	0.8 ± 0.1	0.8 ± 0.1	0.589	0.291	0.472
CI	1.2 ± 0.1	1.1 ± 0.1	1.2 ± 0.1	1.2 ± 0.2	0.917	0.504	0.169

*Note: values expressed as mean ± standard deviation. R-Ri: R-R intervals; LFnu: low frequency in normalized units; HFnu: high frequency in normalized units; NCI: normalized complexity index; CI: complexity index; * significant difference according to the two-way ANOVA statistical test, with post hoc Tukey test. Source: research data.*

modulation) showed an interaction between sex and air pollution exposure, which was higher in women compared to men living in the city of São Carlos.

Moreover, HFnu was higher in women living in São Carlos, compared to those living in São Paulo. On the other hand, LFnu (cardiac sympathetic modulation) and variables related to the HRV complexity (conditional entropy) did not show an impact from pollution or sex.

The main findings of the present study were: 1) there was an impact of sex on mean R-Ri in subjects living the city with the highest concentration of air pollution (São Paulo/SP), as men had higher values than women; 2) there was an impact of sex on cardiac parasympathetic modulation in the city with the lowest concentration of air pollution (São Carlos, SP), as women had greater parasympathetic modulation compared to men; and 3) there was an impact of air pollution on cardiac parasympathetic modulation among women, as women from São Carlos, SP had greater modulation than those from São Paulo, SP.[31,32]

Discussion

The main finding of the present study was that long-term exposure to pollutants, specifically smoke, interferes with cardiac autonomic modulation, and female residents of the city with lower air pollution levels showed greater parasympathetic modulation compared to male residents.

Mean R-Ri at rest was higher in men than in women only in group 1, *i.e.*, among individuals exposed to a higher concentration of pollution, indicating an impact of sex on R-Ri regardless of air pollution levels. This may be explained by the fact that male individuals have a larger heart size[33] and, consequently, greater cardiac output and blood volume ejected by systole, presenting a lower basal heart rate compared to women.[34] A possible adaptive process related to long-term exposure to pollutants in both sexes should also be considered. Furthermore, men had a better functional capacity than women according to the AHA functional classification.[27]

Parasympathetic modulation was greater in women than in men only in group 2 (lower concentration of air pollution). The association of resting HRV with sex, with higher vagal modulation at rest among women, has been observed in several studies,[10,12,35] corroborating our finding. This may be due to a higher resting HRV and greater vagal modulation in women than men.[10,12,13] However, pollution causes a decline in parasympathetic modulation and an increment in sympathetic activity,[36,37] suggesting that a greater exposure to pollution did not equally affect the expected responses in HRV in men and women.

Concerning parasympathetic modulation, the within-sex analysis revealed an impact of air pollution exposure on females, as women in group 2 showed greater modulation than those in group 1. Thus, exposure to a higher concentration of pollution had an unfavorable impact on cardiac autonomic modulation in the study women. This indicates that females are more susceptible to the damage caused by pollution, as the parasympathetic modulation of men in the two cities was not significantly different. Other studies have also reported a reduction in cardiac vagal tone in individuals exposed to pollution, but they did not carry out an analysis by sex, which makes it difficult to make a comparison with the findings of the present study.[8,20]

As previously stated, we observed different HRV between sexes and, therefore, men and women may suffer different effects of the long-term exposure to air pollution on the ANS. This finding may guide future studies regarding the association among these variables.

Regarding the complexity of HRV, assessed by the conditional entropy, no statistical differences were found between the groups (São Paulo vs. São Carlos residents) or between men and women. This is in accordance with the findings of Catai et al.,[11] who assessed various age groups and, for the age range similar to our study, there were no differences between sexes, as women showed lower HRV complexity only after menopause, due to the sharp decline in the estrogen hormone, while men showed a linear decrease throughout the aging process. On the other hand, Voss et al.,[38] who also assessed different age groups, found that in the 25–34-year age range, the complexity indices varied according to sex and were higher in women than in men.

If, on the one hand, the impact of sex on the variables related to HRV is well documented in the literature, on the other hand, the relationship of these same variables with exposure to atmospheric pollution is still poorly known. Existing studies mainly cover short-term pollution,[3,4,6,7,9,36,37] making it difficult to compare their results with ours. In a meta-analysis of epidemiological studies carried out by Pieters et al.,[39] the authors found a reduction in HRV with an increase in air pollution exposure. However, when the literature search encompassed HRV, sex and long-term air pollution, we did not find any studies.

This study has some limitations. The first is that it involved only two cities in São Paulo State and, therefore, the results cannot be generalized; although there are differences in the concentrations of smoke pollution between the cities of São

Paulo and São Carlos, these may not have been enough to cause other significant changes in HRV. It is important to consider that São Carlos is a medium-sized city, with many industries and a large vehicle fleet. If the comparison had been made between São Paulo and a smaller city (and thus with lower air pollution concentrations), perhaps greater differences would have been observed; however, smaller cities usually do not have air quality control, which could lead to spurious conclusions. Also, even though the municipality of São Carlos performs the measurement of smoke indices, these represents only a fraction of the particulate-matter air pollution. Another potential limitation is the small sample size, which may have influenced the results in some of the analyses, such as of HRV complexity (conditional entropy).

Therefore, our study suggests that long-term exposure to air pollution reduces HRV in healthy young adults, especially females, with a reduction in cardiac parasympathetic modulation. Thus, our findings can be considered as a springboard for further studies with a larger sample size, focusing on the assessment of data from different cities and age groups and the relationship between HRV, long-term pollution and sex, in order to confirm and expand our findings.

Conclusion

The results suggest that long-term exposure to pollutants, specifically to smoke, has an unfavorable impact on HRV, with a reduction in cardiac vagal autonomic modulation, in healthy young adults, mainly females.

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Author contributions

Conception and design of the research: Melinski AC, Catai AM, Takito MY. Acquisition of data: Melinski AC, Moura SCG, Milan-Mattos JC. Analysis and interpretation of the data: Melinski AC, Catai AM, Moura SCG, Milan-Mattos JC, Takito MY. Statistical analysis: Catai AM, Milan-Mattos JC, Takito MY. Obtaining financing: Catai AM, Takito MY. Writing of the manuscript: Melinski AC, Catai AM, Moura SCG, Milan-Mattos JC, Takito MY. Critical revision of the manuscript for intellectual content: Melinski AC, Catai AM, Milan-Mattos JC, Takito MY.

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 graduation program.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the EEFE – ESP under the protocol number 2011/36. 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

Epicardial Fat Tissue Thickness and Omentin in Patients with Atrial Fibrillation

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Abstract

Background: Although electrical and structural remodeling has been recognized to be important in the pathophysiology of atrial fibrillation, the mechanisms underlying remodeling process are unknown. There has been increasing interest in the involvement of inflammatory molecules and adipokines released from the epicardial fat tissue in the pathophysiology of atrial fibrillation.

Objectives: In our study, we aimed to investigate the relationship of atrial fibrillation with increased epicardial adipose tissue, inflammatory molecules released from this tissue and omentin.

Methods: Thirty-six patients who were followed up with a diagnosis of permanent AF at the cardiology outpatient clinic 33 individuals without atrial fibrillation (controls) were included in the study. Epicardial adipose tissue thickness of patients was measured by echocardiography. Serum omentin, IL 6, IL 1 beta, TNF alpha and CRP levels were measured. Man-Whitney U test was performed for comparisons and significance was established at 5% ($p<0.05$).

Results: Epicardial adipose tissue thickness was significantly greater in the patient group (6mm [4-5.5]) than controls (4mm [3-5.5]) ($p <0.001$). No significant difference was found in the concentrations of omentin or inflammatory molecules between the groups.

Conclusion: No relationship was found between atrial fibrillation and serum levels or omentin or inflammatory markers. A relationship between epicardial adipose tissue thickness measured by echocardiography and atrial fibrillation was determined.

Keywords: Atrial Fibrillation; Omentin, Inflammation; Intelectin 1; Pericardium; Adipose Tissue; Molecules.

Introdução

Atrial fibrillation (AF) is a severe arrhythmic condition with high mortality and morbidity. AF may have serious complications, and its incidence is increasing day by day. According to current guidelines, there are five types of AF – first diagnosed AF, paroxysmal AF, persistent AF, long-standing persistent AF, and permanent AF.[1] Permanent AF is used when a joint decision by the patient and clinician has been made to no longer pursue a rhythm control strategy.[1] Because of its long duration, permanent AF is more suitable for pathophysiological studies than other types of the disease. [2]

Due to the increasing incidence of AF, new treatment modalities have been developed and implemented. However, the pathophysiology of the disease has not been fully elucidated.[3] In recent years, it has been suggested that that epicardial fat tissue, adipokines and inflammatory molecules released from this tissue may play a role in the pathophysiology of AF.[4-6]

Epicardial adipose tissue is a visceral adipose tissue where molecules associated with inflammation and atherosclerosis are released.[7] As the epicardial adipose tissue thickness increases, the levels of proinflammatory molecules such as interleukin -6 (IL-6) and tumor necrosis

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factor alfa (TNF alpha) also increase in the tissue.[8] We also know that adipokines such as adiponectin, leptin, and omentin are also released from epicardial adipose tissue like other visceral adipose tissues.[9,10] These proinflammatory molecules and adipokines are thought to be related to AF.

There are many studies on the relationship of inflammation and inflammatory molecules with AF and the contribution of the inflammatory process to the formation of AF.[11] Atrial fibrosis, which is an important factor in the formation of AF, is thought to develop as a result of inflammation in the atrial myocardium. Especially in patients with persistent and permanent AF, higher C-reactive protein (CRP) levels indicate this inflammatory process as compared with patients with paroxysmal AF and individuals with sinus rhythm.[12] High detection of IL-1, IL-6, and TNF alpha in patients with AF supports this view. In addition, the higher levels of TNF alpha in patients with chronic AF and valvular AF compared to patients with paroxysmal AF indicates its relationship with chronic inflammation and atrial fibrosis.[13]

Omentin is an adipokine mostly released from visceral adipose tissue.[14] Its anti-inflammatory effects have been shown in experimental studies, and the adipokine has also been detected in epicardial adipose tissue.[10-13] The relationship of omentin released from epicardial adipose tissue with cardiovascular diseases has been shown in various studies.[15] Serum levels of omentin, which suppresses the inflammatory process by multiple pathways, are low in some cardiovascular diseases.[16] Omentin is thought to play a role in the pathophysiology of AF, although there are few studies on this topic.[17]

Thus, in the presen study, we aimed to show the relationship of AF with inflammatory molecules and omentin.

Methods

Study population

Thirty-six patients who were followed up with a diagnosis of permanent AF at the cardiology outpatient clinic were included in the study. In addition, diagnosis of permanent AF was applied to those cases when both physician and patient decided to accept the presence of AF at least one year before. Thirty-three individuals attending the cardiology outpatient clinic, who had sinüs rhythm (electrocardiography, ECG) were included in the control group. They didn't have atrial fibrillation in the ECG Holter monitoring.

Patients with mitral stenosis, moderate or severe mitral insufficiency, mechanical mitral valve, hyperthyroidism, and those who underwent AF ablation were excluded. Patients with cancer, autoimmune disease, connective tissue, and inflammatory bowel disease were also excluded because of the association of these conditions with elevated inflammatory biomarkers.

All subjects underwent conventional echocardiography. Left ventricular end-diastolic and end-systolic diameters, posterior wall and septal thickness, aortic root, left atrial dimension, ejection fraction, aortic and mitral valve maximum and mean gradients, systolic pulmonary artery pressure, and epicardial fat tissue thickness were measured. Ejection fraction was calculated with the Teichholz M-mode formula: (EDV-ESV)/EDVx100. EDV:[7/(2.4+End diastolic diameter(EDd))]xEDd^3; ESV:[7/(2.4+ End systolic diameter (ESd))]xESd^3

EDV = end-diastolic volume; ESV = end-systolic volume; EDd = end-diastolic diameter; Esd = end-systolic diameter

The local ethics committee approved the study protocol (approval date and number 01/29/2015 and 2015/02-30). The study complies with the Declaration of Helsinki.

Measurement of epicardial fat thickness

Echocardiographic examinations of all patients and the control group were performed with the help of the GE M5Sc-D probe of the General Electric Medical Systems Vivid E9 Xdclear device.

Transthoracic echocardiographic images of the patients were obtained with a 2.5-3.5 MHz transducer from parasternal and apical windows. Echocardiographically, epicardial fat thickness was mesaured on the parasternal long-axis and parasternal short-axis images while the patient was lying in the left lateral decubitus position. The area and thickness of epicardial fat between the outer layer of the free wall of the right ventricle and the visceral layer of the pericardium was measured at the end of the systole. Echocardiographic fat tissue thickness measurements were taken in three separate cycles to obtain more accurate values. All echocardiographic and Doppler studies were carried out by the same observer.

Statistical analysis

Statistical analysis was conducted using the SPSS software version 18.0 (SPSS, Inc., Chicago, Illinois). Continuous variables with normal distribution were described as mean and standard deviation, and median and interquartile ranges were used for continuous variables not normally distributed. Categorical variables were presented as percentage.

The Kolmogorov-Smirnov test was used to test the normality of these data distribution. The chi-square test was used to compare nominal and categorical variables. Parametric data were compared using the Student's t-test and non-parametric data were compared using the Mann-Whitney U test. A two-sided p-value <0.05 was considered statistically significant. We calculated the sample size based on a statistical power of 0.95, two-sided alpha error of 0.05, with an odds ratio (OR) of l,[17] using the Gpower software v3.1.9.4 (Erdfelder, Faul, & Buchner, 1996).

Results

Mean age was 68.5 ± 15 years in the patient group and 62.8 ± 10.1 years in the control group. In addition, 58% (21) of the patient group and 51% (17) of the control group were women. The use of antiplatelet agents was different in the patient and control groups. Demographic characteristics of individuals in the study are summarized in Table 1.

