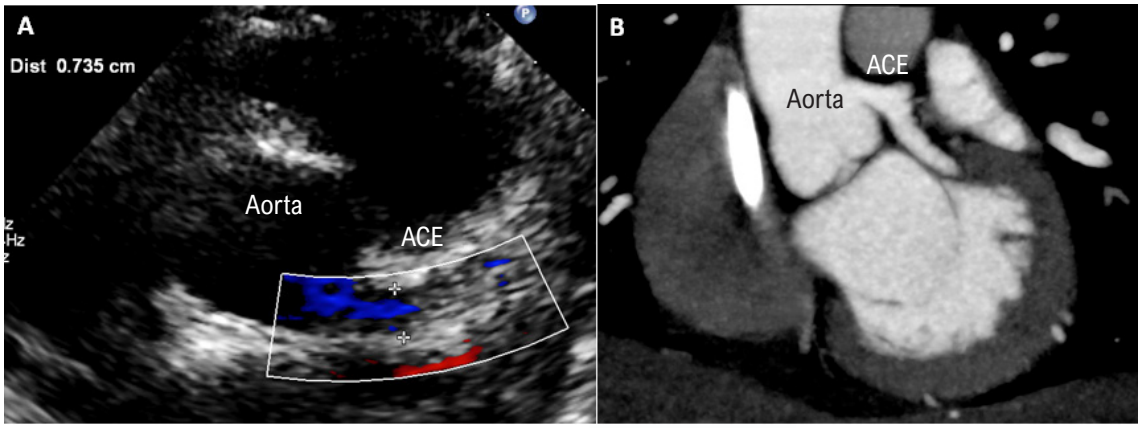
ABC Cardiol
Arquivos Brasileiros de Cardiologia

Volume 117 | Number 5
November 2021

Brazilian Society of Cardiology
ISSN-0066-782X



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JOURNAL OF BRAZILIAN SOCIETY OF CARDIOLOGY - Published since 1943

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Volume 117, Nº 5, November 2021

Indexing: ISI (Thomson Scientific), Cumulated Index Medicus (NLM), SCOPUS, MEDLINE, EMBASE, LILACS, SciELO, PubMed

Address: Av. Marechal Câmara, 160 - 3º andar - Sala 330
20020-907 • Centro • Rio de Janeiro, RJ • Brasil
Phone.: (21) 3478-2700
E-mail: arquivos@cardiol.br
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Association of Hypertension with Severity and Mortality in Hospitalized Patients with COVID-19 in Wuhan, China: A Single-centered, Retrospective Study

You-ping Deng,[1*] Wen Xie,[2*] Tao Liu,[3] Shou-yi Wang,[1] Mei-rong Wang,[4] Yu-xing Zan,[4] Xiao-bo Meng,[1] Yu-qing Deng,[1] Hai-rong Xiong,[4] Xue-dong Fu[1]

Department of Pediatrics, Zhongnan Hospital of Wuhan University,[1] Wuhan - China

Department of Clinical Laboratory, Zhongnan Hospital of Wuhan University,[2] Wuhan - China

Department of Urology, Zhongnan Hospital of Wuhan University,[3] Wuhan - China

State Key Laboratory of Virology/ Institute of Medical Virology, School of Basic Medical Sciences, Wuhan University,[4] Wuhan - China

**Os autores contribuíram igualmente para este trabalho*

Abstract

Background: **Coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has spread worldwide.**

Objective: **To investigate the association between hypertension and severity/mortality in hospitalized patients with COVID-19 in Wuhan, China.**

Methods: **A total of 337 patients diagnosed with COVID-19 at the Seventh Hospital of Wuhan City, from January 20 to February 25, 2020, were enrolled and analyzed in a retrospective, single-center case study. The significance level adopted in the statistical analysis was 0.05.**

Results: **Of the 337 patients with confirmed diagnosis of COVID-19, 297 (87.8%) were discharged from the hospital and 40 patients (22.9%) died. The median age was 58 years (range, 18-91 years). There were 112 (33.2%) patients diagnosed with hypertension at admission (median age, 65.0 years [range, 38-91 years]; 67 [59.8%, 95%CI: 50.6%-69.0%] men, p=0.0209). Patients with hypertension presented a significantly higher portion of severe cases (69 [61.6%, 95%CI:52.5%-70.8%] vs. 117 [52.0%, 95%CI: 45.4%-58.6%] in severe patients and 23 [19.3%, 95%CI:12.9%-28.1%] vs. 27 [12.0%, 95%CI: 7.7%-16.3%] in critical patients, p=0.0014) and higher mortality rates (20 [17.9%, 95%CI: 10.7%-25.1%] vs. 20 [8.9%, 95%CI: 5.1%-12.6%, p=0.0202). Moreover, hypertensive patients presented abnormal levels of multiple indicators, such as lymphopenia, inflammation, heart, liver, kidney, and lung function at admission. The hypertension group still displayed higher levels of TnT and creatinine at approaching discharge.**

Conclusion: **Hypertension is strongly associated with severity or mortality of COVID-19. Aggressive treatment may be considered for COVID-19 patients with hypertension, especially regarding cardiac and kidney injury.**

Keywords: **COVID-19/complications; Betacoronavirus, Severe Acute Respiratoty Syndrome; Hypertension; Comorbidities; Risk Factors**

Introduction

The novel Coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus (SARS-CoV2), emerged in Wuhan in December, 2019, and has spread worldwide, which resulted in great concern to global public health and economics.[1] SARS-CoV-2 was identified as the pathogen of COVID-19 in January 2020, and belongs to a unique clade of the subgenus sarbecovirus, Orthocoronavirinae subfamily.[2] This novel coronavirus is an enveloped, single stranded, positive-sense RNA virus, and recognizes angiotensin-converting enzyme-2 (ACE2) as the functional receptor for host cell entry. ACE2 is a member of the angiotensin-converting enzyme (ACE) family and plays an important role in human physiological functions, especially in blood pressure regulation.[3,4] Emerging data reported the general clinical features and epidemiological characteristics of COVID-19 patients, among which several reports demonstrated that cardiac injury is associated with higher risk of mortality in patients with COVID-19.[5-7]

There is a high prevalence of hypertension worldwide, especially in China. Overall, hypertension was present in 23.2% of the adult Chinese population from 2012 to 2015.[8]

Mailing Address: Xue-dong Fu and Hai-rong Xiong •
Xue-dong Fu, MD, Department of Pediatrics, Zhongnan Hospital of Wuhan University, Wuhan, 169 Donghu Road, Wuhan 430071, China
E-mail: wb001865@whu.edu.cn, hrxiong@whu.edu.cn
Manuscript received July 02, 2020, revised manuscript October 28, 2020, accepted November 11, 2020

DOI: https://doi.org/10.36660/abc.20200733

Hypertension is a major risk factor for cardiovascular disease, the leading cause of death in China.[9,10] With urbanization, rising incomes and an aging population, China's burden of hypertension and cardiovascular disease is increasing.[11,12] Accumulated evidence suggested that hypertension may be related to a growing factor of in-hospital fatality due to COVID-19.[13,14] Therefore, we initiated this retrospective study to analyze data from a single center in Wuhan, China, and examine the association between hypertension and COVID-19. We also monitored the dynamic changes of important biomarkers among the hospitalized patients, which may bring recommendations for the clinical management of hypertensive patients with COVID-19.

Methods

Patients' enrollment

The institutional Ethics board of Zhongnan Hospital, Wuhan University, approved this project (No.2020056K). No.7 Hospital of Wuhan was one of the first COVID-19 designated hospitals, and has been consigned to the Zhongnan Hospital of Wuhan University since January 2020. A total of 337 patients with confirmed diagnosis of COVID-19 hospitalized in four inpatient wards of No.7 Hospital of Wuhan were enrolled in this study, which was conducted from January 20 to February 25, 2020. All patients were diagnosed with COVID-19 and classified in distinct clinical types, according to the diagnostic and treatment guidelines of COVID-19 from the Chinese National Health Commission (version 3-7).[15] Since patients without major complications were assigned to the mobile cabin hospital due to the hierarchical medical system during the early stage of the epidemic, all the patients involved in this study had moderate (101), severe (186), and critical (50) COVID-19. The critical cases were further transferred to the ICU. The throat swab samples were collected and applied for laboratory detection.

Data collection

The medical records, including basic information (age, gender, comorbidities etc.), clinical characteristics, laboratory findings and radiological examinations, as well as treatment and outcomes of each patient with positive SARS-CoV-2 results, were collected. The date of disease onset was specified as the day when any symptom was observed. Clinical outcomes were evaluated and recorded at the time of discharge or transfer to the assigned intensive care hospital. Laboratory confirmation of SARS-CoV-2 was primarily performed in the clinical laboratory at the Zhongnan Hospital of Wuhan University, and partially in the clinical laboratory at No.7 Hospital of Wuhan after the detection system was locally established since late February. SARS-CoV-2 was verified by real-time RT-PCR using the protocol as previously described.[16] The viral nucleic acid detection from throat-swab specimen was performed during the therapeutic process. Besides, the patient samples were also detected for other pathogen infections, such as influenza virus, parainfluenza, Coxsackie virus, adenovirus, echovirus, respiratory syncytial virus, cytomegalovirus etc. All the patients underwent chest computed tomography (CT-scan) or X-ray. Follow-up radiological examination and negative SARS-CoV-2 test results were considered as criteria for cure and hospital discharge.

Clinical manifestations were summarized, including fever, cough, expectoration, myalgia, fatigue, headache, heart palpitations, diarrhea, dyspnea etc. Laboratory examinations were conducted at admission and as the disease progressed, such as routine blood tests, blood biochemistry, blood gas level, blood electrolytes, coagulation function, procalcitonin (PCT), C-reactive protein (CRP), serum amyloid A (SAA), serum creatine kinase and myocardial enzyme spectrum. Medical treatments were recorded, as most patients received the antiviral treatment or a Chinese patent medicine. Patients also received corticosteroid, gamma globulin, probiotics, or respiratory support when necessary.

Statistical analysis

Categorical data were presented as frequencies and percentage rates, and continuous data were described using median and interquartile range (IQR) values. The continuous variables were tested for Gaussian distribution using the D'Agostino-Pearson test for normality and further analyzed by the Mann-Whitney test, when appropriate. The frequencies of categorical variables were compared using the chi-square test, Fisher's exact test, and Kruskal-Wallis when appropriate. Survival curves were generated by the Kaplan-Meier method, with comparisons between groups performed with the log-rank test, SPSS version 19.0. Other statistical analyses and graphs were generated and plotted using the GraphPad Prism software, version 6.00 (GraphPad Software Inc). *P* value lower than 0.05 was considered as statistically significant.

Results

Demographics and clinical characteristics

The study enrolled a total of 337 patients hospitalized with confirmed diagnosis of COVID-19, including 112 (33.2%) patients diagnosed as hypertensive at admission. The median age for all patients was 58 years (18-91), and 171 (50.7%) patients were male. The most common underlying comorbidities were diabetes (49, 14.5%), cardiovascular disease (43, 12.8%), and liver disease (24, 7.1%). Of the 337 patients, 101 (30.0%) were categorized as moderate patients; 186 (55.2%) as severe patients; and 50 (14.8%) as critical patients. Of these 337 patients, 297 (87.8%) were discharged from the hospital and 40 (11.9%) patients died.

Compared with non-hypertensive patients, hypertensive patients were older and most were male. Moreover, patients with hypertension presented significantly higher rates of comorbidities, including diabetes, cardiovascular disease, liver disease, kidney disease and cerebrovascular disease. Patients with hypertension presented a significantly higher portion of severe cases, as 69 [61.6%] vs. 117 [52.0%] in severe patients and 23 [19.3%] vs. 27 [12.0%] in critical patients. Mortality rates were significantly higher among patients with hypertension (20 [17.9%] vs. 20 [8.9%]). (Table 1).

Table 1 – Demographics and clinical characteristics of patients with COVID-19

	No. (%)			
Characteristic	**Total (n=337)**	**Normotension (n=225)**	**Hypertension (n=112)**	**p-value**
Mean age (range)	58(18-91)	54(18-88)	65(38-91)	<0.0001[a]
Sex				.0209[b]
Female	166(49.3)	121(53.8)	45(40.2)	
Male	171(50.7)	104(46.2)	67(59.8)	
Smoking	26(7.7)	18(8.0)	8(7.1)	1.00[b]
Onset of symptoms to hospital admission, median (IQR), d	10 (6-13)	9(6-12)	10(7-15)	.1596[a]
Hospitalization, median (IQR), d	15(11-23)	15.5(11-24)	15(11-22)	.9117[a]
Comorbidity—No. (%)				
Cardiovascular disease	43(12.8)	11(4.8)	32(28.6)	<0.0001[b]
Cerebrovascular disease	6(1.7)	0	6(5.4)	0.0012[b]
Diabetes	49(14.5)	15(6.7)	34(30.4)	<0.0001[b]
Chronic bronchitis	8(2.4)	4(2.2)	4(3.6)	.4480[b]
Asthma	1(0.3)	1(0.8)	0(0)	1[b]
Malignancy	18(5.3)	9(4.0)	9(8.0)	.2924[b]
Liver disease	24(7.1)	9(4.0)	15(13.4)	.0028[b]
Kidney disease	17(5.0)	5(2.2)	12(10.7)	.0022[b]
Allergic physique	13(3.9)	11(4.9)	2(1.8)	.2332[b]
Complication				
Bacterial infection	36(10.7)	23(10.2)	13(11.6)	.7106[b]
Metabolic acidosis	14(4.2)	6(2.7)	8(7.1)	.0784[b]
Heart failure	20(5.7)	10(4.4)	10(8.9)	.1398[b]
ARDS	42(12.5)	18(8.0)	24(21.4)	.0007[b]
Acute liver injury	17(5.0)	11(4.9)	6(5.3)	1[b]
Acute kidney injury	19(5.6)	8(3.6)	11(9.8)	.0244[b]
DIC	4(1.2)	1(0.4)	3(2.7)	.1089[b]
Treatments				
Antiviral treatment	276(81.9)	193(85.8)	83(74.1)	0.0107[b]
Antibiotics	302(89.6)	200(88.9)	102(91.1)	0.5763[b]
Chinese Medicine	186(55.2)	122(54.2)	64(57.1)	0.6430[b]
Glucocorticoid	150(44.5)	90(40.0)	60(53.6)	0.0202[b]
Immune globulin	56(16.6)	36(15.6)	21(18.4)	0.3445[b]
Respiratory support				**0.0041[b]**
Nasal cannula	226(67.1)	158(70.2)	68(60.7)	
Non-invasive ventilation	26(7.7)	10(4.4)	16(14.3)	
Invasive ventilation	16(4.7)	9(4.0)	7(6.3)	
Disease severity				**0.0014[b]**
Moderate	101(30.0)	81(36.0)	20(17.9)	
Severe	186(55.2)	117(52.0)	69(61.6)	
Critical	50(14.8)	27(12.0)	23(20.5)	
Clinical outcomes				**.0202[b]**
Discharge	297(87.8)	205(90.7)	92(82.1)	
Death	40(11.9)	20(8.9)	20(17.9)	

ARDS: acute respiratory distress syndrome; DIC: Disseminated intravascular coagulation; IQR: interquartile range. a: statistical difference (numerical variable) between normotension and hypertension groups were evaluated by the Mann-Whitney U test. b: statistical difference (categorical variable) between normotension and hypertension groups were evaluated by the Chi-square test.

Laboratory findings at Admission

As shown in Table 2, in the overall study population of 337 patients, the median level of CRP and SAA was elevated, and lymphocyte count, total protein and albumin were decreased. However, the other laboratory indicators were within the normal range, including other blood cell counts, blood lipids and electrolytes, cardiac biomarkers, blood gas analysis and other liver and renal function biomarkers.

Compared with non-hypertensive patients, hypertensive patients presented with significantly higher white blood cell and neutrophil count, and lower lymphocyte count. The monocyte and platelet counts of these two groups were similar.

Total cholesterol, high-density lipoprotein (HDL), and small dense Low-Density Lipoprotein (sdLDL) levels did not differ between hypertensive and non-hypertensive patients, but hypertensive patients had higher levels of triglyceride and low-density lipoprotein (LDL). The inflammatory biomarkers, including highly sensitive CRP, procalcitonin, and globulin were significantly higher in hypertensive patients.

It is worth noting that hypertensive patients presented abnormal levels of multiple indicators concerning the heart, liver, kidney, and lung function. Hypertensive patients presented significantly higher levels of cardiac injury biomarkers, including troponin T, creatine kinase-myocardial band test, myoglobin and N-terminal pro-brain natriuretic peptide (NT-proBNP). Moreover, hypertensive patients showed more severe respiratory dysfunction, with lower partial pressure of oxygen (PaO2), and PaO2/fraction of inspired oxygen (FiO2). Furthermore, hypertensive patients also had higher levels of creatinine and urea nitrogen. Hypertensive patients presented higher levels of alanine aminotransferase, aspartate aminotransferase, total bilirubin, direct bilirubin, and lower levels of albumin.

Treatment, complications, and clinical outcome

The median time from symptom onset to admission was ten days (IQR, 7-15) in hypertensive patients, and similar with non-hypertensive patients (Table 1). There was no significant difference in hospitalization time between both groups. During hospitalization, hypertensive patients developed more frequent complications regarding acute respiratory distress syndrome, and acute renal injury when compared with non-hypertensive patients (Table 1). But there were no significant differences regarding the incidence of acute heart failure and acute liver injury between these two groups.

A total of 268 patients (79.5%) underwent respiratory support, and the use of nasal cannula, non-invasive ventilation and invasive mechanical ventilation was necessary for 226 (67.1%), 26 (7.7%), and 16 patients (4.7%), respectively. Most patients received antiviral therapy (276 [81.9%]) and antibacterial therapy (302 [89.6%]) during hospitalization. The proportion of treatment with the Chinese Medicine, glucocorticoid and immunoglobulin was 186 (55.2%), 150 (44.5%) and 56 (16.6%), respectively. Overall, the rates of these treatments had no significant differences in therapies between the group with and without hypertension. However, it is worth noting that hypertensive patients received treatment with glucocorticoid.

According to the diagnostic criteria, there were 73 (65.1%) patients with Grade I, 24 (21.4%) with Grade II and 15 (13.4%) with Grade III hypertension, respectively. All Grade III patients presented the severe or critical type of COVID-19. More than half of the patients with Grade III hypertension died (Table 3).

Eighty-four (75%) hypertensive patients received antihypertensive treatment during hospitalization. Among them, 20 patients (17.8%) used angiotensin-converting enzyme inhibitors (ACEIs)/angiotensin receptor blockers (ARBs), and 64 (57.1%) received other antihypertensive drugs. The disease severity and clinical outcomes between the ACEI/ARB group and non-ACEI/ARB group did not present significant differences (Table 4).

Dynamic changes of levels during hospitalization

Since hypertensive patients presented higher levels of CRP, TnT, Creatinine, and ALT compared to normotensive patients, we further analyzed the dynamic change of these four laboratory markers during hospitalization among the surviving patients (Figure 1). As shown in Figure 1A, the TnT level in hypertensive patients increased significantly during the course of hospitalization compared to non-hypertensive patients (median [IQR], 0.011 [0.008-0.021] vs. 0.008 [0.005-0.014], p=0.0027 at hospitalization and 0.012 [0.008-0.165] vs. 0.006 [0.005-0.012], p=0.0077 at approaching discharge). And no such dynamic escalation of TnT levels was observed in non-hypertensive patients. Likewise, the creatinine level in hypertensive patients increased significantly during the course of hospitalization compared to non-hypertensive patients (median [IQR], 69.0 [59.5-85.5] vs. 63.0 [51.3-75.8], p=0.0227 at hospitalization and 70.0 [59.0-84.0] vs. 64.0 [51.0-75], p=0.0220) at approaching discharge (Figure 1B).

Both groups of patients exhibited high levels of CRP during the course of hospitalization. The CRP of non-hypertensive patients were controlled to normal range (median [IQR], 2.75[1.0-8.075]) with no significant differences comparing to the hypertensive group (median [IQR], 3.8[2.2-10.00]) at the time of approaching discharge (Figure 1C). Similarly, there were no significant differences in the ALT level between these two groups when approaching discharge (Figure 1D).

Hypertension increases the death rate of patients with COVID-19

The relationship between hypertension and death was one of the focuses in our study. We found that mortality rates in hypertensive groups were higher than in normotensive groups. Meanwhile, hypertension was associated with nearly 2.2 more chances of dying due to COVID-19 (OR: 2.093 [95%CI: 1.094-4.006], p=0.024) according to the Chi-square test.

We further conducted a survival curve analysis using the Kaplan-Meier method. Patients with hypertension and those without hypertension had different survival curves during the time from admission to follow-up (mean=31,664, SED=1,424; mean=34.79, SED=0.882; p=0.0155) as shown in Figure 2A. Considering the duration of the illness at the time of admission, we also found that the survival curve of patients with hypertension and those without hypertension had no significant differences during the time from symptom onset

Table 2 – Laboratory results among different groups

	Median (IQR)			
Characteristic	**Total (n=337)**	**Normotension (n=225)**	**Hypertension (n=112)**	**p-value[a]**
Blood cell count				
White blood cell count, ×10⁹/L (normal range 3.5-9.5)	4.81(3.81-6.57)	4.65(3.63-5.97)	5.61(4.08-7.82)	.0005
Neutrophil count, ×10⁹/L (normal range 1.6-6.3)	3.24(2.25-5.02)	2.96(2.13-4.25)	3.91(2.89-6.78)	<0.0001
Lymphocyte count, ×10⁹/L (normal range 1.1-3.2)	0.89(0.63-1.25)	0.97(0.66-1.33)	0.76(0.58-1.10)	0.0011
Monocyte count, ×10⁹/L (normal range 0.1-0.6)	0.37(0.26-0.50)	0.36(0.26-0.49)	0.41(0.26-0.54)	0.1051
Platelet count, ×10⁹/L (normal range 125-350)	181(132-232)	181.5(132.8-227.3)	180(130-238)	0.8235
Blood lipids and electrolytes				
Total cholesterol, mmol/L, (normal range 2.8-5.2)	3.53(3.01-4.17)	3.43(2.99-4.13)	3.70(3.06-4.17)	0.1034
Triglyceride, mmol/L, (normal range 0.56-1.7)	0.93(0.69-1.35)	0.88(0.64-1.31)	1.01(0.77-1.58)	0.0127
HDL, mmol/L, (normal range 0.9-2.1)	1.1(0.92-1.31)	1.11(0.93-1.31)	1.09(0.90-1.30)	0.6562
LDL, mmol/L, (normal range 1-3.35)	2.02(1.64-2.48)	1.92(1.63-2.44)	2.1(1.67-2.61)	0.0463
sdLDL, mmol/L, (normal range 95-538)	121(86-184)	115.0(81-174)	131(93-194)	0.0976
Serum				
Potassium, mmol/L (normal range 3.5-5.3)	3.71(3.38-4.07)	3.72(3.43-4.05)	3.71(3.29-4.17)	0.7970
Calcium, mmol/L (normal range 2.11-2.52)	2.16(2.07-2.26)	2.17(2.09-2.27)	2.14(2.05-2.24)	0.0612
Inflammatory biomarkers				
hsCRP, mg/L (normal range 0-3)	31.70(9.08-65.52)	27.2(6.6-61.3)	44.2(14.55-76.05)	.015
Procalcitonin, ng/mL (normal range 0-0.1)	0.065(0.04-0.14)	0.0525(0.04-0.12)	0.09 (0.05-0.21)	<0.0001
SAA, mg/L (normal range 0-10)	93.61(32.24-196.1)	104.7(27.57-223.3)	86.16(38.77-159.6)	.5855
Cardiac biomarkers				
TnT, ng/mL (normal range 0-0.014)	0.009(0.006-0.014)	0.008(0.005-0.013)	0.012(0.008-0.0215)	<0.0001
Creatine kinase-MB, ng/mL (normal range 0-6.22)	1.12(0.68-2.31)	1.00 (0.66-1.93)	1.53(0.93-3.05)	0.0005
Myoglobulin, ng/mL (normal range 7.4-105.7)	47.20(27.80-86.00)	40.9(25.90-67.45)	67.20(30.65-131.7)	0.0004
NT-proBNP, pg/mL (normal range 0-222)	198.4(55.38-488.7)	124.8(47.75-386.6)	243.8(107.1-809.3)	0.0021
Blood gas analysis				
PaO2, mm Hg (normal range 70-107)	85.0(62.3-118.0	93(74-121.5)	77(56.0-110.0)	0.0095
PaO2/FiO2, mm Hg	376.2(229.3-469.0)	390.5(274.5-504.8)	293.1(168.3-419.1)	0.0003
PaCO2, mm Hg (normal range 35-45)	38(33-44)	39(34-44)	36(32-44)	0.0829
PH (normal range 7.35-7.45)	7.42(7.40-7.46)	7.42(7.40-7.45)	7.43(7.40-7.46)	0.4852

Continuation				
BE, mmol/L, (normal range -3-3)	1.3(-0.7-3.0)	1.4(0-3.1)	0.6(-1.9-2.8)	0.0646
Liver and renal function				
Alanine Aminotransferase, IU/L (normal range 9-50)	25.0(16.0-38.0)	23(15.75-34)	27.0(16.0-47.0)	0.0252
Aspartate Aminotransferase, IU/L (normal range 15-40)	28.0(19.0-40.0)	26(18.0-37.0)	29(20.0-45.0)	0.0382
Total Protein, g/L (normal range 65-85)	63.7(60.2-67.3)	64.10(60.3-67.3)	63.5(59.5-67.2)	0.5332
Albumin, g/L (normal range 40-55)	36.5(33.0-39.3)	37.4(34.1-40.1)	33.7(31.3-38.0)	<0.0001
Globulin, g/L, (normal range 20-40)	27.0 (25.1-30.4)	26.5(24.5-29.0)	28.6(26.2-32.4)	<0.0001
Total bilirubin, μmol/L (normal range 2-23)	7.8(5.6-11.0)	7.2(5.3-9.8)	9.6(6.6-12.5)	0.0001
Direct bilirubin, μmol/L (normal range 0-8)	3.0(2.2-4.4)	2.9(2.1-4.0)	3.3(2.4-4.9)	0.0138
Creatinine, μmol/L (normal range 57-97)	64.0(53.0-75.0)	62(52.3-73.0)	68(54.5-85.8)	0.0144
Urea nitrogen, μmol/L (normal range 3.1-8)	4.24(3.36-5.80)	4.13(3.34-5.37)	4.88(3.51-6.26)	0.0113

IQR: interquartile range; HDL: high-density lipoprotein; LDL: low-density lipoprotein; sdLDL: small dense Low-Density Lipoprotein; hsCRP: high-sensitivity C-reactive protein; TnT: troponin T; NT-proBNP: N-terminal pro–brain natriuretic peptide. a: statistical difference (numerical variable) between normotension and hypertension groups were evaluated by the Mann-Whitney U test.

Table 3 – The association between hypertension grade and disease severity in COVID-19 patients with hypertension

		Hypertension grade			
	Total (n=112)	**I (n=73)**	**II (n=24)**	**III (n=15)**	**p-value**
Disease severity					0.0003[a]
Moderate	20(17.8)	12(16.4)	8(33.3)	0(0)	
Severe	69(61.6)	50(68.5)	13((54.2)	6(40)	
Critical	23(19.3)	11(15.1)	3(12.5)	9(60)	
Clinical outcomes					0.0006[b]
Discharge	92(82.1)	64(87.7)	21(87.5)	7(46.7)	
Death	20(17.9)	9(12.3)	3(12.5)	8(53.3)	

a: Kruskal-Wallis was used to analyze the relationship between disease severity and hypertension grades. b: R X C The Chi-square test was used to analyze the relationship between clinical outcomes and hypertension grades.

to follow-up (mean=51,984, SE=2,703; mean=55,625, SE=2,139; p>0.05, Figure 2B).

Discussion

The world is currently suffering from an emerging infectious disease – COVID-19, which had 30,949,804 confirmed cases and 959,116 deaths until 21 September, 2020.[17] Several studies demonstrated that hypertension has been the most common comorbidity in patients with COVID-19.[1,5] In this cohort study, we provided detailed clinical characteristics and risk factors associated with clinical outcomes in COVID-19 hypertensive or normotensive patients. The overall case fatality rate in mainland China was 5.5% (4,642 deaths out of 84,393 confirmed cases on May 3, 2020).[17] In our study, the prevalence of hypertension in COVID-19 patients was 33.2%, which is consistent with previous studies that reported the proportion of COVID-19 patients with hypertension ranging from 19.4 to 32.6%.[5,13,18] The in-hospital mortality in patients with hypertension is markedly higher than in normotensive patients (17.9% vs. 8.9%, p=0.0202), in line with previous findings.

As we know, the angiotensin converting enzyme-2 (ACE-2), as an enzyme of the renin-angiotensin system (RAS), is

Table 4 – The association between ACEI/ARB use and disease severity in COVID-19 patients with hypertension

		Antihypertensive treatment			
	Total (n=112)	ACEI/ARB treatment (n=20)	Other hypotensive drug (n=64)	No hypotensive treatment (n=28)	p-value
Disease severity					0.3487[a]
Moderate	20(17.8)	3(15)	11(17.2)	6(21.4)	
Severe	69(61.6)	13(65)	36(56.3)	20(71.4)	
Critical	23(19.3)	4(20)	17(26.6)	2(7.1)	
Clinical outcome					1.0000[a]
Discharge	92(82.1)	16(80)	49(76.6)	27(96.4)	
Death	20(17.9)	4(20)	15(23.4)	1(3.6)	

ACEIs: angiotensin-converting enzyme inhibitors; ARBs: angiotensin II receptor blockers. a: R X C Chi-square test was used to analyze the difference between groups.