Epicardial adipose thickness and left atrial size were significantly greater in patients with AF than in the control group. Figure 1 shows the graph comparing epicardial adipose thickness.

Serum TNF-alpha, high-sensitivity CRP, IL-1 beta, IL-6 and omentin levels were not statistically different between the two groups (Figure 2 and Table 2).

Table 1 – Baseline clinical characteristics of the study participants

Characteristics	AF group (n=36)	Control group (n=33)	p
Age, years	68.5±15	62.8±10,1	0.068
Male, n (%)	21 (%58)	17 (%51)	0.666
Body mass index (kg/m2)	28.6±6.4	27.8±4,1	0.535
Coronary artery disease n (%)	10 (%28)	12 (%36)	0.445
Heart Failure n (%)	4 (%11)	5 (%15)	0.728
Hypertension n (%)	19 (%53)	18 (%54)	0.883
Diabetes mellitus n (%)	9 (%25)	7 (%21)	0.710
Dyslipidemia n (%)	9 (%25)	15 (%45)	0.075
Stroke n (%)	1 (%3	0	
Drugs			
Beta blocker n (%)	18 (%50)	12 (%36)	0.254
ACEi/ARB n (%)	21 (%64)	20 (%56)	0.495
Statin n (%)	10 (%28)	5 (%45)	0.127
ASA n (%)	0	13 (%39)	
Oral anticoagulant n (%)	35 (%97)	0	
Oral antidiabetic n (%)	8 (%22)	8 (%24)	0.843
MRA n (%)	6 (%17)	4 (%12)	0.592
Diuretic n (%)	10 (%28)	15 (%45)	0.127

P value < 0.05,
ACEi: angiotensin converting enzyme inhibitors, ARB: angiotensin receptor blockers, ASA: acetylsalicylic acid, MRA: mineralocorticoid receptor antagonist

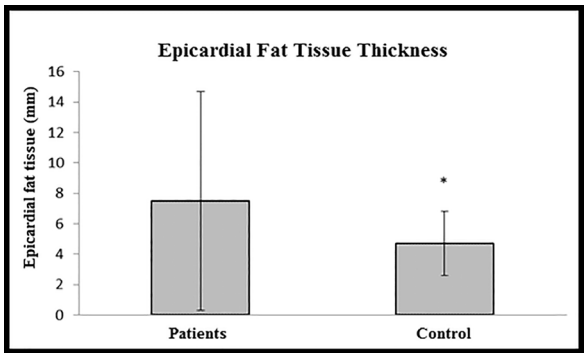

Figure 1 – Measurement of epicardial fat tissue thicknesses in patients (n=36) and controls (n=33).

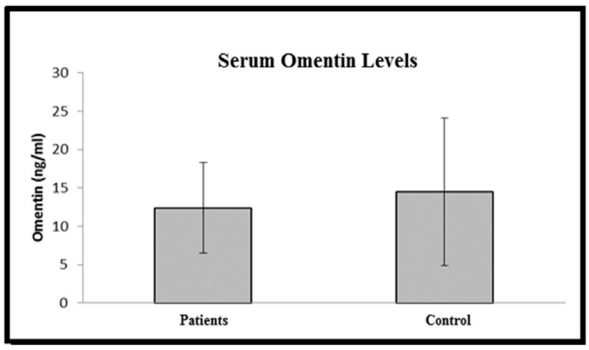

Figure 2 – Serum omentin levels in patients (n=36) and controls (n=33).

Table 2 – Serum inflammatory molecules and serum omentin levels in the study groups

Characteristics	AF group (n=36)	Control group (n=33)	p
Inflammatory molecules			
TNF-alfa (pg/mL)	27.635 (20.658-30.813)	27.935 (21.723-27.935)	0.959
Hs-CRP (mg/mL)	6.69 (2.34-15.21)	6.53 (3.2025-11.52)	0.498
IL-1 beta (pg/mL)	8.61 (6.26-12.22)	9.6 (7.145-11.735)	0.556
IL-6 (pg/mg)	3.64 (2-8.955)	2.37 (1.4825-4.2575)	0.343
Omentin (ng/mL)	13.51 (6.785-20.413)	11.8 (7.425-18.145)	0.555

P value < 0.05
TNF-alfa: tumor necrosis factor alpha, Hs-CRP: high-sensitive c-reactive protein, IL-1 beta: interleukin 1 beta, IL 6: interleukin 6

Discussion

In recent years, new risk factors for AF have been identified. Some of these new risk factors are obesity, and increased epicardial fat tissue, cytokines and inflammatory factors. Epicardial fat tissue is thought to be more specific than obesity in determining AF risk. Therefore, the relation of inflammatory molecules released from epicardial adipose tissue and adipokines with AF will provide a better understanding of the pathophysiology of the disease.[18,19] In our study, we investigated serum levels of inflammatory molecules thought to be released from epicardial adipose tissue and of omentin, which has been poorly addressed.

The thickness of the epicardial fat tissue is related to the biological activity of the tissue, with greater release of cytokines from thick tissues.[20] There is strong evidence that cytokines released from epicardial fat tissue are effective in the pathogenesis of heart disease. Tissue studies have shown that epicardial fat tissue of patients with ischemic heart disease secretes high levels of interleukin 6, tumor necrosis factor-alpha and monocyte chemotactic factor 1, and local concentrations of these cytokine are significantly higher than in systemic circulation. These results suggest that cytokines released from epicardial fat tissue act in the cardiac region.[21-25]

Our finding of increased epicardial adipose thickness in patients with AF was consistent with the literature, and supports the relationship between epicardial adipose tissue and AF.

- Inflammation is one of the new risk factors for AF, and the source of inflammatory cytokines secreted in cardiac diseases seems to be the epicardial fat tissue.[19] This is supported by the increased frequency

of AF in conditions of intense myocardial inflammation, such as pericarditis, myocarditis and cardiac surgery. It is known that atrial fibrosis, which occurs at the end of inflammation, plays an important role in the development of AF. Increased B-type natriuretic peptide (BNP) due to myocyte stretch and increasing high-sensitive troponin levels due to myocyte damage caused by inflammation and fibrosis supports this pathophysiological pathway. High BNP levels have been associated with ischemic complications, and high troponin levels have been associated with cardiovascular mortality in patients with AF.[22,23]

- Inflammatory biomarkers detected in the atrial tissue reinforce the idea of the relationship between inflammation and AF.[19] In atrial biopsies taken during cardiac surgery, high-sensitive CRP, IL-1, IL-6 and TNF alpha levels indicated an inflammatory process. Hıgh serum levels of these molecules, especially in patients with permanent AF, have been reported in previous studies.[11,18,19] In addition, these biomarkers have been investigated in disease prediction and evaluation of prognosis,[11,20] and in treatment response in patients receiving beta-blocker therapy.[24]
- We could not find a significant difference in the levels of inflammatory markers between patients' and control groups in our study. The most important reason for this may be the inclusion of patients with inflammation-related diseases such as coronary artery disease, diabetes and hypertension. Thus, the inclusion of patients from the general population rather than selected patients may have affected the outcomes in this direction. This is supported by the fact that inflammatory molecule levels were not normally distributed.
- Omentin is an anti-inflammatory adipokine released substantially from the epicardial and omentum fat tissues.[14] Although omentin is secreted from the omentum, blood levels of this cytokine fall in obesity. In contrast, the relationship between epicardial fat tissue and blood omentin level are not fully clarified. Omentin has anti-inflammatory properties and suppresses inflammation through several biochemical pathways in experimental studies.[25]
- We thought that the decisive effect of inflammation and increased epicardial fat tissue in the development of AF was by means of omentin release. Epicardial adipose tissue, which is increased in patients with AF, gradually progresses to adipose tissue dysfunction called adiposopathy. This, in turn, reduces the release of the anti-inflammatory cytokine omentin,[26] resulting in inflammation.[27] This inflammation is thought to be one of the causes of AF.[18]
- In our study, there was no significant difference between the two groups for omentin. We confirmed our hypothesis that increased epicardial fat tissue is the basis of AF, with involvement of inflammation and adipokines; however, we could not demonstrate the implication of omentin or biomarkers in it. We have shown that high body mass index is associated with increased epicardial fat tissue thickness, which may explain the association between obesity and AF.
- Our study is the second in the literature to examine the association of serum omentin levels with AF. Tao et al.,[17] showed a negative correlation between serum omentin levels and AF; the adipokine levels were significantly lower in patients with AF. However, in our study, this significant difference was not observed. One of the reasons for this can be that the larger sample size in their study. Also, Tao et al.,[17] did not include patients with chronic diseases. In our study, patients with coronary artery disease, diabetes mellitus, hypertension, and heart failure were included, with no statistical difference in the two groups.
- We also believed that adiposopathy, related to increased epicardial fat tissue, may cause AF through inflammation and omentin. However, in our study, adiposopathy was not detected in patients with increased epicardial fat tissue. We suggest that further studies be done to elucidate the pathophysiology of adiposopathy by different imaging and laboratory techniques.

Study limitations

The small numbers of patients and control subjects is the most important limitation of our study. Another limitation is the presence of diseases that could affect omentin and inflammatory biomarker levels.

Conclusion

Our study showed that increased epicardial fat tissue played an important role in AF, and that it had a positive relationship with body mass index. We could not establish the relationship of omentin and inflammation with AF.

Potential Conflict of Interest

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

Sources of Funding

This study was funded by Turkish Society of Cardiology.

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 Afyon Health Science University under the protocol number 2015/02-30. 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: Onrat E. Acquisition of data: Dural İE. Analysis and interpretation of the data: Emren SV. Statistical analysis: Vurmaz A. Writing of the manuscript: Dural İE. Critical revision of the manuscript for intellectual content: Avşar A.

Erratum

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In Original Article "Epicardial Fat Tissue Thickness and Omentin in Patients with Atrial Fibrillation", with DOI number: https://doi.org/10.36660/ijcs.20200242, published in International Journal of Cardiovascular Science, 35(4). Correct the Orcid of the author Alaeddin Avşar from "https://orcid.org/0000-0001-7865-3915" to "https://orcid.org/0000-0003-0759-0165".

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REVIEW ARTICLE

Depression and Cardiovascular Disease in Women

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Abstract

The prevalence of depression varies from 1 to 17% in different geographic regions, and its incidence is 70% higher in women than men. Today, depression affects more than 300 million people worldwide, affecting twice as many women from adolescence to adulthood. In addition to this earlier onset, depression in women tends to be more severe. Cardiovascular disease and depression are chronic diseases that have a major impact on cardiovascular and all-cause morbidity and mortality, with evidence of a two-way relationship between them, in which depression is a predictor of cardiovascular disease and vice versa. In females, the degree of illness and prognosis are more severe when both diseases are present, than when diagnosed alone. In patients with acute or chronic cardiovascular disease, especially women, a systematic screening for depression should be considered as a preventive strategy of cardiovascular events, aiming to reduce the risk of future events. There are still no clinical studies designed to assess the impact of antidepressant treatment on cardiovascular outcomes in women.

Introduction

Depression is a psychiatric condition characterized by changes in the regulation of mood, behavior, and affection.[1] It represents a heterogenous group of disease that share phenotypical features, with different levels of severity.[1-4]

Clinical presentations of depression include: a) mood swings, identified as feelings of sadness, despair, anxiety, emptiness, discouragement or hopelessness, numbness, and a desire to cry. This profound state of unhappiness (dysphoria) may be either transient or be a symptom of a psychopathological syndrome or clinical disorder; b) a syndrome or association of signs and symptoms that include a depressed mood. Depressive syndromes include major depression, minor depression, or dysthymia (persistent depressive disorder); c) accompanied by a psychiatric disorder such as bipolar disorder, schizophrenia, depressive disorder induced by drugs or other medical conditions.[1-4]

Depression is a cause of disability, with high personal, social and economic costs,[2] requiring a systematic diagnostic investigation and adequate treatment.[1-5]

A prospective study evaluated the relationship of depression and health-related costs in a five-year follow-up of 868 women presenting at the emergency department with suspected acute myocardial infarction (AMI). Depression was associated with up to 53% increases in cardiovascular costs during the follow-up period.[6] This association was more evident among women without significant coronary artery disease (CAD), suggesting that depression may cause higher costs in women without conventional markers of cardiac disease.[6]

Depression has high comorbidity rates, similarly to other psychiatric syndromes (anxiety, eating disorders, psychosis), and other diseases (endocrine, respiratory, rheumatological, cardiovascular and degenerative disorders, and cancers).[1-4]

Keywords

Cardiovascular Diseases; Coronary Artery Disease, Morbimortality/ prevalence; Women; Risk Factors; Prevention and Control.

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The prevalence of depression in different geographic regions worldwide may vary from 1% to 17%, and its incidence is 70% higher among women.[1-3] Approximately 17% of men and 25% of women will have an episode of depression throughout life, and 60% of them will have one or more recurrences.[3-5]

Currently, depression affects more than 300 million people worldwide and, from adolescence onwards, affects twice as many females[7]. In addition to this earlier onset, depression tends to be more severe in women [8].

Several studies have demonstrated that depression is a risk factor and a prognostic factor of cardiovascular disease (CVD) (especially CAD and cerebrovascular disease) in both sexes, but with particularities related to female sex.[8-12]

The primary objective of this study was to summarize the current knowledge about depression as a risk factor for CVD in women, with emphasis on CAD. Other factors including its prognostic impact in patients with CVD, pathophysiological mechanisms that link depression and CVD, and diagnostic and therapeutic strategies were also evaluated, highlighting possible differences between sexes.

Original articles written in English were searched in PubMed (MEDLINE) and Embase databases from 2010 to 2021, and references of the eligible articles were manually searched. The following descriptors ([MeSH Terms]) were used: "coronary heart disease OR disease, ischemic heart AND (woman) AND (depress*). Inclusion criteria were: a) prospective cohort studies or meta-analysis of prospective cohort studies; b) studies on women or studies presenting analysis by sex; c) studies with participants who did not have CVD in the beginning of the study; d) depression as an outcome of interest; e) AMI or CAD as outcomes of interest; f) risk estimate (with 95% confidence interval) of the association between depression and CAD. Study selection and data extraction were performed by two independent investigators; disagreements were resolved by consensus based on the inclusion criteria. Figure 1 depicts the flowchart of study selection.