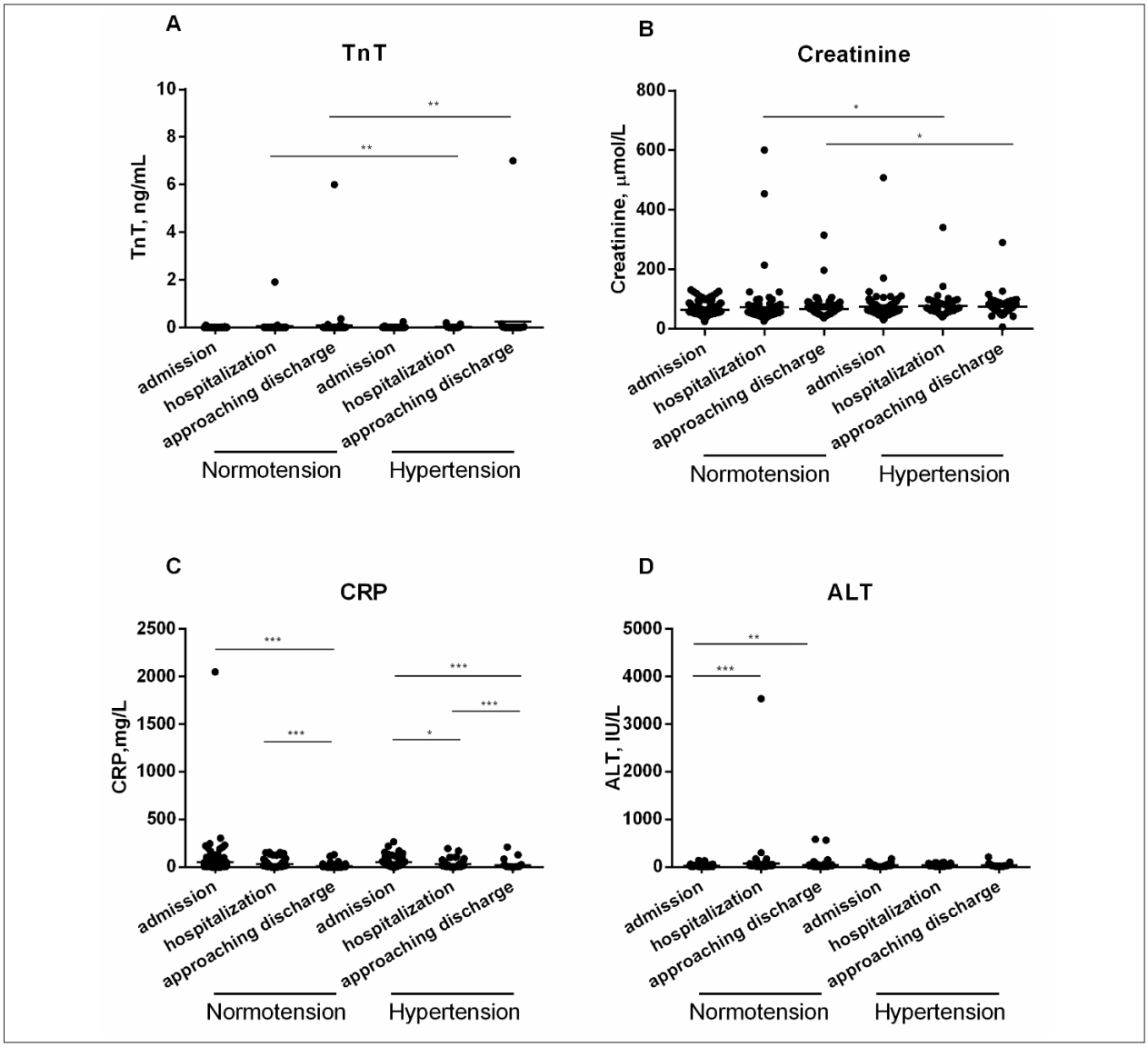

Figure 1 – *Dynamic change of TnT, Creatinine, CRP, and ALT during hospitalization. A.TnT; B. Creatinine; C.CRP; D.ALT. The data were expressed as the median and IQR. Mann-Whitney U test was used. (*p < 0.05, **p < 0.01, ***p < 0.001).*

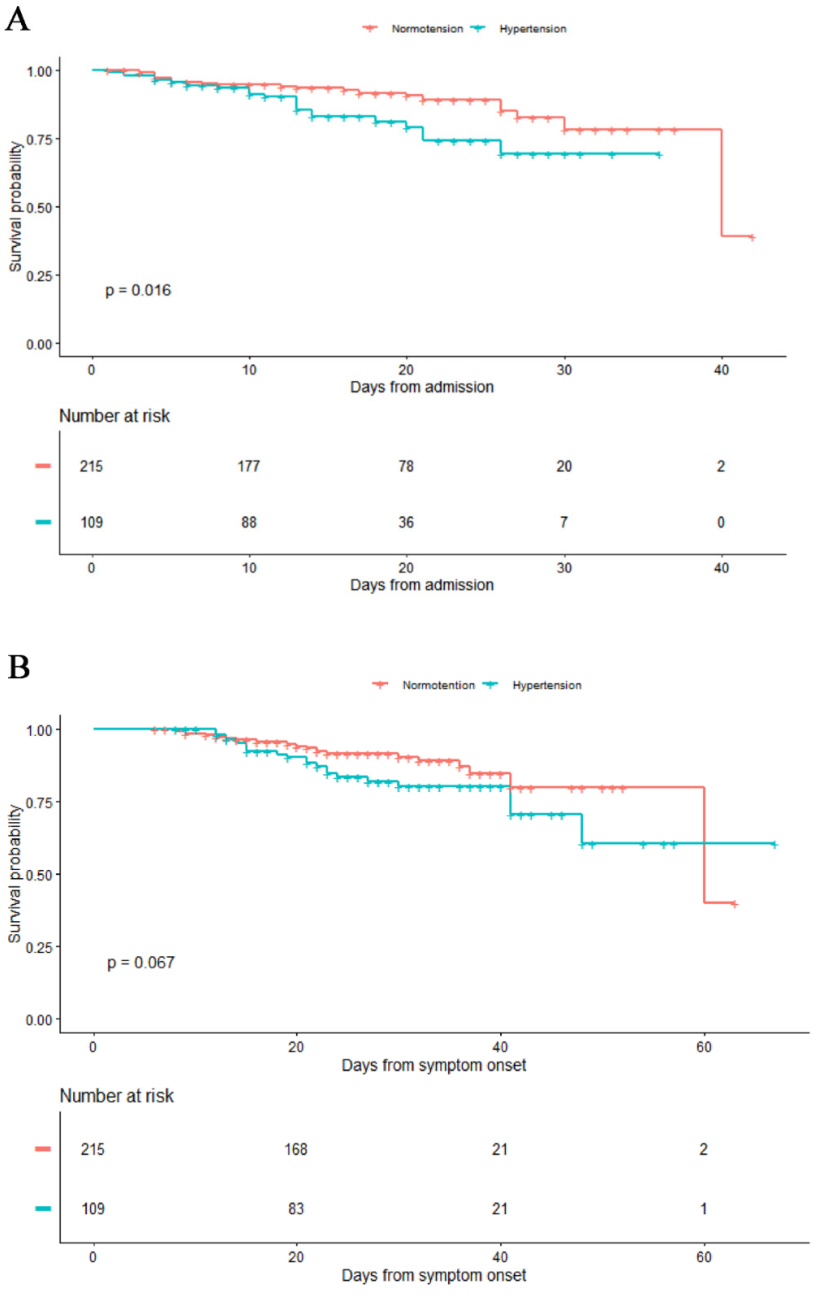

Figure 2 – *Kaplan–Meier plots of survival probability in hospitalized patients with COVID-19. A. Kaplan-Meier survival curves for mortality during the time from admission. B. Kaplan-Meier survival curves for mortality during the time from symptom onset.*

the receptor for SARS-CoV-2 and essential for viral entry.[19] ACE2 is not only expressed in type 2 alveolar epithelial cell in the lungs, but also in the renal tubules of the kidneys, cardiomyocytes in the heart, small intestinal epithelium in the gastrointestinal tract, bile duct epithelial cells and Leydig cells in the testis.[20] Therefore, COVID-19 patients presented multiple extrapulmonary manifestations and possible complications. In our patient cohort, COVID-19 patients with hypertension had more comorbidities, such as diabetes, cardiovascular disease, liver disease, kidney disease and cerebrovascular disease. In this sense, hypertensive patients with COVID-19 presented abnormal levels of multiple indicators concerning the heart, liver, kidney, and lung function at hospital admission. Besides, COVID-19 patients with hypertension displayed higher levels of triglyceride and direct bilirubin. We also summarized other laboratory parameters that may be associated with worse progression of COVID-19 patients with hypertension. It is worth noting that hypertensive patients presented with significantly higher white blood cell count, neutrophil count, and lower lymphocyte count, which indicates that the level of lymphopenia is higher in COVID-19 patients with hypertension. It has been reported that lymphopenia is a common feature in patients with severe COVID-19, who display lower lymphocyte count, higher leukocyte count and neutrophil-lymphocyte ratio (NLR),[21] with a dramatically reduced number of lymphocyte subsets and higher proinflammatory cytokine levels, including IL-2, IL-6, and IL-10.[22] It is curious to determine if COVID-19 patients with hypertension also presented with severe dysregulation of the immune response compared to normotensive patients, but the surveillance of lymphopenia may be helpful in the treatment of COVID-19 patients with hypertension.

We further analyzed the dynamic changes of four biomarker levels during hospitalization, and found that ALT (liver injury) and CRP (inflammatory biomarkers) did not significantly differ between the hypertensive and the normotensive groups. Although the hypertension group displayed a slightly higher ratio of bacterial infection without statistical significance, we found that bacterial infection caused higher chances of death (OR: 5,867, 95%CI: 2,537-13,568, $p<0.001$). Nevertheless, hypertension was still a risk factor independently related to mortality after adjusting the effect of bacterial infection (OR: 2,029, 95%CI: 1,035-3,976, $p<0.05$), and the clinician should pay more attention to the secondary bacterial infection in the group with arterial hypertension regarding the higher levels of CRP. However, the TnT and creatinine levels of the hypertensive group were remarkable higher than those in the normotensive group during hospitalization and at the time of approaching discharge, which implies that more aggressive clinical management regarding cardiac and renal injury may be required for COVID-19 patients with hypertension. It was observed that the components of renin-angiotensin systems may play a pathogenic role for COVID-19 since ACE2 acts directly in hypertension and in SARS-CoV-2 transmission.[4] The balance of the RAS pathway may determine the occurrence of tissue injury, especially in the heart and kidneys.[20] Our data underlined the influence of hypertension on the severity of COVID-19, especially cardiac and kidney injury.

It is not surprising that COVID-19 patients with hypertension are experiencing higher frequency, severe forms, and more complications of COVID-19. Our further analyses found that the hypertension grade was associated with disease severity and clinical outcome in COVID-19 patients with hypertension. However, the mechanisms underlying the relationship between hypertension and COVID-19 are not well understood. As ACE2 acts as the receptor for SARS-CoV-2 to enter host cells, there are emerging concerns regarding the clinical use of ACEIs/ARBs, about whether or not these drugs could increase the susceptibility of a SARS-CoV-2 infection.[23] Our data demonstrated that ACEIs/ARBs would not increase disease severity or the risk of death in COVID-19 patients with hypertension. Recently, a multi-center study including 1,128 COVID-19 patients with hypertension pointed out that the in-patient use of ACEI/ARB was associated with lower mortality in comparison with ACEI/ARB non-users.[14] Combined with our results, these findings suggested that the continuous use of ACEI/ARB during hospitalization should be maintained to control the blood pressure for the patients' benefit, since COVID-19 patients on ACEI/ARB were not at increased risk for adverse outcomes.

However, the present study has several limitations. Firstly, patients without major complications were assigned to the temporary treatment centers (mobile cabin hospitals) due to the limited medical resources, and all of the patients involved in this study had relatively severe cases of COVID-19. Secondly, the follow-up medical data were incomplete, as some critical cases were transferred to the ICU or the a superior hospital. These measures were conducted in accordance with national strategies for major epidemic prevention and control considering the emergency of the COVID-19 outbreak, which have great importance to mitigate the spread of the virus. Thirdly, only 20 patients received the ACEI/ARBs treatment, which may limit the determination of the potential use of ACEI/ARBs in COVID-19 treatment. Further clinical investigations are required.

Conclusion

The present study suggested that hypertension has a significant association with disease severity and fatal outcomes of COVID-19. COVID-19 patients with hypertension presented with severe multiple organ manifestations and complications, especially myocardial and kidney injury, which implies that aggressive treatments may be considered for hypertensive patients diagnosed with COVID-19. Long-term observation and prospective study design on the effectiveness of treatments specific for COVID-19 patients with hypertension are required.

Acknowledgments

We would like to thank all the clinical staff working in No.7 hospital and Zhongnan hospital of Wuhan University for their great effort in taking care of patients with COVID-19.

Author Contributions

Conception and design of the research and Critical revision of the manuscript for intellectual content: Hai-rong X, Xue-

dong F; Acquisition of data: You-ping D, Xie W, Liu T, Shou-yi W, Yu-xing Z, Xiao-bo M; Analysis and interpretation of the data: Xie W, Mei-rong W; Statistical analysis: Yu-qing D; Writing of the manuscript: You-ping D, Hai-rong X.

Potential Conflict of Interest

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

Sources of Funding

There were no external funding sources for this study.

Study Association

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

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The High Pressure of Fighting the COVID-19 Pandemic

Isabela Bispo Santos da Silva Costa[1,2] *and Hugo Bizetto Zampa*[3]

Instituto do Câncer do Estado de São Paulo,[1] *São Paulo, SP - Brazil*

Hospital Sírio Libanês,[2] *São Paulo, SP - Brazil*

Hospital Vila Nova Star - Rede D'Or,[3] *São Paulo, SP - Brazil*

Short Editorial related to the article: Association of Hypertension with Severity and Mortality in Hospitalized Patients with COVID-19 in Wuhan, China: a single-centered, retrospective study

Although we have been facing the challenges posed by the new coronavirus for almost two years, we still have a long way to go. The rapid and easy spread of the virus not only worries the population and scientific society as a whole but also exposes the fragility of the Brazilian public health system. The numbers speak for themselves - the exorbitant rates of infected people and, consequently, the number of deaths made us question the handling of this health crisis.

In this scenario, elderly individuals with comorbidities such as hypertension, diabetes, obesity and coronary artery disease were the ones who suffered most from COVID-19.[1] The virus in the body leads to extensive endothelial dysfunction,[2] mediated by inflammatory cytokines and thrombogenic factors, disseminated microvascular lesions and serious complications, such as pulmonary and systemic embolism, myocardial injury and renal dysfunction.[3] These manifestations proved to be potentially fatal, especially in the group listed here, mainly due to the concomitant presence of cardiovascular diseases (CVD).

Among CVDs, arterial hypertension (AH) stands out for its high prevalence; in Brazil and China, more than 20% of the total population is hypertensive, a figure that reaches 71.7% in individuals over 70 years of age.[4,5] Thus, AH appears as a severe public health problem, 14% of general admissions attributed to it, and it is responsible for the high and rising number of deaths. In 2015, in Brazil, 47.288 deaths from AH were recorded, increasing to 53.022 in 2019.[6]

Deng et al.,[5] in the publication of this issue of the Brazilian Archives of Cardiology, very objectively evaluated the association between AH and severity/mortality in hospitalized patients by COVID-19 in China. In a retrospective cohort of 337 patients, the clinical and laboratory characteristics of 112 hypertensive patients are listed compared to a group of normotensive patients. In the hypertensive group, it was observed that they were older, with more associated comorbidities (such as kidney disease and cerebrovascular disease) and developed more complications in the course of the infection, with a greater need for oxygen supplementation and progression to severe acute distress syndrome.[5]

Consistently, the data presented by these authors show that inflammatory tests such as C-reactive protein and procalcitonin are higher in these patients and higher serum levels of cardiac injury markers (T troponin, creatine kinase MB and NT-proBNP). The degree of arterial hypertension was also associated with greater severity of COVID-19 since 60% of patients with stage III hypertension with COVID-19 developed critical conditions of the disease.[5] The study also showed that AH was associated with almost 2.2 more chances of dying from COVID-19 (OR: 2.093 [CI95%: 1.094-4.006], p=0.024).[5]

Other researchers corroborate the findings presented by these authors and also suggest that AH is the most commonly associated comorbidity with increased mortality in patients with COVID-19.[7] What explains the associated severity between this binomial has not yet been fully elucidated. The hypothesis of a possible interface between the virus and AH with the renin-angiotensin-aldosterone system is suggested,[8] in addition to the endothelial dysfunction that is inherent to both. Cellular invasion by the virus would be facilitated by the angiotensin-2 converting enzyme (ACE-2), which is widely found in cardiac and lung cells. Thus, this passport would be the kick-off for the virus, later, to trigger an exuberant inflammatory cascade, explaining, in part, the severe cardiopulmonary impairment imposed by COVID-19.[9]

In fact, combating the COVID-19 pandemic indeed involves measures of social isolation and mass vaccination. However, actions that promote adequate health care to the population must be equally prioritized and maintained perennially in facing any adverse context, even more evident in this moment in which we live. Thus, providing opportunities for the correct treatment of such prevalent diseases, such as AH, can significantly contribute to the reduction of mortality in COVID-19.

Keywords

COVID-19; Betacoronavirus; Pandemics; Cardiovascular Diseases; Hypertension; Aged; Hospitalization; Comorbidities.

Mailing Address: Isabela Bispo Santos da Silva Costa •
Av. Dr. Arnaldo, 251, 2º andar. Postal Code 01246-000, São Paulo, SP - Brazil
E-mail: isabela.bispo@hc.fm.usp.br

DOI: https://doi.org/10.36660/abc.20210811

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Performance of the Electrocardiogram in the Diagnosis of Left Ventricular Hypertrophy in Older and Very Older Hypertensive Patients

Fernando Focaccia Povoa,[1] Braulio Luna Filho,[2] Henrique Tria Bianco,[1] Celso Amodeo,[2] Rui Povoa,[2] Maria Teresa Nogueira Bombig,[2] Roberto Dischinger Miranda,[1] Simone Matheus Fischer,[2] Maria Cristina Oliveira Izar,[2] Francisco A. H. Fonseca[1]

Universidade Federal de São Paulo - Escola Paulista de Medicina,[1] São Paulo, SP - Brazil

Universidade Federal de São Paulo,[2] São Paulo, SP - Brazil

Abstract

Background: **Left ventricular hypertrophy (LVH) is an important cardiovascular risk factor, regardless of arterial hypertension. Despite the evolution of imaging tests, the electrocardiogram (ECG) is still the most used in the initial evaluation, however, with low sensitivity.**

Objective: **To evaluate the performance of the main electrocardiographic criteria for LVH in elderly and very elderly hypertensive individuals.**

Methods: **In a cohort of hypertensive patients, ECGs and doppler echocardiographies (ECHO) were performed and separated into three age groups: <60 years, Group I; 60-79 years Group II; and ≥80 years, Group III. The most used electrocardiographic criteria were applied for the diagnosis of LVH: Perugia; Pegaro-Lo Presti; Gubner-Ungerleider; Narita; (Rm+Sm) x duration; Cornell voltage; Cornell voltage duration; Sokolow-Lyon voltage; R of aVL ≥11 mm; RaVL duration. In evaluating the performance of these criteria, in addition to sensitivity (Sen) and specificity (Esp), the "Diagnostic Odds Ratios" (DOR) were analyzed. We considered p-value <0.05 for the analyses, with two-tailed tests.**

Results: **In 2,458 patients, LVH was present by ECHO in 781 (31.7%). In Groups I and II, the best performances were for the criteria of Narita, Perugia, (Rm+Sm) x duration, with no statistical differences between them. In Group III (very elderly) the Perugia criteria and (Rm+Sm) x duration had the best performances: Perugia [44,7/89.3; (Sen/Esp)] and (Rm+Sm) duration [39.4%/91.3%; (Sen/Esp), p<0.05)], with the best PAIN results:6.8. This suggests that in this very elderly population, these criteria have greater discriminatory power to separate patients with LVH.**

Conclusion: **In very elderly hypertensive patients, the Perugia electrocardiographic criteria and (Rm+Sm) x duration showed the best diagnostic performance for LVH.**

Keywords: **Electrocardiography/methods; Aged; Hypertrophy, Left Ventricular; Hypertension; Heart Failure; Stroke; Myocardial Infarction.**

Introduction

Left ventricular hypertrophy (LVH) is an important predictor of cardiovascular events. When diagnosed by electrocardiogram (ECG), it is associated with increased risk of events such as stroke, myocardial infarction, heart failure, sudden death, and peripheral vascular disease. Indeed, these outcomes are independent of the presence or absence of systemic arterial hypertension (SAH).[1-3] In this scenario, ECG is a widely used low-cost tool, despite its low diagnostic sensitivity (Se) for LVH.[4] Several ECG criteria for LVH have already been published, with different Ses and specificities (Sps). However, few are used in the clinical practice. This usually results from the low diagnostic accuracy of these criteria when applied in a population with different cardiovascular manifestations and with specific epidemiological characteristics, such as age, race, clinical history, etc.[5] These criteria have good Sp, but low Se. Furthermore, Se varies greatly, depending on the population and on the diseases that led to ventricular hypertrophy.[6]

With population aging, it has become increasingly important to improve understanding on cardiovascular diseases, and SAH stands out with the highest prevalence. In this sense, ECG has an essential role not only on the diagnosis but also on the risk stratification of older individuals, enabling to identify situations that had no clinical expression yet.[7] Few studies in older (≥ 60 and < 80 years) and very older (≥ 80 years) patients with hypertension investigated the diagnostic accuracy of ECG for LVH.[8]

Mailing Address: Henrique Tria Bianco •
Universidade Federal de São Paulo - Escola Paulista de Medicina - Rua Loefgren, 1350. Postal Code 04040-001, São Paulo, SP – Brazil
E-mail: henriquetria@uol.com.br
Manuscript received June 03, 2020, revised manuscript October 08, 2020, accepted November 25, 2020

DOI: https://doi.org/10.36660/abc.20200600

Therefore, the aim of this study is to assess the performance of the main ECG criteria in the diagnosis of LVH in an outpatient sample of older and very older hypertensive patients.

Methods

The present study assessed 2458 ECGs and echocardiographies (ECHOs) of hypertensive patients under treatment and follow-up at the Department of Hypertensive Heart Disease of Universidade Federal de São Paulo from 2006 to 2019. All patients made regular use of antihypertensive drugs. Individuals with the following conditions were excluded: orovalvar disease, acute or chronic coronary artery disease, cardiac rhythm disorders, His bundle branch blocks, pre-excitation syndrome, electrolytic disorders, or ECG changes that could interfere with the analysis, as shown in the flowchart (Fig.1). Patients were classified into three age groups: Group I, age < 60 years; Group II, older adults (60-79 years); and Group III, very older adults (≥ 80 years).[9]

The study protocol was approved by the Research Ethics Committee of Universidade Federal de São Paulo- Escola Paulista de Medicina (CAAE: 29732020.6.0000.5505).

ECG

The 12-lead resting ECG was performed with the patient in the supine position, at a standard velocity of 25 mm/s, and in equipment calibrated for 1.0 mv/cm (Dixtal EP3® and Cardiocare 2000 Bionet®). ECG tracings were analyzed using a duly calibrated caliper and a high-precision magnifying glass, allowing for a nearly five-fold magnification in order to achieve a more accurate analysis. These analyses were conducted by an experienced cardiologist who had no knowledge of patients' clinical and epidemiological characteristics. The following variables were measured: axis, QRS duration, the distance between R waves (R-R interval), QT interval, the amplitude of R waves in leads D_1, aVL, V_5 and V_6, the amplitudes of the S wave in V_1, V_2, V_3 and V_4, and the strain pattern in V_5 and V_6, as well as the largest amplitude of R and S waves in the horizontal plane leads. These data were entered into an Excel® spreadsheet specifically designed for the analysis.

The analysis of reproducibility of measures and application of ECG criteria was conducted by two cardiologists working at the Department of Hypertensive Heart Disease, who independently interpreted 100 ECG tracings randomly selected from the sample. These tracings were selected from a list generated by a dedicated software, in which the first four numbers were associated with patients' records on the database.

LVH descriptors assessed:

1. (Rmax + Smax) x QRS duration: sum of the greatest amplitude of S wave and the greatest amplitude of R wave in the horizontal plane (em mm), multiplied by QRS duration (in seconds). The diagnosis of LVH is established if the result is ≥ 2.8 mm.s.[10]

2. Sokolow-Lyon voltage criteria: $SV_1 + RV_5$ or $V_6 \geq 30$ mm and ≥ 35 mm.[11]

3. Cornell's voltage criteria: $RaVL + SV_3 \geq 20$ mm for women and ≥ 28 mm for men.[12]

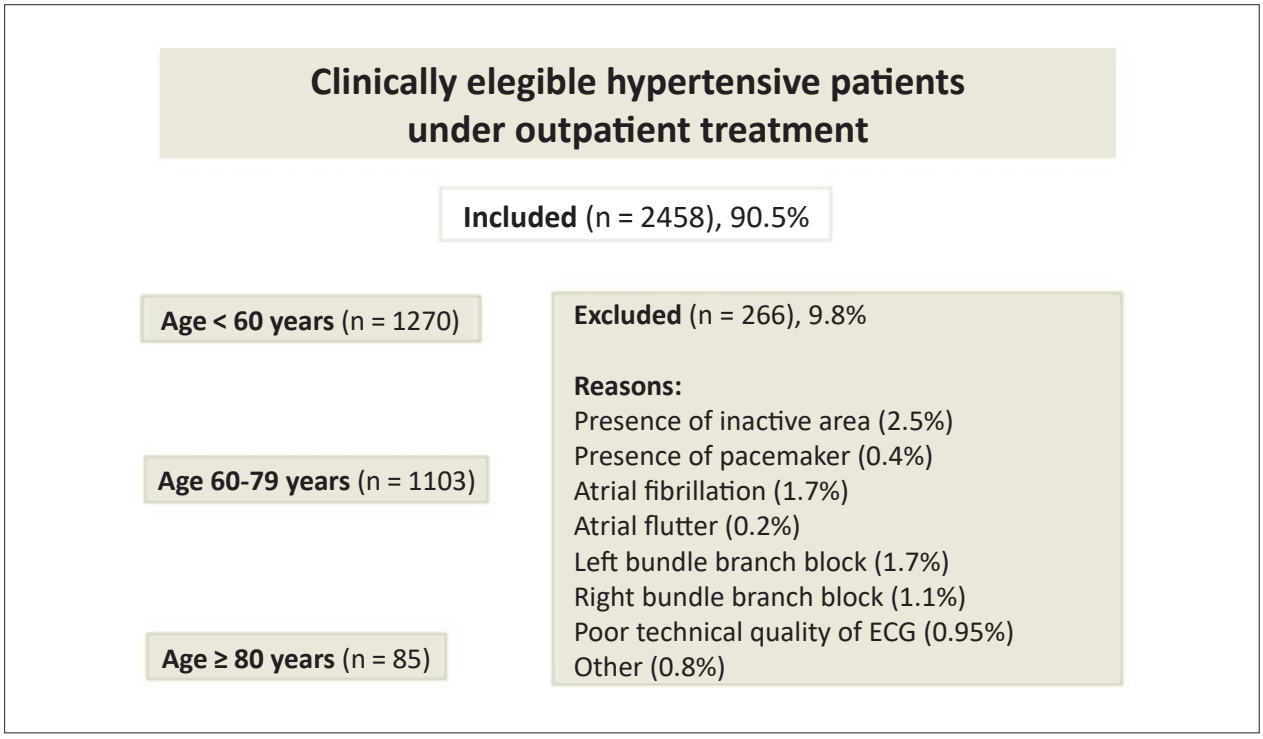

Figure 1 – *Flowchart of the study cohort. ECG: electrocardiogram.*

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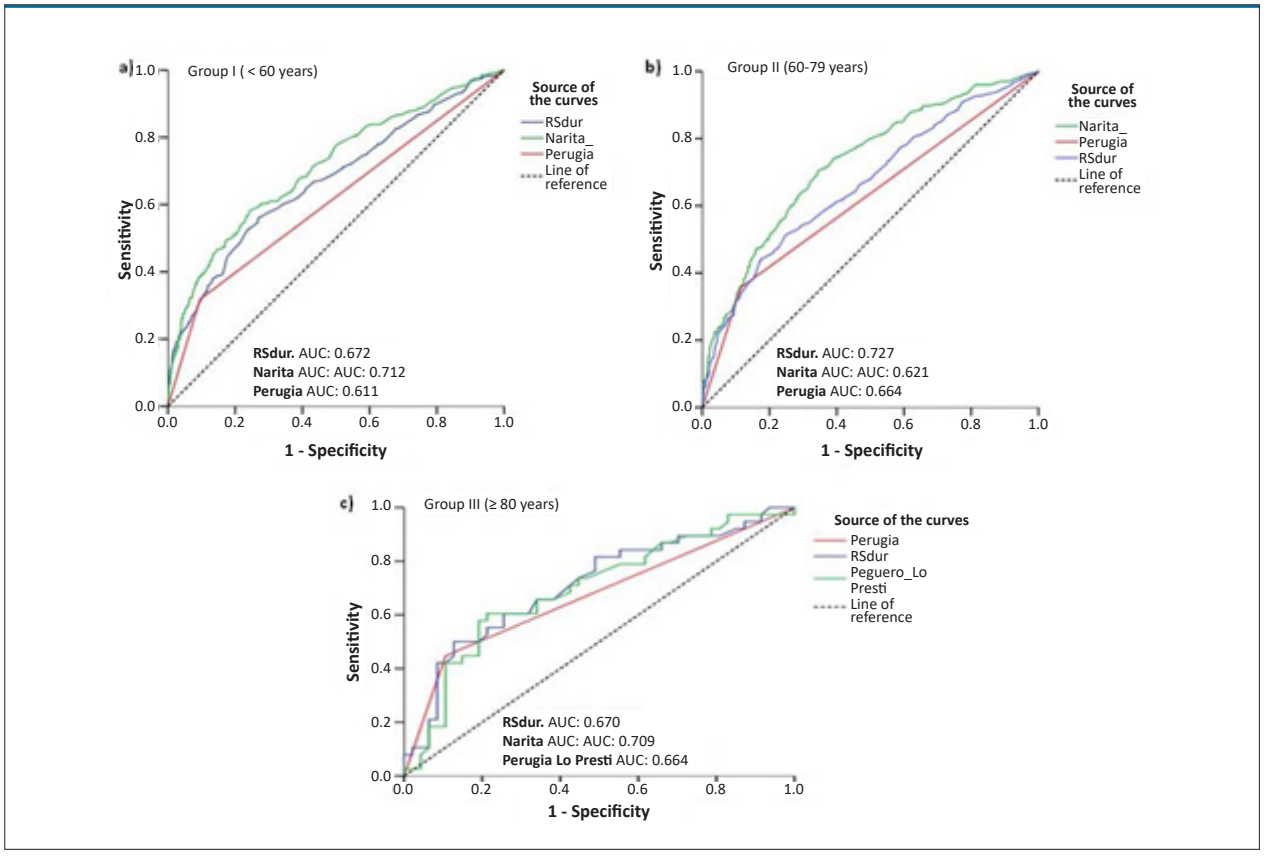

Figure 2 – *ROC curve and area under the curve of the three studied grups.Group I (age <60 years); b) Group II (age 60-79 years); c) (age ≥80 years). OC: Receiver Operating Characteristic Curves, AUC: area under the curve.*

4. Cornell's duration criteria: (RaVL + SV_3) x QRS duration. For women add 8 mm, ≥ 2440 mm.ms.[13]

5. Romhilt-Estes point score system: amplitude of R or S ≥ 30 mm on the horizontal plane or ≥ 20 mm on the frontal plane, strain pattern in V_5 or V_6 (when using digital, the score is only one point) and left atrial growth by the Morris index – these data individually add three points; electrical axis (ÂQRS) above less than 30 degrees adds two points; QRS duration ≥ 90 ms in V_5 or V_6 or ventricular activation time ≥ 50 ms in V_5 or V_6 add one point. Using this score, LVH is diagnosed when the sum of the points is ≥ 5.[14]

6. R wave in aVL ≥ 11 mm.[15]

7. Perugia score: HVE is diagnosed by the presence of one or more of the following findings: Cornell's criteria, considering the values ≥ 20 mm and ≥ 24 mm as limits for women and men, respectively; Romhilt-Estes score; presence of strain pattern.[16]

8. Peguero-Lo Presti criterion: deepest S wave in any lead + SV_4. The diagnosis of LVH is established if the result is ≥ 2.8 mV for men and ≥ 2.3 mV for women.[17]

9. Narita criterion: R wave in limb lead 1 D_1 + S wave in V_4, if ≥ 1.6 mV in men and ≥ 1.4 mV in women.[18]

10. Gubner-Ungerleider score: RD_1 + SV_3 > 25 mm.[19]

11. RaVL product: RaVL x QRS duration ≥ 1030 mm.ms.[20]

12. V_6/V_5 ratio > 1.[21]

Transthoracic Doppler ECHO

The tests were performed in the Service of Doppler Echocardiography of Hospital São Paulo/Unifesp with the device ATL® 1500, USA, according to specialized protocols and guidelines, by skilled professionals with more than 15 years of experience. The patient was placed on the left lateral decubitus position and the images were obtained from the assessed views (paraesternal long axis, paraesternal short axis, four-chamber, two-chamber, and M-mode views) simultaneously with the recording of the ECG. According to the recommendations of the Penn Convention, the following measurements were obtained: left ventricle (LV) size in systole and diastole; interventricular septum in diastole; end diastolic left ventricular posterior wall thickness; end systolic and diastolic volumes.[22] LV mass was indexed for body surface area to adjust differences in heart size, depending on each patient.

LV mass for the diagnosis of HVE was calculated by Doppler ECHO, according to 2015 recommendations of the American Society of Echocardiography/European Association of Echocardiograph, considering LVH when the left ventricular mass index (LVMI) is ≥ 96 g/m² for women and ≥ 116 g/m² for men.[23]

Statistical analysis

Continuous variables were expressed in mean (SD). Categorical variables were presented in percentages. For

the analysis of the performance of the ECG criteria in LVH, measures of Se and Sp with their respective 95% confidence intervals (95%CIs), in addition to diagnostic odds ratio (DOR), which expresses the overall efficacy of a measure without the influence of prevalence, as it occurs with positive and negative predictive value. We also built receiver operating characteristic (ROC) curves for the three groups (GI, GII, GIII), considering the ECG criteria that had the best performances. DOR was also a measure of accuracy, used to estimate the discriminative power and to compare the accuracy between the tests.[24]

Interobserver reproducibility was assessed by the kappa method.[25] In this test, values above 0.75 are defined as excellent agreement; from 0.40 to 0.75, as good agreement; and bellow 0.40, as poor agreement. Statistical significance was investigated using the McNemar's test.[26] This test was applied to assess the statistical differences between the results for ECG criteria for LVH with regard to Se and Sp. The level of significance was set at $p < 0.05$. All analyses were executed with the software SPSS® (version 17.0, SPSS Inc., Chicago, IL, USA).

Results

Of the 2458 participants, 753 were men (30.6%) and 1705 were women (69.4%). Of this total, 1270 (51.6%) were included in Group I (<60 years); 1103 (44.8%) in Group II (from 60 to 79 years); and 85 (3.5%) in Group III (age 80 years or older). The presence of LVH in ECHO occurred in 345 (27.1%) in Group I; 398 (36.0%) in Group II (older adults), and in 38 (44.7%) in Group III (very older adults), as shown in Table 1.

Table 2 describes Se and Sp for the ECG criteria for LVH and their respective 95%CIs. DOR for the assessed criteria are described in Table 3. Patients in Group I and II were found to have similar performances for the Narita, Perugia and (Rmax + Smax) x duration criteria, which showed the best results. Conversely, Group III, with very older patients, had a better performance only in the Perugia (Se 44.7% and Sp 89.3%) and (Rmax + Smax) x duration (Se 39.4% and Sp 91.3%) criteria. The DOR of these ECG criteria also showed better results (DOR = 6.8), showing better efficacy to detect or rule out LVH (Table 3).

In the assessment of reproducibility of ECG analysis, the level of interobserver agreement was 0.82 and 0.94 (kappa index), which are considered excellent numbers. The first figure corresponded to QRS duration, and the latter to the agreement of ECG criteria. ROC curves were constructed for the three groups studied with their respective areas under the curve (AUC) (Figure 2).

Discussion

LVH is an important cardiovascular risk factor, regardless of other manifestations or comorbidities.[25] Therefore, its detection by low-cost, easily available diagnostic methods is extremely relevant. In hypertensive patients, LVH is one of the most frequent pre-clinical manifestations of lesion of target-organ whose identification leads to changes in risk stratification and a more aggressive treatment.[27] Conversely, ECG is a low-cost test that has low Se but high Sp and reproducibility, which explains its wide use. However, this test may be influenced by several factors, such as obesity, smoking, gender and especially age.[28]

Table 1 – Characteristics of the sample according to age group, gender, age, and presence or absence of LVH on echocardiography

Age group	<60 years	60-79 years	≥80 years
N total: (2458)	1270	1103	85
Sex, n (%)			
Male	362 (28.5%)	365 (33.1%)	26 (30.5%)
Female	908 (71.5%)	738 (66.9%)	59 (69.4%)
Age (years), mean (SD)	50.1 (7.4)	67 (5.2)	84 (3.9)
Weight (kg), mean (SD)	74.4 (16.1)	70.5 (12.9)	64.8 (12.8)
Height (m), mean (SD)	1.61 (0.09)	1.60 (0.07)	1.59 (0.09)
BMI, mean (SD)	28.58 (5.61)	27.53 (4.63)	25.65 (4.51)
BS (m^2), mean (SD)	1.75 (0.21)	1.70 (0.18)	1.63 (0.18)
LF cavities (cm), mean (SD)			
IV septum	0.98 (0.17)	1.00 (0.17)	1.02 (0.15)
Posterior wall	0.95 (0.16)	0.96 (0.15)	0.96 (0.13)
Diastolic diameter	4.78 (0.52)	4.79 (0.57)	4.80 (0.65)
No LVH on ECO	924	705	47
LVH on ECHO, n (%)	345 (27.1%)	398 (36.0%)	38 (44.7%)
LVMI (g/m^2), mean (SD)	93.03 (28.79)	98.33 (27.65)	102.70 (32.74)

BMI: body mass Index; BS: body surface; LV: left ventricle; IV Septum: interventricular septum; LVH: left ventricular hypertrophy; ECHO: echocardiography; LVMI: left ventricle mass index. Note: data are expressed as mean (SD).

Table 2 – Characteristics of the study population according to age group, gender, age, and presence or absence of LVH on echocardiography

Criteria for LVH	GI (<60 years)		GII (60-79 years)		GIII (≥80 years)	
	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity
	(95%CI)	(95%CI)	(95%CI)	(95%CI)	(95%CI)	(95%CI)
Perugia	32.2	91.7	35.6	88.5	44.7	89.3
	(27.3-37.1)	(89.8-93.3)	(31.1-40.5)	(85.9-90.6)	(30.1-60.2)	(77.4-95.3)
(Rmax + Smax) x duration	33.8	88.9	32.4	88.9	39.4	91.3
	(29.0-38.9)	(86.7-90.8)	(28.0-37.1)	(86.4-91.0)	(25.6-55.2)	(79.6-96.5)
Peguero-Lo Presti	20.2	96.6	17.8	96.7	34.2	89.3
	(16.3-24.7)	(95.2-97.6)	(14.3-21.9)	(95.1-97.8)	(21.2-50.1)	(77.4-95.3)
Narita	39.6	89.3	38.1	87.5	26.3	91.4
	(34.5-44.8)	(87.2-91.2)	(33.5-43.0)	(84.8-89.7)	(14.9-42.0)	(80.0-96.6)
Romhilt-Estes	16.1	96.4	14.5	95	21	93.6
	(12.6-20.4)	(95.0-97.4)	(11.4-18.3)	(93.1-96.4)	(11.0-36.3)	(82.8-97.8)
Cornell's voltage [≥28 mm (m); ≥20mm (f)]	18.2	97.1	17.3	90.6	21	91.4
	(14.5-22.6)	(95.9-98.0)	(13.9-21.3)	(88.3-92.5)	(11.0-36.3)	(80.0-96.6)
Sokolow-Lyon voltage (≥30 mm)	23.7	92.1	20.8	92.6	21	93.6
	(19.5-28.4)	(90.1-93.6)	(17.1-25.1)	(90.4-94.3)	(11.0-36.3)	(82.8-97.8)
Sokolow-Lyon voltage (≥35 mm)	14.7	97.1	12	97.1	15.7	97.8
	(11.3-18.8)	(95.9-98.0)	(9.2-15.6)	(95.6-98.1)	(7.4-30.4)	(88.8-99.6)
Cornell's voltage duration (≥2440 mm.ms)	20.5	96.1	20.1	95.3	21	91.4
	(16.6-25.0)	(94.6-97.1)	(16.4-24.3)	(93.5-96.6)	(11.0-36.3)	(80.0-96.6)
Gubner-Ungerleider (≥25 mV)	18.5	97.2	16	97	15.7	93.6
	(14.7-22.9)	(96.0-98.1)	(12.8-20.0)	(95.4-98.0)	(7.4-30.4)	(82.8-97.8)
RaVL (≥11 mm)	11.8	96.6	12.3	95.8	15.7	93.6
	(8.8-15.6)	(95.2-97.6)	(9.4-15.9)	(94.1-97.1)	(7.4-30.4)	(82.8-97.8)
V_6/V_5 (>1)	15.3	88.1	14	90	13.1	87.2
	(11.9-19.4)	(86.9-90.1)	(11.0-17.8)	(87.6-92.0)	(5.7-27.3)	(74.8-94.0)
RaVL x duration	8.9	98.2	11.8	97.5	7.8	97.8
	(6.3-12.4)	(97.2-98.9)	(9.0-15.3)	(96.1-98.4)	(2.7-20.8)	(88.8-99.6)

LVH: left ventricular hypertrophy. Note: Values of sensitivity and specificity are expressed with their respective 95% confidence intervals (95%CIs), using the McNemar's statistical test.

The best assessment of ventricular mass is achieved by nuclear magnetic resonance imaging (NMRI); nevertheless, economic reasons make its routine use unfeasible in the evaluation of hypertensive patients.[29] In this sense, ECHO is used as a gold standard for the assessment of left ventricular mass with a high level of correlation and excellent intra- and interobserver reproducibility. In the present study, the reference test for the diagnosis of LVH was transthoracic ECHO. The modified Devereux formula was applied to calculate LV mass, which has a good correlation with the actual heart mass ($r = 0.90$; $p < 0.001$).[30]

The older and very older population has been increasingly growing worldwide. It has already been acknowledged that the control of risk factors, which are highly prevalent in this population, increases their life expectancy.[31] Conversely, age is known to interfere with ECG Se in the detection of LVH.[32] With the purpose of identifying the best ECG criteria to diagnose the presence of LVH in older adults, an increasingly more frequent situation in doctor's offices and outpatient clinics, we assessed the main ECG indices described in the literature and used in epidemiological studies.

Table 3 – DOR for ECG criteria for LVH according to age group

Criteria for LVH	GI (<60 years)	GII (60-79 years)	GIII (≥80 years)
Perugia	5.2 (3.8-7.2)	4.2 (3.1-5.8)	6.8 (2.2-20.9)
(Rmax + Smax) product ≥ 2.8 mm.s	4.1 (3.0-5.5)	3.8 (2.8-5.2)	6.8 (2.0-23.0)
Peguero-Lo Presti	7.3 (4.6-11.3)	6.4 (3.9-10.4)	4.3 (1.3-13.7)
Narita	5.5 (4.0-7.4)	4.3 (3.2-5.8)	3.8 (1.09-13.4)
Romhilt-Estes	5.2 (3.3-8.1)	3.2 (2.1-5.0)	3.9 (0.9-15.9)
Cornell's voltage: ≥ 28 mm (h); ≥ 20 mm (m)	7.6 (4.7-12.3)	2.0 (1.4-2.8)	2.8 (0.7-10.3)
Sokolow-Lyon voltage ≥ 30 mm	3.6 (2.5-5.1)	3.3 (2.2-4.7)	3.9 (0.95-15.9)
Sokolow-Lyon voltage ≥ 35 mm	5.9 (3.6-9.7)	4.6 (2.7-8.0)	8.6 (0.99-75.12)
Cornell's voltage duration ≥ 2440 mm.ms	6.3 (4.1-9.7)	5.1 (3.3-7.8)	2.8 (0.7-10.3)
Gubner-Ungerleider ≥ 25 mV	8.1 (5.0-13.2)	6.2 (3.7-10.3)	2.7 (0.6-11.8)
RaVL ≥ 11 mm	3.8 (2.3-6.2)	3.2 (2.0-5.2)	1.9 (0.3-12.1)
V_6/V_5 ratio > 1	1.3 (0.9-1.9)	1.4 (1.0-2.1)	1.03 (0.29-3.6)
RaVL.dur QRS > 103 mm.ms	5.5 (3.0-10.3)	5.4 (3.0-9.5)	3.9 (0.39-39.5)

Note: Data expressed as DOR and its respective 95% confidence interval (95%CI). HVE: left ventricular hypertrophy; DOR: diagnostic odds ratio.

In our cohort, Perugia score was the criterion with the highest Se (44.7 %) in older and very older patients (35.6%) without leading to a significant loss in Sp. This criterion was described by Schillaci et al.[16] in 1994 and diagnoses LVH in hypertensive patients whose ECG findings show at least one of the three following parameters (strain pattern; modified Cornell's voltage criteria: SV_3 + RaVL > 2.4mV in men and 2.0 mV in women; or Romhilt-Estes score ≥ 5). The authors reported Se of 34% and Sp of 93%, with a fair improvement in individual Se for the three criteria with no decrease in Sp. Although these authors investigate the performance of the proposed criteria with regard to gender and degree of LV mass, they did not mention the influence of age. In our study, patients younger than 60 years of age (Group I) had Se of 32.2% and Sp of 91.7%, percentages similar to those reported by Schillaci et al.,[16] and there was a progressive increase in Se among older (Group II) and very older adults (Group III).[16]

The criterion that considered the sum of the highest amplitude of the R wave and the highest S wave multiplied by QRS duration [(Rmax + Smax) x duration] also showed good Se in the very old population (39.4%), with Sp of 91.3%. In the original publication, there was no distinction between age groups, and Se and Sp were 35.2% and 88.7%, respectively.[10] Although being simple, this criterion had a result equivalent to that of Perugia score, because there was no statistically significant difference between the two criteria.

Recently, a new ECG criterion was proposed. The so-called Peguero-Lo Presti criterion had Se of 62% and Sp of 90%.[17] In our study, Se 34.2% and Sp of 89.3% in very older patients (Group III), and of 17.8% and 96.7% in older patients (Group II), respectively. Finally, 1270 patients younger than 60 years of age (Group I) showed Se 20.2% and Sp of 96.6%, results different from those reported here. We considered that the two samples were different; the sample assessed by Peguero- Lo Presti consisted of more severe patients with a high prevalence of LVH (60%). Obviously, diagnostic tests tend to have greater Se in a population of individuals with more severe disease.

In our sample, the percentage of LVH in the group of young, older, and very older adults were 44.7%, 36.0%, and 27.1%, respectively. The Narita criterion, which considers the sum of R wave in D_1 and the amplitude of S wave in V_4, showed good Se in young and older adults (39.6% and 38.1%), respectively, but it reached only 26.3% in very older adults. Romhilt-Estes score, Cornell's voltage and duration, and Sokolow-Lyon ≥ 35 mm had very similar Se in the three age groups studied, with relatively low values ranging from 16.1 to 21%. Although recommended by several guidelines on arterial hypertension, these criteria had a lower performance.[26,33] The remaining assessed criteria in our cohort did not show satisfactory results with regard to Se, ranging from 8.9 to 18.5%.

The ECG indices that had the best performance took into account the amplitude of the S wave in V_3 or V_4 or the greatest S wave. This may be due to the fact that LVH generates higher vector projection of the QRS complex to the posterior horizontal plane. In LVH, the cavity grows posteriorly and to the left, changing the direction and the magnitude of the main depolarization vector. Hence, there will be an increase in the amplitude of the S wave in precordial V_3 and V_4.

We found that most ECG criteria used in the diagnosis of LVH lose Se as sample age increases. However, this did not occur with regard to Perugia score and (Rmax + Smax) x duration criterion, especially in Group III. When we assessed the DOR, which evaluates the efficacy of a measure independently from prevalence and allows to estimate the overall efficacy of the parameter, we observed that the Perugia score and the (Rmax + Smax) x duration criterion yielded the highest values: DOR = 6.8. Thus, in Groups I and II, the greatest Se (39.6 and 38.1%) was observed for the Narita criterion, which also demonstrated high Sp (89.3% and 87.5%). However, for very old patients (Group III), the best performances for the diagnosis of LVH were found for Perugia score and the (Rmax + Smax) x duration, with Se of 44.7% and 39.4%; and Sp of 89.3% and 91.3%, respectively. The

Sokolow-Lyon criteria, which have been widely used in several studies and may be the most well-known to physicians, due to the simplicity of its analysis, exhibited low Se in all age groups.

Our study showed that advanced age leads to loss of performance for several diagnostic criteria for LVH, exactly for a population at high cardiovascular risk. Therefore, the main contribution of our observations was detecting two ECG criteria that revealed to be superior in the detection of LVH among very older hypertensive patients. Furthermore, diagnostic imaging methods such as ECHO are not promptly available in many regions and health care facilities. Hence, ECG may be a useful, easily accessible and low-cost tool of practical interpretation and applicable to the diagnosis of LVH, using the criteria with better performance, especially in the very older population.

Study limitations

In this study, coronary artery disease was ruled out by clinical history, specific imaging tests, or by the presence of pathological q waves on ECG. There was a lower number of patients in the group of very older adults compared to younger patients.

Conclusions

The results obtained in this study suggest that, in very old adults with hypertension, the ECG criteria of Perugia and [(Rmax + Smax) x duration] showed the best diagnostic performance for the presence of LVH.

Author Contributions

Conception and design of the research: Povoa FF, Povoa R, Miranda RD, Fonseca FAH; Acquisition of data: Povoa FF, Povoa R, Fonseca FAH; Analysis and interpretation of the data: Povoa FF, Bianco HT, Amodeo C, Povoa R, Bombig MTN, Fonseca FAH; Statistical analysis: Luna Filho B, Bianco HT; Writing of the manuscript: Povoa FF, Bianco HT, Povoa R, Fischer SM, Izar MCO, Fonseca FAH; Critical revision of the manuscript for intellectual content: Povoa FF, Luna Filho B, Bianco HT, Amodeo C, Povoa R, Bombig MTN, Izar MCO, Fonseca FAH.

Potential Conflict of Interest

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

Sources of Funding

There were no external funding sources for this study.

Study Association

This article is part of the thesis of doctoral submitted by Fernando Focaccia Povoa, from Universidade Federal de São Paulo.

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Electrocardiographic Diagnosis of Left Ventricular Hypertrophy

Claudio Leinig Pereira da Cunha[1]

Universidade Federal do Paraná - Cardiologia,[1] *Curitiba, PR – Brazil*

Short Editorial related to the article: Performance of the Electrocardiogram in the Diagnosis of Left Ventricular Hypertrophy in Older and Very Older Hypertensive Patients

Left Ventricular Hypertrophy (LVH) is defined as an increase in left ventricular (LV) mass, which may be secondary to an increase in wall thickness (concentric LVH), increased cavity size (eccentric LVH), or both. The presentation of hypertrophied LV depends mainly on the underlying disease, with concentric LVH resulting in most cases from LV pressure overload (hypertension or aortic stenosis), while eccentric LVH mainly depends on LV volume overloads (mitral and aortic insufficiency) and dilated cardiomyopathies. Other causes of LVH include ventricular septal defects, hypertrophic cardiomyopathy, and physiological changes associated with athletic training.[1]

The presence of LVH is clinically meaningful because it is associated with an increased incidence of heart failure, ventricular arrhythmias, peripheral vascular insufficiency, aortic dilatation, cerebrovascular events and sudden death or after myocardial infarction.[2]

LVH can be diagnosed by electrocardiogram (ECG) or echocardiogram, which is the procedure of choice because it has a much greater sensitivity than the ECG.[3] The ECG is a useful but imperfect tool in detecting LVH; its usefulness is mainly due to its low cost and universal availability, routinely performed in cardiac evaluations. Echocardiography is more expensive but not unreasonable and has also been widely available. Yet, to assess the ventricular mass, the most accessible techniques of the method are used. In few situations, cardiac magnetic resonance imaging may be necessary, only when technical conditions make echocardiographic assessment unfeasible.[4]

The calculation of left ventricular mass by echocardiography can be performed using different techniques – one-dimensional, two-dimensional or three-dimensional, but always to quantify the myocardium in that chamber, based on common fundamentals and, therefore, with similar results. Standards of normality are recommended by the international associations of echocardiography (ASE, EACI)[5] and endorsed by most authors.[6] Thus, echocardiography shows uniformity of LVH results based on few studied parameters.[5,6]

In electrocardiography, the situation is the opposite. As early as 1969, Romhilt et al.[7] described 33 electrocardiographic criteria for diagnosing LVH, and all showed low sensitivity.[7] Over the years, some criteria have solidified as the most used in clinical practice for diagnosing LVH on the ECG, but there is still no consensus in this selection. In a recent article, Wang et al.[8] studied the performance of seven ECG criteria in Chinese patients with LVH on echocardiography. They found a sensitivity of 15%-31.9% and a specificity of 91.6%-99.2% in the global sample, with better sensitivity in concentric LVH. The best LVH descriptors in this research[8] were the Sokolow-Lyon voltage, Cornell voltage, Cornell product and R aVL voltage criteria.

Povoa et al.,[9] in a publication in this journal, studied 13 electrocardiographic criteria for LVH in 2458 hypertensive patients submitted to echocardiography, classified by age group and submitted to rigorous statistical analysis. Among patients aged ≥ 80 years, the Perugia criteria performed better (sensitivity 44.7%, specificity 89.3% and DOR - diagnostic odds ratio: 6.8) and (Rmax + Smax) x duration (sensitivity 39.4 %, specificity 91.3%, DOR 6.8). In patients aged < 80 years, in addition to these indices mentioned above, the Narita criterion, described in 2019,[10] also performed well. In this research, traditional indices had lower diagnostic sensitivity: Sokolow-Lyon voltage > 35 mm with 12%-15.7% in different age groups and Cornell voltage with 17.3%-21% sensitivity.[9]

In conclusion, we understand that the electrocardiogram remains an important tool in daily cardiology practice, quite valuable when it indicates LVH, but with still modest diagnostic sensitivity, despite new research in this area.

Keywords

Hypertrophy, Left Ventriculat; Diagnostic Imaging; Electrocardiography/methods; Echocardiography/methods; Cardiomyopathy, Hypertrophic; Ventricular Dysfunction, Left.

Mailing Address: Claudio Leinig Pereira da Cunha•
Rua Olavo Bilac, 181. Postal Code 80440-040, Curitiba, PR – Brazil
E-mail: cpcunha@cardiol.br

DOI: https://doi.org/10.36660/abc.20210868

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Determinants of Functional Capacity in Patients with Chagas Disease

Whesley Tanor Silva,[1] Henrique Silveira Costa,[1] Pedro Henrique Scheidt Figueiredo,[1] Márcia Maria Oliveira Lima,[1] Vanessa Pereira Lima,[1] Fábio Silva Martins da Costa,[2] Matheus Ribeiro Ávila,[1] Vanessa Amaral Mendonça,[1] Ana Cristina Rodrigues Lacerda,[1] Maria Carmo Pereira Nunes,[2] Manoel Otávio Costa Rocha[2]

Laboratório de Reabilitação Cardiovascular, Escola de Fisioterapia, Faculdade de Ciências Biológicas e da Saúde, Universidade Federal dos Vales do Jequitinhonha e Mucuri (UFVJM),[1] Diamantina, MG - Brazil

Programa de Pós-graduação em Infectologia e Medicina Tropical, Departamento de Medicina Interna, Faculdade de Medicina e Hospital das Clínicas da Universidade Federal de Minas Gerais (UFMG), [2] Belo Horizonte, MG - Brazil

Abstract

Background: Chagas disease leads to reduced functional capacity. However, the stage at which functional impairment is detectable remains unclear.

Objectives: The present study was addressed to compare the functional capacity of patients at different stages of Chagas disease and healthy individuals and to verify the determinants of peak oxygen uptake (VO2peak).

Methods: In a cross-sectional study, 160 individuals were selected, 35 healthy and 125 with Chagas disease. In the Chagasic group, 61 (49%) were in the indeterminate form of the disease, 45 (36%) with Chagas cardiomyopathy (ChC) and preserved cardiac function and 19 (15%) with cardiac dysfunction and dilated ChC. The data were analyzed using univariate and multivariate regression analysis. Statistical significance was set at 5%.

Results: Patients in the indeterminate form of disease showed similar functional capacity to healthy individuals ($p>0.05$). Patients with ChC and preserved cardiac function had lower VO2peak than patients in the indeterminate form ($p<0.05$), but showed similar VO2peak values than dilated ChC ($p=0.46$). The age, male sex, NYHA functional class, diastolic blood pressure, ratio of the early diastolic transmitral flow velocity to early diastolic mitral annular velocity, left ventricular ejection fraction (LVEF) and left ventricular end-diastolic diameter were associated with functional capacity. However, only age, male sex, LVEF and NYHA functional class, remained associated with VO2peak in the final model (adjusted $R2=0.60$).

Conclusion: Patients with ChC had lower functional capacity than patients in the indeterminate form. LVEF, age, male sex and NYHA functional class were determinants with VO2peak in patients with Chagas disease.

Keywords: Chagas Disease; Chagas Cardiomyopathy; Exercise Test/methods/métodos; Heart Failure/complications; Thromboembolism; Trypanosoma Cruzi.

Introduction

Chagas disease, an infection caused by the protozoan *Trypanosoma cruzi*, still remains a serious public health problem more than 100 years after its discovery.[1] The disease affects about six to seven million people in Latin America,[2] with a dramatic increase in non-endemic areas such as the United States and Europe.[3,4]

Most people remain asymptomatic in the chronic phase but infected in the indeterminate form of the disease. In the indeterminate form, infected individuals have similar prognosis to healthy subjects.[5] Therefore, patients are usually referred to as asymptomatic or Chagasic patients without apparent cardiopathy.[6] Clinical findings in the indeterminate form include minor echo or electrocardiographic changes, such as chronotropic incompetence, exercise-induced ventricular arrhythmias, and segmental changes on the echocardiogram, with no changes in left ventricular systolic function and with no significant electrocardiographic changes.[7] About 30% to 40% of these patients will develop the cardiac form.[5]

The cardiac form, also called Chagas cardiomyopathy (ChC), is the most common and severe clinical manifestation, with important electrocardiographic changes, progressive worsening of the systolic function with ventricular dilation. Dilated ChC, the end stage of heart disease, may evolve with heart failure, thromboembolism, and malignant arrhythmias.[8,9]

Fatigue and dyspnea are common clinical findings of cardiac involvement[5] and, consequently, the reduction in functional capacity and exercise tolerance is expected. However, it remains unclear at what stage functional impairment can be detected. Some authors have reported that the reduced functional capacity is detectable only in dilated ChC due to

Mailing Address: Whesley Tanor Silva •
Rodovia MGT 367 - Km 583, nº 5000. Postal Code 39100-000, Alto da Jacuba. Diamantina, MG - Brazil
E-mail: whesleytanor@gmail.com
Manuscript received May 12, 2020, revised manuscript September 24, 2020, accepted December 02, 2020

DOI: https://doi.org/10.36660/abc.20200462

heart failure. Others demonstrated that functional impairment may occur in the early stages of cardiopathy,[10] even preceding systolic dysfunction.

The stage identification is desirable for risk stratification and the adoption of effective preventive measures. Thus, the present study was addressed to evaluate the functional capacity in different stages of Chagas disease in order to compare the functional capacity, as well as clinical, demographic, and echocardiographic variables, at different stages of the disease, as compared to healthy patients, and to verify the factors associated with VO2peak in patients with Chagas disease.

Methods

This cross-sectional study was conducted at the Referral Outpatient Center for Chagas Disease and at a Cardiovascular Rehabilitation Laboratory, Brazil, between June 2013 and June 2018. All the patients voluntarily gave their written informed consent prior to participating in this study. The research was carried out in accordance with the Declaration of Helsinki[11] and was approved by the institutional ethics committee.

Study design

The sample was comprised of healthy subjects and patients with a wide spectrum of Chagas disease. The post hoc sample size calculations were performed using the software GPower, version 3.1. Considering that 125 subjects with Chagas disease were evaluated for convenience, an alpha error of 5% and 4 predictors, a statistical power of 95% was obtained. The criteria for inclusion in the Chagas disease group were the presence of two or more positive serological tests for *Trypanosoma cruzi*. The healthy sample consisted of subjects without significant clinical changes or systemic diseases.

The Chagasic group was stratified according to the clinical presentation (indeterminate form, ChC with preserved cardiac function or dilated ChC). Patients in the indeterminate form should present an absence of significant clinical symptoms suggestive of functional impairment due to Chagas disease and a chest X-ray with a normal cardiac silhouette and conventional ECG within the normal limits.[12]

Criteria for inclusion for ChC were clinical, electrocardiographic, or echocardiographic findings compatible with ChC[9] and a stable clinical condition. Patients were included in the dilated ChC group when they demonstrated a left ventricular ejection fraction (LVEF) of lower than 52% (for men) or 54% (for women)[13] and a left ventricular end-diastolic diameter (LVDd) of higher than 55mm. Exclusion criteria for all patients were the presence of systemic or heart disease by any other causes, associated comorbidities, and the inability to perform exercise testing.

The overall study population underwent clinical evaluation, echocardiography, and a maximal exercise test. Echocardiography was performed according to recommendations of the American Society of Echocardiography.[13] LVEF was obtained through the modified Simpson´s rule. Early diastolic velocity (e') at the medial border of the mitral annulus was obtained and the ratio between peak mitral E and e' (E/e' ratio) was calculated. All subjects performed a symptom-limited exercise test on a treadmill (Digistress Pulsar, Micromed, Brasilia, Brazil), using the standard Bruce protocol. Peak oxygen uptake (VO2peak), which was estimated by a specific formula [VO2peak (mL/kg/min) = 2.33 (time in min) + 9.48],[14] was considered for functional evaluation.

Statistical analysis

The normal distribution of data was assessed by the Kolmogorov-Smirnov test. Continuous variables were shown as mean and standard deviation (normal distribution) or median and interquartile range (non-normal distribution), while categorical variables were demonstrated as absolute number and percentage.

Categorical variables were compared by the Chi-squared test. Differences among groups were verified by one-way ANOVA with Bonferroni corrections or the Kruskall Wallis test with Dunn's multiple comparison test for post-hoc analyses, as appropriate. The determinants of VO2peak were verified by univariate and backward multivariate linear regression. The variables associated with VO2peak in the univariate analysis ($p<0.1$) were included in the multivariate model. In the linear regression analysis, four assumptions were adopted: linearity, distribution of residuals, homoscedasticity, and the absence of multicollinearity. The linearity of the independent variables and residuals was checked by scatter plots and the distribution of residuals was analyzed by the histogram. The homoscedasticity was verified by the scatter plot and characterized by the residuals equally distributed in the regression line. The absence of multicollinearity was defined as the variance inflation factor (VIF) values below 10.0. Additionally, the auto-correlation of the variables was verified by the Durbin-Watson test and values between 1.5 and 2.5 show that there is no auto-correlation in the data. Statistical significance was set at 5%. Data were analyzed with SPSS version 17.0 (SPSS Inc., Chicago, IL, USA).

Results

A total of 160 individuals were selected and evaluated: 35 (22%) healthy individuals, 61 (38%) patients with Chagas disease in the indeterminate form, 45 (28%) with ChC and preserved cardiac function, and 19 (12%) with dilated ChC. Demographic, clinical, echocardiographic, and functional features of the sample are presented in Table 1, stratified by clinical presentation.

Differences between healthy subjects and patients in different clinical forms of Chagas disease

In the comparison between healthy individuals and patients with Chagas disease in the indeterminate form, there was no significant difference in any variables. In contrast, patients with ChC and preserved cardiac function were predominantly female ($p=0.025$), older, with worse NYHA functional class, lower values of systolic and diastolic blood pressure, lower functional capacity, higher E/e' ratio, and a lower LVEF ($p<0.001$ for all), when compared to healthy individuals.

Table 1 – Demographic, clinical, echocardiographic, and functional characteristics of the evaluated sample stratified by clinical presentation (n=160)

Variables	Healthy individuals (n=35)	Patients with Chagas disease			p-value*
		Indeterminate form (n=61)	ChC and preserved cardiac function (n=45)	Dilated ChC (n=19)	
Age (years)	47.0 (36.7-52.0)	43.5 (38.0-51.0)	52.0 (43.7-61.5)[a,b]	52.5 (45.7-58.2)[a,b]	**<0.001**
Male sex (%)	21 (60)	28 (46)	16 (35)[a]	12 (63)[c]	0.083
BMI (kg/m^2)	25.9 (23.8-29.4)	25.9 (23.6-29.3)	26.8 (23.5-29.4)	25.6 (22.2-30.9)	0.875
NYHA functional class					**0.035**
I	35 (100)	61 (100)	32 (71)	5 (26)	
II	0	0	13 (29)	6 (32)	
III	0	0	0	8 (42)	
SBP (mmHg)	127.3±14.7	120.0±12.7	118.7±19.8[a]	102.3±17.0[a,b,c]	**<0.001**
DBP (mmHg)	86.3±8.5	84.1±7.5	74.2±9.8[a,b]	66.5±7.0[a,b,c]	**<0.001**
HR (bpm)	69.4±7.7	72.2±11.3	71.6±18.9	64.8±11.3	0.255
E/e' ratio	5.1 (4.3 – 6.4)	5.7 (4.4 – 7.2)	8.5 (6.7 – 11.4)[a,b]	9.7 (6.8 – 12.3)[a,b]	**<0.001**
LVEF (%)	70.0±5.4	68.1±5.1	64.9±7.1[a]	38.8±7.9[a,b,c]	**<0.001**
LVDd (mm)	47.2±5.5	48.6±4.2	48.7±4.9	62.9±10.6[a,b,c]	**<0.001**

*Data presented as mean and standard deviation (normal distribution), median and interquartile range (non-normal distribution) or number and percentage (categorical variables). BMI: body mass index; NYHA: New York Heart Association functional class; SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate; LVEF: left ventricular ejection fraction; LVDd: left ventricular end-diastolic diameter; E/e' ratio: ratio of the early diastolic transmitral flow velocity to early diastolic mitral annular velocity. *p-value of the comparison among the four groups by One-way ANOVA. a, b, c represent a p-value < 0.05 verified by Bonferroni post-hoc analyses when compared to: ahealthy subjects; bpatients with Chagas disease in the indeterminate form; cChagas cardiomyopathy with preserved cardiac function.*

Patients with dilated ChC were older, with a worse NYHA functional class, lower values of systolic and diastolic blood pressure, lower functional capacity, higher E/e' ratio, lower LVEF, and higher LVDd (p<0.001 for all), when compared to healthy individuals.

Demographic, clinical, echocardiographic, and functional differences among the clinical forms of Chagas disease

Patients with Chagas disease in the indeterminate form were younger, showed better NYHA functional class, higher diastolic blood pressure, and a lower E/e' ratio (p<0.001 for all), when compared to ChC and preserved cardiac function. Additionally, patients in the indeterminate form were younger, showed a better NYHA functional class, higher systolic and diastolic blood pressures, a lower E/e' ratio, a higher LVEF and a lower LVDd (p<0.001 for all), when compared to patients with dilated ChC.

Finally, patients with ChC and preserved cardiac function are predominantly female (p=0.040), when compared to dilated ChC, as well as with a better NYHA functional class, higher values of systolic and diastolic blood pressure, a higher LVEF, and a lower LVDd (p<0.001 for all).

Functional differences between healthy subjects and patients with Chagas disease, and among the clinical forms of Chagas disease

The results of the functional capacity assessment are shown in Figure 1. In the overall study population, significant differences were found among the groups (p<0.001). Patients in the indeterminate form of Chagas disease presented a VO2peak that was similar to healthy patients. Patients with ChC and preserved cardiac function showed a significant reduction in functional capacity in relation to healthy participants and patients with Chagas disease in the indeterminate form (p<0.001 for both), with a mean of difference of 15.7 mL.kg.min (95% CI 10.5 – 20.8) and 16.1 mL.kg.min (95% CI 11.6 – 20.6), respectively. Finally, patients with dilated ChC had a lower VO2peak when compared to healthy subjects and patients in the indeterminate form (p<0.001 for both), and the mean differences were of 20.0 mL.kg.min (95% CI 13.3 – 26.6) and 20.3 mL.kg.min (95% CI 14.2 – 26.5), respectively. No difference was found in VO2peak between patients with dilated ChC and with ChC and preserved cardiac function (p=0.467).

Determinants of VO2peak in patients with Chagas disease

In the univariate analysis, age, male sex, NYHA functional class, diastolic blood pressure, E/e' ratio, LVEF, and LVDd were associated with the VO2peak. However, in the final multivariable model, only age, male sex, NYHA functional class, and LVEF remained as determinants of the VO2peak, with an adjusted R^2 of 0.60 (Table 2).

In the visual analysis of the linear regression assumptions, the linearity of the independent variables, the normal distribution and the homoscedasticity of the residuals were verified. The Durbin-Watson test demonstrated the absence of

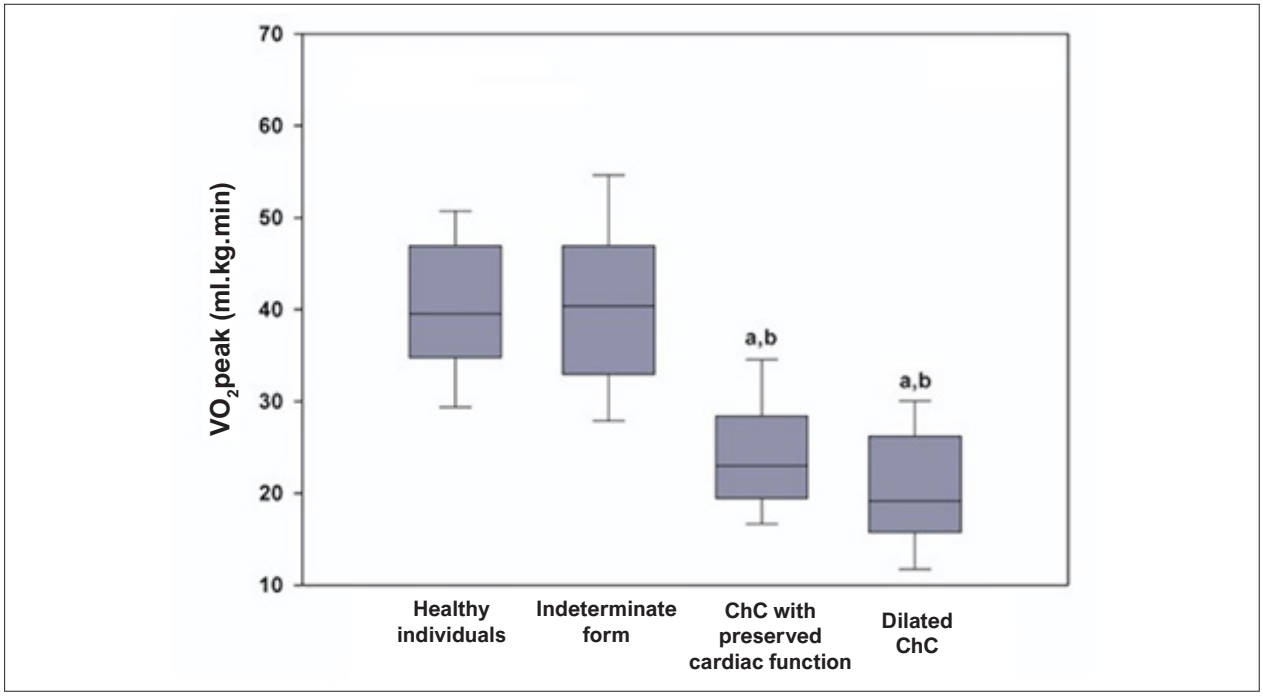

Figure 1 – *Peak oxygen uptake (VO2peak) in healthy individuals and in patients with Chagas disease with different clinical forms. [a]: p<0.001 compared to healthy individuals; [b]: p<0.001 compared to the indeterminate form of Chagas disease.*

Table 2 – Factors associated with the VO2peak in the uni and multivariate analysis of the Chagasic population (n=125)

Variables	Univariate analysis				Multivariate analysis*			
	B-coefficient	95% CI	r	p-value	B-coefficient	95% CI	p-value	Collinearity statistics (VIF values)
Constant	-	-	-	-	29.5	13.5 to 46.4	**<0.001**	
Age (years)	-0.6	-0.8 to -0.5	0.5	**<0.001**	-0.2	-0.5 to -0.2	**0.038**	**1.13**
Male sex	10.9	7.5 to 14.3	0.5	**<0.001**	9.6	6.3 to 13.4	**<0.001**	**1.18**
BMI (kg/m^2)	-0.3	-0.7 to -0.1	0.1	0.209	-	-	-	
NYHA class	-11.8	-14.9 to -8.6	0.5	**<0.001**	-4.2	-8.3 to -0.1	**0.041**	**1.92**
SBP (mmHg)	0.1	-0.1 to 0.1	0.1	0.352	-	-	-	
DBP (mmHg)	0.4	0.2 to 0.5	0.3	**<0.001**	-	-	-	
HR (bpm)	-0.1	-0.1 to 0.1	0.1	0.982	-	-	-	
E/e' ratio	-0.5	-1.5 to 0.7	0.3	**<0.001**	-	-	-	
LVEF (%)	0.5	0.3 to 0.6	0.5	**<0.001**	0.3	0.2 to 0.5	**<0.001**	**1.99**
LVDd (mm)	-0.4	-0.6 to -0.1	0.2	**0.003**				

*r: correlation coefficient; LV: left ventricular; BMI: body mass index; NYHA: New York Heart Association functional class; SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate; bpm - beats per minute; E/e' ratio: ratio of the early diastolic transmitral flow velocity to early diastolic mitral annular velocity; LVEF: left ventricular ejection fraction; LVDd: left ventricular end-diastolic diameter; VIF: variance inflation factor. * The R2 value for the final multivariate model was 0.60.*

auto-correlation in the data (d = 1.6). In addition, VIF values highlight the absence of multicollinearity (Table 2).