Depression as a Cardiovascular Risk Factor

Depression has been recognized as an emerging, non-conventional risk factor for CAD and cerebrovascular disease in both sexes, but with a greater impact on women than men.[8-12]

The risk of cardiovascular disease in women with a diagnosis of depression throughout life is 30-50% higher in women than men, especially among the young.[8] Studies have indicated that hormonal changes,

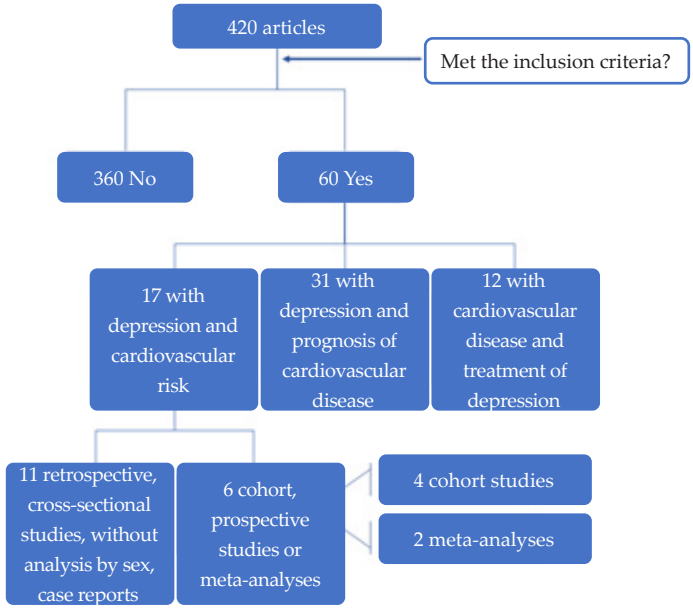

Figure 1 – Flow chart of study selection

such as menopausal transition, have been associated with a higher risk for the first depressive episode. In addition, depression in perimenopausal women has been associated with a higher frequency of a history mood disorder.[2,13]

A prospective, a 15-year longitudinal study of a representative sample of US adults (n=7,641), aged 17 to 39 years, showed that depression was associated with an increased risk of death for CAD, with an adjusted hazard ratio of 3.70 (95% CI, 1.32-10.35) for depression in both men and women, and a 15-fold adjusted risk of CVD among women (14.57 [95% CI, 2.65-80.10]).[14]

A nine-year prospective cohort study of 998 women (mean age of 57 years, 28-96 years), without a history of CAD, referred for routine mammography, showed that 185 (18.5%) were diagnosed with depression at year two; 24 of them (13.0%) developed one or more ischemic events by year 10, which was significantly higher than the incidence of 6.5% in control group (p<0.001). In a logistic regression model, adjusted for other cardiovascular risk factors, including age, depression was the only significant predictive factor for CAD in women aged less than <65 (OR = 6.56, 95% CI 1.07-40.09, p = 0.042). The authors drew attention to the finding that in women aged 65 years and over, age was the only significant predictive factor for CAD.[15]

A prospective longitudinal study of 860 women followed for 18 years showed that depression was associated with a twice higher incidence of CAD.[16]

A meta-analysis of 30 prospective cohort studies (n=893,850 and 59,062 cases of CAD), with a follow-up period ranging from two to 37 years, showed a significant, independent association of depression with an increased risk of chronic CAD and AMI in both sexes.[17]

Another meta-analysis on the association between depression, risk of AMI and death for CAD included 19 prospective cohort studies, with a total of 323,709 participants followed for 4-37 years demonstrated that depression was associated with a significantly increased risk of myocardial infarction and coronary mortality in both sexes.[18]

Regarding the important relationship between depression and CAD, it is worth discussing the results of the VIRGO (Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients) Study,[19] the Women's Health Initiative (WHI)[20] and the Nurse's Health Study.[21]

The VIRGO Study was an observational study on clinical presentation, treatment and outcomes of 2,000 young women and 1,000 young men (aged from 18 to 55 years old) with AMI, seen at 100 participating hospitals. The study showed that 50% of women and 25% of men had a history of depression and, at the moment of the ischemic episode, 39% of women and 29% of men had depression.[19]

Data from the WHI Observational Study,[20] which followed up 93,676 postmenopausal women for an average of 4.1 years, demonstrated that depression was significantly related to CVD risk (odds ratio of 1.60 for cerebrovascular disease or angina). In women without a history of cardiovascular disease, depression was an independent predictor of death for CVD (relative risk, 1.50) and all-cause mortality (relative risk. 1.32) after adjustment for age, race, education, income, diabetes, hypertension, smoking, high cholesterol level requiring medication, body mass index, and physical activity. The authors called attention to the fact that, so far, whether early treatment with antidepressants of patients without a history of CVD will lower the risk for the disease is still unknown.[20]

In a cohort study of 63,469 women without cardiovascular disease, followed for four years, a diagnosis of depression was significantly associated with fatal and nonfatal AMI.[18] The authors highlighted that sudden cardiac death in depressive women may be more associated with sympathetic nervous system activation, higher resting heart rate and greater use of antidepressants.[21]

Based on the large amount of evidence supporting that depression is an independent risk factor for CVD in men and especially in women,[22] it has been included in many guidelines on CVD prevention.[8-12,22,23] However, depression has not been included in any of the current cardiovascular risk scores.[11,12,23]

Depression as a Prognostic Factor in Cardiovascular Disease Patients

Depression has also been regarded as a predictor of worse prognosis in men and women diagnosed with AMI, unstable angina, and stroke, and those with angiographic confirmation of chronic CAD.[8-11,24]

Epidemiological studies have reported a higher prevalence of depression in patients with CVD than in general population and that individuals with depression are more likely to develop AMI, heart failure and stroke.[8-10]

Depression is two to three times more prevalent in CAD patients (up to 30% in this population) and two times higher in women than men.[8]

In a prospective study of patients with AMI, the diagnosis of depression was more frequent in women than in men; women with depression had a two-fold higher rate of complications such as reinfarction, recurrent ischemia, cardiogenic shock, cardio-respiratory arrest and in-hospital death.[25]

In post-acute myocardial infarction patients, a diagnosis of depression increased the risk for recurrent cardiovascular event within two years.[25]

In a post-hoc analysis of a randomized, double-blind study (Darapladib vs. placebo) of 15,828 patients with chronic CAD (19% women), followed for a median of 3.7 years, women with depression had a higher risk of infarction, stroke, and cardiovascular death.[26]

In patients with stroke, depression is associated with higher mortality and recurrence rates. As compared with men, women with stroke are twice more likely to have depression, and early onset of treatment has a positive impact on physical and cognitive recovery in these cases.[24]

A meta-analysis of eight studies, involving 125,763 patients, demonstrated a prevalence of 21.5% of depression in patients with heart failure. The presence of depression was associated with a worse prognosis and higher mortality, especially in older patients and in those taking antidepressants, with no difference between sexes.[27] The authors discussed the importance of a tailored antidepressant prescription to this group of patients, considering symptoms, and severity of heart failure, depression and other conditions,[27] since treatment with antidepressant may contribute to higher mortality in these patients.

In addition to the above, in general, depression also contributes to a poorer adherence to treatment, self-care practices and rehabilitation programs,[16-19] with a negative impact especially on women. In the presence of CAD and/or cerebrovascular disease, depression is associated with persistence of symptoms, poorer quality of life, early and frequent readmissions and higher mortality rates in women.[16-19]

These data support the need for a systematic investigation of depression in patients with acute and chronic CVDs, considering the frequent association between these diseases and its potential devastating effect, on these individuals, particularly on women.[16-19]

Mechanisms that Link Depression to Cardiovascular Diseases

Depression and CVD are chronic diseases that have a great impact on cardiovascular morbidity and mortality. Evidence supports a two-way relationship between these conditions, in which depression is a predictor of cardiovascular disease and vice versa.[28] In women, the combination of depression and CVD leads to more severe disease and a poorer prognosis, than when presented alone.[29]

However, despite increasing data supporting that both depression and CVD share etiological pathways related to the immune system and inflammation, studies to elucidate this association and how women are more affected during hormonal changes related to reproductive events (menstrual cycle, pregnancy, menopause) are still needed. [5,24,28-30]

The current hypothesis is that in women, the low-grade chronic inflammation contributes to the development of both depression and CVD, when associated to dysregulation of some biological systems, such as the hypothalamic–pituitary–adrenal axis, the renin-angiotensin-aldosterone system, and the serotonin-kynurenine pathway.[5,24,28-30] Dysregulation of these systems is accompanied by increases in inflammatory markers, endothelial dysfunction, platelet activation and coagulation, as well as increase in sympathetic tone.[28-31] These changes, combined with traditional and/or emerging cardiovascular risk factors and reproductive hormonal fluctuations, may generate an even worse inflammatory response that contributes to the development or aggravation of the depression-CVD relationship.[29-31]

In a cohort study,[32] where participants were followed from birth to the age of 18 years, individuals with at least one episode of depression had higher levels of C-reactive protein and triglycerides, greater insulin resistance and a higher mass index corporal, and this association was more frequent in female participants.[32] These findings corroborate the hypothesis of the association between depression, inflammation, and cardiovascular risk. [5,28-30,32]

The pattern of inflammatory response in women may vary over the years according to the exposure to endogenous sex hormones (estrogens and progesterone), especially estradiol (one of the endogenous estrogens), which seems to be more directly associated with suppression of inflammatory cytokines (interleukin-6 and TNF-alpha) and increase of anti-inflammatory cytokine production (interleukin-10). Regarding plasma levels, high and low levels of estradiol are associated with an anti-inflammatory and a pro-inflammatory response, respectively, while progesterone has predominantly anti-inflammatory effects.[28]

Thus, in women, hormonal variations throughout life can have a great impact on their cardiovascular health and contribute to the developing of mood disorders. Therefore, menarche, early menopause and peri-menopause are periods that increase the risk of developing of CVD, while the perinatal period and menopause increase the chance of both occurring in association.[28]

With respect to the use of exogenous sex hormones for contraceptive purposes, relief of menstruation-related abdominal pain, and treatment of polycystic ovary syndrome and endometriosis, there is still little evidence supporting that it may increase the risk for depression and CVDs.[28] However, it is worth to mention that the use of oral contraceptives like estrogen plus progesterone may raise the risk of systemic arterial hypertension, thromboembolism, and ischemic stroke.[28]

Diagnosis

All professionals involved in the management of CVD patients must be aware of this important and close relationship between depression and CVD, considering the potential role of the former in favoring the development and worsening the prognosis of the latter.[8-21] In addition, these healthcare providers must recognize the worse impact of this association among women.[7,16-19]

Similar to other diseases, the diagnosis of depression initially depends on clinical history and physical examination, with history being the most important component of this assessment. This should be taken from the patient and complemented by information given by family members and other physicians, with patient's consent and respecting the confidentiality of the information obtained.[1,3,4]

Symptoms of depression include persistent feeling of sadness, loss of interest or pleasure in daily activities, insomnia or hypersomnia, significant weight gain or loss (5% or more within a month), decrease or increase in appetite, fatigue or low energy, decreased capacity to concentrate or to make decisions, sense of uselessness, inappropriate or excessive guilt, frequent thoughts of death, and suicide ideation or attempt.[1,3,4]

Psychomotor retardation (slowed speech, decreased speech production, slowed movement) or agitation (restlessness, wringing of hands, inability to keep still, pulling clothes or skin) can be identified during physical examination, which can be confirmed by other people over time.[1,3,4]

The assessment of a person with depression should include the analysis of the chronology of depressive symptoms – current symptoms, history of depression events, the course and treatment of disease – the impact of depressive episodes on occupational and interpersonal functioning, and presence of attenuating or aggravating factors (life-stressing events, and social or occupational circumstances), psychiatric diseases and other concomitant conditions.[1-4]

In patients with acute or chronic CVDs, the screening for depression should be considered as a preventive strategy against cardiovascular events.[8-10] This investigation should be performed during hospitalization and at regular intervals thereafter.[33]

This recommendation for the investigation of depression in CVD patients has been progressively included in guidelines on primary and secondary cardiovascular prevention, calling attention to specificities of depression in women with CVDs. [8,9,11,21,22,31,33]

There are several diagnostic tools for depression, with good sensitivity, specificity and negative predictive value, that can be used in clinical practice.[8,31,33] Application of these instruments requires specific training and should be done by experienced professionals, with the supervision of a psychiatrist.[8] However, there are self-answered questionnaires that have been validated and used in several studies, and used in the screening and diagnostic confirmation of depression in patients with CVDs.[25,31]

In this regard, we recommend the Patient Health Questionnaire (PHQ)-2 (which contains two questions on depression) as a first-step approach, and patients who screen positive should be further evaluated with the nine-question "Patient Health Questionnaire" (PHQ)-9 (with nine questions) for confirmation of the diagnosis. [8,10,11,22,31,33] These questionnaires have a sensitivity of 96% and specificity of 71% (PHQ-2) and 72% (PHQ-9),[31] and can be freely accessed at https://bit.ly/2VvPHIG (PHQ-2) e https://bit.ly/2PY3INz (PHQ-9).[31]

Treatment

Except for heart failure,[27] there is evidence suggesting that treatment of depression in CVD patients improves depressive symptoms, adherence to other therapies and tends to reduce depressive events, although it has no effect on reducing cardiovascular mortality and all-cause mortality.[8-11,21-23, 31,33,34]

In patients with CVDs, several therapeutic interventions for depression have been investigated in observational studies and clinical trials and shown to be effective either alone or in combination – psychotherapy, psychodynamic therapy, behavioral cognitive therapy, stress management, use of antidepressants, electroconvulsive therapy, and exercises.[2,8,33,34]

The benefits of the treatment of depression to the course of patients with CVD seem to be greater when there is an association of psychotherapy, especially cognitive behavioral therapy, with antidepressant drugs.[8,31,33] These data reinforce the need for a multiprofessional and multidisciplinary intervention that may include, in addition to a cardiologist, a psychiatrist, a psychologist, a physical educator, among others.[23]

Different psychotherapeutic approaches help depressed individuals understand how their ideas, feelings and behaviors contribute to worsening of depression, and provide them with coping strategies that may help these patients retake control of themselves.[8,23] When used alone, psychotherapy is as effective as antidepressant drugs in improving depressive symptoms, but several reports have shown that better results are achieved when these both strategies are used in combination.[8]

In addition, physical exercise, especially aerobic exercise seems effective in the treatment of depression and may be complementary to the effect of antidepressants in patients considered "poor responders" to these medications.[8]

The currently available antidepressants for the treatment of depression include selective inhibitors of serotonin uptake (fluoxetine, sertraline, paroxetine, fluvoxamine, citalopram, escitalopram), inhibitors of serotonin and norepinephrine uptake (desvenlafaxine, duloxetine, levomilnacipran, milnacipran, venlafaxine), and antidepressants with new mechanisms of action (bupropion, mirtazapine, mianserin, nefazodone, trazodone).[8,31,33,34]

Four randomized clinical trials evaluated the effect of antidepressants (bupropion, citalopram, escitalopram, mirtazapine, sertraline e venlafaxine) versus conventional treatment in post-AMI patients diagnosed with depression.[31] Three studies, involving 2,091 patients, have shown a significant improvement of depressive symptoms with treatment during a follow-up of six to 30 months. However, in a study with 331 patients followed for 18 months, no difference was found in depressive symptoms between the groups.[31] None of the studies demonstrated that the treatment of depression was effective in reducing events, hospitalization, and all-cause and cardiovascular mortality, after a mean follow-up of 16 months.[28] One study showed that the use of antidepressant resulted in better symptom control in women than men.[31] None of the studies reported adverse effects of the therapy used.

A randomized clinical trial[34] with 300 post-AMI patients with depression (39.3% were women), investigated the use of escitalopram vs. placebo for 24 months and showed a significant reduction in reinfarction during a follow-up period of eight years, with no significant difference in cardiovascular and all-cause mortality.

Levine et al.,[35] pointed out that the analysis of data of numerous studies conducted with depressed patients after hospitalization for acute CAD has revealed that the failure of treatment with antidepressants is associated with higher risk of mortality and cardiovascular events in the follow-up of these patients.[35]

It is important to mention that fluoxetine and paroxetine should not be administered to patients with breast cancer, due to their inhibitory effect on tamoxifen.[21]

In addition, tricyclic antidepressants should be avoided in patients with structural CVD because of their effects on cardiac conduction, seen in the electrocardiogram as prolongation of the PR interval, QRS complex and QT interval, and T-wave flattening.[8,27,31] These effects increase the likelihood of malignant ventricular arrhythmias and sudden cardiac death, mainly in women and older patients with conduction disturbances, heart failure, or chronic or acute CAD.[8,27,31]

So far, there is no study evaluating the impact of antidepressant treatment on cardiovascular outcomes in women.[23]

Table 1 describes the currently used drugs for the treatment with depression in patients with CVD, including daily doses, main side effects and impact on QT interval.

Electroconvulsive therapy, which has a successful rate of approximately 80%, and should be used as the last therapeutic option, after failure of other treatments. It also should be postponed in patients with hemodynamic instability and new-onset, still uncontrolled, arterial hypertension, to minimize the risk of complications (persistent hypertension, ischemia, arrythmias, prolonged asystole, and heart failure).[8]

Due to the frequent association between menopause, CVD and depression, it is important to stress out that hormone therapy should not be used for primary

Table 1 – Currently used drugs in the treatment of depression in patients with cardiovascular diseases

DRUG	DAILY DOSE (mg)	EFFECT ON QT INTERVAL	COMMON SIDE EFFECTS% AND OTHER FINDINGS
INIBIDORES SELETIVOS DA RECEPTAÇÃO DA SEROTONINA			
Citalopram	20 - 40	Little	Insomnia (D), orthostatic hypotension (D), weight gain (D), sexual dysfunction (M)
Escitalopram	10 - 20	Little	Insomnia (D), orthostatic hypotension (D), weight gain (D), sexual dysfunction (M)
Fluoxetine	20 - 60	Little	Insomnia (D), orthostatic hypotension (D), weight gain (D), sexual dysfunction (M) Inhibits the effect of tamoxifen; not recommended for breast cancer patients
Fluvoxamine	50 - 200	Little or none	Insomnia (VL), orthostatic hypotension (VL), weight gain (VL), sexual dysfunction (M)
Paroxetine	20 - 40	Little or none	Insomnia (VL), orthostatic hypotension (L), weight gain (L), sexual dysfunction (H). Inhibits the effect of tamoxifen; not recommended for breast cancer patients
Sertraline	50 - 200	Little or none	Insomnia (VL), orthostatic hypotension (VL), weight gain (VL), sexual dysfunction (M)
INHIBITORS OF SEROTONIN AND NOREPINEPHRINE UPTAKE			
Desvenlafaxine	50 - 100	None	Insomnia (VL), sexual dysfunction (VL)
Venlafaxine	75 - 375	Little	Insomnia (VL), sexual dysfunction (M)
Duloxetin	60 - 120	None	Insomnia (VL), sexual dysfunction (VL)
SELECTIVE INHIBITORS OF SEROTONIN-DOPAMINE UPTAKE			
Bupropion	300	Little	Insomnia (L)
ALPHA-1 RECEPTOR ANTAGONISTS			
Mirtazapine	15 - 45	Little	Wight gain (H), sexual dysfunction (VL)
Mianserin	60 - 120	Little	Weight gain (H), sexual dysfunction (VL)
SEROTONIN MODULATORS			
Nefazodone	300 - 600	None	orthostatic hypotension
Trazodone	200 - 500	Little	orthostatic hypotension (VL or M), Weight gain (VL), sexual dysfunction (VL)
Vilazodone	40	None	Insomnia (L), sexual dysfunction (L)

**Side effect degree: H: high; M: medium; L: low; VL: very low*

or secondary prevention of CVD or treatment of depression.[2,9,21]

Final Considerations

So far, scientific evidence has indicated the presence of common biomarkers between depression and CVD, which determines a worse prognosis for patients with both conditions, especially among women. Considering that depression is more prevalent in women and that depressed women are more likely to have cardiovascular risk factors and more severe forms of CVD than men, a systematic screening for depression and its adequate treatment in women with suspected or confirmed CVD is warranted. Besides, randomized, clinical trials to investigate the impact of treatment of depression on cardiovascular outcomes in men and women with CVD are urgently needed.

Author contributions

Conception and design of the research: Rivera MAM, Rivera IR. Acquisition of data: Rivera MAM, Rivera IR, Avila W, Marques-Santos C, Costa FA, Ferro CR, Fernandes JMG. Analysis and interpretation of the data: Rivera MAM, Rivera IR, Avila W, Marques-Santos C, Costa FA, Ferro CR, Fernandes JMG. Writing of the manuscript: Rivera MAM, Rivera IR. Critical revision of the manuscript for intellectual content: Rivera MAM, Rivera IR, Avila W, Marques-Santos C, Costa FA, Ferro CR, Fernandes JMG. Maria Alayde Mendonça Rivera MAM, Ivan Romero Rivera IR, Walkiria Avila W, Celi Marques-Santos C, Francisco Assis Costa FA, Carlos Romério Ferro CR, Jose Maria Gonçalves Fernandes JMG.

Potential Conflict of Interest

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

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Study Association

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Erratum

Int J Cardiovasc Sci. 2022 Issue vol 35(4), pages 537-545.

In Review Article "Depression and Cardiovascular Disease in Women", with DOI number: https://doi.org/10.36660/ijcs.20200416, published in the journal International Journal of Cardiovascular Sciences, 35(4):537-545, in page 543, in Table 1, correct "INIBIDORES SELETIVOS DA RECEPTAÇÃO DA SEROTONINA" to "SELECTIVE INHIBITORS OF SEROTONIN RECEPTION"

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CASE REPORT

Vascular Spectrum of Imaging Findings in COVID-19: Ischemic, Hemorrhagic, and Thromboembolic Complications

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Abstract

Ischemic strokes secondary to occlusion of large vessels have been described in patients with COVID-19. Also, venous thrombosis and pulmonary thromboembolism have been related to the disease. Vascular occlusion may be associated with a prothrombotic state due to COVID-19-related coagulopathy and endotheliopathy. Intracranial hemorrhagic lesions can additionally be seen in these patients. The causative mechanism of hemorrhage could be associated with anticoagulant therapy or factors such as coagulopathy and endotheliopathy. We report on cases of ischemic, thrombotic, and hemorrhagic complications in six patients diagnosed with SARS-CoV-2 infection. Chest computed tomography (CT) showed typical SARS-CoV-2 pneumonia findings in all the cases, which were all confirmed by either serology or reverse transcription polymerase chain reaction (RT-PCR) tests.

Case 1

A 29-year-old woman who was 5 weeks pregnant, previously healthy, was diagnosed with COVID-19 12 days before hospital admission, when both immunoglobulins (IgM and IgG) were positive. While in home quarantine, the patient manifested sudden right hemiplegia and aphasia 48 hours before hospital admission. Upon arrival to the emergency room, she was disoriented and had right hemiplegia.

Keywords

COVID-19/complications; Pneumonia; Hemorrhage; Thromboembolism/complications; Spectrum Analysis/methods; Diagnostic Imaging/methods.

Brain magnetic resonance (MR) angiography revealed occlusion at the left internal carotid bifurcation extending to the corresponding middle cerebral artery and A1 segment of the ipsilateral anterior cerebral artery. There were areas of hyperintense signal on fluid-attenuated inversion recovery (FLAIR) sequence and restricted diffusion in the left caudate, internal capsule, putamen, insula, centrum semiovale, and cortical territories of the ipsilateral middle cerebral artery, with mild sulcal effacement, indicating subacute ischemic injury. Susceptibility weighted imaging (SWI) demonstrated hematic material in the left putamen (Figure 1).

Chest CT showed peripheral ground-glass opacities associated with foci of consolidation, typical of COVID-19 pneumonia[1]. Brain CT showed an ischemic lesion with a small hemorrhagic area (Figure 2). The patient was transferred to the intensive care unit for supportive treatment.

Case 2

A 59-year-old man presented with fever, myalgia, arthralgia, headache, and dyspnea. Because of the patient's clinical worsening status and need for supplemental oxygen, hospitalization was required. RT-PCR testing was positive for SARS-CoV-2 infection. Chest CT showed ground-glass opacities and bilateral consolidations, typical of COVID-19 pneumonia (Figure 3).

After 2 days of hospitalization, the patient had respiratory failure requiring orotracheal intubation. There was an increase in D-dimer level. Chest CT with contrast showed pulmonary thromboembolism in the lingular and left lower lobe branches (Figure 4, arrows). Anticoagulation therapy was implemented.

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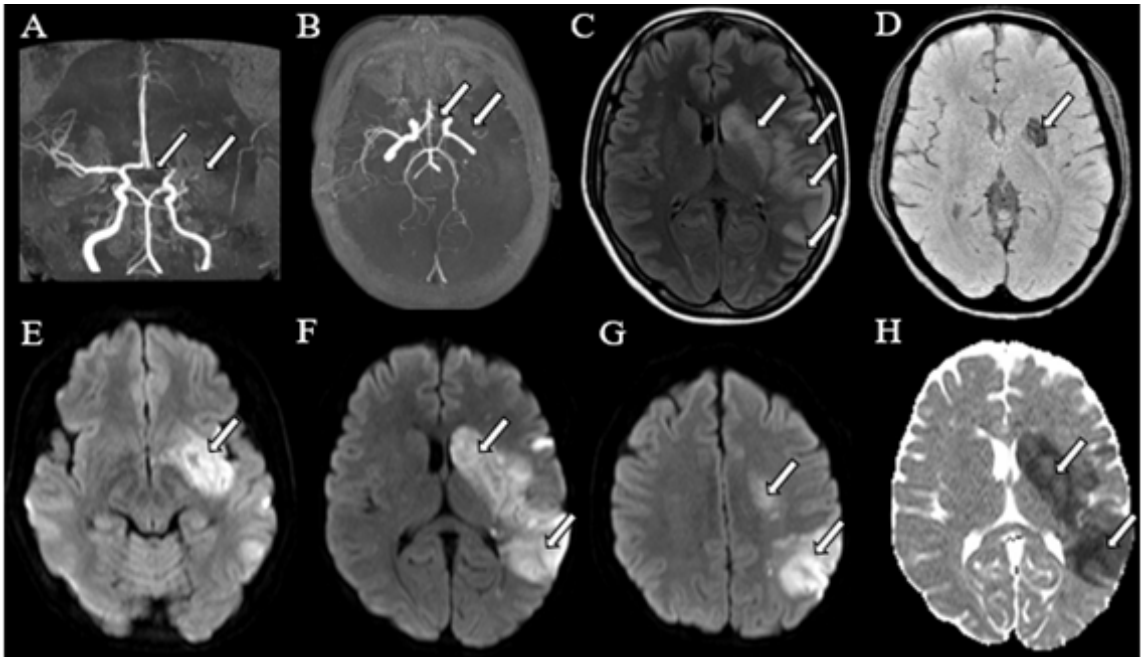


Figure 1 – 3D-TOF MRA (A, B) demonstrates occlusion at the left ICA bifurcation extending to the MCA and ACA stems; FLAIR image (C) shows hyperintensity in left MCA territory, including basal ganglia; SWI (D) hypointensity in left basal ganglia indicating hemorrhagic foci; DWI (E, F,G) and ADC-map demonstrate markedly restricted diffusion, indicating subacute stroke.