Discussion

Patients with Chagas disease usually evolve with progressive fatigue and dyspnea, and exercise intolerance is a common clinical finding in this population.[15] However, the stage of the disease at which functional impairment is detectable remains unclear. The main findings of the present study were: (1) Chagas disease patients in the indeterminate form had similar functional capacity to healthy patients; (2) the VO2peak in patients with ChC was significantly lower than in patients in the indeterminate form; and (3) the LVEF, together with age, male sex, and NYHA functional class, explains 60% of the variations in functional capacity. The present study suggests that, even without significant myocardial damage, patients with ChC and preserved cardiac function have functional impairment. These findings are useful in understanding the impact of the disease in the functional capacity and risk stratification of the patient, and demonstrate the importance of periodic functional assessment in this population, as well as assist in identifying patients who need supervised exercise training.

Patients in the indeterminate form of Chagas disease are known to be asymptomatic and have a good medium-term prognosis. However, studies have shown that more accurate examinations, such as exercise testing, are able to detect changes in this population when compared to healthy individuals.[16] Costa et al.[17] reported the higher prevalence of exercise-induced ventricular arrhythmias and vagal dysfunction by respiratory sinus arrhythmias in indeterminate patients versus healthy subjects. However, the authors found no difference in functional capacity ($p>0.05$). During exercise testing, Rocha et al.[18] demonstrated an increased prevalence of exercise-induced ventricular arrhythmias and chronotropic incompetence in patients with Chagas disease without heart disease, as compared to healthy subjects, with no difference in the functional capacity ($p>0.05$). Similarly, the present study also found no difference in functional capacity between the two groups. It is believed that subclinical changes may be present in patients in the indeterminate form of Chagas disease but without changes in exercise capacity.

On the other hand, patients in the cardiac form of the disease, both with preserved cardiac function and with ventricular dysfunction, showed a reduction in the systolic function, diastolic function, and functional capacity in relation to patients in the indeterminate form of Chagas disease and healthy individuals. Many studies have failed to determine the stage of the disease at which functional impairment is detectable. A previous study has shown that the reduction of functional capacity occurs in the early stages of heart disease.[10] Another study demonstrated that functional impairment is detectable in patients with Chagas disease only in the presence of advanced cardiomyopathy.[19] Recently, a systematic review with meta-analysis[15] reported that functional impairment occurs in ChC, even in patients with preserved ventricular function. However, this review included few studies and the results should be interpreted with caution. Few studies have included the main forms of Chagas disease in a single manuscript. Moreover, our results are consistent with the systematic review, showing that patients with ChC and preserved cardiac function presented lower a VO2peak and LVEF values than healthy individuals and patients with Chagas disease in the indeterminate form, even with values within normal limits. Dilated ChC showed lower VO2peak than healthy individuals and all other forms of Chagas disease.

In addition, our results showed a reduction in the diastolic function in patients with ChC and preserved cardiac function when compared to the indeterminate and healthy groups, which could lead to a reduction in VO2peak. In fact, the E/e' ratio was associated with the VO2peak in the univariate analysis; however, it did not remain in the final multivariate model. Thus, it seems that the diastolic function, although reduced in the group with ChC and preserved cardiac function, is not a determinant of functional capacity in patients with Chagas disease.

The present study also demonstrated the factors associated with functional capacity in patients with Chagas disease. The LVEF is a determinant of functional capacity, and together with age, male sex, and NYHA functional class, it explains 60% of variations in the VO2peak. Age and sex are well-established predictors of functional capacity in the general population. There is an inverse relationship between age and exercise capacity, just as women tend to have a lower VO2peak than men.[20-22] In fact, muscle mass and strength can be reduced by 30% to 50% between 30 and 80 years of age by the loss of muscle fibers and atrophy of the type II muscle fiber.[23,24] Regarding sex, women have smaller left ventricular chambers and lower stroke volumes,[25] lower diastolic compliance,[26] greater prevalence of obesity,[25] and less lean mass than men,[27] which would explain the lower exercise capacity.

Regarding LVEF, many studies failed to demonstrate an association between LVEF and functional capacity,[28,29] reporting that other factors, such as right ventricular function and left atrium, are more related to exercise than LVEF. However, another study has found significant differences in patients with ChC and preserved LVEF and ventricular dysfunction,[30] since both the VO2peak and LVEF tend to decrease with disease progression. It is believed that the reduction in LVEF leads to poor skeletal muscle perfusion during exercise,[31] causing fatigue and dyspnea, and contributing to exercise intolerance. However, further studies are needed to confirm the hypothesis.

The present study has limitations and strengths. One limitation of this study was the performance of the stress test using conventional maximal exercise testing, without gas analysis. The indirect assessment of the VO2peak has been established to be correlated with the direct measurement,[32] while other authors have reported a considerable discrepancy between the estimated and evaluated VO2peak values.[33] Despite the conflicting results, it is emphasized that the endemic areas in Chagas disease generally have few technological resources and, according to a recent systematic review, 77% of the studies that aimed to verify the functional capacity in this population used the indirect measure of the VO2peak without gas analysis. Therefore, we believe that the use of the estimated VO2peak for functional assessment is a limitation, but it does not invalidate the results, especially considering the setting of Chagas disease. In addition, our

sample consisted of patients followed up by a referral center for the treatment of parasitic diseases, and they are regularly evaluated and are undergoing optimized therapy. Despite the importance of the findings of this neglected population, the results may not reflect the functional capacity of all patients with Chagas disease, especially those in an endemic area. Moreover, the intra and interobserver analysis in the assessment of functional capacity was not verified. However, all tests were performed by only two experienced cardiologists, certified by the Brazilian Society of Cardiology, which possibly reduced the bias and may not have changed the results of the functional assessment. Finally, the present study included only one parameter of diastolic function (E/e' ratio), which is necessary to verify whether other diastolic function variables are associated with the functional capacity of this population. As a strength, the present study was the first that demonstrated the LVEF as a determinant of functional capacity. Furthermore, the significant reduction in the VO2peak in patients with ChC,a s compared to those in the indeterminate form, suggests that patients with ChC, regardless of cardiac function, should undergo supervised exercise training to prevent severe functional impairment.

Conclusion

Patients with ChC, even with preserved ventricular function, presented a lower functional capacity than did patients in the indeterminate form. In patients with Chagas disease, LVEF, age, male sex, and NYHA functional class are determinants of functional capacity.

Author Contributions

Conception and design of the research: Costa HS, Figueiredo PHS, Lima MMO, Mendonça VA, Rocha MOC; Acquisition of data: Silva WT, Costa HS, Ávila MR, Lacerda ACR; Analysis and interpretation of the data: Figueiredo PHS, Lima MMO, Lima VP, Nunes MCP; Statistical analysis: Costa FSM, Lacerda ACR, Nunes MCP, Rocha MOC; Writing of the manuscript: Ávila MR; Critical revision of the manuscript for intellectual content: Silva WT, Costa HS, Lima VP, Mendonça VA, Nunes MCP, Rocha MOC.

Potential Conflict of Interest

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

Sources of Funding

There were no external funding sources for this study.

Study Association

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

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Universidade Federal dos Vales do Jequitinhonha e Mucuri (UFVJM) under the protocol number CAAE 16379719.5.0000.5108. 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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Diagnostic and Prognostic Importance of Functional Capacity in the Different Evolutionary Forms of Chagas Disease

João Marcos Barbosa-Ferreira,[1,2] Charles Mady,[1] Fábio Fernandes[1]

Instituto do Coração do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo,[1] São Paulo, SP – Brazil

Universidade do Estado do Amazonas,[2], Manaus, AM – Brazil

Short Editorial related to the aticle: Determinants of Functional Capacity in Patients with Chagas Disease

The manuscript published by Silva et al.[1] in this issue brings us an important reflection on the evolution of the different forms of Chagas disease (CD), by demonstrating that patients with the indeterminate form (IF) have similar functional capacity, measured through peak oxygen uptake (VO_2peak), to healthy individuals without CD. On the other hand, patients with Chagas' heart disease without ventricular dysfunction had similar functional capacity to patients with ventricular dysfunction.[1]

The IF of CD has been studied under different aspects for several years. Some studies in asymptomatic patients that are included in the definition of IF for not presenting electrocardiographic and chest X-ray alterations, demonstrated incipient alterations in complementary exams that may suggest the possibility of evolution to the more severe forms of CD over the years. Evaluations made through echocardiography showed alterations in variables such as tissue Doppler and study of myocardial deformity through two-dimensional strain.[2,3] There has also been demonstration of changes in the Autonomic Nervous System, especially in the parasympathetic branch, which can be potential pathways for worsening in the stage disease over the years.[4,5] Studies performed with magnetic resonance have demonstrated the presence of myocardial fibrosis in 12% of patients with IF of the disease.[6] However, despite these small changes, the long-term evolution of these patients has been shown favorable and similar to that of healthy individuals without CD. Ianni et al.[7] studied patients with the IF based on ECG findings for 8 years and concluded that the IF of CD represents a benign condition with a favorable long-term prognosis.[7] However, in a small group of patients, there may be evolution for chronic Chagas cardiopathy (CCC) or digestive tract disease in about 10 to 20 years after acute infection. Sabino et al.,[8] in a 10-year retrospective cohort study, suggested a rate of progression to cardiomyopathy of 1.85% per year in patients with FI of the disease.[8] Therefore, studies that identify markers that can predict the possibility of this evolution are needed and the evaluation of the functional capacity of these patients is important in this aspect.

The presence of electrocardiographic alterations suggestive of cardiac involvement, characteristic of CD, in a symptomatic or asymptomatic individual, characterizes the chronic cardiac form of CD. This group of patients may present only with an altered electrocardiogram (ECG), but without symptoms or presence of ventricular dysfunction, or present with symptoms of heart failure and significant grade of left ventricular systolic dysfunction. Studies with magnetic resonance have shown the presence of up to 94% of myocardial fibrosis in patients with altered ECG, even without ventricular dysfunction.[6] These findings suggest that this group of patients should have a rigorous clinical follow-up and the assessment of functional capacity is also important into this spectrum.

On the other hand, patients with CCC and severe ventricular dysfunction represent a group of patients who have a worse prognosis than other cardiomyopathy etiologies. Mady et al.[9] demonstrated that functional capacity, as well as ejection fraction, is an important predictor of survival in this group of patients.[9] In addition, physical training and cardiac rehabilitation are important components of clinical improvement in these patients and VO_2peak is also important in this monitoring.[10]

All these aspects suggest that the study of CD needs to increasingly address themes that seek predictors of its evolution, which varies from individual to individual, and the study of functional capacity is important in this context.

Keywords

Chagas Disease; Exercise; Chagas cardiomyopathy; Exercise Test/methods; Heart Failure/complications; Thromboembolismi; Trypanosoma Cruzi.

Mailing Addess: Fábio Fernandes •
Instituto do Coração do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo - Av. Dr. Enéas C. Aguiar, 44. Postal Code 05403-000, São Paulo, SP - Brazil
E-mail: fabio.fernandes@incor.usp.br

DOI: https://doi.org/10.36660/abc.20210808

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Original Article

Mortality Due to Heart Failure and Socioeconomic Development in Brazil between 1980 and 2018

Sonia Carvalho Santos,[1] *Paolo Blanco Villela,*[1] *Gláucia Maria Moraes de Oliveira*[1]

Universidade Federal do Rio de Janeiro – Cardiologia,[1] *Rio de Janeiro, RJ – Brazil*

Abstract

Background: Studies on mortality from heart failure (HF) in Brazil and in the country's Geographic Regions (GRs) are scarce.

Objective: To analyze the temporal progression of HF mortality rates by sex and age group in Brazil and its GRs and Federative Units (FUs) from 1980 to 2018, and the associations between mortality rates at each FU and the Municipal Human Development Index (MHDI).

Methods: Time series analysis of deaths due to HF categorized by sex and age groups in Brazil and Brazilian GRs and FUs from 1980 to 2018. Death and population data were obtained from the DATASUS for estimation of crude and standardized mortality rates per 100,000 inhabitants (direct method, Brazilian population in the year 2000). We calculated the 3-year moving averages of the standardized rates. The MHDIs of the FUs in 1991 and 2010 were obtained from Atlas Brasil and were correlated with mortality rates using Pearson's correlation at a 5% significance level.

Results: Mortality due to HF decreased in Brazil after 2008, reaching a similar level at the end of 2018 in the GRs and FUs, and was higher in men during almost all periods and age groups, except for those over the age of 60 years after 1995 in the South region. There was an inverse relationship between MHDI and reduction in mortality rates (0.73).

Conclusion: There was a progressive reduction in mortality rates due to HF in Brazil from 2008 to 2018, with similar levels in 2018 in the GRs and FUs and higher rates in men. These reductions appear to be related more to the 2010 MHDI than the percentage increase over time.

Keywords: Heart Failure; Development Indicators; Mortality Registries.

Introduction

Annual mortality rates are higher for cardiovascular diseases (CVDs) than any other cause, making these the first causes of death worldwide. About 17.9 million people are estimated to have died from CVDs in 2016, representing 31% of all global deaths and more than three-quarters of CVD deaths in low- and middle-income countries.[1] Among all CVDs, heart failure (HF) stands out for its high and increasing morbidity and mortality rates.[2]

Mortality rates due to HF are not estimated in the Global Burden of Disease (GBD) data since this condition is considered to be the common end to several diseases (also known as garbage code, *i.e.*, a nonspecific, incomplete code that does not identify clearly the underlying cause of death)[3] and redistributes the deaths by the conditions that were responsible for their occurrence. According to the GBD, the prevalence and standardized rates of HF per 100,000 inhabitants in Brazil were 670,194.8 (95% uncertainty interval [UI] = 589,952.6; 753,672.6) and 818.1 (95% UI = 718.1; 922.8) in 1990 and 1,686,320.1 (95% UI = 1,478,563.8; 1,890,537.3) and 777.2 (95% UI = 680.0; 874.80) in 2017, with a percentage reduction of -5% (95% UI = -7.1; -3) in the standardized prevalence rate over 27 years.[3]

Studies on HF mortality in Brazil based on data from the Mortality Information System in Geographic Regions (GRs) and Federative Units (FUs) with different levels of socioeconomic development are scarce. A study on underlying causes of death carried out between 2004 and 2011 observed that the proportional mortality due to HF increased with age, and that the highest percentages in Brazil and its GRs were observed among elderly women.[4] The authors found ischemic heart disease to be the most frequent cause for the occurrence and development of HF, and suggested that regional differences may be a consequence of socioeconomic conditions and health care structures, among other factors.[5] A recent study conducted between 2008 and 2015 in Paraíba, the state with the lowest socioeconomic development, has reported that the HF mortality in absolute numbers had a nonsignificant decline between 2008 and 2015 (R = -0.513), and that the same happened in Brazil (R = -0.412), with no observed statistically significant differences regarding sex and age

Mailing Address: Gláucia Maria Moraes de Oliveira •
Universidade Federal do Rio de Janeiro - Rua Visconde de Pirajá, 330. Postal Code 21941-901, Sala 1114, Rio de Janeiro, RJ – Brazil
E-mail: glauciamoraesoliveira@gmail.com
Manuscript received August 13, 2020, revised manuscript November 03, 2020, accepted December 02, 2020

DOI: https://doi.org/10.36660/abc.20200902

groups.[6] However, the relationships of HF and social and economic indicators in Brazil have not been much explored in the literature.

The Human Development Index (HDI) is a summary measure of the population's health, education, and income that evaluates long and healthy life, access to knowledge, and standard of living. This index appears to be a good socioeconomic indicator to assess the complex relationships between social determinants and CVD. Since 2009, the HDI has been composed of the life expectancy at birth, average years of schooling for the adult population and expected years of schooling for children (school enrollment rate), and the gross national income per capita.[7]

The present study aimed to analyze the temporal evolution of HF mortality rates according to sex and age group in Brazil and in the country's GRs and FUs over the last 39 years, and the associations of the mortality rates with the MHDI, an index chosen to compare the socioeconomic development among the FUs.

Materials and Methods

This was an ecological and descriptive study of historical series of death certificates related to deaths due to HF that occurred in Brazil between 1980 and 2018, across all age groups and in both sexes.

Information on the underlying cause of death was retrieved from the website of the Brazilian Mortality Information System (*Sistema de Informação de Mortalidade*, SIM) of the Department of Informatics of the Unified Health System (DATASUS) of the Ministry of Health.[8] After downloading the database, the original files in a .CSV format were converted into a .XLS format using the program Microsoft Excel,[9] which was also used for the data analysis and construction of graphs and tables. For identification of deaths with HF as the underlying cause, we used the categories 428 of the ICD-9[10] for deaths that occurred between 1980 and 1995, and I50 of the ICD-10[11] for deaths that occurred after 1996.

Information on the resident population was also retrieved from the DATASUS website,[8] which in turn considered the census data from the Brazilian Institute of Geography and Statistics (*Instituto Brasileiro de Geografia e Estatística*, IBGE) from 1980, 1991, 2000, and 2010, intercensal projections until 2012, and population projections from 2013 onwards.

The annual crude and standardized mortality rates in the FUs per 100,000 inhabitants were estimated by the direct method,[12] using as standard the age structure of the Brazilian population in 2000. For each FU, we calculated the moving averages of the standardized rates every 3 years, disregarding the initial 2 years of the series (1980 and 1981 for all FUs; 1989 and 1990 for Tocantins) until 2018. The FUs were grouped into their GRs (North, Northeast, Southeast, South, and Midwest). Of note, after 1989, the North region started incorporating data from Tocantins, a FU created in 1988.

We estimated the crude mortality rates by GR in three age groups (up to 29 years, 30–59 years, and 60 years or more) over seven periods of 5 years and in a period of 4 years (2015 to 2018), with subsequent calculation of the ratio rates of men/women.

The MHDI of each FU corresponding to the years 1991 and 2010 were obtained from the website Atlas Brasil.[13] The data result from adapting the calculation of the country's global HDI to municipal and state levels, carried out by the United Nations Development Programme (UNDP - Brazil), by the Institute for Applied Economic Research (IPEA), and by the João Pinheiro Foundation, thus creating the Municipal HDI (MHDI), which can be interpreted the same way as the global HDI but at a municipal and state level. Next, we calculated the percentage variation of the MHDI for each FU between 1991 and 2010, and its correlation with the percentage variation of the standardized mortality rates in the respective FUs between 1990 and 2018 using Pearson's correlation coefficient, adopting as significant a value below 0.05. Of note, we chose the year 1990 in this case for the beginning of the temporal series so that all FUs could be evaluated with the same time interval, considering the incorporation of Tocantins in 1988. We correlated the 2010 MHDI with the percentage variation of the standardized mortality rates in the respective FUs between 1990 and 2018.

Results

We found 1,185,120 deaths between 1980 and 2018, of which 49.3% (584,155) occurred in men. Regarding the distribution of the deaths by GR, 48,533 occurred in the North, 245,898 in the Northeast, 602,105 in the Southeast, 218,496 in the South, and 70,088 in the Midwest. The complete data used for the study are available in Supplemental Tables 1, 2, 3, and 4.

Figure 1 shows the 3-year moving averages of the mortality rates standardized by age per 100,000 inhabitants at each FU grouped into the five GRs (Figures 1A to 1E) and the overall national rates (Figure 1F) between 1982 and 2018. In the North region, with the exception of Rondônia and Acre, in which the averages increased in the first and second decades of observation, respectively, all other FUs showed a progressive decline and, after 2008, the averages were similar in all FUs, with small oscillations until 2018 (Figure 1A). Since Tocantins was incorporated in 1988, this state's data are presented from 1989 onwards, and in this case, the calculation of the moving averages began after 1991 (Figure 1A). In the Northeast region (Figure 1B), Alagoas had the highest averages at the beginning of the period and, despite the downward trend, showed increases between 1998 and 2008, a similar trend to that observed in Piauí. Following the same trend of the North region, the averages of all FUs in the Northeast region after 2008 were similar to each other, showing the same evolutionary trend in the last 10 years of observation.

The FUs of the Southeast region (Figure 1C) showed increased averages at the beginning of the period followed by a progressive decline over the years, especially in Espírito Santo, which after 2010 stood out for presenting the lowest averages in the region, in a stable and sustained pattern. The FUs in the South region (Figure 1D), as observed in the Southeast region, presented increased averages at the beginning of the observation period and, with the exception of Paraná, which showed an increase throughout the 1990s, all other FUs showed a progressive decline, reaching values

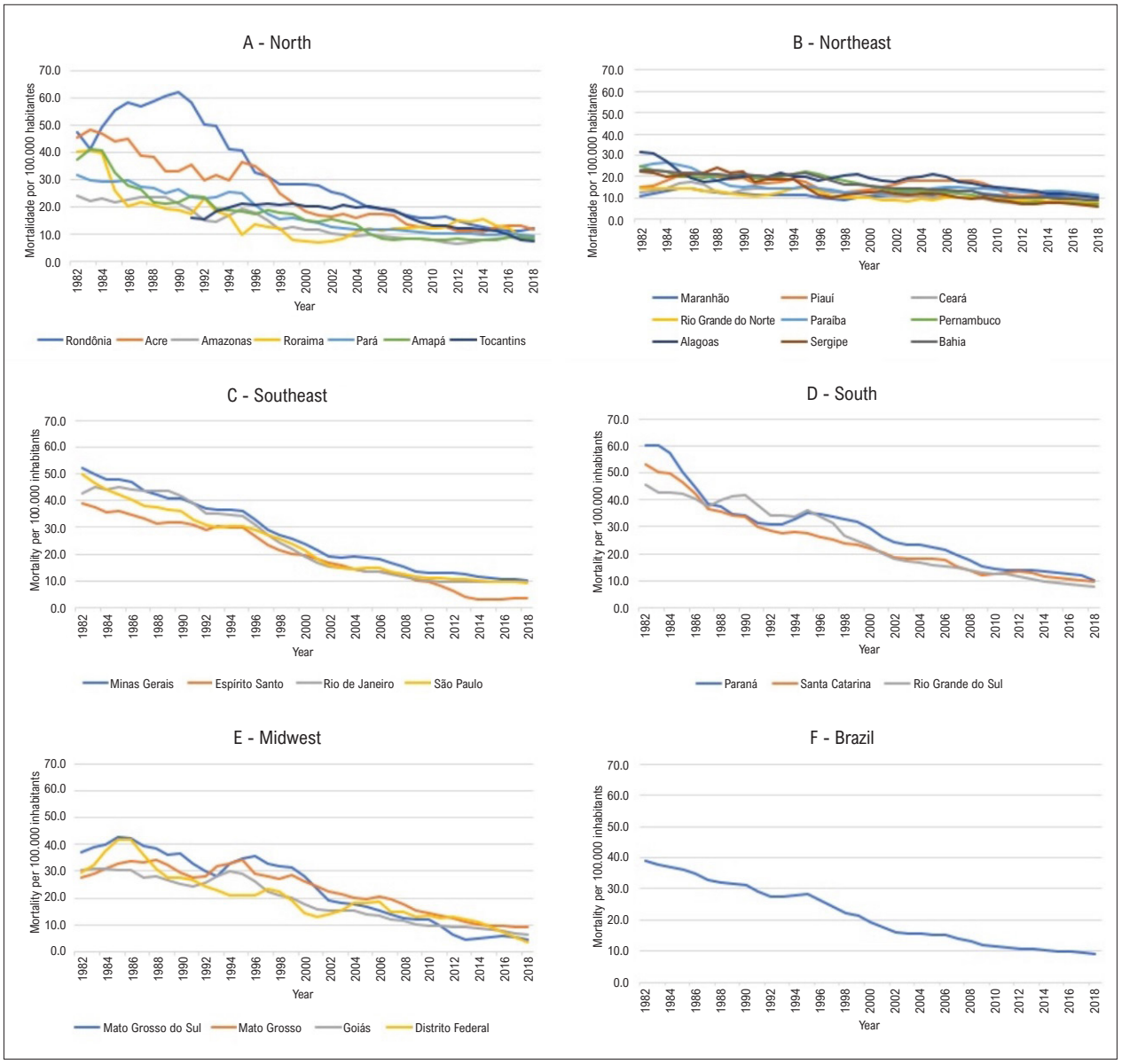

Figure 1 – *Shows the 3-year moving averages of the mortality rates standardized by age per 100,000 inhabitants at each FU grouped into the five GRs, (A- North, B-Northeast, C- Southeast, D- South, E-Midwest and the national total (F).*

similar to those of the Southeast region in the final observation period. Figure 1E shows important fluctuations across the FUs in the Midwest region along the first three decades, trending toward linearity only over the last 10 years of observation. As seen separately in each region, the national trend pointed downward in the period (Figure 1F). After starting from intermediate values at the beginning of the series, small fluctuations occurred, especially in the 1990s, with a later trend toward linearity after the beginning of the 2000s.

Table 1 shows the ratio of the mortality rates between men and women across the five GRs at 5-year periods and in all three age groups. The rates in men were greater during almost all periods and age groups observed, reaching the highest proportions in the age group between 30–59 years in all GRs. The mortality rates among women were only higher (ratio <1) in the age group up to 29 years in brief periods in the North and Northeast regions, and in the age group above 60 years after 1995 in the South region (Table 1).

The Pearson's correlation coefficient of the variation in mortality rates between 1990 and 2018 and the variation in MHDI between 1991 and 2010 for each FU was 0.73 (strong correlation), with p = 0.000. Figure 2A shows a scatter plot of the correlation across all FUs, while Figure 2B shows the correlation of mortality rates and MHDI in 2010, with a coefficient of 0.72. In line with Figure 1, in relation to the moving averages over a longer period, all FUs showed reductions and, therefore, a negative variation in mortality rates comparing the years 1990 and 2018 (Figure 2A, Y axis).

Table 1 – Ratio between crude mortality rates in men and women in different age groups and by geographic region over 5-year periods

Age Group	Region/Period	1980-1984	1985-1989	1990-1994	1995-1999	2000-2004	2005-2009	2010-2014	2015-2018
0-29	North	1.0	0.9	1.2	1.0	1.2	1.3	1.3	1.8
	Northeast	0.9	1.0	1.0	1.1	1.1	1.4	1.4	1.5
	Southeast	1.1	1.2	1.3	1.3	1.2	1.6	1.5	1.8
	South	1.1	1.2	1.2	1.6	1.5	1.3	1.5	1.1
	Midwest	1.1	1.1	1.1	1.1	1.9	1.5	2.7	1.0
30-59	North	1.5	1.4	1.5	1.4	1.6	1.9	1.8	1.5
	Northeast	1.2	1.3	1.4	1.3	1.3	1.4	1.5	1.6
	Southeast	1.4	1.5	1.6	1.5	1.6	1.7	1.6	1.5
	South	1.4	1.5	1.5	1.4	1.4	1.5	1.4	1.2
	Midwest	1.2	1.5	1.6	1.6	1.8	1.9	1.7	1.7
60+	North	1.1	1.1	1.1	1.1	1.2	1.3	1.3	1.2
	Northeast	1.2	1.2	1.2	1.1	1.2	1.2	1.2	1.2
	Southeast	1.1	1.1	1.0	1.0	1.0	1.0	1.0	1.0
	South	1.1	1.0	1.0	0.9	0.9	0.9	0.9	0.9
	Midwest	1.1	1.1	1.0	1.0	1.1	1.1	1.1	1.2

Figure 2 – *Shows a scatter plot. A) Correlation between the percentage variations of the MHDI between 1991 and 2010 and the mortality rates between 1990 and 2018, in each Federation Unit (Acronyms) in Brazil. B) Correlation between the absolute MHDI in 2010 and the percentage change in mortality rates between 1990 and 2018, in each Federation Unit (acronyms) in Brazil.*

In contrast, all FUs showed an increase and, therefore, a positive variation in the MHDI between 1991 and 2010 (Figure 2A, X axis). As shown in Figure 2A, the FUs with the greatest reductions in mortality rates were those with the smallest increases in MHDI. In turn, those FUs with the smallest reductions in mortality rates were the ones that showed the largest increases in MHDI. Figure 2B shows the inverse relationship between the 2010 MHDI and the percentage changes in mortality rates. Table 2 shows the 2010 MHDI and the MHDI variations between 1991 and 2010 for each FU.

Discussion

Worldwide, HF affects approximately 26 million people. This number tends to increase with population aging, increased prevalence of cardiovascular risk factors, survival of patients

Table 2 – Municipal Human Development Index (MHDI) by Federative Unit and variation between 1991 and 2010

Federative Unity	2010 MHDI	Δ% 1991-2010
Rondônia	0.690	69.5
Acre	0.663	64.9
Amazonas	0.674	56.7
Roraima	0.707	54.0
Pará	0.646	56.4
Amapá	0.708	50.0
Tocantins	0.699	89.4
Maranhão	0.639	79.0
Piauí	0.646	78.5
Ceará	0.682	68.4
Rio Grande do Norte	0.684	59.8
Paraíba	0.658	72.3
Pernambuco	0.673	53.0
Alagoas	0.631	70.5
Sergipe	0.665	63.0
Bahia	0.660	71.0
Minas Gerais	0.731	52.9
Espírito Santo	0.740	46.5
Rio de Janeiro	0.761	32.8
São Paulo	0.783	35.5
Paraná	0.749	47.7
Santa Catarina	0.774	42.5
Rio Grande do Sul	0.746	37.6
Mato Grosso do Sul	0.729	49.4
Mato Grosso	0.725	61.5
Goiás	0.735	50.9
Distrito Federal	0.824	33.8

Δ% 1991-2010 = percentage change between 1991 and 2010.

to acute coronary events, and therapeutic improvements in HF.[14] Estimates in the United States project more than 8 million people with HF by 2030, with the numbers increasing due to population aging.[15]

Mortality rates due to HF have decreased in Brazil over the 29 years analyzed in the present study, showing a trend toward a progressive reduction after 2008 and reaching similar levels across GRs and FUs by the end of 2018 (Figure 1). This trend was similar to that observed in a study with 5,823 patients followed up for 1 year across different regions worldwide, which showed a proportional mortality of 9% in South America. The authors observed high mortality rates in Africa (34%) and India (23%), followed by intermediate rates in Southeast Asia (15%) and lower rates in China and the Middle East (7%), which persisted despite adjustment for multiple clinical variables, medication therapy, and socioeconomic factors. The authors hypothesized that the quality, access, and infrastructure of the health services, as well as genetic and environmental factors, could be involved in this complex phenomenon.[16]

Another important aspect is that the average age of the patients with HF was a decade younger in low- and middle-income countries compared with high-income countries,[17] which may be related to the delay in diagnosis and treatment that could lead to a worse prognosis for less favored patients, adding to the low life expectancy in these countries.[14,18] In a

cohort of 4 million individuals from the Clinical Practice Research Datalink (CPRD) and representative of the UK population, socioeconomically disadvantaged individuals were more likely to develop HF than wealthy individuals (rate ratio incidence 1.61, 95% CI 1.58–1.64), and did so earlier in life (adjusted difference -3.51 years, 95% CI 3.77-3.25) and with more comorbidities despite the younger age. They also observed an increase in the socioeconomic gradient in the age at the first HF presentation between 2002 and 2014.[19]

Mortality rates due to HF in men were higher during almost all periods and age groups observed, except in the age group above 60 years after 1995 in the South region (Table 1), probably related to the ischemic etiology of HF, except at more advanced ages, which may be associated with longer longevity in women, as observed in a meta-analysis of about 240,000 patients with acute and chronic HF.[17] Another study of 88,416 patients also from the UK database CPRD observed that the risks of adverse outcomes were greater in individuals who are older, men, with socioeconomic limitations, and in those whose HF diagnosis was established during hospitalization. They also observed worse outcomes in women over the past two decades. The authors concluded that these disparities probably reflect the growing burden of non-CVDs in patients with HF, which will require changes in the contemporary approach and, in turn, will need to incorporate management and improvement in socioeconomic status.[20]

Previous studies have shown that patients have HF at a younger age in countries with lower compared with higher HDI,[17] and that economic limitations are associated with a higher incidence of HF at a national level.[21,22] A study with more than 17,100 patients with HF and reduced left ventricular ejection fraction from a Universal Health System has reported that low income was associated with a higher risk of death from all causes, readmission within 12 months from the HF diagnosis, longer hospital stay, and higher hospital mortality rate.[23]

An inverse trend was observed between the variation in mortality rates in the FUs between 1990 and 2018 and the variation of the respective MHDIs between 1991 and 2010. Thus, although the FUs that presented the greatest reductions in mortality rates showed the smallest increases in MHDI (Figure 2A - RJ, DF, SP, RS, SC, ES), they all reached MHDI equal to or greater than 0.7 in 2010 (Table 2). In contrast, none of the FUs with the largest increments in MHDI (Figure 2A - TO, MA, PI, PB, AL, BA) had an MHDI greater than 0.7 in 2010 (Figure 2B). This fact suggests that in relation to HF mortality, more important than the degree of MHDI increase is the final MHDI level. A study evaluating 1,802 UK patients with HF and reduced left ventricular ejection fraction using an Index of Multiple Deprivation found that all-cause mortality and mortality due to noncardiac causes adjusted for age were associated with a high risk of socioeconomic limitation, but not with mortality from cardiovascular causes. This excess risk was attributed to excess noncardiac mortality and hospitalizations and cannot be associated with the lack of medication for evidence-based HF. The authors suggest that socioeconomic interventions need to be implemented to reduce the personal risks and economic burden of the disease in patients with HF and low socioeconomic status.[24]

In the present study, we did not evaluate multiple causes of death, only the underlying causes of death selected from the information recorded in the death certificates. This fact becomes a limitation because the codes related to HF are generally discarded after the application of the rules for the selection of underlying causes by the World Health Organization,[25] which can lead to an undersized estimate of deaths due to HF. However, as these are rules of global applicability, it is believed that there is no loss when comparing deaths between different countries and/or regions.

Another point to be highlighted is that since this is a study that directly evaluates the underlying cause of death, the quality of the information depends on the proper completion of the death certificate. Errors in completion and incompleteness of the certificates caused by lack of knowledge of the declarant[26] represent potential problems that can interfere with official statistics. However, because they are systemic in nature, possible errors could affect all the causes of death, influencing not only those deaths due to HF.

Despite including data related to income, education level, and life expectancy, the HDI represents only a partial view of the socioeconomic status of a given country or region, thus not assessing phenomena such as inequality or quality of life and their influences on HF mortality. However, since this index is available worldwide, it allows for comparing, with proper dimensioning, different populations.

In addition to representing an enormous burden for society, HF is the main cause of hospitalization in western countries.[27] The increasing prevalence of HF, especially in younger individuals, and the inefficient public spending on health care in developing countries, which already have important social inequalities, will require a reconsideration of the economic impact of HF, especially in a country with continental dimensions like Brazil.

Few data are known about the epidemiology of HF, especially in middle-income countries like Brazil, where the prevalence of HF is believed to be increasing, and an increasing association has been reported with ischemic heart disease, rheumatic disease, Chagas disease, and hypertension, among others.[28] The reduction in HF mortality may be a consequence of advances in the treatment of ischemic heart disease, but it must also be related to the progression in HF treatment itself, especially after the introduction of neurohumoral blocker therapy.[4]

Efforts must be made to expand access to health care and toward more effective control of cardiovascular risk factors, dyslipidemia, obesity, physical inactivity, and diabetes, as well as social determinants that contribute to both mortality from HDI and HF. It is within this context that the scope of the Family Health Program can play an important role, which in addition to attributing the model of the care to primary care, increases the coverage of the National Health System, reducing the proportion of unattended deaths, improving the quality of vital information in Brazil, and decreasing hospitalizations due to chronic diseases such as HF.[29] Future studies must be carried out to analyze the association of the installed capacity of health care resources, and the multiple causes represented by risk factors as contributors to the complex

process of death to improve the guidance of public health policies regarding HF in Brazil.

Conclusion

This study evaluating HF mortality in Brazil over 39 years at each FU of the GRs demonstrated that, despite variations, all FUs showed a reduction in mortality rates, especially in the last 10 years of observation. A predominance of deaths in men was observed in the age group of 30–59 years. There was a trend toward an inverse relationship between the percentage of increase in MHDI and reduction in mortality rates, the latter potentially related to the absolute level of MHDI achieved in 2010. These findings could, at least in part, be justified by improved access to the health system in HF treatment and socioeconomic conditions of the population over almost four decades.

Author Contributions

Conception and design of the research, Acquisition of data, Analysis and interpretation of the data, Obtaining financing, Writing of the manuscript and Critical revision of the manuscript for intellectual content: Santos SC, Villela PB, Oliveira GMM.

Potential Conflict of Interest

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

Sources of Funding

There were no external funding sources for this study.

Study Association

This article is part of the thesis of master submitted by Sonia Carvalho Santos, from Universidade Federal do Rio de Janeiro.

Ethics approval and consent to participate

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

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*Supplemental Materials

For additional information, please click here.

Socioeconomic Indicators and Mortality from Heart Failure: Inseparable Parameters?

Helder Jorge de Andrade Gomes[1,2] *and Carlos Eduardo Lucena Montenegro*[3,4]

Group of Investigation on Multimorbidity and Mental Health in Aging (GIMMA) - Faculdade de Medicina de Jundiaí,[1] *Jundiaí, SP - Brazil*
Hospital Samaritano de São Paulo,[2] *São Paulo, SP - Brazil*
PROCAPE (Pronto Socorro Cardiológico de Pernambuco) - Universidade de Pernambuco,[3] *Recife, PE - Brazil*
Centro Cardiológico Ovídio Montenegro,[4] *Recife, PE - Brazil*

Short Editorial related to the article: Mortality Due to Heart Failure and Socioeconomic Development in Brazil between 1980 and 2018

Cardiovascular diseases (CVD) are still the leading cause of death, accounting for approximately one third of deaths worldwide. In June 2021, the World Health Organization (WHO) underscored its concern about the impact caused by CVD in low- and middle-income countries, where more than three quarters of their deaths occur.[1] Heart failure (HF) is a common final route of heart diseases. It is an out-of-control global pandemic, with increasing prevalence, as a consequence of factors such as population aging, a greater presence of cardiovascular risk factors such as obesity, sedentary lifestyle or diabetes mellitus, despite therapeutic advances that reduce mortality.[2]

The connection between worse socioeconomic conditions and higher mortality from HF seems to have been well established in recent years in different populations[3-5] and is partially justified by the worse access to diagnostic methods and pharmacological treatment. However, this relationship is more confusing in low- and middle-income countries, where clinical, demographic, and socioeconomic variables explain little about the variability between one-year HF mortality rates across Africa, India, Southeast Asia, Middle East, South America and China, as observed in the INTER-CHF prospective cohort study.[6]

In the past decades, Brazil has shown a gradual decline in inequality, measured by the Gini coefficient — especially from the mid-1990s and reaching its lowest levels in 2010[7] — as well as a progressive improvement in the Human Development Index (HDI) and its equivalent locally determined index (LHDI), which report three basic dimensions of human development: longevity, education and income.[8] Along the same lines, the publication by Malta et al.[9] presented recent data confirming that the adjusted cardiovascular mortality rate has also declined in Brazil over the past years, although a heterogeneity among the states of Brazil has already drawn attention. A study published in this issue of ABC[10] analyzes the relationship between the temporal evolution of human development and mortality rates from heart failure in different regions of Brazil, shedding some important light on this topic.

According to this study,[10] reduced mortality from HF actually occurred in all states of Brazil. However, although the reduction in mortality in the states where there was a smaller increase in the LHDI (Rio de Janeiro, Brasília, São Paulo, Rio Grande do Sul, Santa Catarina and Espírito Santo) was greater, all of these states already had a high LHDI (>0.7). On the other hand, the authors note that the LHDI has also improved in all Brazilian states. Despite the rates lower than 0.7, the states that showed the highest increases in the LHDI (Tocantins, Maranhão, Piauí, Paraíba, Alagoas and Bahia), had smaller reductions in mortality from HF. These data strongly suggest, therefore, that to achieve large reductions in the HF mortality rate, "more important than the level of LHDI increase is the final level it reaches" – as stated by the authors.

Apparently, mortality from a chronic non-contagious disease such as heart failure and socioeconomic indicators are not such inconsistent parameters. On the contrary, it may be that these two lines meet over time in case of a reduction in inequalities and all regions reach good development rates (LHDI >0.7). Or these lines may stand apart even further if the worsening of health indicators in Brazil observed in the recent years persists, with increasing poverty rates, cuts in social policies and freezing of health investment produced by Constitutional Amendment no. 95, as recently cited.[9,11] Although the HDI represents only a partial view of the socioeconomic status of a population, and cannot be directly assessed on the relationship of inequality and mortality due to HF, it is reasonable to infer that important variations in the HDI between regions reveal spots of inequality across Brazil. A low HDI reflects, in most cases, a poor population with a significant educational deficit, which leads to greater difficulties in understanding, acquiring and sticking to such a complex medical treatment such as HF.

The study confirms the impression that good socioeconomic and educational conditions seem to be intrinsically linked to better cardiovascular outcomes. As Brazil is a country with continental dimensions and high levels of inequality, recognizing the importance of the epidemiological assessment mechanisms available in its public health system (DATASUS, SIM, etc.), the Brazilian Institute of Geography and Statistics (census, intercensus and projections), the United Nations Development Program (HDI, LHDI, etc.), and others, is essential to direct socio-sanitary policies for the application of robust scientific evidence available and updated recently for the diagnosis, treatment and prevention of heart failure and cardiovascular health in general.[11,12]

Keywords

Cardiovascular Diseases; Heart Failure; Mortality, Risk Factor; Social Class; Human Development.

Mailing Address: Carlos Eduardo Lucena Montenegro •
Rua Aviador Severiano Lins, 182. Ap. 2301. Postal Code 51020-060, Boa Viagem, Recife, PE – Brazil
E-mail: ce_montenegro@yahoo.com.br

DOI: https://doi.org/10.36660/abc.20210826

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The Heart of Pediatric Patients with COVID-19: New Insights from a Systematic Echocardiographic Study in a Tertiary Hospital in Brazil

Maria de Fátima Rodrigues Diniz,[1] Maira Freire Cardoso,[1] Karen Saori Shiraishi Sawamura,[1,2,3] Carolina Rocha Brito Menezes,[1] Alessandro Cavalcanti Lianza,[1,3] Maria Fernanda Badue Pereira,[1] Nadia Litvinov,[1] Juliana Ferreira Ferranti,[1] Silvana Forsait,[1] Andreia Watanabe,[1] Sylvia Costa Lima Farhat,[1] Nadia Emi Aikawa,[1] Lucia Maria Arruda Campos,[1] Artur Figueiredo Delgado,[1] Magda Carneiro-Sampaio,[4] Werther Brunow de Carvalho,[5] Clovis Artur Silva,[5] Gabriela Nunes Leal[1,2,6]

Universidade de São Paulo Instituto da Criança,[1] São Paulo, SP - Brazil

Hospital do Coração,[2] São Paulo, SP - Brazil

Hospital Israelita Albert Einstein,[3] São Paulo, SP - Brazil

Universidade de São Paulo Hospital das Clínicas - Faculdade de Medicina,[4] São Paulo, SP - Brazil

Universidade de São Paulo - Faculdade de Medicina,[5] São Paulo, SP - Brazil

Hospital Sírio-Libanês,[6] São Paulo, SP - Brazil

Abstract

Background: **COVID-19 pandemic represents a huge burden to the health system in the world. Although pediatric COVID-19 patients have been relatively spared compared with adults, recent reports showed an increasing number of critically ill patients with multisystemic inflammatory syndrome in children (MIS-c), with marked cardiovascular impairment. Nevertheless, little is known about the relationship between cardiac abnormalities and inflammatory and coagulation biomarkers.**

Objectives: **To investigate echocardiographic abnormalities in pediatric patients with COVID-19 admitted to tertiary hospital.**

Methods: **This was a retrospective longitudinal study, based on the review of medical records and echocardiograms of patients (0-19 years) admitted to a tertiary hospital between March 30 and June 30, 2020. For statistical analysis, the significance level was set at 5% ($p < 0.05$).**

Results: **Forty-eight patients were enrolled, 73% with preexisting diseases, 20 (41.7%) with MIS-c. Median age was 7.5 (0-18.6) years; 27 (56.2%) were male. Median duration of hospitalization was 15.4 (2-92) days and seven (14.6%) patients died. A total of 70 echocardiograms were performed; 66.7% patients were scanned only once and 33.3% multiple times. Twenty-three (48%) patients showed echocardiographic abnormalities: eight (16.6%) left ventricle (LV) systolic dysfunction, six (12.5%) right ventricle (RV) systolic dysfunction and 12 (25%) coronary dilatation (Z-score>+2.5). Echocardiographic abnormalities were significantly associated with MIS-c, admission to the pediatric intensive care unit, multiple organ dysfunction, ventilatory/vasoactive support, and death ($p<0.05$). Significantly higher d-dimer (ng/mL) levels were detected in patients with LV dysfunction [16733(4157-115668) vs. 2406.5(190-95040)], RV dysfunction [25769(3422-115668) vs. 2803.5(190-95040)] and coronary artery dilation [9652.5(921-115668) vs. 2724(190- 95040)] ($p<0.05$).**

Conclusion: **Echocardiographic abnormalities in COVID-19 pediatric patients were frequent and associated with worse clinical outcomes. Exacerbation of the inflammation and coagulation pathways may play an important role in cardiovascular injury in those patients.**

Keywords: **COVID-19; Pandemics; Betacoronavirus; Biomarkers; Inflammation; Child; Heart Failure; Echocardiography/methods.**

Introduction

The coronavirus disease 19 (COVID-19) pandemic represents a huge burden to the health system in the world. In its severe presentation, COVID-19 is a systemic illness characterized by hyperinflammation, cytokine storm and elevated myocardial injury markers.[1] Cardiac involvement appears to be a prominent feature of the disease in adults, occurring in 20% to 30% of hospitalized patients and contributing to 40% of deaths.[2] Although children have been relatively spared compared to adults, recent reports showed an increasing number of critically ill children with multisystem inflammatory syndrome (MIS-C, multisystem inflammatory syndrome in children), accompanied by severe cardiovascular impairment.[3] Ventricular dysfunction, pericardial effusion, valvar regurgitation and coronary artery inflammation were documented in many case series. A Kawasaki-like phenotype was also described in some MIS-C patients, although recent literature suggests these are two different illnesses with overlapping clinical features. To date, MIS-C

Mailing Address: Maria de Fátima Rodrigues Diniz •
Universidade de São Paulo Instituto da Criança - Serviço Auxiliar de Diagnóstico e Terapia - Avenida Dr. Eneas Carvalho de Aguiar, 647. Postal Code 05403-000, Cerqueira Cesar, São Paulo, SP – Brazil
E-mail: mariafrdiniz@hotmail.com
Manuscript received August 19, 2020, revised manuscript October 19, 2020, accepted November 11, 2020

DOI: https://doi.org/10.36660/abc.20200920

occurs predominately in older children, with a median age of 9-10 years, whereas Kawasaki disease typically affects patients younger than five years. Cardiovascular shock, rarely seen in Kawasaki disease, is a striking feature of MIS-C.[3]

Nevertheless, the real incidence of overall cardiac abnormalities among pediatric COVID-19 patients and their relevance to clinical outcomes are yet to be determined. Little is known about the relationship between cardiac abnormalities, and inflammatory and coagulation markers in this group.[4] Consequently, there is an urgent need to better understand the interactions between COVID-19 and the heart in the pediatric population.

The present study aimed to investigate echocardiographic abnormalities of pediatric COVID-19 patients admitted to a tertiary hospital in São Paulo, the epicenter of coronavirus pandemic in Brazil. Possible associations of clinical and laboratory data with echocardiographic findings were also explored.

Methods

Study design and population

This is a longitudinal retrospective study, based on the review of medical records and echocardiogram reports from children and adolescents (0-19 years) admitted to the pediatric ward and intensive care unit due to COVID-19, between March 30 and June 30, 2020. Patients with and without MIS-c were included, according to the World Health Organization (WHO) classification.[5] Exclusion criterion was the absence of echocardiograms during the follow-up period.

Clinical, laboratory and therapeutic parameters

Patients' electronic medical records were carefully reviewed for clinical, laboratory and therapeutic data. Pre-existing diseases and previous echocardiogram reports were also registered. The Institutional Research Ethics Committee has approved the study.

Patients were classified as having MIS-C if they fulfilled the following criteria:

1. Children and adolescents (0-19 years) with fever for three or more days;
2. And at least two of the following:
   a. Rash, bilateral non-purulent conjunctivitis, or mucocutaneous inflammation signs (oral, hands or feet).
   b. Hypotension or shock
   c. Features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities (including echocardiographic findings or elevated cardiac enzymes).
   d. Evidence of coagulopathy (by elevated d-dimers, prothrombin time, partial thromboplastin time)
   e. Acute gastrointestinal problems (diarrhea, vomiting or abdominal pain).
3. And: elevated inflammatory markers such as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) or procalcitonin.
4. And: no other obvious microbial cause of inflammation
5. And: severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) confirmed infection by real time-polymerase chain reaction (RT-PCR) and/or serology, or likely contact with patients with COVID-19.

RT-PCR in respiratory specimens were performed to detect SARS-CoV-2 RNA. Serologic tests included two different methods during the COVID-19 pandemic: immunochromatography assay for SARS-Cov-2 specific IgM/IgG antibody detection and anti-SARS-CoV-2 enzyme-linked immunosorbent assay (ELISA) for IgG antibodies detection.[6]

MIS-C and non-MIS-C patients were compared regarding age, sex, clinical signs and symptoms at presentation, frequency of echocardiographic abnormalities, confirmed SARS-CoV-2 infection and death. The following laboratory data were compared: frequency of anemia, lymphocytopenia and thrombocytopenia, evidence of coagulopathy, peak levels of d-dimer, CRP, ferritin, troponin, and creatine kinase-MB. Pro-brain natriuretic peptide (BNP), procalcitonin and fibrinogen were not included in the analysis, because these biomarkers were not assessed routinely in all patients.

Anemia was defined as hematocrit at or below the 2.5th percentile for age, race and gender;[7] lymphocytopenia was defined as a lymphocyte count was lower than 4,500/mm^3 in children under eight months of age and 1500/mm^3 in older ones;[8] and thrombocytopenia was defined as platelet count lower than 100,000/microL.[9]

Echocardiography

All echocardiographic tests were performed by two experienced pediatric cardiologists, according to the guidelines of the American Society of Echocardiography (ASE).[10] The analyses included M and two-dimensional (2D) modes, besides standard Doppler examinations with color flow mapping. The equipment used was a Philips Affinity 70, CX50 and Innosight compact ultrasound, with multi-frequency transducers (S5-1 and S8-3). Echocardiographic studies also followed the ASE statement on protection of patients and echocardiography service providers during COVID-19 outbreak.[11] Since one of the equipment used in our institution during the COVID-19 pandemic was originally designed as a point-of-care ultrasound (Philips Innosight), it was not possible to obtain 2D derived left ventricular ejection fraction (LVEF) (Simpson's method) in all scans. For that reason, M-mode derived LVEF (Teichholz method) was chosen for this study purpose, although Simpson's method would be undoubtedly more accurate.[10] Left ventricular (LV) systolic dysfunction was defined as a LVEF lower than 55%; it was considered mild if the LVEF was $\geq$ 45% and $<$ 55%, moderate if the LVEF was $\geq$ 30% and $<$ 45%, and severe if the LVEF was $<$ 30%.[10]

Right ventricular (RV) systolic function was evaluated by tricuspid annular plane systolic excursion (TAPSE). RV systolic dysfunction was detected when TAPSE z-score was lower than -2.[12]

Coronary arteries were evaluated according to the American Heart Association Statement for Diagnosis, Treatment and Long-Term Management of Kawasaki Disease.[13]

Dilation was detected when the coronary artery internal lumen diameter z-score was higher than higher than +2.5.[14] A z-score between +2.5 and +5 defined small aneurisms; between +5 and +10, medium aneurisms; equal or greater than +10, giant aneurisms. Other echocardiographic signs frequently described in coronary artery inflammation, like enhanced perivascular brightness and lack of tapering, were also registered.[13]

Pulmonary artery systolic pressure (PASP) was estimated through tricuspid regurgitation; pulmonary hypertension (PH) was diagnosed when the pulmonary artery systolic pressure was greater than 35 mmHg. Mild PH was diagnosed if 35 mmHg < PASP ≤ 45 mmHg, moderate if 45 mmHg < PASP ≤ 50 mmHg and severe if PASP > 50 mmHg.[15]

Pericardial effusion presence was also described, as well as eventual signs of pericardial tamponade.

Patients were divided according to the presence or absence of echocardiographic abnormalities and compared regarding age, gender, presence of MIS-c, pediatric intensive care unit (PICU) admission, presence of multiple organ dysfunction, ventilatory/vasoactive support, renal replacement therapy, use of intravenous (IV) immunoglobulin, corticosteroids, acetylsalicylic acid and low molecular weight heparin, length of hospital stay, and death.

Images were digitally acquired, and intra and interobserver variability of LVEF, TAPSE and coronary arteries diameter was evaluated. The same examiner repeated analysis of 10 randomly selected exams. A second observer (CRB), unaware of previous results and of patient's clinical condition, also performed offline echocardiographic measures.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics 22. Categorical data were reported as percentages and continuous data as mean (standard deviation - SD) or median (range). Fisher exact test was chosen to compare categorical data. The Kolmogorov and Smirnov test was used to verify if data were sampled from a Gaussian distribution. Unpaired Student's t test was used to assess continuous data with normal distribution, and the Mann-Whitney U test to assess continuous data without normal distribution. The significance level was set at 5% ($p < 0.05$). Intra and interobserver variability for echocardiographic measures was assessed using Bland Altman Plot and intraclass correlation coefficient (ICC), with good correlation being defined as ICC > 0.8.

Results

Clinical presentation

Forty-eight pediatric patients were hospitalized due to COVID-19 during the study period. The median age was 7.5 (0 - 18.6) years; 21 (43.8%) were female. The median in-hospital stay was 15.4 (2 - 92) days. By the end of the study, 33 (68.7%) patients have been successfully discharged, eight (16.7%) were still in the pediatric ward or PICU, and seven (14.6%) patients died. All deaths occurred in the MIS-c group. There was no statistically significant difference between survivors and deceased patients regarding the use of corticosteroids, IV immunoglobulin or low molecular weight heparin.

Twenty (41.7%) patients fulfilled the WHO criteria for MIS-c and 28 (58.3%) did not. Among MIS-c patients, 11 (55%) had confirmed SARS-CoV-2 infection by RT-PCR and/or serology and nine (45%) patients did not. All nine MIS-c patients without confirmed SARS-CoV-2 infection have had intimate contact with COVID-19 patients in the last four weeks before symptoms. Five of those nine patients had also typical findings on chest computed tomography (ground-glass opacities with surrounding consolidation (halo sign).

In the non-MIS-c patients (n=28), the SARS-CoV-2 infection was confirmed by PCR and/or serology.

MIS-c was associated with seizures, shock, evidence of coagulopathy, echocardiographic abnormalities, and death. Significantly higher peak values of serum d-dimer, CRP and troponin were detected among MIS-c patients ($p<0.05$). The incidence of respiratory and gastrointestinal symptoms was similar between MIS-c and non-MISC-c patients ($p>0.05$). Likewise, there was no difference between the frequency of anemia, lymphocytopenia, thrombocytopenia or preexisting diseases between the two groups of patients ($p>0.05$). Only one patient had with mucocutaneous inflammation signs. No patient fulfilled the diagnostic criteria for Kawasaki disease (Table 1).

Preexisting diseases were detected in 35 (73%) patients: immunosuppression in 26 (54.2%), malignancies in 14 (40%), chronic kidney disease in nine (25.7%), chronic neuropathy in eight (22.8%), congenital/acquired heart disease in five (14.2%), chronic pneumopathy in five (14.2%), hepatopathy in four (11.4%), dysmorphic syndromes in three (6.3%), Duchenne muscular dystrophy in one (2.8%), juvenile systemic lupus erythematosus in one (2.8%), previous orthopedic surgery in 1(2.8%), previous gynecologic surgery in one (2.8%) and previous heart transplantation in one (2.8%). Two (4.2%) patients were neonates born to COVID-19 mothers and one of them was also preterm. Among the seven deceased patients, three were oncologic (two solid tumors and one leukemia), one had primary immunodeficiency, one had Edwards syndrome with congenital heart disease and two were healthy.

Echocardiographic evaluation

The 48 patients had at least one echocardiogram performed during hospitalization. Thirty-two patients (66.7%) had only one exam and 16 (33.3%) were scanned multiple times. A total of 70 exams were carried out throughout the study. All patients with preexisting diseases were already followed at our institution and had previous echocardiogram reports in their medical records. Five (14.2%) patients had previous echocardiographic abnormalities: one with small ventricular septal defect and bicuspid aortic valve (Edward's syndrome), one with small residual ventricular septal defect and discrete aortic coarctation, one with echogenic mass invading inferior vena cava (adrenal tumor), one with discrete left ventricle hypertrophy secondary to chronic kidney disease and one with moderate left ventricle systolic dysfunction secondary to chemotherapy (sarcoma).

Table 1 – Demographic data, clinical and laboratory data of COVID-19 pediatric patients with and without multisystem inflammatory syndrome in children (MIS-C), according to the World Health Organization criteria (WHO)

Demographic, clinical and laboratory data	MIS-C (*n*= 20)	Non-MIS-C (*n* = 28)	p
Age (years)	8.4 (0.1-16.4)	6.7 (0 – 18.6)	0.33
Sex (male)	10 (50%)	17 (60.7%)	0.56
Preexisting diseases	15 (75%)	20 (71.4%)	1
Respiratory symptoms	10 (50%)	14 (50%)	1
Gastrointestinal symptoms	6 (30%)	7 (25%)	0.75
Rash/ Non-purulent bilateral conjunctivitis/ mucocutaneous inflammation signs	1 (5%)	0 (0%)	0.41
Seizures	5 (25%)	0 (0%)	0.009
Shock	12 (60%)	0 (0%)	<0.0001
Evidence of coagulopathy (↑PT, ↑PTT, ↑D-dimer)	20 (100%)	18 (64.3%)	0.0028
Anemia*	14 (70%)	21 (75%)	0.75
Thrombocytopenia**	4 (20%)	7 (25%)	0.74
Lymphocytopenia***	8 (40%)	14 (50%)	0.56
Echocardiographic abnormalities	19 (95%)	4 (14.3%)	<0.0001
D-dimers (ng/ml)****	9652.5 (921 - 115668)	1722 (190 - 95040)	0.0003
C-reactive protein (mg/L)****	119.6 (0.38 - 447.7)	14.6 (0.30 – 324)	0.0046
Ferritin (ng/ml)****	1159 (58-35967)	655 (25-2567)	0.07
Troponin (ng/L)****	25 (9-385)	16 (3-1050)	0.028
Creatine kinase (CK-MB) (ng/ml)****	1.78 (0.3-30)	1.65 (0.18-28.9)	1
Death	7 (35%)	0 (0%)	0.001
Confirmation of Sars-CoV-2 infection (RT-PCR/serology)	11 (55%)	28 (100%)	0.0001

*Values are expressed as n (%) or as median (range). Fisher exact test was used to compare categorical data. Mann-Whitney U test was used to compare non-normally distributed continuous variables. *Hematocrit at or below 2.5th percentile for age, race, and sex at admission. **Platelet count < 100000/ microL at admission; ***Lymphocyte count < 4,500/mm^3 in children under 8 months and < 1500/mm^3 in older ones at admission; ****Values correspond to the highest serum level obtained from each patient. PT: prothrombin time; PTT: partial thromboplastin time*

Twenty-three (48%) patients had echocardiographic abnormalities and 19 (39.6%) of them showed new echocardiographic findings potentially associated with COVID-19 as follows: left and RV systolic dysfunction, coronary dilation, PH, and pericardial effusion. Of note, only one patient with previous echocardiographic abnormalities presented with new echocardiographic findings: LV systolic dysfunction secondary to chemotherapy progressed from moderate to severe and coronary dilation was also detected.

Echocardiographic abnormalities were associated with MIS-c, PICU admission, multiple organ dysfunction, ventilatory and vasoactive support, use of IV immunoglobulin, corticosteroid, acetylsalicylic acid and low molecular weight heparin, and death (Table 2). Patients with echocardiographic abnormalities also had significantly higher length of hospital stay.

Ten (20.8%) of the 48 patients received low molecular weight heparin during hospitalization, only one patient without echocardiographic abnormalities. Therapeutic anticoagulation was introduced in two patients: one with left main coronary artery (LMCA) z-score of +10 and one with LV severe systolic dysfunction and subclavian vein thrombosis. The remaining eight patients received prophylactic low molecular weight heparin due to prolonged hospitalization, concomitant malignancies, and prolonged catheter use.

LV systolic dysfunction was detected in eight (16.6%) patients: six with mild, one with moderate and one with severe dysfunction. Global hypokinesia of left ventricle was found in all but one patient, who exhibited apical akinesia suggestive of Takotsubo syndrome. Four patients with LV systolic dysfunction had also coronary arteries abnormalities. Patients with LV systolic dysfunction showed significantly higher peak levels of d-dimer, CRP, ferritin, and troponin (Table 3). Five patients with LV systolic dysfunction received IV immunoglobulin and only one received corticosteroids. No patient received interleukin blockers. Five patients showed improvement of LV systolic function during the follow-up.

Six (12.5%) patients showed RV systolic dysfunction. These patients showed significantly higher peak levels of d-dimer and troponin (Table 3). Two patients had mild PH and three had also LV systolic dysfunction. RV systolic function improved in three patients during follow-up.

Table 2 – Demographic data e clinical outcomes according to the presence or absence of echocardiographic abnormalities

Demographic data, treatment strategies and clinical outcomes	Echocardiographic abnormalities		
	Present (*n* = 23)	Absent (*n* = 25)	p
Age (years)	7.8 (0.1-16.4)	6.4 (0-18.6)	0.87
Sex (male)	11 (47.8%)	16 (64%)	0.38
MIS-c according to WHO criteria	19 (82.6%)	1 (4%)	<0.0001
Pediatric Intensive Care Unit	15 (65.2%)	5 (20%)	0.003
Multiple organ dysfunction syndrome	8 (34.8%)	0 (0%)	0.0013
Respiratory system	6 (26%)	0 (0%)	
Cardiovascular system	6 (26%)	0 (0%)	
Renal system	5 (21.7%)	0 (0%)	
Hepatic system	2 (8.7%)	0 (0%)	
Neurological system	4 (17.4%)	0 (0%)	
Hematological system	4 (17.4%)	0 (0%)	
Ventilatory support	15 (65.2%)	7 (28%)	0.02
Oxygen by nasal catheter	8 (34.8%)	3 (12%)	
Venturi mask	3 (13%)	1 (4%)	
Non-rebreather mask	0 (0%)	1 (4%)	
High-flow oxygen therapy	6 (26%)	1 (4%)	
Noninvasive ventilation	5 (21.7%)	1 (4%)	
Conventional Mechanical ventilation	10 (43.5%)	3 (12%)	
High-frequency ventilation	1 (4.3%)	0 (0%)	
Vasoactive drug support	10 (43.5%)	1 (4%)	0.0015
Epinephrine	4 (17.4%)	0 (0%)	
Norepinephrine	10 (43.5%)	1 (4%)	
Vasopressin	2 (8.7%)	0 (0%)	
Milrinone	5 (21.7%)	1 (4%)	
Dobutamine	3 (13%)	0 (0%)	
Renal replacement therapy	5 (21.7%)	2 (8%)	0.23
Peritoneal dialysis	0 (0%)	2 (8%)	
Conventional hemodialysis	1(4.3%)	0 (0%)	
Sustained low-efficiency dialysis	1 (4.3%)	0 (0%)	
Continuous hemodialysis	3 (13%)	0 (0%)	
IV Immunoglobulin	14 (60.8%)	0 (0%)	<0.0001
Corticosteroids	4 (17.4%)	0 (0%)	0.04
Acetylsalicylic acid	9 (39%)	0 (0%)	0.0005
Low molecular weight heparin	9 (39.1%)	1 (4%)	0.0038
Length of stay (days)	23 (2-92)	8.3 (2-26)	0.0074
Deaths	6 (26%)	1 (4%)	0.04

Values are expressed as n (%) or as median (range). Fisher exact test was used to compare categorical data. Mann-Whitney U test was used to compare non-normally distributed continuous variables.

Table 3 – Laboratorial profile of patients according to the echocardiographic abnormalities detected throughout the study

Laboratory*	LV systolic dysfunction			RV systolic dysfunction			Coronary artery abnormalities		
	Present (n = 8)	Absent (n = 40)	p	Present (n = 6)	Absent (n = 42)	p	Present (n =12)	Absent (n = 36)	p
D-dimers (ng/ml)	16733 (4157 -115668)	2406.5 (190 - 95040)	0.0015	25769 (3422 - 115668)	2803.5 (190 - 95040)	0.037	9652.5 (921 - 115668)	2724 (190 - 95040)	0.04
CRP (mg/L)	303.16 (30 - 423)	35.9 (0.3 - 447.7)	0.0017	113.95 (2 - 407.21)	53.95 (0.3 - 447.70)	0.46	109.9 (0.38 – 423)	33.75 (0.38 - 447)	0.10
Ferritin (ng/ml)	3734 (839 - 35967)	499 (25 - 8000)	0.0026	1301 (123 - 35967)	663 (25 - 8000)	0.18	389.50 (58 - 35967)	790 (25 - 8000)	0.8
Troponin (ng/L)	88 (20 - 342)	16 (3 - 1050)	0.0018	108.5 (3 - 385)	17 (3 - 1050)	0.04	19.5 (9 - 125)	19 (3 - 1050)	0.57
CK-MB (ng/ml)	2.2 (0.7 - 28)	1.6 (0.18 - 30.7)	0.62	4 (0.18 - 30.7)	1.6 (0.3 -28.9)	0.58	1.78 (0.3 -18.2)	1.65 (0.18 – 30.7)	0.9

*Mann-Whitney U test was used to compare non-normally distributed continuous variables. *Values correspond to the highest level obtained from each patient and are expressed as median (range).*

Coronary abnormalities were detected in 12 (25%) patients and most of them exhibited mild ectasia, except for an adolescent (15 years old) with a LMCA z-score of +10 (Figure1). Besides dilation, six patients had also enhanced perivascular brightness. Dilatation of the LMCA was observed in 11 patients, with a median z-score of +4 (+2.8 - +10); dilation of the left descending coronary artery (LDCA) in six, with a median z-score of +4 (+3.6 - +4.2); dilatation of the left circumflex coronary artery (LCCA) in three, with a median z-score of +4.6 (+3.9 - +5); and dilatation of the right coronary artery (RCA) in four, with a median z-score of +3.3 (+2.6 - +4.3). Patients with coronary arteries abnormalities had significantly higher peak levels of d-dimers (Table 3). In four patients, coronary abnormalities were not present in the first echocardiographic evaluation and were detected in subsequent scans.