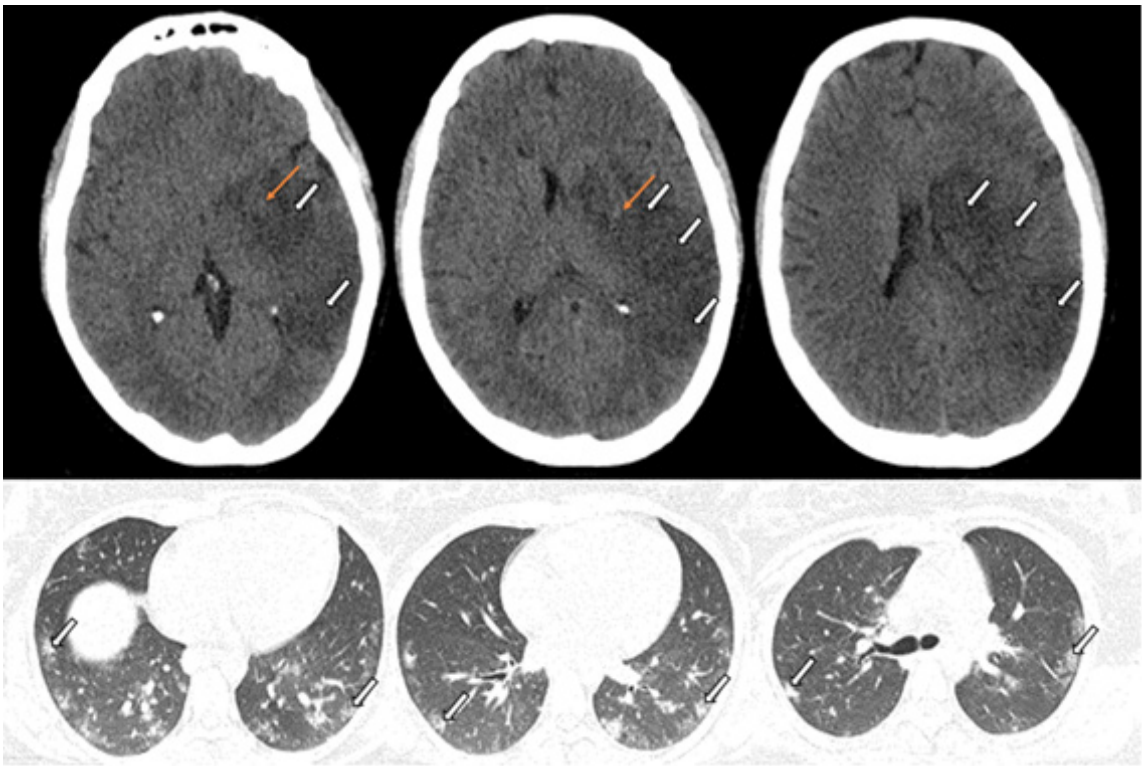
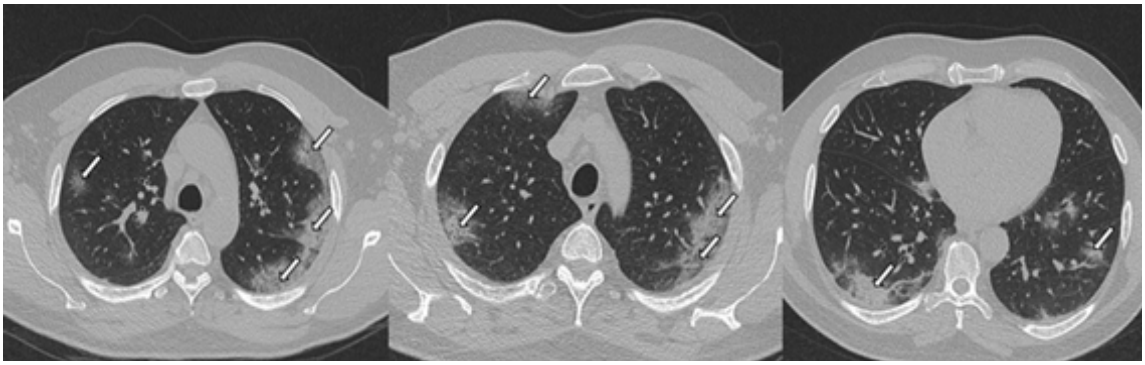


Figure 2 – Unenhanced brain CT scan (top row) demonstrates hypodense areas in MCA territory, including basal ganglia, suggestive of a subacute stroke with subtle hyperdense foci, indicating hemorrhage. Chest CT scan (bottom row) shows bilateral patchy peripheral ground-glass opacities associated with consolidation foci, typical CT imaging features for COVID-19[1].



Figue 3 – Chest CT scan shows bilateral, multifocal rounded and peripheral ground-glass opacities with superimposed intralobular septal thickening and consolidation, which are typical features for COVID-19 pneumonia[1].

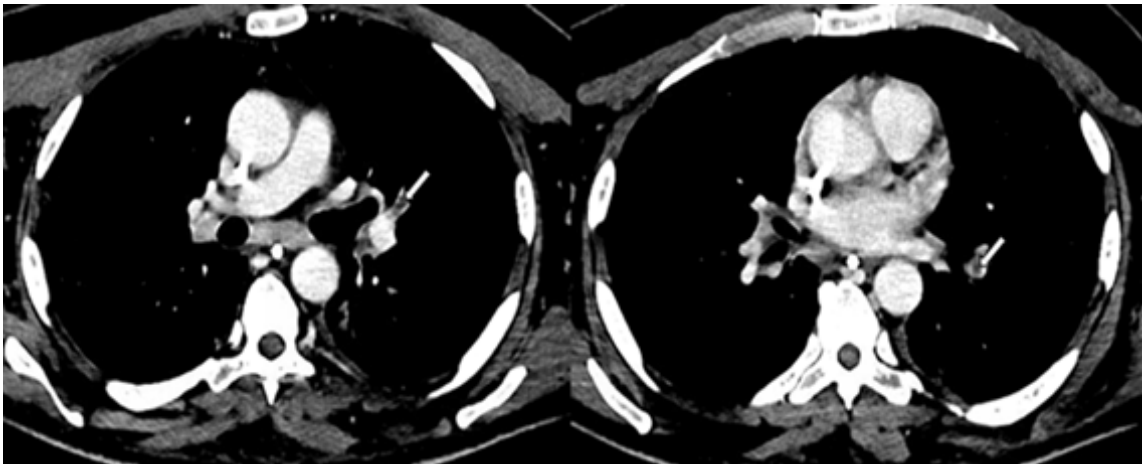


Figure 4 – CT pulmonary angiography shows filling defects within the lingular and left lower lobe branches, suggestive of acute pulmonary embolism (arrows).

On the 30th day of hospitalization, the patient had cardiac arrest with asystole, which was reversed after 5 minutes. Brain CT showed massive intraparenchymal hemorrhage in the left frontal region associated with subarachnoid hemorrhage (Figure 5). Surgical evacuation of the hematoma was performed.

Subsequent MRI showed post-surgical changes and subcortical and deep microbleeds in both cerebral hemispheres and corpus callosum, which may be associated with thrombotic microangiopathy (Figure 6). In addition, a FLAIR hyperintense signal was demonstrated in the thalami and caudate nuclei, probably related to a hypoxic-ischemic injury (Figure 7).

Case 3

A 30-year-old woman presented with severe respiratory failure and reversed cardiac arrest in the emergency room. Chest CT demonstrated ground-glass opacities and bilateral peripheral consolidations, typical of COVID-19 pneumonia[1] (Figure 8). Brain CT demonstrated hypodensity in the cerebral cortex bilaterally, as well as in the putamina and caudate nuclei, indicative of severe hypoxic-ischemic injury (Figure 9). The patient was transferred to the intensive care unit for supportive treatment. RT-PCR testing was positive for SARS-CoV-2 infection.

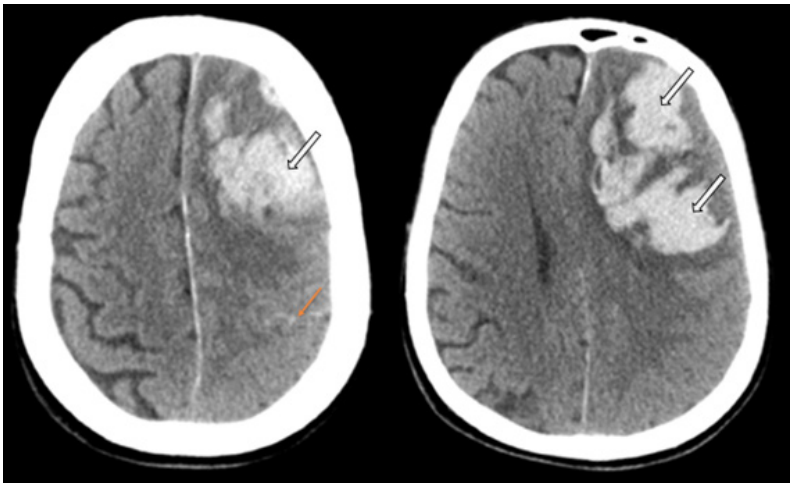


Figure 5 – Unenhanced brain CT scan shows left frontal lobe hematoma and subarachnoid hemorrhage.

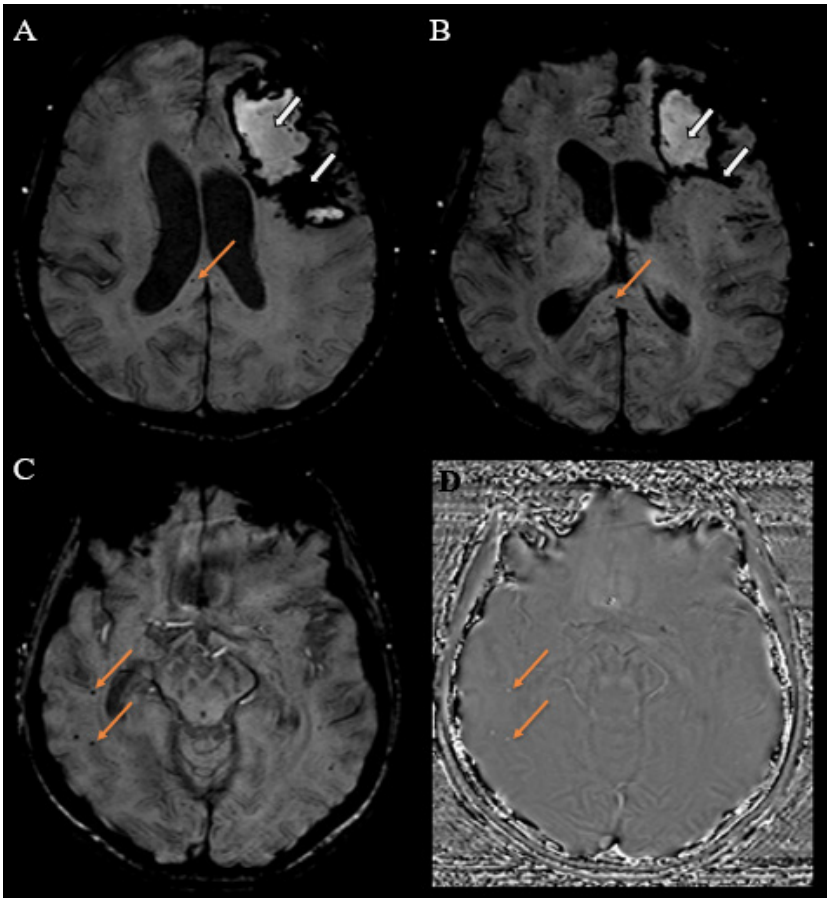


Figure 6 – MRI SWI (a, b, c) and phase-map image (d) demonstrate surgical changes and blood degradation products in left frontal lobe. Note multiple subcortical and deep microbleeds in both cerebral hemispheres and corpus callosum, what may be associated with thrombotic microangiopathy.

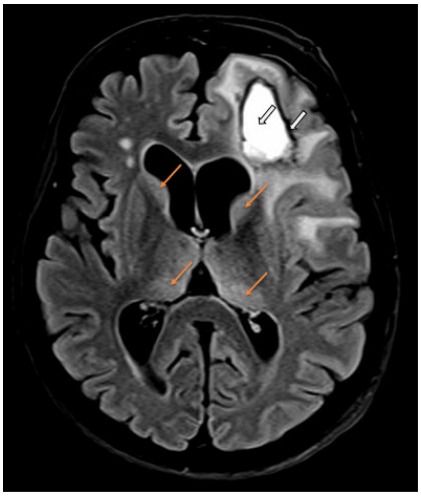


Figure 7 – FLAIR image shows surgical changes and blood degradation products in left frontal lobe and hyperintensity in thalami and caudate nuclei, probably related to hypoxic-ischemic injury.

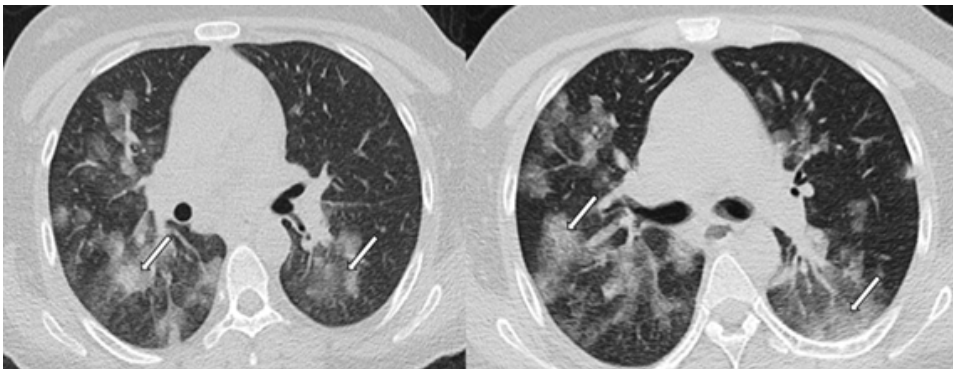


Figure 8 – Chest CT shows bilateral round ground-glass opacities and bilateral patchy consolidations.