Eleven (91.7%) of the 12 patients with coronary dilatation received IV immunoglobulin. One had coronary dilatation detected belatedly, after being afebrile for more than one week. Nine (75%) of the 12 patients with coronary dilatation received acetylsalicylic acid and three (25%) corticosteroids. Acetylsalicylic acid was contraindicated in three of the 12 patients with coronary artery inflammation, due to thrombocytopenia and/or peptic ulcer. No patient exhibited normalization of coronary arteries z-score during the follow-up.

Four patients had mild tricuspid and mitral regurgitation and one patient had mild aortic regurgitation. All of them were MIS-c patients.

Four (8,3%) patients had mild PH, which was associated with MIS-c: 4 (20% with MIS-c) x 0 (0% Non-MIS-c).

Eight (16.6%) patients had discrete transient pericardial effusion, which was also associated with MIS-c: eight (40%) x 0 (0%); $p = 0.0003$. Five patients had concomitant LV systolic dysfunction, two had RV systolic dysfunction and only one PH.

Intra- and interobserver variability of echocardiographic measures

Reproducibility of LVEF, TAPSE and coronary arteries was considered good, as demonstrated by ICC ≥ 0.85 for intra and interobserver variability (Table 4).

Discussion

The present study stands out for the systematic echocardiographic evaluation of a cohort of pediatric COVID-19 patients, with high prevalence of preexisting diseases. Significant associations of cardiac abnormalities with clinical, laboratorial and therapeutic parameters were clearly demonstrated, reinforcing the pivotal role of rigorous echocardiographic follow-up of this population.

Studies published since April, 2020, conducted in the UK, France, Italy, Switzerland and North America have reported that MIS-c is temporally related to SARS-CoV-2, and is frequently associated with cytokine storm, severe cardiovascular impairment, PICU admission and death.[16] Differently from the present study, most of their children and adolescents did not have underlying comorbidities, which may have contributed to the better clinical outcomes. While Feldstein et al.[17] reported 2% of deaths in a population where 73% were previously healthy patients, this study showed 14.6% of deaths in a population with 27% of healthy subjects. Like in the majority of published papers, the present MIS-C patients had less positive RT-PCR tests than the non-MIS-C ones, suggesting that this syndrome is a post-infectious phenomenon related to a hyperimmune response, occurring a couple of weeks after the acute phase. Only one patient presented with mucocutaneous inflammation signs, reinforcing that MIS-c and Kawasaki disease are really different illnesses sharing some clinical features.[3]

Table 4 – Reproducibility for LV ejection fraction, TAPSE and coronary artery internal diameter

Parameter	Bias	95% limits of agreement	ICC
Intraobserver variability			
LVEF (%)	0.2	-1.82 a 2.22	1
TAPSE (cm)	-0.09	-0.42 a 0.24	0.92
LMCA (mm)	0	-0.01 a 0.02	0.9
LDCA (mm)	0	-0.01 a 0.01	1
LCCA (mm)	0	-0.02 a 0.01	0.95
RCA (mm)	0	-0.01 a 0.01	0.98
Interobserver variability			
LV ejection fraction (%)	0.4	-3.95 a 4.75	0.98
TAPSE (cm)	-0.08	-0.49 a 0.33	0.85
LMCA (mm)	0.01	-0.01 a 0.02	0.9
LDCA (mm)	0	-0.02 a 0.02	1
LCCA (mm)	0	-0.02 a 0.03	0.99
RCA (mm)	0	-0.02 a 0.01	0.98

LVEF: left ventricular ejection fraction; TAPSE: tricuspid annular plane systolic excursion; LMCA: left main coronary artery; LDCA: left descending coronary artery; LCCA: left circumflex coronary artery; RCA: right coronary artery.

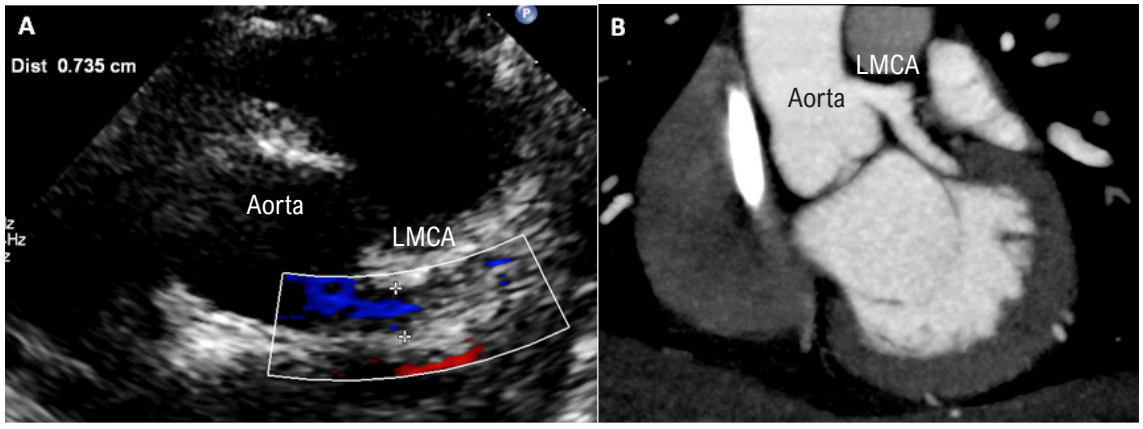

Figure 1 – *A) Echocardiogram showing dilated left main coronary artery (LMCA) in a 15-year old girl; B) Computed tomography of the same patient.*

The largest global echocardiographic survey already published reveled cardiac abnormalities in 46% of adult patients with COVID-19, without preexisting cardiac diseases. Similarly, the present study documented non-previously described echocardiographic abnormalities in 39.6% of pediatric COVID-19 patients, potentially related to SARS-CoV-2 infection.[18]

Most studies reporting cardiac abnormalities in pediatric patients with COVID-19 enrolled many centers, without a common protocol of echocardiographic evaluation. To date, in one of the largest published series that included 186 patients with MIS-c from 26 states in the United States, LVEF was assessed either quantitatively or qualitatively.[17] The standardization of echocardiographic methods and the inclusion of intra/interobserver variability tests in this study may have contributed to more reliable estimation of the incidence of cardiac abnormalities among pediatric COVID-19 patients. For instance, twice as much LV systolic dysfunction was found in MIS-c patients (40%), compared with the study of Feldstein et al. (20%).[17]

Although ventricular systolic dysfunction in pediatric patients with COVID-19 has been extensively described, the pathophysiological mechanisms involved in myocardial injury were scarcely investigated.[19,20] Viral particles have been

observed in the myocardium and vascular endothelium in adult patients with COVID-19 and cardiogenic shock.[21,22] In addition, autopsies showed inflammatory infiltrates composed of macrophages, CD4+ and T cells, associated with regions of cardiomyocyte necrosis. It is still unclear how much of the cardiac injury can be directly attributable to viral infection versus systemic inflammatory response.[1] In spite of the mechanism involved, adult patients with elevated biomarkers of myocardial injury (troponin, pro-BNP) are at significantly higher risk of death.[23] In the present study, higher levels of troponin were found in patients with left and RV systolic dysfunction, highlighting the possible contribution of cardiac impairment to worse clinical outcomes in pediatric COVID-19 patients. Indeed, patients with echocardiographic abnormalities required more aggressive ventilatory and vasoactive drug support and longer hospitalization and had a higher mortality rate than those with normal echocardiograms.

Serum levels of inflammatory markers such as ferritin and CRP are also known to be higher in non-survivors than in survivors of COVID-19, reflecting deleterious effects of amplified inflammatory response to multiple organs, including the heart.[24] Higher levels of serum ferritin and CRP were detected among patients with LV systolic dysfunction in the present study, which may have contributed to low cardiac output, tissue hypoperfusion and multiple organ dysfunction.

It is important to emphasize that no patient received interleukin-blockers during the study period, since at that time there was still limited information regarding their use in pediatric patients with COVID-19.

Another relevant mechanism of myocardial damage that must be pointed out is the microvascular injury, with microthrombi formation in the myocardial vasculature and consequent ischemia.[1] Recently, Duarte-Neto et al.[25] have identified small thrombi in myocardial vessels by ultrasound-guided minimally invasive autopsy in adults with COVID-19. That may explain why higher levels of d-dimer were found among patients with left and RV systolic dysfunction. Interestingly, recent guidelines regarding pediatric patients with COVID-19 still do not advocate routine prophylactic anticoagulation for all MIS-c patients. Moreover, therapeutic anticoagulation is restricted to patients with LVEF $< 30\%$ or with giant coronary aneurysms (coronary z-scores $\geq +10$).[26] The present findings suggest there may be some benefit in administrating prophylactic low molecular weight heparin to MIS-c patients, aiming to prevent myocardial ischemia and ventricular dysfunction. Prospective studies with greater number of pediatric patients will be necessary to confirm our hypothesis.

High incidence (25%) of coronary artery abnormalities was found among the patients studied. In fact, the extent of coronary artery involvement in children with COVID19 is still a matter of concern. Whereas some authors describe 14% of MIS-C patients with coronary dilatation,[19] others have found 41% of prominent and echogenic coronary arteries on admission, despite normal diameters.[20] These discrepancies probably reflect different protocols of evaluation: in some studies, only coronary z-scores were considered, while in others, early signs of coronary artery inflammation were also included (like enhanced perivascular brightness and lack of tapering). Moreover, the longitudinal design of the present study may have enabled more accurate detection of coronary abnormalities, since 33.3% of patients were scanned multiple times throughout hospitalization. Indeed, one third of them did not have coronary arteries abnormalities in their first scan, only in subsequent evaluations.

Coronary abnormalities in COVID-19 have been previously linked to cytokines storm in MIS-C, specially interleukine-6.[27] The higher levels of d-dimer among patients with coronary dilation in the present study highlights an important pathophysiological pathway to be further investigated in MIS-C patients. Based on the emerging role of immunothrombosis in pediatric conditions, like sepsis and autoimmune rheumatic diseases, one can hypothesize that blocking coagulation cascade may contribute to dampen the inflammatory response.[28] In fact, several publications have described the non-anticoagulant properties of heparin, such as inhibiting neutrophil chemotaxis and leukocyte migration, neutralizing the positively charged complement factor C5a and sequestering acute phase proteins, with a consequent decrease of inflammatory biomarkers.[29] Thus, heparin could also work as an adjuvant anti-inflammatory therapy in MIS-c patients with coronary artery inflammation, together with IV immunoglobulin, corticosteroids and immunobiological agents.

Limitations

The present study is limited by its retrospective nature, although echocardiographic evaluations were reasonably standardized and intra/interobserver variability was proven adequate. The study group was formed predominantly by patients with preexisting diseases, which may make extrapolation of results to previously healthy children difficult. For instance, the striking prevalence of malignancies among the referred COVID-19 patients may have contributed to the hypercoagulation state, as well as to subclinical ventricular dysfunction. Likewise, patients with chronic kidney disease or rheumatologic diseases were prone to inflammation, not necessarily caused by COVID-19. Finally, immunosuppression may have contributed to the low frequency of SARS-CoV-2 positive serology among our MIS-c patients.

Conclusions

Echocardiographic abnormalities in pediatric patients with COVID-19 are frequent and associated with worse clinical outcomes. Associations between echocardiographic abnormalities and inflammation/coagulation biomarkers provided possible pathophysiological pathways to explain myocardial injury in our pediatric patients with COVID-19. Further studies should be conducted to determine which therapeutic strategies will reduce cardiovascular impairment in this population, taking into account the different mechanisms of myocardial damage. The follow-up of pediatric COVID-19 survivors with cardiac abnormalities will be necessary. Echocardiography is well placed to help further this understanding, as an inexpensive, portable, and widely accessible technology.

Author Contributions

Conception and design of the research: Diniz MFR, Silva CA, Leal GN; Acquisition of data: Diniz MFR, Cardoso MF, Sawamura KSS, Menezes CRB, Lianza AC, Ferranti JF, Leal GN; Analysis and interpretation of the data: Diniz MFR, Cardoso MF, Sawamura KSS, Menezes CRB, Pereira MFB, Litvinov N, Forsait S, Delgado AF, Silva CA, Leal GN; Statistical analysis: Leal GN; Writing of the manuscript: Diniz MFR, Leal GN; Critical revision of the manuscript for intellectual contente: Lianza AC, Pereira MFB, Litvinov N, Ferranti JF, Forsait S, Watanabe A, Farhat SCL, Aikawa NE, Campos LMA, Delgado AF, Carneiro-Sampaio M, Carvalho WB, Silva CA, Leal GN.

Potential Conflict of Interest

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

Sources of Funding

There were no external funding sources for this study.

Study Association

This article is part of the thesis of master submitted by Gabriela Nunes Leal, from Departamento de pediatria da Faculdade de Medicina da Universidade de São Paulo.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Hospital das Clínicas da Faculdade de Medicina da USP under the protocol number 4.139.678. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013.

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Original Article

Cardiovascular Manifestations in the Pediatric Population with COVID-19, What is the Real Relevance?

Andressa Mussi Soares[1,2] *and Bernardo Mussi Soares*[3]

Hospital Evangélico de Cachoeiro de Itapemirim,[1] *Cachoeiro de Itapemirim, ES – Brazil*
Faculdade de Medicina da Universidade de São Paulo,[2] *São Paulo, SP – Brazil*
Fundação Técnico Educacional Souza Marques,[3] *Rio de Janeiro, RJ – Brazil*

Short Editorial related to the article: The Heart of Pediatric Patients with COVID-19: New Insights from a Systematic Echocardiographic Study in a Tertiary Hospital in Brazil

Although COVID-19 usually has mild manifestations in children, multisystem inflammatory syndrome (MIS) may occur in 0.6% of the cases. MIS in children (MIS-C), already well defined by the World Health Organization (WHO), is characterized by hyperinflammation with cytokine storm and high levels of myocardial injury markers, with involvement of one or more organs of the cardiac, renal, respiratory, gastrointestinal or neurological systems.[1]

The combination of the timing of MIS-C cases with positive serology and negative PCR in most patients suggests that MIS-C is a post-infectious (up to six weeks after the insult), immune-mediated complication rather than of the acute infection. The pathophysiology of MIS-C is thought to be due to a hyperimmune response to the virus in a genetically susceptible child. The symptoms of MIS-C can overlap with those of Kawasaki disease, toxic shock syndrome, macrophage activation syndrome, bacterial sepsis, and cytokine release syndrome ("cytokine storm"). Cytokine storm is characterized by persistent fever, and markedly elevated inflammatory markers and pro-inflammatory cytokines such as interleukin.[2] There increasing evidence on cardiovascular involvement in COVID-19 and MIS-C.[3,4]

In a recent European multicenter study, Valverde et al.[5] demonstrated acute cardiovascular manifestations in 286 children with an average age of 8.4 years (3.8 to 12.4 years), whose most common complications were shock, cardiac arrhythmia, pericardial effusion, coronary dilation, and troponin elevation in 93% of the cases. There were one death due to ventricular arrhythmia and one patient listed for heart transplantation.[5] In another study with 186 patients with MIS-C in 26 American states, cardiovascular involvement was observed in 80% of patients, and 33% of these had left ventricular ejection fraction (LVEF) less than 55% and 5% had LVEF less than 30%. Increased troponin and B-type natriuretic peptide (BNP) e levels were found in 50% and 73% of patients, respectively, pericardial effusion in 26%, cardiac arrhythmia in 12%, and coronary involvement in 8%.[6] A Latin American study[7] that also included the participation of Brazilian centers showed that children with COVID-19 with cardiovascular involvement had more severe clinical presentation, more laboratory abnormalities, greater hemodynamic instability and the greater need for vasoactive drugs and intensive care unit admission, when compared to those without cardiovascular involvement.[7]

The potential mechanisms of myocardial injury in COVID-19 range from direct viral cardiotoxicity, as first reported by the group of the Instituto da Criança of HCFMUSP - São Paulo - Brazil, about a case of an 11-year-old child affected by MIS-C, who developed ventricular tachycardia and died within 28 hours of admission, and had viral particles detected in the cardiac tissue,[8] to several other factors such as microthrombosis, microvascular dysfunction, endothelial injury, hyperinflammatory state, hypoxemia, increased metabolic demand and hypotension.[9]

Echocardiography has emerged as a robust tool both in diagnosis and in clinical follow-up in the pediatric population with COVID-19 and has already been indexed in the clinical guideline for MIS-C.[2] Several parameters are evaluated by echocardiography, such as left ventricular systolic and diastolic function, pericardial effusion, valvular alterations, coronary involvement such as increased hyperechogenicity, parietal irregularities, dilation, and aneurysms by measurement of the of coronary artery diameter and analysis using z-score. In several series published during the pandemic, coronary involvement in MIS-C occurred from 8 to 36%, probably due to endothelial dysfunction associated with cytokine storm caused by SARS-CoV-2.[2]

In the study "The Heart of Pediatric Patients with COVID-19: New Insights from a Systematic Echocardiographic Study in a Tertiary Hospital in Brazil",[10] the authors retrospectively evaluated 48 pediatric patients, 73% with pre-existing diseases and 41.7% with MIS-C. Standardized echocardiographic assessments were performed with adequate intraobserver and interobserver variability. Echocardiographic abnormalities were significantly associated with MIS-C, admission and longer stay in the pediatric intensive care unit, multiple organ dysfunction, ventilatory/vasoactive support, and death. There was an interesting, statistically significant correlation of echocardiographic findings with changes in inflammatory markers and myocardial injury. Patients with left ventricular dysfunction had higher levels of D-dimer, C-reactive protein, ferritin and troponin; those with right ventricular

Keywords

COVID-19; Coronavirus; Inflammatory Syndrome; Cardiovascular Dseases; Child; Biomarkers; Echocardiography/methods; Strain.

Mailing Address: Andressa Mussi Soares •
Rua Papa João XXIII, 1 apto 1202. Postal Code 29303-297, Gilberto Machado, Cachoeiro de Itapemirim, ES - Brazil
Email: amussisoares@gmail.com

DOI: https://doi.org/10.36660/abc.20210835

dysfunction had higher levels of D-dimer and C-reactive protein; and those with coronary abnormalities had higher levels of D-dimer only. Due to these findings, the authors highlight the importance of immunothrombosis in MIS-C and raise the hypothesis of blocking the coagulation cascade to decrease the inflammatory response, emphasizing the non-anticoagulant properties of heparin, such as the inhibition of neutrophil chemotaxis and migration of leukocytes, with a consequent decrease in inflammatory biomarkers. The use of heparin, in addition to its antithrombotic function, would enhance the anti-inflammatory therapy together with the immunomodulation performed by intravenous human immunoglobulin, corticosteroids and immunobiological agents in patients with MIS-C.[11]

Another important tool that has added value to echocardiography is the use of the strain assessed by the speckle tracking technique in pediatric patients with SIM-P both in the acute phase and in the follow-up (Figure 1). Matsubara et al.[12] demonstrated that systolic and diastolic cardiac dysfunctions might occur frequently, probably due to the presence of a state similar to myocarditis. Even in patients with preserved ejection fraction, subtle changes in myocardial deformation were detected, suggesting subclinical myocardial dysfunction. In addition, these authors demonstrated that even patients whose ejection fraction was normalized, remained with ventricular diastolic changes in the echocardiographic assessment by speckle tracking over time, reinforcing the need for the follow-up of patients with MIS-C with complementary exams (troponin, BNP, electrocardiogram, Holter, echocardiogram and magnetic resonance in some cases).

The cardiovascular manifestations of COVID-19 are frequent in patients with MIS-C and can lead to high morbidity and consequent deaths. The understanding of the SARS-CoV-2-related syndrome in the pediatric population is growing. All knowledge gained to date reflects the current evidence available together with expert opinion. There is a lot to learn about MIS-C in COVID-19, towards better diagnosis, treatment and follow-up of these patients.

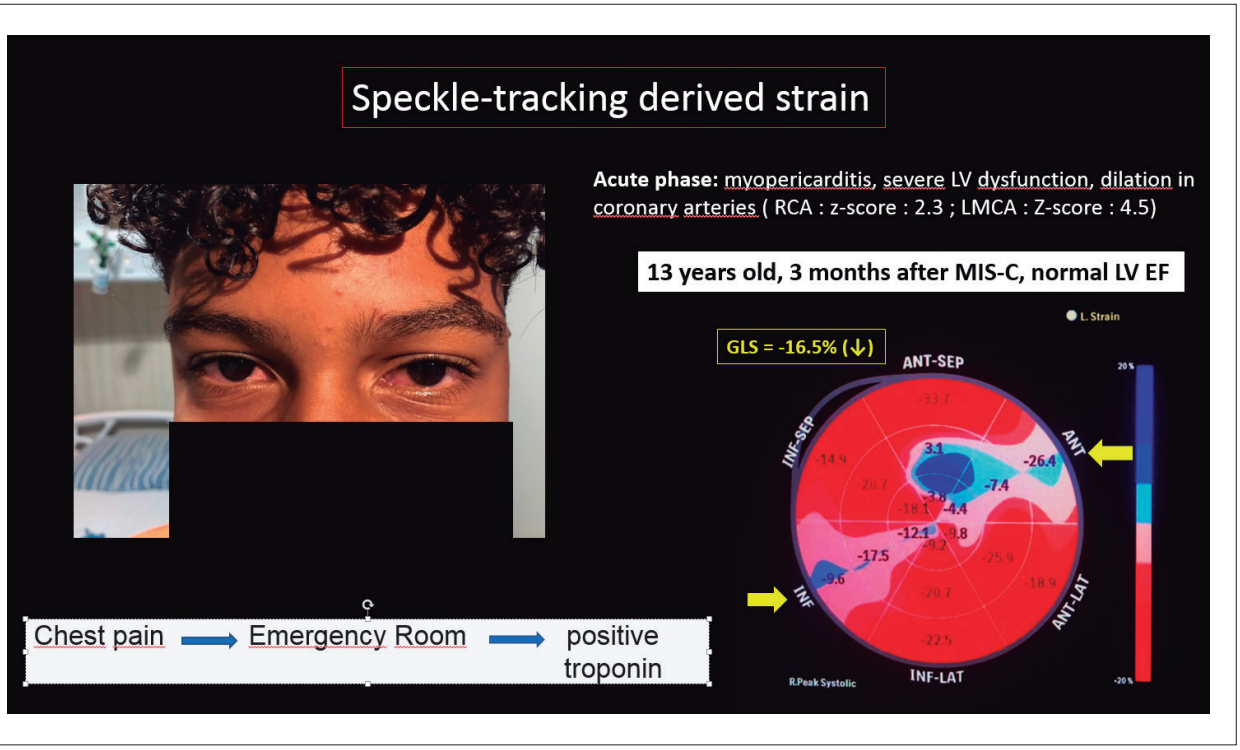

Figure 1 – *A 13-year-old teenager presenting with fever and chest pain, showed conjunctival hyperemia and positive troponin. Acute-phase echocardiogram revealed myopericarditis, left ventricular dysfunction, right coronary artery (RCA) dilation (z-score: 2.3) and small left main coronary artery (LMCA) aneurysm (z-score: 4.5). After three months of multisystem inflammatory syndrome, despite normalization of the left ventricular function (by two-dimensional echocardiogram), the patient still had abnormal myocardial strain (yellow arrows) and decreased global longitudinal strain (bull's eye-plot).*

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Original Article

Prevalence and Associated Factors of SARS by Covid-19 in Adults and Aged People with Chronic Cardiovascular Disease

Karina Mary de Paiva,[1] Danúbia Hillesheim,[1] Cassiano Ricardo Rech,[1] Rodrigo Sudatti Delevatti,[1] Rodrigo Vasconi Sáez Brown,[1] Ana Inês Gonzáles,[1,2] Patricia Haas[1]

Universidade Federal de Santa Catarina (UFSC),[1] Florianópolis, SC – Brazil

Centro Universitário Estácio de Santa Catarina,[2] São José, SC – Brazil

Abstract

Background: The presence of Cardiovascular Disease (CVD) in individuals infected with COVID-19 may imply a worse prognosis.

Objective: To describe the prevalence of Severe Acute Respiratory Syndrome (SARS) by COVID-19 and to analyze the factors associated with this condition in adults and the elderly with cardiovascular disease in Brazil until the 30th Epidemiological Week of 2020.

Methods: Cross-sectional study conducted with data from the Influenza Epidemiological Surveillance Information System (Sistema de Informação de Vigilância Epidemiológica da Gripe – SIVEP-Gripe), referring to the SARS notification forms of hospitalized individuals in Brazil, between the 1st and 30th Epidemiological Week of 2020. Adults and the aged (≥ 18 years old) with CVD. The dependent variable was SRAG confirmation by COVID-19 and factors related to sociodemographic characteristics, signs and symptoms, and clinical factors were analyzed. Poisson regression with robust variance was applied. The level of significance adopted was 5%.

Results: Notifications from 116,343 individuals were analyzed. Of these, 61.9% were diagnosed with SARS by COVID-19. The prevalence of the outcome was 4% lower in women (95%CI: 0.94–0.99) and 18% lower in rural areas (95%CI: 0.77–0.87). There was a higher prevalence in the 50 to 59 age group (95%CI: 1.09–1.48) and in the northeast region (95%CI: 1.72–1.91). Fever, cough, admission to the ICU, use of ventilatory support, and nosocomial cases were also significantly associated with a higher probability of SRAS by COVID-19 in these individuals.

Conclusion: There is a high prevalence of SARS by COVID-19 in adults and aged people with CVD in Brazil. Factors associated with sociodemographic and clinical characteristics, signs, and symptoms were associated.

Keywords: Adult; Aged; Cardiovascular Diseases; COVID-19; Severe Acute Respiratory Syndrome; Epidemiology; Prevalence; Comorbidity; Hospitalization.

Introduction

Severe Acute Respiratory Syndrome (SARS) is one of the outcomes related to coronavirus infection, called Sars-CoV-2, and has been configured in a pandemic that has generated social, financial, and psychological implications worldwide.[1] The disease was characterized as a pandemic, with 15,581,009 confirmed cases and 635,173 deaths worldwide as of August 23rd, 2020.[2]

The presence of Cardiovascular Disease (CVD) in individuals infected with COVID-19 may result in a worse prognosis, in addition to being associated with a higher lethality rate.[3] Data suggest that acute cardiac injury, cardiogenic shock, and cardiac arrhythmia were present, respectively, in 7.2, 8.7, and 16.7% of patients after infection by COVID-19, and highlight that the stay in the Intensive Care Unit (ICU) can increase this prevalence.[4]

CVD stand out as an important public health problem in low- and middle-income countries, in view of their increased burden, whether in relation to their related comorbidities, or due to the public spending involved.[5] According to data from the National Health Survey (*Pesquisa Nacional de Saúde* – PNS), the prevalence of CVD among Brazilian adults aged 18 years old and older was 4.2%, presenting an increasing gradient with the increasing age, highlighting the prevalence of 11.4% among the aged.[6]

Studies involving national data at a time of pandemic help to understand and direct more effective actions and long-term planning. The social isolation actions adopted to face COVID-19 are different among Brazilian macro-regions. The

Mailing Address: Karina Mary de Paiva •
Universidade Federal de Santa Catarina – campus Trindade P.O.476.
Postal Code 88040-970, Florianópolis, SC – Brazil
E-mail: kmvianna@gmail.com
Manuscript received August 27, 2020, revised manuscript October 22, 2020, accepted November 11, 2020

DOI: https://doi.org/10.36660/abc.20200955

concerns about pre-existing morbidities are highlighted, as is the case of CVD; patients are instructed to follow activity restrictions that impose limitations which may compromise the control of complications resulting from living with CVD, in addition to restricted medical follow-up during this period.

Given this context, the objective of this study was to describe the prevalence of SARS by COVID-19 and to analyze the factors associated with this condition in adults and aged people with chronic CVD in Brazil until 30th Epidemiological Week of 2020.

Methods

Study design and data source

This is a cross-sectional study carried out using data from the Influenza Epidemiological Surveillance Information System (*Sistema de Informação de Vigilância Epidemiológica da Gripe* – SIVEP-Gripe), made available through the opendatasus platform, available at https://opendatasus.saude.gov.br/. The Ministry of Health (MH), through the Health Surveillance Secretariat (*Secretaria de Vigilância em Saúde* – SVS), has been developing SARS surveillance in Brazil since 2009. In 2020, COVID-19 was incorporated into the surveillance network for Influenza and other respiratory viruses. Data from the SARS notification forms of hospitalized individuals were used in this study.

SARS cases are defined by individuals who meet the following criteria: (a) fever, even if self-reported; (b) cough or sore throat; (c) dyspnea or O_2 saturation <95% or respiratory distress; and (d) who have been hospitalized or died, regardless of previous hospitalization.[7]

This study included adults and aged subjects (≥ 18 years old) with CVD hospitalized with SARS. Individuals should present a complete diagnosis of the case on the notification form (SARS or SARS by COVID-19). The analysis period occurred until the 30th Epidemiological Week of 2020.[8]

Dependent variable

The dependent variable was the confirmation of SARS by COVID-19 (no; yes). The variable "final classification of the case", present in the database, consisted of the following response categories: SARS due to influenza; SARS by other respiratory viruses; SARS by another etiological agent; unspecified SARS; and COVID-19. Thus, the categories of SARS were grouped and the dependent variable was categorized into "other types of SARS" and "SARS by COVID-19". Among the cases analyzed, 95.9% were diagnosed in the laboratory, 0.4% through epidemiological relation, and 3.7% clinically.

Independent variables

The variables were analyzed in three different blocks: sociodemographic factors, signs and symptoms, and clinical factors. Sociodemographic factors included: gender (male; female), age group (18 to 29; 30 to 39; 40 to 49; 50 to 59; 60 to 69; 70 to 79; 80 years old or older), race (white; black; yellow; brown; indigenous), macroregion of residence (South; Southeast; Midwest; Northeast; North) and patient's residence area (urban; rural; peri-urban). Signs and symptoms included: fever (no; yes), cough (no; yes), dyspnea (no; yes), and O_2 saturation <95% (no; yes). Regarding clinical factors, the following were analyzed: ICU admission (no; yes), use of ventilatory support (no; yes, invasive; yes, non-invasive) and nosocomial case, that is, case of SARS with acquired infection after hospitalization (no; yes).

Data analysis

A descriptive analysis of all variables was performed by calculating the relative frequencies. To identify the factors associated with the confirmation of SARS by COVID-19, the prevalence of the outcome was initially estimated according to the research variables, using Pearson's X^2 test, with a significance level of 5%. Subsequently, the Poisson model with robust variance, both bivariate and multivariate, was applied. The raw and adjusted prevalence ratios (PR) of the data were estimated, along with their respective 95% confidence intervals (95%CI). PR was used as a measure of association as it was more conservative in view of the high prevalence of outcomes.[9]

For the entry of the variables in the multivariate analysis, a p-value lower than 0.20 was considered in the bivariate analysis. The variables were introduced at once (direct method of variable selection). In the final model, variables with a p-value ≤ 0.05 were considered associated. The analyses were performed using the Stata software, version 14.0 (https://www.stata.com).

Ethical aspects

As they are secondary data, available in the public domain and without the identification of the participants, the approval of the Ethics Committee in Research with Human Beings (*Comitê de Ética em Pesquisa com Seres Humanos* – CEPSH) was waived, according to resolution No. 510, of April 7th, 2016, of the National Health Service Council (Conselho Nacional de Saúde – CNS).[10]

Results

Notifications of 116,343 patients with CVD were analyzed in this study. Of these, 61.9% were diagnosed with SARS by COVID-19. Regarding the characterization of the sample, the majority were male (52.8%), white (51.3%), from the southeastern macro-region (58.3%), and lived in urban areas (95.7%). In addition, a higher prevalence of individuals aged 60 years old or older was observed (73.6%). Regarding the bivariate analysis, all variables were associated with a higher prevalence of SARS by COVID-19, except for the age group of 80 years old or older and individuals living in peri-urban areas (Table 1).