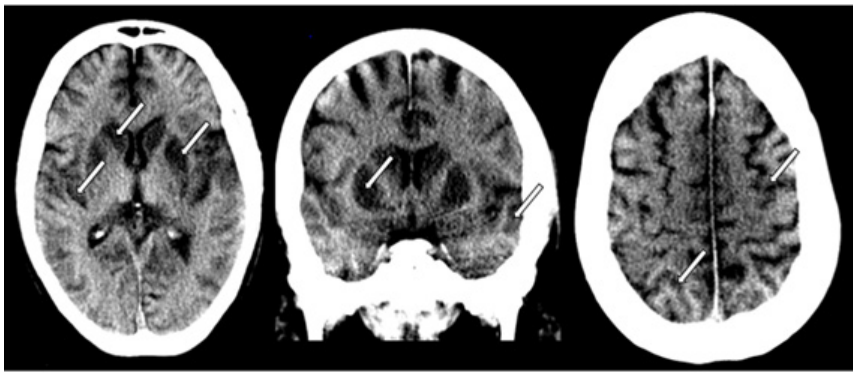


Figure 9 – Brain CT scan demonstrates brain volume loss associated with hypodensity in the cerebral cortex bilaterally, as well as in the putamina and caudate nuclei, indicative of severe hypoxic-ischemic injury.

Case 4

A 70-year-old man without comorbidities presented with fever, anosmia, and dyspnea for 4 days. At the emergency department, chest CT demonstrated peripheral ground-glass opacities, crazy-paving pattern, and parenchymal bands (Figure 10). RT-PCR testing was positive for SARS-CoV-2 infection. Upon hospitalization, the patient received full-dose enoxaparin. After 2 days, the patient had a decrease in his level of consciousness. Brain CT demonstrated a large intraparenchymal hematoma in the left frontotemporoparietal region, associated with intraventricular hemorrhage (Figure 11).

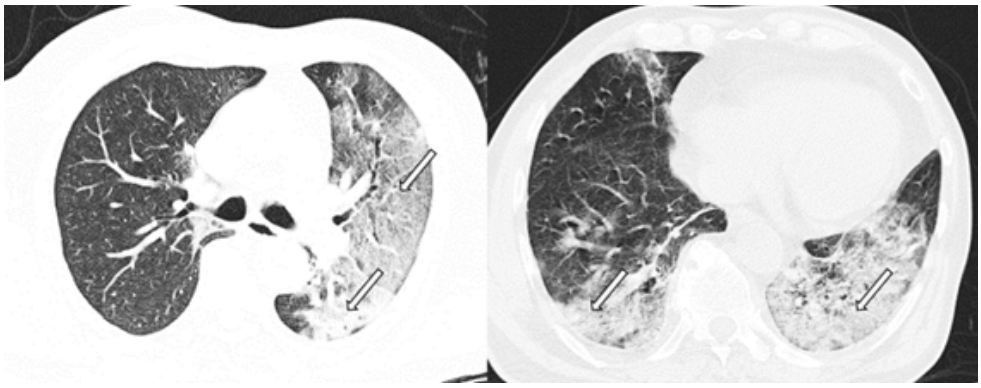


Figure 10 – Chest CT scan shows bilateral ground-glass opacities with superimposed interlobular septal thickening and visible intralobular lines ("crazy-paving") and consolidations.

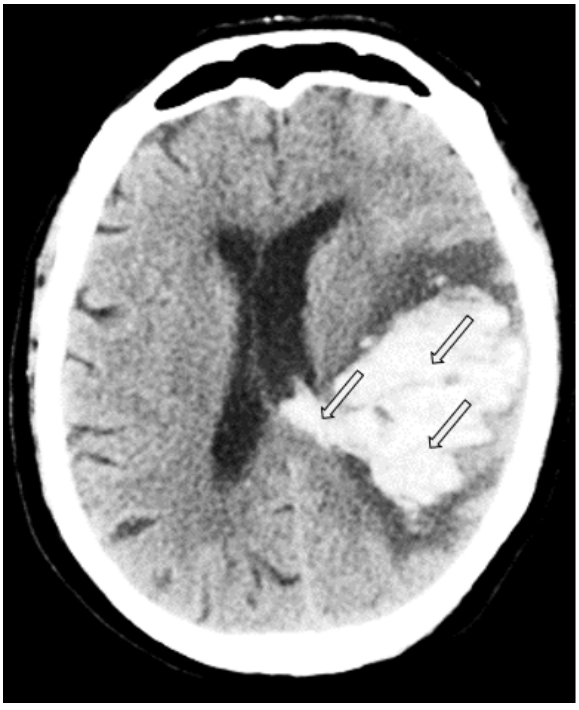


Figure 11 – Brain CT scan demonstrates a large intraparenchymal hematoma in left frontal and parietal lobes, associated with intraventricular hemorrhage.

Case 5

A 78-year-old man had hypertension, diabetes, and chronic obstructive disease. After 7 days of flu-like symptoms, the patient developed dyspnea and was admitted to the emergency room. CT revealed bilateral ground-glass opacities, typical of COVID-19 pneumonia[1] (Figure 12). RT-PCR testing was positive for SARS-CoV-2 infection.

The patient was hospitalized for 23 days, during which he was treated with antibiotics and corticosteroids. With the improvement of symptoms, the patient was discharged from hospital. After 7 days at home, he presented with severe respiratory distress and returned to the emergency department. Oxygen saturation was 70% with an increase to 95% after oxygen supplementation. There was an increased D-dimer level.

Chest CT angiography showed a filling defect in the right posterior basal segment branch, compatible with pulmonary thromboembolism (Figure 13). In addition, there was a deterioration in the pulmonary ground-glass opacities, with more than 50% of the lungs compromised (Figure 14). Doppler ultrasonography of left upper limb demonstrated thrombosis of the left cephalic vein. The patient underwent orotracheal intubation and was transferred to the intensive care unit.

Case 6

A 45-year-old man had flu-like symptoms and diarrhea for 2 days. Chest tomography performed in the emergency room showed a typical pattern for COVID-19 pneumonia, with pulmonary involvement estimated at less than 25% by visual analysis[1] (Figure 15, A). The patient was discharged from hospital with prescribed cefuroxime and azithromycin and reported improvement in fever and diarrhea during antibiotic therapy.

After 10 days of discharge, the patient returned to the emergency room with severe abdominal pain, refractory to medication, and desaturation of 89%, without respiratory distress. Chest CT showed significant worsening of pulmonary findings, with an estimated involvement of more than 50% (Fig 15, B). Laboratory tests revealed a significant increase in D-dimer level, slightly increased lactate, and elevated urea and creatinine.

On the 4th day of hospitalization in the intensive care unit, while using 1 mg/kg of enoxaparin twice daily, the patient developed leukocytosis, pain, and abdominal distension without signs of peritoneal irritation. He underwent CT angiography of the chest, abdomen, and pelvis, which revealed thrombosis in the proximal portion of the superior mesenteric artery and branch (Figure 16).

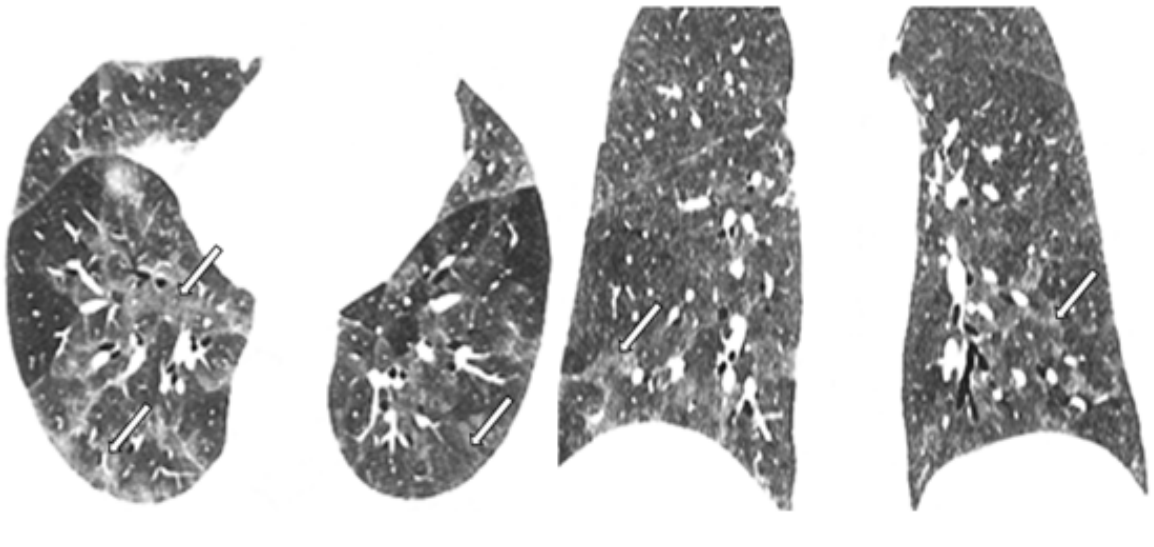
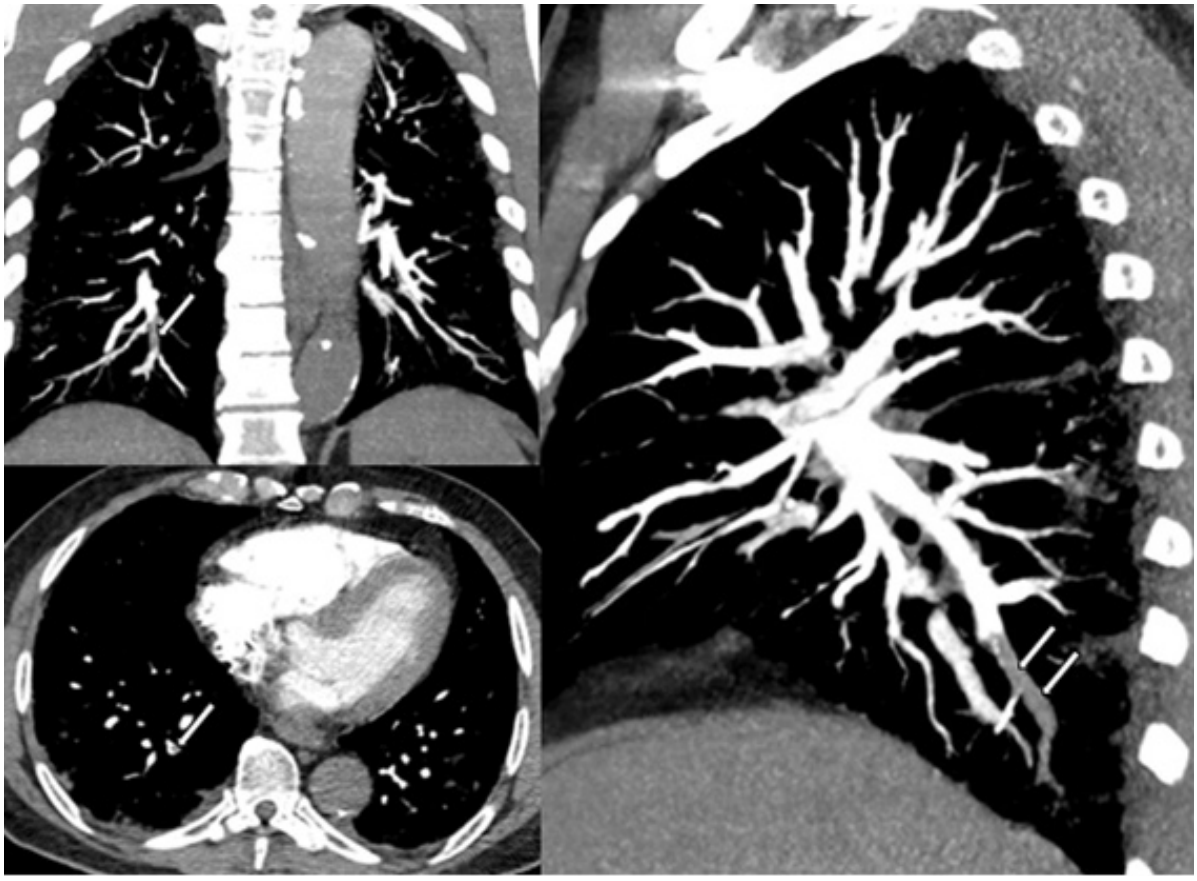


Figure 12 – CT scan reveals bilateral ground-glass opacities, typical of Covid-19 pneumonia[1].



Figue 13 – CT pulmonary angiography shows filling defects within right posterior basal segment branch, suggestive of acute pulmonary embolism.

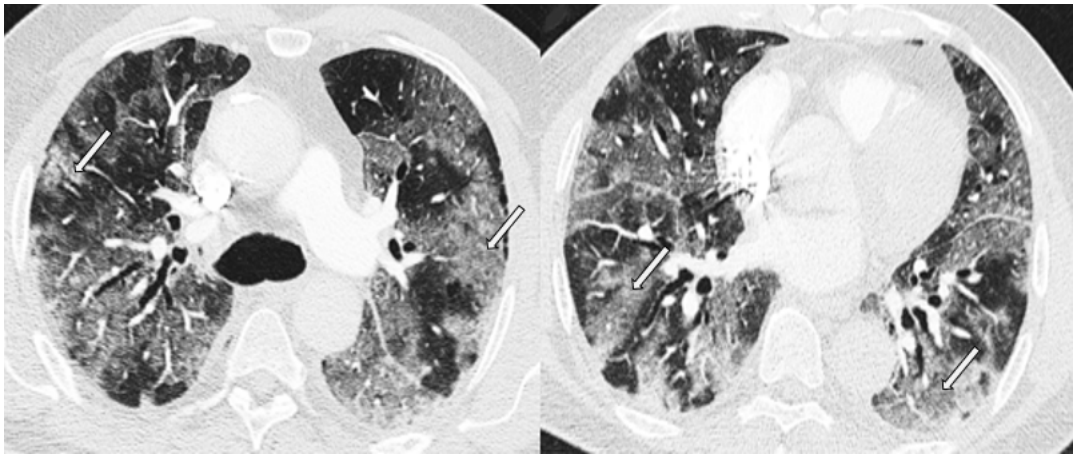


Figure 14 – CT scan reveals worsening of the pulmonary bilateral ground-glass opacities, now associated with superimposed interlobular septal thickening and intralobular lines.