With regard to signs and symptoms, the majority presented fever (69.5%), cough (79.3%), dyspnea (82.8%), and O_2 saturation <95% (74.0%). Regarding clinical factors, the majority did not need to be admitted to the ICU (59.9%) and it was not a nosocomial case (96.7%). However, 50% of the individuals required invasive ventilatory support. The signs and symptoms associated with the higher prevalence of

Table 1 – Characterization and bivariate analysis of sociodemographic factors associated with confirmation of SARS by COVID-19 in adults and the aged with chronic cardiovascular disease. Brazil, 2020. (N=116,343)

Characteristic	Percentage of the total sample %	Prevalence of SARS by COVID-19 %	p*	Raw PR (95%CI)
Gender			<0.001	
Male	52.8	63.8		1.00
Female	47.2	59.8		0.93 (0.92-0.95)
Age range			<0.001	
18 to 29	0.7	53.3		1.00
30 to 39	2.8	63.6		1.19 (1.07-1.32)
40 to 49	7.6	67.3		1.26 (1.14-1.39)
50 to 59	15.3	67.4		1.26 (1.14-1.39)
60 to 69	23.4	65.2		1.22 (1.11-1.34)
70 to 79	25.0	61.1		1.14 (1.04-1.26)
80 or more	25.2	54.9		1.02 (0.93-1.13)
Race			<0.001	
White	51.3	55.0		1.00
Black	7.7	60.8		1.10 (1.06-1.14)
Yellow	1.6	64.0		1.16 (1.08-1.24)
Brow	39.2	65.1		1.18 (1.16-1.20)
Indigenous	0.2	73.3		1.33 (1.12-1.58)
Macro-region			<0.001	
South	10.9	39.9		1.00
Southeast	58.3	61.3		1.53 (1.49-1.58)
Mid-West	5.6	61.8		1.54 (1.48-1.61)
Northeast	18.8	73.1		1.82 (1.77-1.88)
North	6.8	72.0		1.80 (1.73-1.87)
Residence area			<0.001	
Urban	95.7	61.7		1.00
Rural	3.9	53.1		0.86 (0.82-0.89)
Peri-urban	0.4	57.8		0.93 (0.81-1.07)

**Pearson's χ^2 test; p-value <0,05; 95%CI: 95% confidence interval.*

SARS by COVID-19 were: fever, cough, and O_2 saturation <95% (p<0.05). Regarding clinical factors, the outcome was associated to ICU admission, use of ventilatory support, and nosocomial case (Table 2).

In the final adjusted model, the prevalence of SARS by COVID-19 was 4% lower in women, when compared to men (PR=0.96; 95%CI: 0.94–0.99) and 18% lower in individuals who lived in rural areas (PR=0.82; 95%CI: 0.77–0.87), when compared to individuals who lived in urban areas. On the other hand, it is noteworthy the prevalence 1.27 times higher in the age group of 50 to 59 years old (95%CI: 1.09–1.48), and 1.81 times higher in the northeast region (95%CI: 1.72–1.91). Fever (PR=1.24; 95%CI: 1.20–1.27), cough (PR=1.12; 95%CI: 1.09–1.16), admission to the ICU (PR=1, 08; 95%CI: 1.05–1.11), use of invasive ventilatory support (PR=1.14; 95%CI: 1.09–1.19), use of non-invasive ventilatory support (PR=1.11; 95%CI: 1.07–1.14), and nosocomial case (PR=1.12; 95%CI: 1.05–1.20) were statistically associated with an increased likelihood of SARS by COVID-19 (Table 3).

Discussion

Among hospitalized adults and aged people with CVD, 61.9% were diagnosed with SARS by COVID-19. The prevalence of the outcome was 4% lower in women and 18% lower in individuals living in rural areas. On the other hand, a higher prevalence was observed in the age group from 40 to 69 years old and in the northeast region. Fever, cough, ICU admission, use of ventilatory support, and nosocomial case were significantly associated with an increased likelihood of SARS by COVID-19.

Chronic diseases can be considered risk factors for COVID-19 infection due to their susceptibility to greater associated morbidity and mortality.[11,12] Thus, individuals with previous CVD may be more vulnerable to more severe infections,[13] considering the

Table 2 – Characterization and bivariate analysis of signs and symptoms and clinical factors associated with confirmation of SARS by COVID-19 in adults and the aged with chronic cardiovascular disease. Brazil, 2020. (N=116,343)

Characteristic	Percentage of the total sample %	Prevalence of SARS by COVID-19 %	p*	Raw PR (95%CI)
Fever			<0.001	
No	30.5	49.3		1.00
Yes	69.5	67.4		1.36 (1.34-1.39)
Cough			<0.001	
No	20.7	52.1		1.00
Yes	79.3	64.2		1.23 (1.20-1.25)
Dyspnea			0.271	
No	17.2	61.6		1.00
Yes	82.8	61.2		0.99 (0.97-1.01)
O_2 Saturation <95%			<0.001	
No	26.0	57.4		1.00
Yes	74.0	62.3		1.08 (1.06-1.10)
Hospitalized in the ICU			<0.001	
No	59.9	58.6		1.00
Yes	40.1	65.7		1.19 (1.10-1.13)
Use of ventilatory support			<0.001	
No	25.7	55.5		1.00
Yes, invasive	24.3	66.7		1.20 (1.17-1.22)
Yes, non-invasive	50.0	61.7		1.12 (1.09-1.13)
Nosocomial case			<0.001	
No	96.7	60.0		1.00
Yes	3.3	66.4		1.10 (1.05-1.15)

**Pearson's χ^2 test; In bold, p-value <0,05; ICU: Intensive Care Unit; 95%CI: 95% confidence interval.*

fragility of each individual's system, thus providing the potential action of the virus and corroborating with the data found in this research, whose prevalence of confirmed diagnosis for COVID -19 in hospitalized CVD patients was high.

Even before the pandemic, CVD were common comorbidities in diagnoses of SARS, which can elevate the risk of associated mortality by twelve fold.[14,15] Although the deaths among the participants were not evaluated, a study developed by Zhang,[16] in Wuhan, China, showed that mortality from COVID-19 in patients with CVD had a higher prevalence (22.2%) in relation to the general population of the study (9.8%).

Studies indicate that men are at greater risk of evolving to a more severe condition of COVID-19,[17] indicating a possible influence of biological factors intrinsic to gender as well as socio-cultural and behavioral factors. These data seem to be better consolidated in Chinese[18] and European[19,20] populational studies, in which data disaggregated by gender show similar absolute numbers of contamination between men and women, but with a worse evolution in men, especially with CVD. In a recent publication in the journal "Biology of Sex Differences", epidemiological data from countries such as Italy, China, Spain, France, Germany, and Switzerland were analyzed and reinforced this hypothesis. These grouped data also indicate that this difference in infection rates and a worse prognosis between genders may be more pronounced in middle-aged individuals (50 to 59 years old).[17]

One of the possible explanations for the lower prevalence of SARS by COVID-19 in women is the variation between the immune response and the susceptibility to viral infections between the genders, which can lead to differences in the severity and evolution of the disease.[17] In addition, there seems to be significant differences in the regulation and expression of proteins that participate in the pathophysiological process of SARS-CoV-2 between the genders. Data such as the difference between circulating level, activity, and expression of angiotensin-converting enzyme 2[21,22] and transmembrane serine protease type 2[23] corroborate this theory. In addition, a study carried out in Brazil pointed out that women with and without noncommunicable diseases (NCD) use health services more when compared to men.[24] This fact can be attributed to a greater perception of the signs and symptoms of diseases, a higher prevalence of exams, and greater health promotion and prevention practices, contributing to better health outcomes and lower infection rates.[24]

Despite an 18% lower prevalence of SARS by COVID-19 in rural areas, probably due to the low population density, there is also a high incidence and mortality in rural and remote regions, such as Amazonas and Amapá, which can be justified by the

Table 3 – Multivariate analysis assessing sociodemographic factors, signs and symptoms, and clinical factors associated with confirmation of SARS by COVID-19 in adults and the aged with chronic cardiovascular disease. Brazil, 2020

Characteristics	Final model	
	Adjusted PR (95%CI)	p-value*
Gender		0.010
Male	1.00	
Female	0.96 (0.94-0.99)	
Age range		
18 to 29	1.00	
30 to 39	1.17 (0.99;1.38)	0.056
40 to 49	1.25 (1.07-1.46)	0.004
50 to 59	1.27 (1.09-1.48)	0.002
60 to 69	1.21 (1.04-1.41)	0.010
70 to 79	1.17 (0.96-1.29)	0.148
80 or more	0.99 (0.85-1.16)	0.981
Macro-region		
South	1.00	
Southeast	1.45 (1.39-1.51)	<0.001
Mid-West	1.35 (1.26-1.45)	<0.001
Northeast	1.81 (1.72-1.91)	<0.001
North	1.71 (1.62-1.82)	<0.001
Residence area		
Urban	1.00	
Rural	0.82 (0.77-0.87)	<0.001
Peri-urban	0.92 (0.76-1.12)	0.451
Fever		
No	1.00	
Yes	1.24 (1.20-1.27)	<0.001
Cough		
No	1.00	
Yes	1.12 (1.09-1.16)	<0.001
Hospitalized in the ICU		
No	1.00	
Yes	1.08 (1.05-1.11)	<0.001
Use of ventilatory support		
No	1.00	
Yes, invasive	1.14 (1.09-1.19)	<0.001
Yes, non-invasive	1.11 (1.07-1.14)	<0.001
Nosocomial case		
No	1.00	<0.001
Yes	1.12 (1.05-1.20)	

*In the final model, the variables were adjusted to each other; *In bold, p-value <0,05; ICU: Intensive Care Unit; 95%CI: 95% confidence interval.*

difficulty in access to intensive care.[25,26] Corroborating these findings, an epidemiological analysis carried out in the United States identified a higher rate of SARS-CoV-2 infection in the urban population; however, black individuals, aged between 25 and 49 years, smokers, and obese were related to increased prevalence rates of COVID-19 in rural areas.[25]

The highest prevalences observed in the northern and northeastern macro-regions may present themselves as a potential public health problem, provided the Brazilian regional inequalities.[27] This pandemic situation exposes weaknesses in health care and assistance in Brazil and reinforces the issues of inequality in the north and northeast regions, with regard to the contingency of professionals, infrastructure, and capacity for the production and performance of diagnostic tests, whose issues date prior to the pandemic and persisted in the current epidemiological situation.[28]

A report produced by the Oswaldo Cruz Foundation (FIOCRUZ) (2020)[29] sought to classify vulnerability indicators (A-less vulnerable to E-most vulnerable) at the municipal level, in order to create an estimate of the risk of COVID-19 spreading in Brazilian states. For this, factors such as life expectancy at birth, GINI index — which measures inequality and income distribution —, education component of the human development index (IDHedu), % of population living in extreme poverty, % of population living in urban areas, % of people in households with inadequate water supply and sewage, % of households with running water, and % of households without electricity. The data showed that the municipalities in the north and northeast regions were considered more vulnerable, belonging to classes C, D, and E, and that the less populous capitals, such as Teresina, Maceió, Aracajú, Palmas, Rio Branco, and Porto Velho had high potential for dissemination.

In this study, it was observed that the most frequent signs and symptoms associated with the confirmation of SARS by COVID-19 were dyspnea, cough, and fever, with a statistically significant association only for fever and cough. Data analysis of 4,203 Chinese patients identified that the most common symptoms associated with COVID-19 infection were fever, cough, and dyspnea (80.5, 58.3, and 23.8%); with regard to comorbidities, they were hypertension, CVD, and diabetes (16.4, 12.1, and 9.8%).[30] In a retrospective study developed by Zhang,[16] with a sample consisting of 380 individuals and confirmation for COVID-19, it was found that cough with sputum production was the most common condition in patients with CVD when compared to the general population.

In a study conducted by Fang[12], factors associated with a greater severity of the disease in the general population were considered, with a greater chance of a worse prognosis, admission to the ICU (RR: 5.61, 95%CI: 2.68–11.76) and the use of invasive ventilation (RR: 6.53, 95%CI: 2.70-15.84). The study by Wang,[4] on the other hand, showed that individuals with comorbidities had the most severe form of the disease, with greater need for ICU admission, in addition to the association found between the use of ventilatory support and ICU admission for patients with CVD and confirmed infection for COVID -19, corroborating the findings of this study.

Despite efforts to control COVID-19 infections acquired in a hospital environment, studies show that nosocomial infection is an aggravating factor in the control of the disease.[4,30] In the present study, nosocomial infection was significantly associated with confirmed cases of SARS by COVID-19. A study carried out in Wuhan, China, the epicenter of the beginning of the pandemic, showed a prevalence of nosocomial infection of 41% of SARS attributed to COVID-19 infection, having a higher prevalence in relation to diagnoses of SARS in general.[4,30] Even more worrying, in the study by Zhou,[31] the proportion of nosocomial infections among patients confirmed for COVID-19 in the initial outbreaks of the disease was 29.3%, reiterating the importance of adequate protection, especially in a hospital environment.

It is highlighted that some limitations must be considered when interpreting the results of this study. Data from adults and aged people hospitalized with CVD were analyzed and, therefore, the results cannot be generalized to other populations. In this context, the lack of available variables representative of CVD control, such as medication used and lifestyle data, limits the adjustment of the findings for the CVD status/control factor. Still, there is the influence of the quality of information completion in notification forms and their heterogeneity in the Brazilian regions, as well as the underreporting of cases. In addition, 4.1% of cases were not diagnosed in the laboratory. This fact can be attributed to the lack of diagnostic tests and certified laboratories to perform them in some regions of the country.[32] However, other forms of diagnosis were recognized by the Ministry of Health.[33]

The study presented its strengths, highlighting that the analysis of secondary databases is one of the best ways to assess the epidemiological situation of a given population, especially banks with national coverage.

Conclusion

It was concluded that there is a high prevalence of SARS by COVID-19 in adults and aged people with CVD in Brazil. Factors related to sociodemographic characteristics, clinical characteristics, signs, and symptoms were associated with this condition. Finally, the data presented in this study will contribute to facing this pandemic by presenting findings from national data. They will also be able to highlight important aggravating factors associated with the confirmation of COVID-19, with the possibility of carrying out monitoring actions in the target audience.

Author Contributions

Conception and design of the research: Paiva KM, Hillesheim D, Gonzáles AI, Haas P; Acquisition of data: Hillesheim D; Analysis and interpretation of the data: Paiva KM, Hillesheim D, Delevatti RS, Brown R, Gonzáles AI, Haas P; Statistical analysis: Paiva KM, Hillesheim D, Delevatti RS; Writing of the manuscript: Paiva KM, Hillesheim D, Brown R, Gonzáles AI, Haas P; Critical revision of the manuscript for intellectual contente: Paiva KM, Hillesheim D, Delevatti RS, Gonzáles AI, Haas P.

Potential Conflict of Interest

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

Sources of Funding

There were no external funding sources for this study.

Study Association

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

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Severe Acute Respiratory Distress Syndrome (ARDS) Caused by COVID-19: A Regional Factor

Jussara A. Oliveira Baggio,[1] *Ana Luiza Exel,*[2] *Ana Carolina do Nascimento Calles,*[2] *Vinicius Minatel*[2]

Universidade Federal de Alagoas,[1] *Arapiraca, AL - Brazil*

Centro Universitário Tiradentes,[2] *Maceió, AL - Brazil*

Short Editorial related to the article: Prevalence and Associated Factors of SARS by Covid-19 in Adults and Aged People with Chronic Cardiovascular Disease

The COVID-19 (Coronavirus disease-19), a disease caused by the SARS-CoV-2, was identified in China at the end of 2019 and announced as a pandemic by the World Health Organization (WHO) in March 2020, with more than 20 million cases confirmed in Brazil, and more than 583 thousand deaths from complications of the disease, by the end of epidemiological week 35, on September 4, 2021.[1-3] According to the WHO, Brazil is the third country in number of cases, with the USA on the top of the list, followed by India,[1-3] which is also considered an emerging country with problems similar to those faced by the Brazilian population.

Symptoms of the SARS-CoV-2 infection may vary from a flu-like syndrome, with mild symptoms and signs like fever, cough, nasal congestion and fatigue, to acute respiratory distress syndrome (ARDS), with symptoms including dyspnea, O_2 saturation ≤ 93%, respiratory rate ≥ 30 breaths per minute, partial pressure of oxygen (PaO2)/fraction of inspired oxygen (FiO2)< 300, lymphopenia, and alveolar edema.[4,5] Nearly 1,775,816 cases of ARDS secondary to COVID-19 were recorded in Brazil and 32.2% of the cases progressed to death.[6] Of the 342,636 deaths for ARDS due to COVID-19 recorded up to the epidemiological week 36 in 2021, 59.5% had at least one comorbidity, with heart diseases, cerebrovascular diseases, systemic arterial hypertension and diabetes mellitus (DM) as the most common ones.[6,7]

Considering the high prevalence of cardiovascular diseases (CVDs), especially in the elderly, and its association with more severe cases of the disease, Paiva et al.[8] aimed at describing the prevalence of ARDS due to COVID-19 and evaluating the factors associated with this condition in adults and elderly with chronic CVD in Brazil up to the 30th epidemiological week in 2020. The authors used data from the epidemiological surveillance system on influenza (*Sistema de Informação de Vigilância Epidemiológica da Gripe*, SIVEP-Gripe) and included individuals with CVDs, aged over 18 years old, hospitalized for ARDS. In their study, 116,343 patients were included, 61.9% of them received a diagnosis of ARDS due to COVID-19. The authors found clinical features, signs and symptoms that were similar to those described in the literature.[9] Factors associated with ARDS due to COVID-19 were fever, cough, intensive care unit admission, use of invasive and non-invasive ventilation, and nosocomial infection. The results indicated a higher prevalence of ARDS in individuals aged over 60 years from the southeast of Brazil.

The results of Paiva et al.[8] reflect what has already been pointed out in previous studies.[10] The main contribution of the study is the data on the prevalence of ARDS by COVID-19 analyzed by each variable. The authors found that most cases of ARDS in the north and northeast regions of Brazil were caused by COVID-19, which differed from the cases in the south of the country, where 39.9% of the cases were caused by COVID-19. These data indicate that the prevalence of COVID-19-related ARDS has a regional factor, and reflect the difference in the access to healthcare and social inequalities among the regions. A study published by Baggio et al.,[11] in Alagoas, showed a high incidence of COVID-19 in the cities with the highest human development indexes, as well as in those with high social vulnerability. However, the highest mortality rates were found in the poorest cities. The highest prevalence of comorbidities was observed in patients hospitalized for COVID-19, which explain in part the highest risk of death in this region.[12,13] Besides, one should consider the morbidity profile, healthcare infrastructure (number of beds, trained professionals), and access to diagnostic tests and intensive therapy with qualified and safe processes by the patients.

The inclusion of data about the presence of other comorbidities, in addition to CVDs, like physical activity level and clinical follow-up for CVDs, would aid to improve the analysis conducted by the authors. Also, the inclusion of other comorbidities and physical activity level to the multivariate analysis would allow the establishment of survival and mortality curves associated to other comorbidities, including DM, obesity, sedentary lifestyle, among other common conditions that play an important role in the development of severe cases of COVID-19.

Keywords

Cardiovascular Diseases; COVID-19; Severe Acute Respiratory Syndrome.

Mailing Address: Jussara A. Oliveira Baggio •
Avenida Manoel Severino Barbosa, s/n. Postal Code 57309-005, Bairro Bom Sucesso, Arapiraca, AL - Brazil
E-mail: jussarabaggio@gmail.com

DOI: https://doi.org/10.36660/abc.20210803

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The Prognosis of Coronary Artery Disease in a Brazilian Community Hospital: Findings from the ERICO Study

Tatiana Cristina Bruno,[1] Marcio Sommer Bittencourt,[1] Alessandra V. L. Quidim,[1] Itamar Santos,[1] Paulo Lotufo,[1] Isabela Bensenor,[1] Alessandra Goulart[1]

Universidade de São Paulo, Hospital Universitário de São Paulo - Centro de Pesquisa Clínica e Epidemiológica,[1] São Paulo, SP - Brazil

Abstract

Background: Long-term prognosis post-acute coronary syndrome (ACS) in secondary care is not well-known. The severity of coronary artery disease (CAD) as a predictor of long-term mortality was evaluated in a community hospital in Brazil.

Objective: We aimed to compare short and long-term prognosis after an ACS event according to severity of obstructive disease in patients attended in a secondary community hospital from prospective CAD cohort in Brazil (the Strategy of Registry of Acute Coronary Syndrome, ERICO study).

Methods: Survival analyses were performed by Kaplan-Meier curves and Cox proportional hazard models (hazard ratios (HR) with respective 95% confidence interval (CI) to evaluate cumulative all-cause, CVD and CAD mortality according the coronary artery obstruction: no-obstruction (reference group), 1-vessel-disease, 2-vessel-disease, multivessel-disease) among 800 adults from an ERICO study during a 4-year-follow-up. HR are presented as crude and further adjusted for potential confounders from 180 days to 4-year follow-up after ACS. A p-value <0.05 was considered statistically significant.

Results: Poorer survival rates were detected among individuals with multivessel-disease (all-cause, CVD and CAD, p-log rank< 0.0001). After multivariate adjustments, multivessel-disease |(HR; 2.33 (CI 95%; 1.10-4.95)) and 1-vessel-disease obstructed (HR; 2.44 (CI 95%; 1.11-5.34)) had the highest risk for all-cause mortality compared to those with no obstruction at 4-year follow-up.

Conclusions: Not only multivessel-disease, but also 1-vessel-disease patients showed a high long-term mortality risk post-ACS. These findings highlight the importance of having a better approach in the treatment and control of cardiovascular risk even in apparently low-risk individuals attended to in secondary care.

Keywords: Survivorship; Mortality; Acute Coronary Syndrome; Coronary artery disease; Public Hospital; Epidemiology.

Introduction

Cardiovascular disease (CVD), particularly coronary artery disease (CAD), is still the main cause of death worldwide, including in Brazil.[1,2] Acute Coronary Syndrome (ACS), which includes unstable angina (UA), acute myocardial infarction (MI) with segment elevation (STEMI) and non-ST elevation myocardial infarction (NSTEMI), places a substantial burden on low- to middle-income countries, including Brazil.[3] National statistics reveal a higher burden of mortality among those with lower social strata, working, and younger age populations when compared to more affluent populations.[2,3] Most data reporting long-term prognosis in CAD comes from prospective studies performed in developed countries.[4-6] In those studies from specialized centers with tertiary care level cardiology units, higher long-term mortality rates were described among those with a higher number of obstructed arteries and CAD severity when compared to those patients with no obstruction (<50%).[7-9] In this scenario, long-term survival after an ACS event is not well-known among patients evaluated in secondary and primary care. Moreover, the lack of access to more specialized cardiologic approach and treatment after an acute coronary event is a huge public healthcare problem, particularly in developing countries. For instance, previous studies have already indicated a worse prognosis in CAD patients admitted into primary and secondary care who were not referred to specialized care.[10-12] The same is true for Brazil, where the difficulties to access tertiary care also seems to be responsible for higher mortality rates.[13] Thus, this study sought to compare short and long-term prognosis after an ACS event according to the severity of obstructive disease in patients attended to at a secondary community hospital from a prospective CAD cohort in Brazil (the Strategy of Registry of Acute Coronary Syndrome, ERICO study).

Mailing Address: Tatiana Cristina Bruno •
USP - Hospital Universitário - Av. Lineu Prestes, 2565. Postal Code 05508-900, Butantã, Cidade Universitária, São Paulo, SP – Brazil
E-mail: taticbruno@gmail.com
Manuscript received April 29, 2020, revised manuscript October 01, 2020, accepted December 02, 2020

DOI: https://doi.org/10.36660/abc.20200399

Methods

Sample design and population

All patients were participants in the ERICO study, a prospective cohort of ACS individuals recruited at the University Hospital from the University of São Paulo (HU-USP,

in Portuguese) from February 2009 to December 2013. Further details about the ERICO study are presented elsewhere.[14]

In brief, the ERICO study is an ongoing cohort from HU-USP, a secondary community hospital with 260 hospital beds in the district of Butantã, which ha a population of 428,000 inhabitants in 2010.[15,16] Although Butantã has some socioeconomic indicators above the city's average (e.g., average family income), it is a region characterized by broad inequalities.[16]

Here, the present study evaluated all participants (n=800/1085, 73.7%), admitted to the emergency department of HU-USP, with confirmed ACS submitted to invasive angiography for the diagnosis of coronary obstruction and posterior clinical decision after acute phase (exclusive clinical treatment, percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG)). All exams were performed during the acute phase of a coronary event in our main cardiologic referral center, *Instituto do Coração* (InCor), a reference center in cardiology nearly eight kilometers from HU-USP. Since HU-USP is a non-specialized hospital, there is no availability of cardiac catheterization procedures or CABG.

Definition of Acute Coronary Syndrome (ACS)

All patients with suspected ACS at the emergency department of HU-USP were screened to participate in the ERICO study. The eligibility for taking part in the ERICO study requires the patient to be diagnosed as having an ST elevation myocardial infarction (STEMI), a non-ST elevation myocardial infarction (NSTEMI), or unstable angina (UA); the criteria used to define ACS were:[14-17]

1) Myocardial infarction: the presence of symptoms consistent with cardiac ischemia within 24 hours of hospital admission and troponin I levels above the 99th percentile with a test-specific coefficient of variation < 10%.

1a) ST elevation myocardial infarction: the presence of criteria for coronary artery disease (CAD) plus one of the following: persistent ST segment elevation equal to or greater than 1mm in two contiguous electrocardiographic leads or the presence of a new or presumably new left bundle branch block.

1b) Non-ST elevation myocardial infarction: the presence of criteria for myocardial infarction but not STEMI.

2) Unstable angina: symptoms consistent with cardiac ischemia 24 hours prior to hospital admission, absence of myocardial infarction criteria, and at least one of the following: history of coronary artery disease; positive coronary disease stratification test (invasive or noninvasive); transient ST segment changes equal to or greater than 0.5mm in two contiguous leads, new T-wave inversion equal to or greater than 1mm and/or pseudonormalization of previously inverted T-waves; troponin I equal to or greater than 0.4 ng/ml (which guarantees troponin I levels above the 99th percentile regardless of the utilized kit); or diagnostic concordance of two independent doctors.

Coronary artery disease classification

The classification of coronary disease was based on the presence of ≥50% obstruction of at least 1 major coronary artery or any of its major branches: anterior descending artery (AD), circumflex artery (CX), and right coronary artery (RCA). The following categories of coronary obstruction was made up of: Group 1: no obstruction when all vessels had <50% obstruction, Group 2: 1-vessel-disease when ≥50% obstruction was present in one major coronary artery or any of its major branches, Group 3: 2-vessel-disease coronary obstruction ≥50% in two major coronary arteries or its major branches, and Group 4: multivessel-disease with obstruction in all three major coronary artieries (or its major branches) or Left Main(LM) ≥50% obstruction or presence of previous coronary artery bypass grafting (CABG).

Study Protocol

Upon hospital admission for ACS, after having signed the informed consent form, all participants provided baseline information based on standardized questionnaires that included sociodemographic data, main cardiovascular risk factors (hypertension, diabetes, obesity, dyslipidemia, smoking, personal or family history of coronary artery disease, physical inactivity, cocaine use, and menopause) and the use of previous medication. Clinical conditions were self-reported.

Three physicians were independently responsible for reviewing information and validating ACS cases. The study protocol also included a blood sample for laboratory testing, such as: troponin I, MB-creatine kinase, hemogram, and lipid profile (including total cholesterol, HDL and LDL- cholesterol (C), and triglycerides).

After 30 days of the acute event, all participants were invited to update their information about cardiovascular risks. At six months and annually after the initial event, patients were contacted by phone to update their information, their vital status, cardiovascular history, and medication use. Whenever a patient reported a new potential ACS event, an investigation was initiated to acquire further information. ERICO has been described in detail elsewhere.[14]

Results

Information on the three fatal endpoints: all-cause, CVD and CAD mortality were record by the ERICO study. Vital status was updated through medical records and death certificates. Mortality data was confirmed by official death certificates in collaboration with the city of São Paulo's health statistics system (PRO-AIM, Program for Improvement of Mortality Information in the Municipality of São Paulo) and State's health offices (SEADE foundation, Healthcare Data Analysis System of the State of São Paulo's Health) and the Brazilian Ministry of Health. On a regular basis, the research team prepared a list of individuals who were reported as dead or with whom contact had been lost. State and municipal health agencies searched their databases for death certificates reporting results to the ERICO study research team. In the present study, the basic cause of death was used. Two physicians independently analyzed the death certificate and, when necessary, the underlying cause of death was reclassified. If there was disagreement between them, a third doctor performed the analysis of the death certificate, followed by a discussion and consensual decision. Participants were defined to have

died from cardiovascular cause ("cardiovascular mortality") when the cause of death could be classified as "Diseased of Circulatory System", according to the International Classification of Diseases, version 10 (ICD-10), chapter IX, or if the cause of death was identified following ICD-10 code R57.0 "Cardiogenic Shock". Each identified event was adjudicated using predefined international criteria.[18,19] Participants' mortality was classified as "post-IM mortality" whenever fatal CAD was identified as the main cause of death. For CAD as the cause of death, the definition of myocardial infarction (I21.X) was used, which was also present in Chapter IX of circulatory diseases of the ICD-10. All-cause mortality refers to the deceases regardless of underlying causes.

The study protocol was approved by the Institutional Review Board addressing research in human beings. All subjects provided a written informed consent form for the study.

Statistical Analysis

Descriptive analyses of ERICO participants were presented according to the predefined groups of coronary obstruction described above. Categorical variables, presented in absolute and relative frequencies, were analyzed using the chi-squared test. As no parametric distribution was observed by a normality test of Kolmogorov-Smirnov, continuous variables are presented as median values with a respective interquartile range (IQR) and the distribution among coronary obstruction subgroups were compared using Kruskal-Wallis tests.

Survival analyses were performed by applying Kaplan-Meier curves[20] and Cox proportional hazards models (hazard ratios (HR) with respective 95% CI)[21] to evaluate cumulative all-cause, CVD, and CAD mortality according the number of obstructed major coronary arteries or any of their major branches (no-obstruction: reference group, 1-vessel-disease, 2-vessel-disease, multivessel-disease). For all patients in this sample there was a 7-year follow-up period, with the median follow up time of 1,460 days, corresponding to 4 years. Therefore, we opted to do Cox Regression analysis and Hazard Ratio in 180 days and yearly up to 4 years after an acute event. The Cox regression models were calculated as follows: crude, adjusted for age-sex, and the full model adjusted for the history of the previous CAD, ACS subtype (UA, NSTEMI, STEMI), smoking (past, current, and never), hypertension, diabetes, dyslipidemia, and type of procedure performed (medical therapy, percutaneous or surgical). Additional models adjusted for LDL-cholesterol, previous use of aspirin, lipid-lowering drugs, angiotensin-converting enzyme inhibitor (ACE), and β-blocker were also evaluated.

All tests were two-tailed with a significance of <0.05. All statistical analyses were performed using the statistics program, SPSS® Statistics, version 25.0, made available by IBM®.

Results

Casuistic

Of the 800 participants who underwent invasive angiography (February 2009 and December 2013), 343 (42.9%) underwent conservative treatment, including at least three of the following medications: aspirin, β blocker, ACE inhibitor or angiotensin II converting enzyme inhibitor, and lipid lowering medications (statin or fibrate). Among those under conservative treatment, 15 (4.4%) underwent chemical thrombolysis. Regarding invasive therapeutic strategies, 400 participants (50.0%) underwent percutaneous coronary intervention (PCI) with a stent implant (75.8% metal stent, 13.3% balloon angioplasty, 10.9% drug-eluting stent) and 57 (7.1%) underwent CABG.

Clinical and sociodemographic characteristics

Clinical and sociodemographic characteristics according to the number of obstructed major coronary arteries are shown in Table 1. The presence of obstructed major coronary arteries was as follows: 107 (13.4%) with no obstruction, 304 (38.0%) 1-vessel-disease, 169 (21.1%) 2-vessel-disease, and 220 (27.5%) multivessel-disease.

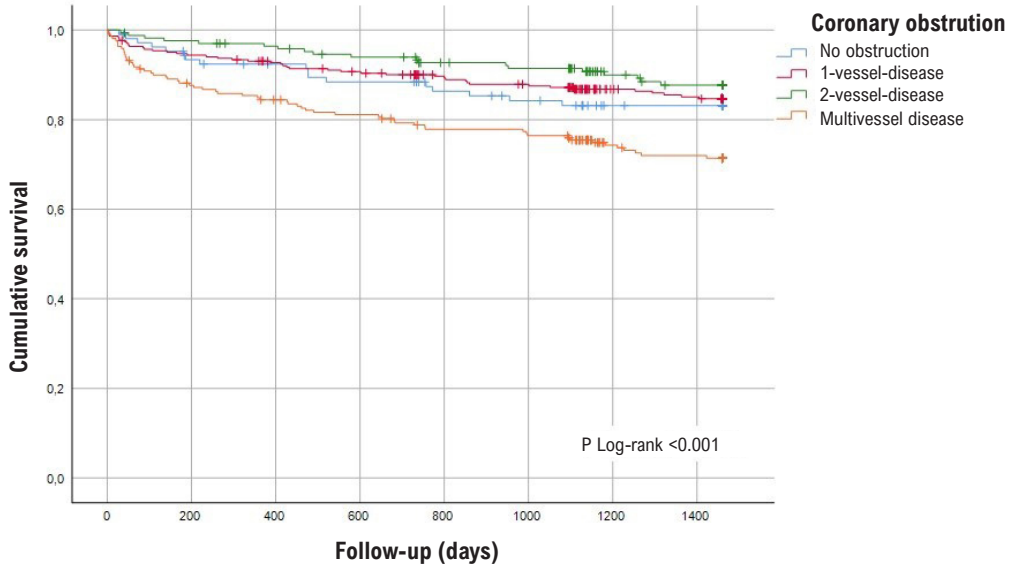
Most cardiovascular risk (CVRF) were more frequent among those patients with multivessel-disease. However, higher frequencies of current smokers, STEMI and slightly higher levels of LDL-C were noticed among individuals with 1-vessel-disease when compared to those with multivessel-disease. A significant difference was also found in the history of previous CAD across subgroups: with no obstruction, 15 (15.6%); 1-vessel-disease, 57 (19.9%); 2-vessel-disease, 36 (22.4%); and multivessel-disease, 74 (36.1%), with $p<0.0001$. Further, the higher the level of obstruction, the more frequent the previous history of heart failure: no obstruction (24.5%), 1-vessel-disease (13.6 %), 2-vessel-disease (13.5%). and multivessel-disease (26.2%), with $p=0.001$. Likewise, the higher the severity of coronary obstruction, the lower the ejection fraction: with no obstruction (median 59, IQR: 43-66), 1-vessel-disease (median 60, IQR: 50-67), 2-vessel-disease (median 60, IQR:45-67), and multivessel-disease (median 51, IQR: 41-65), $p=0.001$).