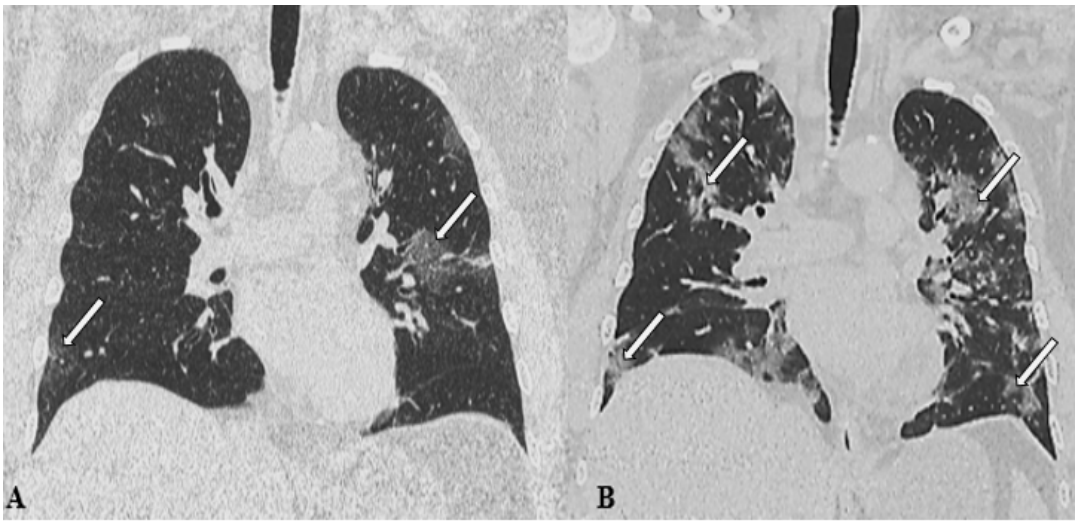


Figure 15 – Chest CT on the first emergency care, revealing typical findings of Covid-19 pneumonia (A). Examination after 10 days reveals worsening of the findings (B).

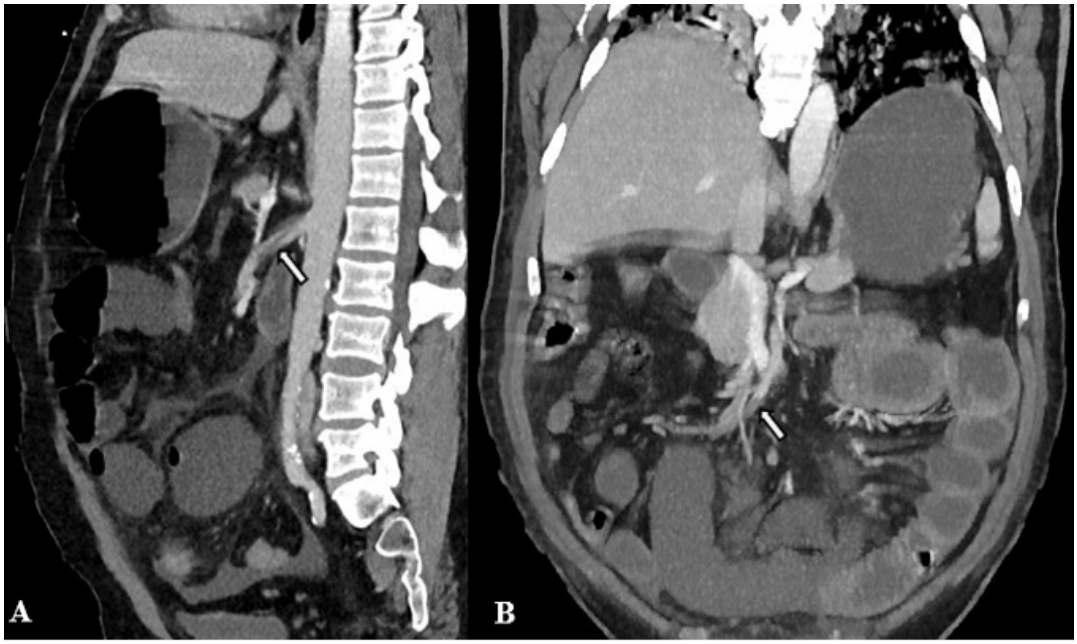


Figure 16 – Angiotomography 2 days after admission, revealing a thrombus in the upper mesenteric artery (A, arrow). MIP reformatation demonstrates thrombosis in one of its branches (B, arrow).

Upon diagnosis, the patient underwent mechanical thrombectomy and intra-arterial thrombolysis in occluded branches as well as angioplasty with stenting in the proximal third of the superior mesenteric artery. There was partial reperfusion of the branches occluded at the end of the procedure.

Discussion

SARS-CoV-2 emerged in December 2019 in Wuhan, China, and has since spread worldwide.[2] The World Health Organization declared the coronavirus outbreak a pandemic in March 2020.[3] The severe forms of COVID-19 manifest mainly as acute pulmonary respiratory syndrome. However, the involvement of other systems, such as the gastrointestinal and nervous systems, has also been demonstrated.[4] The involvement of the central nervous system may include encephalitis, myelitis, and cerebrovascular disease.[5-8]

The patterns of brain ischemia in patients with COVID-19 may include large vessel occlusion with territorial infarct and hypoxic-ischemic injury related to hypoxemia or cardiopulmonary arrest.[9] Severe hypoxic-ischemic injury manifests in regions of greater metabolic demand, such as the cortex, basal ganglia, and thalamus.[10] The patient in case 2 presented with lesions in the thalamus and caudate. In case 3, there were lesions in the cortex, putamen, and caudate. The presence of severe hypoxic-ischemic injury may be implicated in a longer hospital stay, larger neurological sequelae, and a dismal prognosis.

Also, an increase in the incidence of ischemic strokes secondary to occlusion of large vessels has been reported in patients infected with SARS-CoV-2.[7] Case 1 demonstrates a young patient, without cardiovascular risk factors or other comorbidities, presenting with ischemic stroke due to occlusion of large vessels during the course of COVID-19. Case 6 demonstrates thrombosis in the superior mesenteric artery and branch. Likewise, a rising prevalence of venous thrombosis and pulmonary thromboembolism has been related to the disease.[8] Cases 2 and 5 demonstrate this form of vascular complication.

Vascular occlusion could be connected to a prothrombotic state related to angiotensin-converting enzyme 2 (ACE2) downregulation and inflammation-induced coagulopathy in COVID-19.[8] Additionally, changes in coagulation with increased D-dimer level and fibrin/fibrinogen degradation products may be seen in these patients.[11] Such abnormalities may be related to a higher incidence of thrombotic events, including ischemic stroke related to large vessel occlusions, as well as pulmonary thromboembolism related to venous thrombosis.

The vascular endothelium is an extensive and active paracrine, endocrine, and autocrine organ that has an important role in controlling vascular tone and homoeostasis.[12] When this hemostatic balance is disturbed by a viral infection eliciting endothelial dysfunction, it produces vasoconstriction, hypoxia, and acute vascular wall inflammation[13]. Apoptosis of the endothelial cells leads to exposure of the intima (smooth muscle cells, extracellular matrix, collagen 1) generating platelet activation (hypercoagulability) and activation of innate and adaptable immunological responses (inflammation in situ and microvasculature dysfunction).[13]

Endotheliopathy, disseminated intravascular coagulation, and sepsis-associated coagulopathy may be related to multiple organ failure in critically ill patients, including those with COVID-19.[11] Thrombotic microangiopathies, such as disseminated intravascular coagulation, can manifest as diffuse cerebral microbleeds.[14] The patient in case 2 exhibited cortico-subcortical and deep microbleeds, including the corpus callosum, possibly related to this pattern of vasculopathy.[15] However, factors such as hypoxia and endotheliopathy may be implicated somehow.[15]

Intracranial hemorrhagic lesions can also be seen in these patients.[4,8,9] The causative mechanism of hemorrhage can be mainly associated with clinically indicated anticoagulant therapy; however, it is not clear whether factors such as coagulopathy and COVID-19-related endotheliopathy may be involved in some way. Cases 2 and 4 demonstrate large intraparenchymal hematomas in patients treated with anticoagulation during SARS-CoV-2 infection.

Finally, the vascular complications that may occur during COVID-19 are of great therapeutic importance. Cerebral infarction related to thrombosis of large vessels requires the implementation of immediate recanalization therapy, if the patient is eligible. In addition, other approaches that may still be required are

full anticoagulation for pulmonary thromboembolism as well as surgical evacuation of intracranial hematomas. The medical team must be aware of the presence of coagulopathy and a prothrombotic state in these patients, which may be related to the higher incidence of some of these complications and directly interfere with the treatment.

Author contributions

Conception and design of the research: Castro P, Chagas L, Machado D. Writing of the manuscript : Castro P, Chagas L, Wajnberg E. Critical revision of the manuscript for intellectual content : Cougo P, Santos R, Machado D.

Potential Conflict of Interest

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Study Association

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

Ethics approval and consent to participate

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

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CASE REPORT

Takotsubo Cardiomyopathy and Myocardial Perfusion Image: Unusual Binomial in the Investigation of Acute Coronary Syndrome without Obstructive Lesions

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Introduction

Takotsubo cardiomyopathy (TC), also known as broken heart syndrome or stress-induced cardiomyopathy, was primarily described in Japan in 1990, is named after its morphological similarity to the vase used by Asian people to catch octopuses, which has a rounded bottom and a narrow bottleneck.[1] This condition is characterized by transient left ventricular (LV) systolic dysfunction, commonly preceded by physical or emotional stress, mimicking the presentation of acute myocardial infarction.[2] In the present article, we describe a case of TC focusing on its updated approach, highlighting the applicability of myocardial perfusion scintigraphy (MPS) in the acute phase of chest pain and presenting images rarely described in this scenario.

Description

A 66-year old woman with hypertension and dyslipidemia using aspirin, angiotensin receptor blocker (ARB), statin, and beta-blocker (BB) presented at the emergency department due to smoke inhalation after a fire in her house. Under observation, she evolved into typical chest pain, her electrocardiogram (ECG) showed sinus rhythm and ST-segment elevation in the inferior wall (Figure 1). Laboratory tests revealed high troponin levels. reaching 1106 pg/mL (reference value < 14 pg/mL), and physical examination did not show abnormalities. The patient was treated as having acute coronary syndrome (ACS) with ST-segment elevation, thus receiving dual antiplatelet aggregation therapy, low-molecular weight heparin, and vasodilators, and was referred to a referral hospital.

On admission, patient's pain improved, and ST segments remained elevated. She was then referred to the department of hemodynamics for primary coronary angioplasty, which did not find any significant obstructive lesion (Figure 2). Ventriculography was not performed due to periprocedural hemodynamic instability. The patient was kept under monitoring for stabilization and diagnostic investigation, and she had an InterTAK score of 61, which means non-high probability of TC, according to the European Society of Cardiology (ESC). Transthoracic echocardiography was performed, showing reduced ejection fraction (36%), mid-apical segmental akinesis, and basal segmental hyperkinesis.

During hospitalization, the patient evolved into a new episode of typical chest pain, with spontaneous relief, in which T-wave inversion was identified in precordial leads V3 to V6. On that occasion, the procedure of choice was MPS with sestamibi-^{99m}Tc, which showed reduced myocardial perfusion in LV juxta-apical segments and preserved basilar segments; furthermore, rest ejection fraction was estimated at 34%. There were also findings suggestive of subendocardial necrosis and myocardial stunning, compatible with the diagnosis of TC (Figure 3).

The patient remained stable during the 4 days de hospitalization, follow-up tests showed a decrease in troponin levels, and inflammatory workup was negative. She was discharged with optimized doses of BB, angiotensin-converting enzyme inhibitors (ACEIs), statin, and aspirin. On patient's follow-up outpatient visit after 4 weeks, recovery of ventricular function was observed on control echocardiography.

Keywords

Takotsubo Cardiomyopathy; Chest Pain; Acute Coronary; Ventilation-Perfusion Scan.

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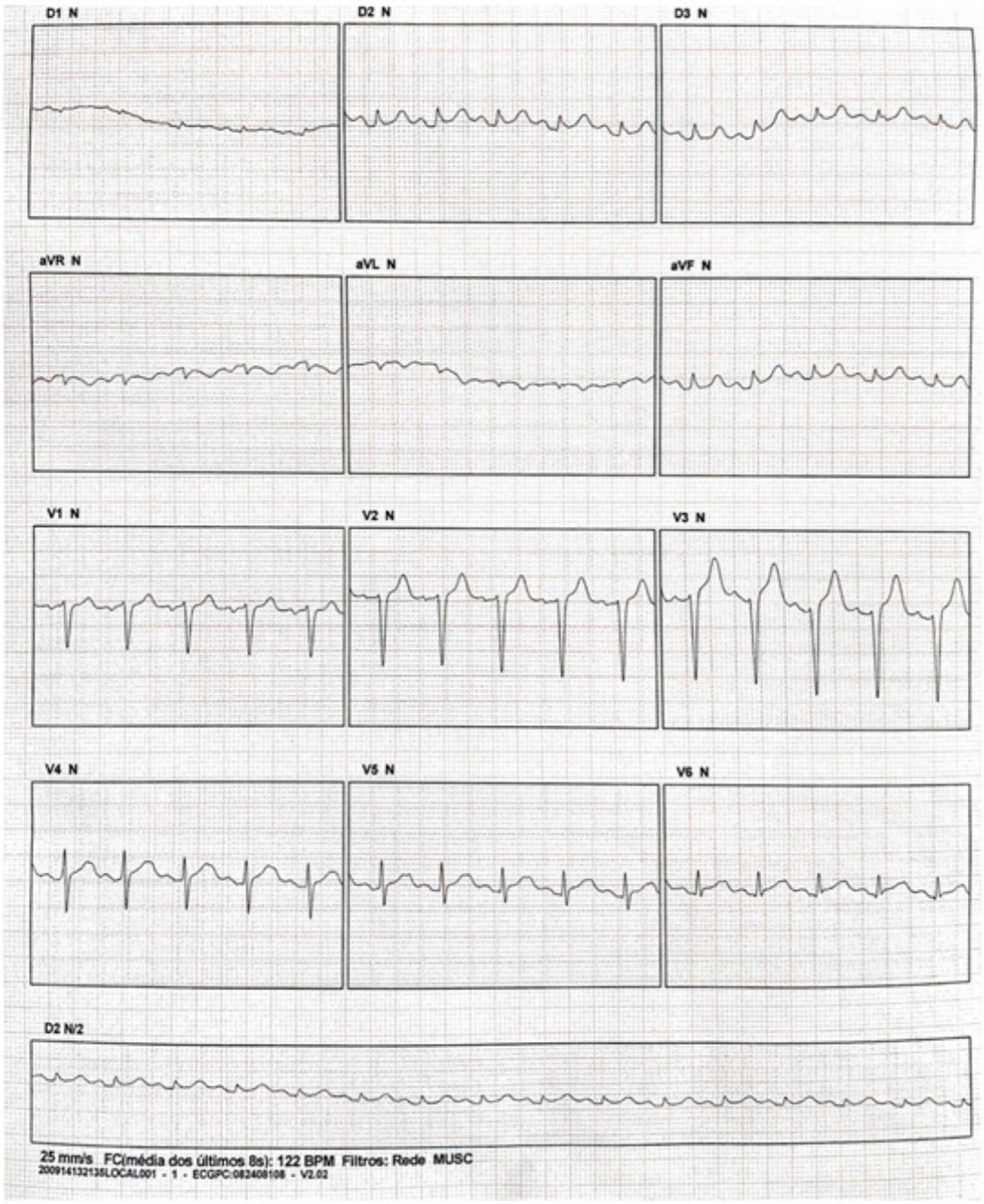

Figure 1 – 12-lead electrocardiogram showing ST-segment elevation in the inferior wall.
Source: the author.

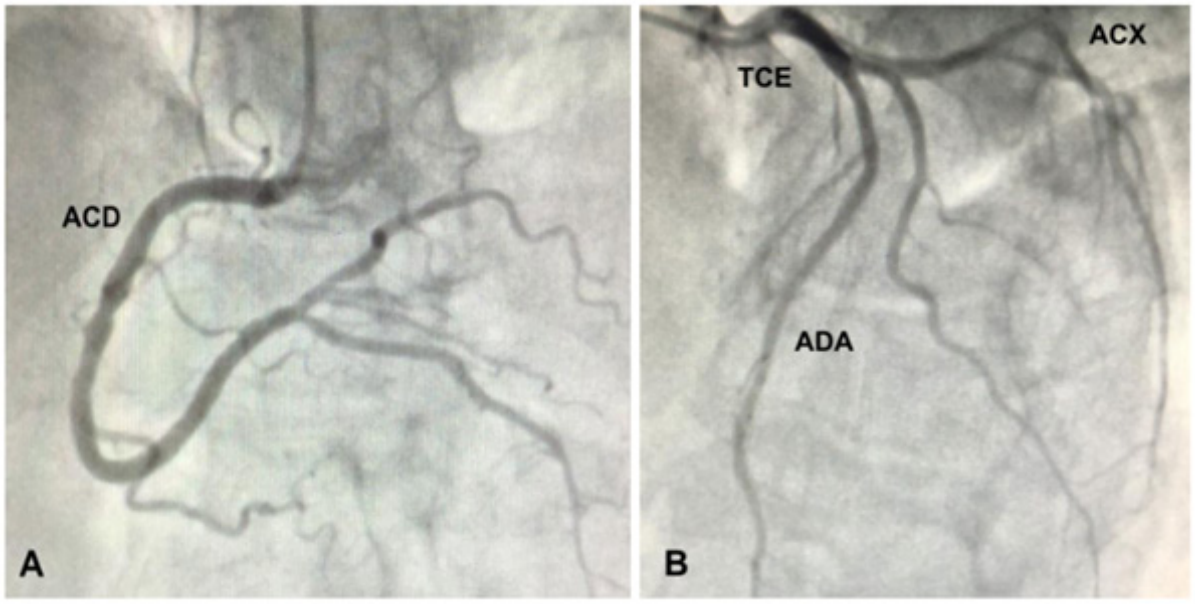

Figure 2 – Coronary angiography of the right (A) and left (B) coronary arteries, showing absence of obstructive lesions. ACD: right coronary artery; TCE: left coronary trunk; ACX: circumflex artery; ADA: anterior descending artery.
Source: the author.

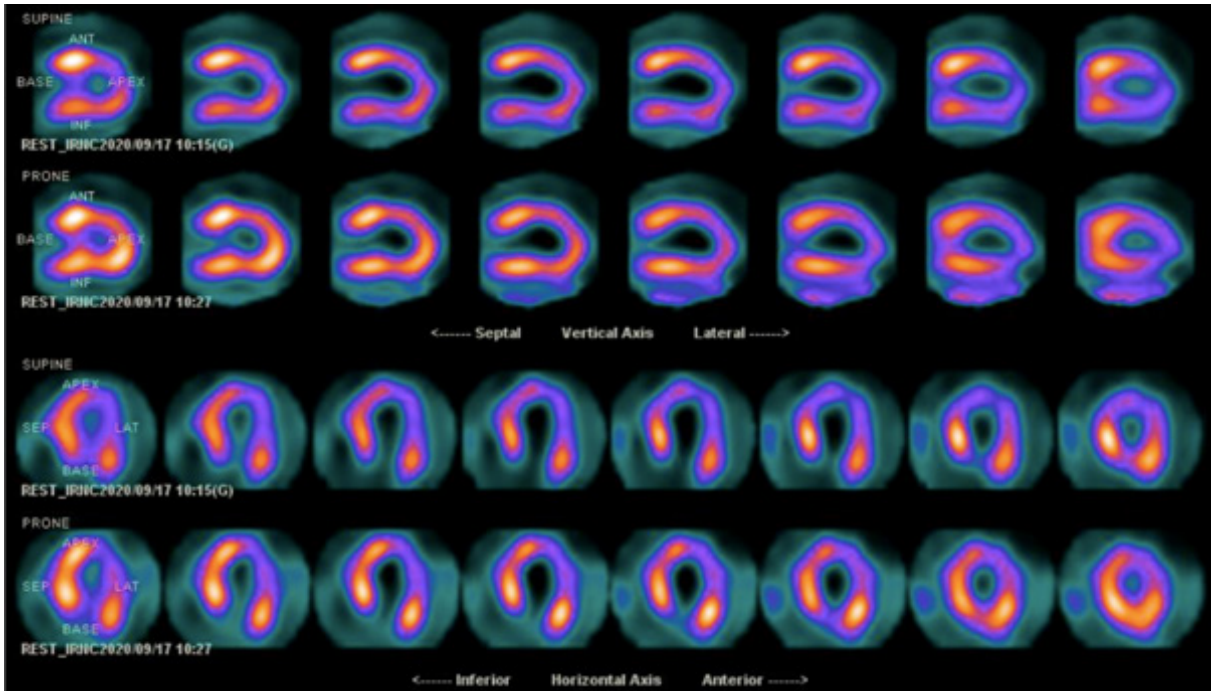

Figure 3 – Myocardial scintigraphy with sestamibi-99mTc at rest. It shows an abnormal distribution in myocardial perfusion, with moderate reduction in the apex and mid-apical segments of the lateral wall, with a slight inferolateral extension, affecting 20-25% of the LV area (SRS = 15). The basal regions are preserved.
Source: the author.

Discussion

TC is an underdiagnosed condition with an estimated prevalence of 1-2% among patients diagnosed with ACS.[3] The most common forms of ventricular involvement are apical ballooning in 75-80% of the cases, and mid-ventricular ballooning in 10-20%.[4]

Although the relationship between TC and the autonomous central nervous system has only recently been known, thanks to neuroimaging tests, increased blood flow in hippocampus, basal ganglia, and brainstem was identified during the acute phase of TC, showing the involvement of the limbic system in the pathophysiological mechanism of the disease.[5] An hypothesis to explain this activation would be catecholaminergic storm, which would induce both microvascular vasospasm and direct toxicity to the vascular endothelium, resulting in myocardial stunning.[6]

TC classically occurs in postmenopausal women with history of anxiety disorder and a factor of emotional stress within the last 5 days.[2] Emotional triggers include death, romantic conflicts, violence, natural disasters, and great financial losses. Conversely physical triggers encompass critically-ill patients, major surgical procedures, severe pain, sepsis, and exacerbation of chronic lung diseases.[3]

Chest pain was the predominant symptom in more than 75% of the cases of TC, making its diagnosis challenging.[4] For this reason, the InterTAK score was created as an auxiliary diagnostic tool in 2017 and was incorporated to the International Consensus published by the ESC in the following year. Its variables are: female sex, emotional stress, physical stress, absence of ST-segment depression, former psychiatric disorder, former neurological disorder, and prolonged QT interval. These variables score 25, 24, 13, 12, 11, 9 and 6 points, respectively. An InterTAK score higher than 70 points suggests high probability of TC and recommends transthoracic echography. Conversely, a score lower or equal to 70 suggest ACS and indicates angiography.[7]

One of the most accepted criteria are those of the Mayo Clinic, published in 2008, which include: transient hypokinesis, akinesis, or dyskinesis of LV mid segments, with or without apical involvement (regional wall-motion abnormalities extend beyond a single epicardial vascular distribution); a stressful trigger is often, but not always, present; absence of obstructive coronary artery disease or angiographic evidence of acute plaque rupture; new ECG abnormalities (either ST elevation and/or T-wave inversion) or modest elevation in cardiac troponin; absence of pheochromocytoma or myocarditis.[8]

Some ECG characteristics suggest TC with high sensitivity and specificity, such as: T-wave inversion; prolonged QT interval; absence of reciprocal change; absence of abnormal Q waves; and greater ST elevation in leads V4 to V6 compared to that observed in V1 to V3.[9] Biomarkers of myocardial injury are modestly elevated, with a typical discrepancy between the expected level and the significant degree of myocardial compromise.[4]

Imaging tests are essential in diagnostic procedures. According to indication and urgency, cineangiocoronariography should be prioritized. Transthoracic echocardiogram is the preferred non-invasive test, since it enables to identify LV outflow obstruction and acute mitral insufficiency, complications with the worst prognosis.[7] Cardiac magnetic resonance (CMR) has an important role in the diagnosis of myocarditis, being able to reveal inflammation and myocardial edema, and late gadolinium-enhanced CMR may be used in cases of scars and fibrosis.[10] However, it is still a high-cost test not commonly available in hospitals.

Cardiac perfusion imaging, a technique based on nuclear medicine, is an attractive option for the additional evaluation of chest pain. Ideally, it should be performed with the patient at rest, up to 6 hours after pain improved, which is the period with greater sensitivity for abnormalities.[11] In TC, most reports show essentially normal perfusion.[12] In this report, moderate hypoperfusion was observed in the dysfunctional myocardial regions, indicating that MPS with sestamibi-^{99m}Tc is a promising additional tool for the understanding of TS pathophysiology, as well as for its diagnosis. Conversely, scintigraphy with iodinated meta-iodobenzylguanidine MIBG^{123} (which has a structure similar to that of noradrenaline, ie, selective to sympathetic nerves) is consolidated as diagnostic method, even days after injury, thus corroborating its pathophysiology.[11]

With regard to treatment, it is based on clinical and hemodynamic support. In the long term, it is necessary to approach risk factors and triggers, such as anxiety disorders and depression.[7] ACEIs have shown to improve survival and reduce disease recurrence, with no strong evidence for BBs in this scenario.[4,7] Anticoagulant agents may be considered in cases of severe LV compromise to prevent intracavitary thrombi.[7]

Although intra-hospital mortality due to TC is relatively low, complications such as acute mitral insufficiency, LV outflow obstruction, arrhythmia, and ventricular thrombi

should be monitored.[4,7] Recovery usually takes from 1 to 2 weeks, but may extent up to 6 weeks. Recurrence is common, with a rate of approximately 3% per year, reaching up to 20% in a decade.[4]

Conclusion

We reported a case of TC with a good outcome, highlighting the practical applicability of the current approach and the importance of MPS as an additional tool in the understanding of TC pathophysiology. We presented an unusual scan obtained from this imaging modality in this scenario, with apical myocardial hypoperfusion in the acute phase of disease, a finding rarely described in the literature using this imaging modality.

Potential Conflict of Interest

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

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Ethics approval and consent to participate

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Author contributions

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ERRATUM

Int J Cardiovasc Sci. 2022 Issue vol 35(3), pages 297-301.

In Editorial “An Updated View on the Approach to Tricuspid Regurgitation”, with DOI number: https://doi.org/10.36660/ijcs.20200325, published in the journal International Journal of Cardiovascular Sciences, 35(3):297-301, in page 297, correct the title “An Uptated View on the Approach to Tricuspid Regurgitation” to “An Updated View on the Approach to Tricuspid Regurgitation”.

Int J Cardiovasc Sci. 2022 Issue vol 35(4), pages 537-545.

In Review Article “Depression and Cardiovascular Disease in Women”, with DOI number: https://doi.org/10.36660/ijcs.20200416, published in the journal International Journal of Cardiovascular Sciences, 35(4):537-545, in page 543, in Table 1, correct "INIBIDORES SELETIVOS DA RECEPTAÇÃO DA SEROTONINA" to "SELECTIVE INHIBITORS OF SEROTONIN RECEPTION".

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