Regarding drug therapy upon hospital admission, patients with 1-vessel-disease had the lowest percentage of β blocker administration (25.2%) when compared to the others ($p=0.048$). No significant differences were identified regarding standard medication use for CAD during follow-up, regardless of the number of obstructed major coronary arteries (Supplemental Table 1).

Mortality and survival

Overall, the present study observed 140 deaths post-ACS (88 deaths due to CVD, of which 52 were due to CAD). The poorer survival rates were also detected among individuals with multivessel-disease (all-cause, CVD, and CAD, p-log rank$<$ 0.0001) (Figures 1-3). After multivariate adjustment that included age, sex, and main CVRF, either individuals with multivessel disease or those with 1-vessel-disease had a higher risk of more than twice for all-cause mortality as compared to those without obstruction at 4-year follow-up (Table 2).

We also found higher HRs (adjusted by age and sex) for CVD mortality at 180 days and for CAD mortality at 180 days, and 1, 2, and 4 years of follow-up among those with



Coronary obstruction	Deaths/Total (%)	Mean survival time		
		Mean (days)	Mean time) days 95% Confidence interval (CI)	
			Lower	Upper
No obstruction	17/107 (15.9)	1.290	1.212	1.367
1-vessel-dissease	44/304 (14.5)	1.316	1.272	1.359
2-vessel-dissease	19/169 (11.2)	1.365	1.320	1.410
Multivessel-dissease	60/220 (27.3)	1.174	1.106	1.241
Total	140/800 (17.5)	1.284	1.255	1.313

Figure 1 – *Kaplan Meyer survival curve for all-cause mortality during 4 years of follow-up.*

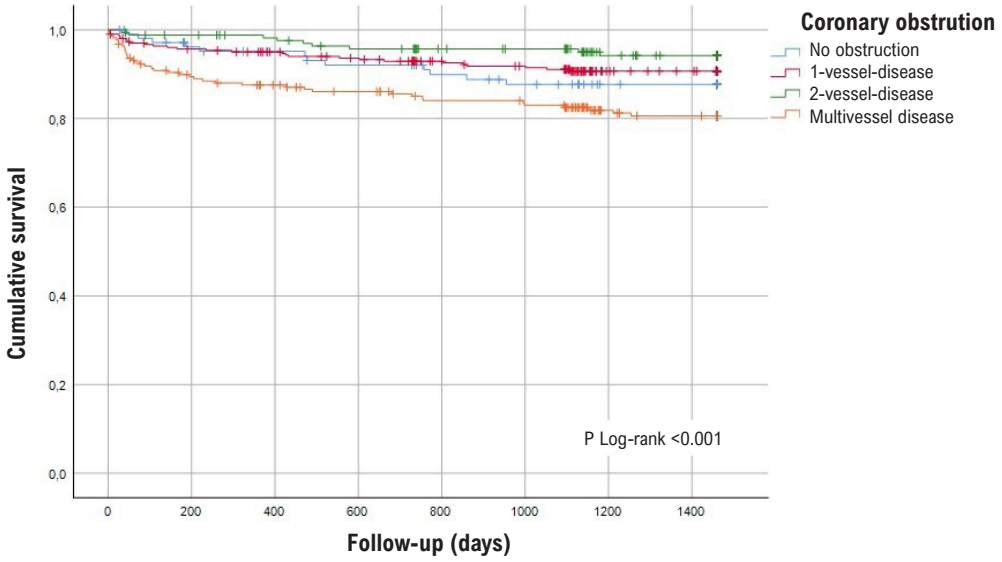
multivessel disease. However, after multivariate adjustments, no significant risks were detected for CVD and CAD mortality according coronary obstruction during the follow-up (Tables 3 and 4). Sensitivity analysis, excluding those with STEMI, did not change the direction of our main findings regarding all-cause mortality after 4 years among those with 1-vessel-disease [HR; 2.09 (CI 95%; 0.64-6.78); p = 0.22] and for those with multivessel-disease [HR; 2.39 (CI 95%; 0.76-7.44); p = 0.13]. Further adjustments for LDL-cholesterol, previous use of aspirin, lipid-lowering drugs, angiotensin-converting enzyme inhibitor (ACE), and β-blocker did not change our main findings.

Discussion

In the ERICO study, our study found a higher risk of death (all-cause mortality) in both subgroups with 1-vessel-disease and multivessel-disease compared to individuals with no obstruction (< 50% obstruction) four years after the acute event. Among those with multivessel-disease, higher hazard ratios for CVD and CAD mortality were also observed but not after the multivariable adjustment.

Our results are in accordance with most data published in CAD that described high mortality and poor survival among patients with multivessel disease.[7-9] However, our study also described high mortality among those with 1-vessel disease. Similarly, Porter et al. described the long-term prognosis within a sample of young adults who underwent a coronary angiography after an ischemic event.[22] This study described comparable prognosis among patients with a 1-vessel-disease with those with multivessel-disease (1-vessel-disease had a lower survival rate (63%) vs. multivessel-disease (65%) p=0.001).[22] As in our sample, most participants were male (88%), with a higher frequency of current smokers (58%). These similarities may well have contributed to similar results in both cohorts.

By reviewing baseline risk factors that may have led to worse long-term prognosis for 1-vessel-disease patients, this study observed the highest frequencies of STEMI and current smokers, and the lowest frequency of beta-blocker users upon hospital admission in the ERICO study. Our study shows similarity with other studies that showed a higher mortality rate when associated with smoking in the presence of CAD. In the study of Yudi et al., which was performed with



Coronary obstruction	Deaths/Total (%)	Mean survival time		
		Mean (days)	Mean time (days) 95% Confidence interval (CI)	
			Lower	Upper
No obstruction	17/107 (11.2)	1.388	1.271	1.405
1-vessel-dissease	27/304 (8.9)	1.360	1.323	1.398
2-vessel-dissease	9/169 (5.3)	1.408	1.372	1.443
Multivessel-dissease	40/220 (18.2)	1.248	1.186	1.311
Total	88/800 (11.0)	1.337	1.311	1.362

Figure 2 – *Kaplan Meyer survival curve for CVD mortality during 4 years of follow-up.*

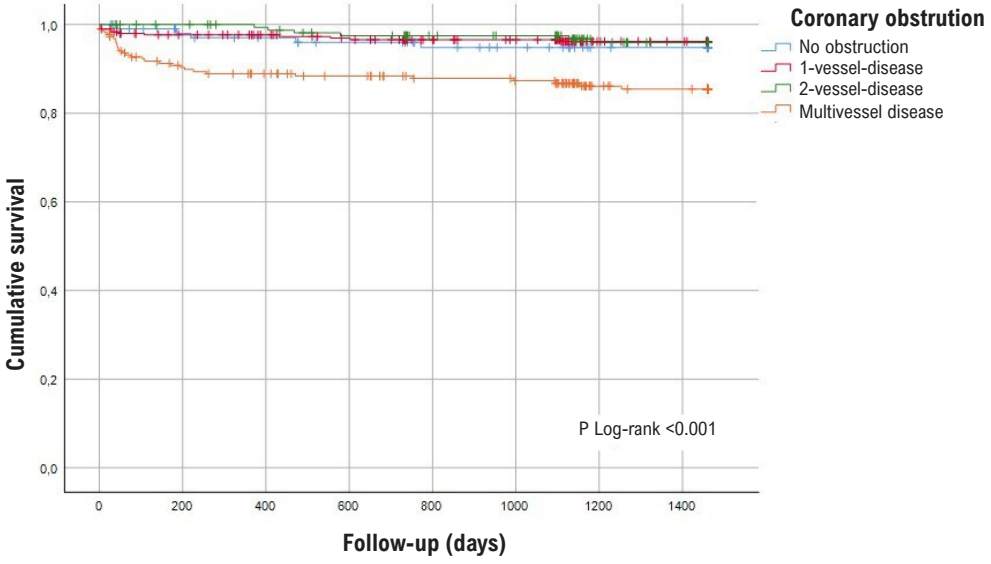
individuals with ACS, those who continued to smoke have an 80% risk of lower survival, while those who quit showed a survival rate comparable to lifelong non-smokers.[23] Although information about smoking during follow-up is scarce, the smoking status can lead to a poor prognosis among 1-vessel-disease participants.

When the medication was analyzed, at baseline, 1-vessel-disease patients in particular have taken less β-blockers than those with multivessel-disease (25.2% versus 28.1%, p=0.048). In a Brazilian study conducted by Nicolau et al., the early administration of β-blockers during hospital admission decreased the survival rate in a long-term follow-up. This study showed that β-blocker administration within the first 24 hours in NSTEMI patients contributed to a better prognosis over the long-term: higher mean survival time (11.86 ±0.4 years vs 9.92 ±0.39 years p<0.001).[24] Furthermore, another Brazilian multicenter study showed that the secondary prevention to CAD according to guidelines is linked to higher income and better access to health services. Overall, most of the Brazilian population living with a lower-middle income has some barriers to access public health care services. Moreover, as previously mentioned, the ERICO participants come from a neighborhood characterized by broad inequalities.[25]

In addition, 1-vessel-disease individuals, who were the lowest frequency of β-blocker users and the highest frequency of smokers at baseline, had the most severe subtype of ACS (STEMI). Sensitivity analysis, excluding those with STEMI, resulted in a non-significant mortality risk among those with 1-vessel. Although our study considered the ACS subtype, smoking, and β-blocker use as confounding variables in the Cox regression models, one cannot rule out the possibility that a residual effect of low adherence and poor control of CVRF could interfere in the high risk of mortality among individuals with only 1-vessel-disease in the ERICO study.

Moreover, the prognosis of CAD is also related to the area of the myocardium at risk and analyzing the most affected coronary artery in patients with 1-vessel-disease, this study found that 45.4% of the cases involved the anterior descending artery (AD). The AD is responsible for supplying a large part of the myocardium; therefore, the fact that 1-vessel-disease patients have a high percentage of obstruction of this coronary artery may have led to a worse prognosis in those patients.

Since our results differ from those found in other studies, mostly performed in tertiary care in developed countries,[4-6]



Coronary obstruction	Deaths/Total (%)	Mean survival time		
		Mean (days)	Mean time (days) 95% Confidence interval (CI)	
			Lower	Upper
No obstruction	5/107 (4.7)	1.403	1.353	1.452
1-vessel-dissease	11/304 (3.6)	1.415	1.389	1.442
2-vessel-dissease	6/169 (3.6)	1.430	1.405	1.445
Multivessel-dissease	30/220 (13.6)	1.290	1.231	1.349
Total	52/800 (6.5)	1.382	1.361	1.404

Figure 3 - *Kaplan Meyer survival curve for CAD mortality during 4 years of follow-up.*

regarding patients with 1-vessel-disease, the comparison of mortality rates according to the number of major coronary arteries in post-ACS must be interpreted with prudence. There are differences in how obstructive CAD can be classified. Furthermore, there are also differences in the selection of patients and treatment options offered at hospitals. Moreover, the advent of technology in treatment in recent decades may be partially responsible for the differing results in our study.

Our study has some strengths. It provides consistent evidence about the relationship between the larger number of major coronary arteries with CAD, higher mortality, and lower survival rates. Our study reported information of prognosis for 1-vessel-disease that needs to be considered less benign than they seem. This fact reinforces the importance of adequate treatment and control of cardiovascular risk factors after an ACS event. The ERICO population study has low socioeconomic level and was attended to at a community hospital, but with the ability to transfer patients to a specialized cardiology referral center without difficulty. In addition, we monitored the medications indicated for the treatment of ACS over a period of one year and evaluated the intake according to the extent of the obstructive disease. All of these factors, coupled with the significant number of patients in our study and the four-year follow-up time frame provides a single opportunity to evaluate the association among mortality rates (all-cause, CVD, and CAD) according to the severity of coronary disease four years after the acute event. Nonetheless, some limitations need to be pointed out here. Invasive angiography for the diagnosis of coronary obstruction was not performed by a single or a restricted team of professionals which might have generated a source of bias. However, a cardiologist from the ERICO study revised all cases and performed the classification according the extension of the obstructive disease.

Conclusion

In the ERICO study, multivessel-disease, as well as 1-vessel-disease, presented high long-term all-cause mortality after ACS. Therefore, our study reinforces the importance of designing a better approach to controlling and treating patients within all cardiovascular risk ranges, including those at apparently low risk attended to in secondary care.

Author Contributions

Conception and design of the research: Bruno TC, Bittencourt MS, Santos I, Lotufo P, Bensenor I, Goulart A; Acquisition of data: Bruno TC, Bittencourt MS, Quidim AVL, Santos I, Bensenor I, Goulart A; Analysis and interpretation of the data: Bruno TC, Bittencourt MS, Santos I, Bensenor I, Goulart A; Statistical analysis: Bruno TC, Bittencourt MS, Santos I, Goulart A; Writing of the manuscript: Bruno TC, Bittencourt MS, Quidim AVL, Lotufo P, Bensenor I, Goulart A; Critical revision of the manuscript for intellectual content: Bruno TC, Bittencourt MS, Quidim AVL, Santos I, Lotufo P, Bensenor I, Goulart A.

Potential Conflict of Interest

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

Sources of Funding

There were no external funding sources for this study.

Study Association

This article is part of the thesis of master submitted by Tatiana Cristina Bruno, from Universidade de São Paulo.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the HU-USP under the protocol number CAAE: 82801318-0-0000-0076 / Registro CEP/HU/USP 1692/18. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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*Supplemental Materials

For additional information, please click here.

Prognosis of Coronary Artery Disease in Public Hospitals in Brazil: The ERICO Study and the Application of Knowledge in Public Health

Fatima Marinho[1,2]

Programa de Pós-Graduação em Saúde Pública, Faculdade de Medicina, Universidade Federal de Minas Gerais,[1] *Belo Horizonte, MG – Brazil*
Organização Internacional de Saúde Pública Vital Strategies,[2] *New York - USA*

Short Editorial related to the article: The Prognosis of Coronary Artery Disease in a Brazilian Community Hospital: Findings from the ERICO Study

The group of cardiovascular diseases (CVD) includes the leading causes of death in Brazil and in all developing countries.[1,2] Ischemic heart disease (IHD) or coronary artery disease (CAD) has been the leading cause of death for many years in the Brazilian population,[1] with the exception of the year 2020,[3] when the disease caused by the novel coronavirus (COVID-19) was the leading cause of death, followed by IHD. IHD was the main cause of years of life lost in the Brazilian population in 2016.[4]

In 2017, the prevalence of CAD was estimated to be of 1.75% (2,500,000 individuals) in the Brazilian population over 20 years of age.[1] The highest prevalence was found in the South and Southeast Regions, with a decreasing standardized mortality rate, but an increased prevalence, since 1990.[1] With an estimated incidence of about 121,000 cases per year in 2017,[1] CAD has been an important public health problem in Brazil.

The ERICO study,[5] a cohort of patients with episodes of acute coronary syndrome (ACS) who were treated at a secondary hospital, among other studies, is an important element in the production of knowledge about the short- and long-term prognosis of patients receiving secondary care and CAD.

Questions that need to be asked for patients with ACS include the following: What is the best intervention, what is the evidence, and what is the prognosis? How are we to inform patients and families about the chances of long-term survival if there is still no consolidated knowledge? Many questions have yet to be answered in the Brazilian context, for example, the impact of social determinants[6] on prognosis. What is the evidence regarding the best treatment?

Cardiovascular statistics[1] published in 2020 revealed that "78,575 coronary angioplasties were performed by the SUS in 2018, with hospital mortality of 2.96% and average hospital stay of 4.5 days." With this number of angioplasties, the possibility of applying the best evidence to provide information about the best care and procedures increases the chances of benefiting not only individual patients, but the thousands of patients with ACS, thus reducing population mortality and improving quality of life. In 2019, 10% of hospitalizations in the SUS were due to CVD.[7]

The use of technology for diagnosis and treatment during an acute manifestation of the disease (particularly stroke or acute myocardial infarction) has been instrumental in many countries for reducing deaths and prolonging life when CVD manifests.[8]

In their article, Bruno et al.,[9] reveal that, "Not only patients with multiple vessel disease, but also those with single vessel disease had a high risk of long-term post-ACS mortality. These findings highlight the importance of having a better approach to treatment and control of cardiovascular risk factors, even in individuals with apparently low risks, who are treated in secondary care."

The emergence and rapid growth of cardiovascular risk factors in developing countries are responsible for the prominent increase in morbidity and mortality related to IHD in recent decades, bringing about the need for an epidemiological control plan, with the aim of preventing CVD in developing countries.[4,5,7,10]

Greater mortality due to CAD is related to lower socioeconomic level,[5] and higher income countries have lower mortality rates than middle-income countries.[1,4] New treatments for CAD with the use of new technologies have reduced mortality, but they cannot reduce the disease burden and the loss of health[1,4] associated with CAD. Risk factors, such as obesity, diet, tobacco use, and sedentary lifestyle, have increased the risk of developing the disease.[1,2,4-6,9] The growing association of CAD and diabetes has contributed to an increased risk of death.[11-13]

The baseline of the ERICO study[6] showed that, "Average age was 62.7 years; 58.5% were men, and 77.4% had 8 years of schooling or less. The most common cardiovascular risk factors were hypertension (76%) and sedentary lifestyle (73.4%). Only 29.2% had prior history of coronary disease."[6]

During the period from 1990 to 2017, the prevalence of CAD increased in both sexes (from 1.08% to 1.75%), more prominently in men than in women, increasing with the aging of the population.[1,8]

Considering the importance of treating cardiovascular morbidity and its acute events, the trend of reduced mortality due to CAD and, consequently, the increased survival of patients with ACS and coronary obstruction have made it necessary to enhance knowledge about treatment,[9] better use of clinical information for prognosis,[8,13] and prevention

Keywords

Coronary Artery Disease; Prognosis; Hospitals, Public; Epidemiology; Public Health; Risk Factors; COVID-19; Mortality

Mailing Address: Fatima Marinho •
Rua São Bento, 470 Cj 104. Postal Code 01010-905, São Paulo, SP – Brazil
E-mail: fmarinho@vitalstrategies.org

DOI: https://doi.org/10.36660/abc.2021-0825

of cardiovascular risk factors.[4] It is, therefore, fundamental to understand health professionals' practice and their level of adherence to good practice recommendations.[14]

Thus, understanding more in depth, producing evidence, seeking impact on the population level,[8,13,14] and, at the same time, placing public health policies at the center of the debate on reducing the prevalence and incidence of ACS and CAD[8] in order to face the growing increase in cardiovascular risk factors are the most effective way to reduce health losses and lost years of life due to CAD.[4]

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Cost-Effectiveness Analysis of Evolocumab Therapy in Patients at High Risk of Cardiovascular Events in the Context of the Brazilian Unified Health System

Luisa Latado,[1] Rodrigo Morel Vieira de Melo,[1,2] Sóstenes Mistro,[3] Adriana Lopes Latado,[1] Harrison Floriano do Nascimento,[4] Yasmin Menezes Lira,[5] Natalia Ferreira Cardoso de Oliveira,[5] Yuri de Santana Galindo,[1] Tainá Viana,[2] Luiz Carlos Santana Passos[1,2]

Universidade Federal da Bahia - Faculdade de Medicina,[1] Salvador, BA – Brazil

Hospital Ana Nery - Serviço de Cardiologia,[2] Salvador, BA – Brazil

Universidade Federal da Bahia. Instituto Multidisciplinar em Saúde - Programa de Pós-Graduação em Saúde Coletiva,[3] Vitória da Conquista, BA - Brazil

Hospital Universitário Professor Edgard Santos - Pesquisa e Inovação Tecnológica,[4] Salvador, BA – Brazil

Escola Bahiana de Medicina e Saúde Pública,[5] Salvador, BA – Brazil

Abstract

Background: **Hypertrophic cardiomyopathy (HCM) and left ventricular hypertrophy (LVH) secondary to systemic hypertension (HTN) may be associated with left atrial (LA) functional abnormalities.**

Objectives: **We aimed to characterize LA mechanics in HCM and HTN and determine any correlation with the extent of left ventricular (LV) fibrosis measured by cardiac magnetic resonance (CMR) in HCM patients.**

Methods: **Two-dimensional speckle tracking-derived longitudinal LA function was acquired from apical views in 60 HCM patients, 60 HTN patients, and 34 age-matched controls. HCM patients also underwent CMR, with measurement of late gadolinium enhancement (LGE) extension. Association with LA strain parameters was analyzed. Statistical significance was set at $p<0.05$.**

Results: **Mean LV ejection fraction was not different between the groups. The E/e' ratio was impaired in the HCM group and preserved in the control group. LA mechanics was significantly reduced in HCM, compared to the HTN group. LA strain rate in reservoir (LASRr) and in contractile (LASRct) phases were the best discriminators of HCM, with an area under the curve (AUC) of 0.8, followed by LA strain in reservoir phase (LASr) (AUC 0.76). LASRr and LASR-ct had high specificity (89% and 91%, respectively) and LASr had sensitivity of 80%. A decrease in 2.79% of LA strain rate in conduit phase (LASRcd) predicted an increase of 1cm in LGE extension ($r^2=0.42$, β 2.79, $p=0.027$).**

Conclusions: **LASRr and LASRct were the best discriminators for LVH secondary to HCM. LASRcd predicted the degree of LV fibrosis assessed by CMR. These findings suggest that LA mechanics is a potential predictor of disease severity in HCM.**

Keywords: **Cardiomyopathy, Hypertrophic; Hypertension; Echocardiography/methods; Magnetic Resonance Spectroscopy/methods; Left Ventricular Hypertrophy.**

Introduction

Cardiovascular diseases (CVDs) are the main cause of mortality in Brazil and in the world.[1] In Brazil, they account for 29% of deaths in individuals ≥ 20 years old, according to the Informatics Department of the Brazilian Unified Health System (DATASUS), in 2015.[2] Among the CVDs, atherosclerotic cardiovascular disease (ASCVD) stands out: a disease of which pathogeny is intrinsically related to modifiable or non-modifiable risk factors.[3]

High levels of low-density lipoprotein (LDL) cholesterol play an important role in the ASCVD risk. Lipid-lowering therapies to reduce LDL levels are essential in this scenario, and statins are efficient and effective in preventing cardiovascular outcomes.[4] It is estimated that, for each 39mg / dL decrease in LDL cholesterol with statins, there is a relative reduction in major cardiovascular events in the order of 21%.[5]

Pro-protein convertase subtilisin-kexin type 9 (PCSK9) inhibitors are a new class of medication for hypercholesterolemia, represented in the Brazilian market by evolocumab and alirocumab. PCSK9 is a protease capable of inhibiting the recycling of LDL receptors (LDL-R) expressed on the surface of hepatocytes, decreasing the hepatic uptake of LDL and increasing its plasma levels.[6] Consequently, the inhibition of PCSK9 enables

Mailing Address: Rodrigo Morel Vieira de Melo •
Universidade Federal da Bahia - Departamento de Medicina - Praça XV de novembro, s/n. Postal Code 40110-060, Largo do Terreiro de Jesus, Salvador, BA – Brazil
E-mail: rodrigo.morel@ufba.br, morel@cardiol.br
Manuscript received August 07, 2019, revised manuscript October 23, 2020, accepted December 02, 2020, corrected September 09, 2024

DOI: https://doi.org/10.36660/abc.20200690

the recycling of LDL-R and increases the clearance of circulating LDL-cholesterol.

The FOURIER study demonstrated an additional 59% reduction in LDL cholesterol levels and 15% in cardiovascular outcomes with the use of evolocumab (compared with placebo) in patients at high cardiovascular risk already using statins.[7] According to updates of the specialty guidelines, evolocumab is recommended for the secondary prevention of events in patients treated with a high-potency statin who have not reached the recommended LDL cholesterol levels.[8]

Economic analyses of the use of these new drugs are still very scarce but extremely necessary, since their direct cost is very high. A recent North-American study showed that evolocumab was not cost-effective when compared to statin use alone.[9] The present study aims to evaluate the cost-effectiveness of using evolocumab in comparison to the standard therapy for patients at high risk of cardiovascular events monitored in the Brazilian Unified Health System (SUS, *Sistema Único de Saúde*).

Methods

Study design and sampling

This is a cost-effectiveness economic evaluation study that compared the standard lipid-lowering therapy with atorvastatin 80 mg/day *versus* atorvastatin 80 mg/day combined with evolocumab 140 mg/mL every 15 days, in the estimated reduction of cardiovascular atherosclerotic events in patients with a previous history of acute coronary syndrome (ACS). Costs and benefits were assessed from the perspective of society, particularly in the context of the Brazilian public health system.

The economic model of the study was applied using a convenience sample obtained from a prospective cohort of patients undergoing secondary prevention followed at the coronary artery disease (CAD) outpatient clinic in a public referral hospital in the state capital city of Salvador, state of Bahia, Brazil. The inclusion criteria for this cohort were ACS occurring less than 1 year ago, associated with failure to achieve an LDL target of less than 50 mg/dL under conventional treatment with a high-potency statin, with or without ezetimibe, for at least 12 weeks. The exclusion criteria included: concomitant disease outside the therapeutic perspective, estimated survival of less than 1 year, and participation in another similar research protocol. The eligibility criteria were applied only to patients who agreed to participate in the study and signed an informed free and informed consent form.

From this cohort, patients who additionally met the eligibility criteria for the FOURIER[7] clinical trial were selected for the study, namely: age between 40 and 85 years, LDL-cholesterol level ≥ 70 mg/dL, and optimized use of a high-potency statin or, at least, 20mg daily dose of atorvastatin.

Statistical analysis

Descriptive statistics were used to summarize the variables of interest in the sample. The Kolmogorov-Smirnov test was used to verify the normality of continuous variables, with p values > 0.05 indicating a normal distribution. Continuous variables with normal distribution were described as means and standard deviations, and categorical variables were described as their absolute and percentage values.

Economic model

The patients included in the study had their risk of outcomes resulting from ASCVD stratified in 10 years, according to the presence of comorbidities, as shown in a previous publication.[10] The highest risk category in which the patient was classified was considered, and the risk was estimated by calculating the average of the risk interval, as described in Table 1.

Based on the estimated 10-year risk and a hypothetical intervention to reduce cardiovascular events with the PCSK9 inhibitor in these patients, a cardiovascular risk reduction

Table 1 – High-risk categories for cardiovascular disease at 10 years for patients on statin therapy, based on published clinical trial data

Category	Projected risk over 10 years (%)
Clinical ASCVD + diabetes	28-38
With chronic kidney disease	28-43
Without chronic kidney disease	26-29
Clinical ASCVD + chronic kidney disease	34-35
Recent ACS (<3 months)	32
CAD + poorly controlled risk factors	28-41
CAD + Peripheral vascular disease	43-55
CAD + ≥ 65 years old	21-54
IS/Transient ischemic attack	31
CAD + Familial hypercholesterolemia (LDL cholesterol ≥ 190mg/dL)	41

ASCVD: atherosclerotic cardiovascular disease; ACS: acute coronary syndrome; CAD: coronary artery disease; IS: ischemic stroke. Adapted from Robinson et al.[10]

model was developed with evolocumab for the study sample. This model was based on data from the FOURIER[7] clinical trial, which demonstrated an additional 59% reduction in LDL levels with evolocumab in patients already using statins, and data from the CTT[5] (Cholesterol Treatment Trialists) meta-analysis, which found that for every 39 mg/dL of decrease in the LDL-cholesterol value, there was a reduction in the number of cardiovascular events greater than 21%. Although the FOURIER study has a 26-month follow-up, the observed results were extrapolated to the 10-year period in the present study.

The cost-effectiveness assessment was performed using a Markov model, as depicted in Figure 1, which used as a primary outcome the combination of major cardiovascular events: non-fatal myocardial infarction (MI); non-fatal ischemic stroke (IS), coronary revascularization (RV); and cardiovascular death. Although Robinson et al.[10] do not consider RV as one of the evaluated outcomes, it is understood that coronary interventions are often performed after a MI, and, since its cost is not included in the payment for hospitalization for AM, this outcome was considered for the analysis.

The hospitalization costs for MI, IS and RV were obtained through the Management System of the List of Procedures, Medication, and Orthotics/Prosthetics and Special Materials - OPM (SIGTAP) of SUS, while the direct costs related to medication were obtained from data from the State Health Department of the state of Bahia.[11] The indirect costs related to early cardiovascular death were calculated according to the schematic representation shown in figure 2. The calculation was made by multiplying the number of years lost due to early death, considering the average life expectancy of the Brazilian individual and the average age of the assessed population, by the average annual financial gain of the Brazilian individual.[12] The salary used in this study was the average wage of the Brazilian population in 2017 corrected for the unemployment rate in the same period. Data was obtained through the Brazilian Institute of Geography and Statistics (IBGE, *Instituto Brasileiro de Geografia e Estatística*).[13]

The costs related to the treatment with high-potency statins were estimated based on the wholesale purchase price by our institution of a unit of atorvastatin tablet in the dose of 40mg. Regarding evolocumab, since it is not a medication acquired in the context of SUS, the retail price of a syringe unit at the dose of 140mg was used.

The results were presented using the Incremental Cost-Effectiveness Ratio (ICER), defined as the additional cost of the therapy with evolocumab, expressed in R$, divided by the additional achieved health gain, expressed by avoided cardiovascular outcome, when compared with standard therapy with high potency atorvastatin. For the calculation, a discount rate of 5% per year was considered.

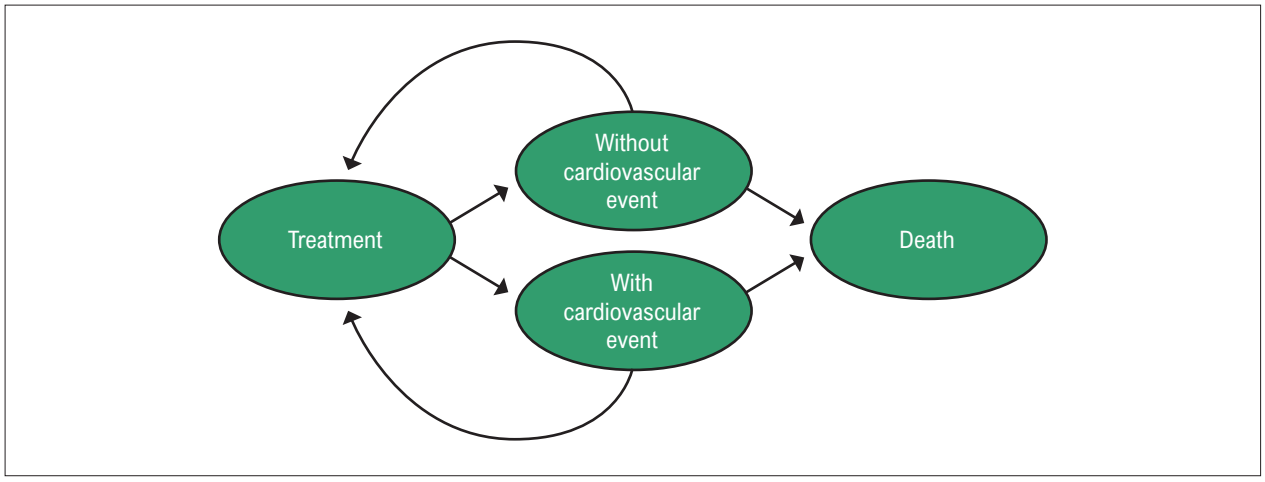

Figure 1 – *Schematic representation of the Markov Model used in the comparison between Atorvastatin 80mg versus Atorvastatin + Evolocumab.*

$$\text{Cost of 1 cardiovascular death} = \left[\begin{array}{c} \text{Number of years lost} \\ \text{X} \\ \text{Average annual gain} \end{array} \right]$$

Figure 2 – *Formula used to estimate the cost of cardiovascular death. Adapted from Siqueira et al.[11]*

Sensitivity analysis

To assess the robustness of the model, deterministic and probabilistic sensitivity analyses were performed. In the deterministic analysis, the parameters of the model were varied by up to 20% more or less, to obtain a range of ICER variation. The probabilistic analysis was performed to assess the uncertainty of the ICER calculated values. To this end, a Monte Carlo analysis was conducted by microsimulation including 1,000 random attempts. From this analysis, the acceptability curve was generated to assess the probability that one treatment is more cost-effective than another, as a limit function of the willingness to pay for an additional unit of effectiveness. The analyses were performed using the TreeAge Pro 2020 R.2 software.

Ethical considerations

According to resolution 466/2012 of the National Health Council, the present study was approved by the local research ethics committee, CAAE number 68053317.9.0000.0045, and all procedures were performed in accordance with the declaration of Helsinki.

Results

According to the inclusion criteria, 61 patients were evaluated in the present study and their clinical and demographic characteristics were compared to those of the population monitored by the FOURIER study, demonstrating a moderate heterogeneity between the two groups, as shown in table 2. The sample had a mean age of 63 (±11) years old, 32 (52%) were males and the most prevalent cardiovascular risk factors were hypertension (83%), followed by diabetes mellitus (42%) and smoking (31%). Of these patients, 54% had suffered a previous MI and had an average LDL-cholesterol level of 111 (±34) mg/dL, with 57% of them having an LDL value ≥100 mg/dL.

The average individual 10-year risk of MI, IS, RV or cardiovascular death among the study patients was 35%, if using isolated therapy with atorvastatin. The costs of hospitalization for MI, IS and RV were, respectively, R$ 588.12, R$ 463.21, and R$ 6,756.37, while the value of an atorvastatin 40mg tablet was R$ 1.00 and that of a 140 mg syringe of evolocumab was R$ 901.61.

To calculate the cost of early cardiovascular death, the mean age of patients was 63 years old and the average age of death was 68 years considering that, in a period of 10 years, death would occur, on average, after 5 years. Adjusting to the proportion of men and women, the average life expectancy of the study sample was 75 years and 8 months with a loss of 7.7 years of life if the death event occurred, and the average annual gain corrected for the unemployment rate was R$ 22,128.00. Thus, an early cardiovascular death in the studied population would cost R$ 170,385.60.

According to the estimate, treatment with evolocumab would reduce the average LDL-cholesterol level of the population from 111 mg/dL to 45.5 mg/dL, which would represent a relative risk reduction of 35% in comparison to the isolated use of atorvastatin 80mg/day. Thus, patients using the combined therapy of atorvastatin and evolocumab would have an individual risk of 22.75% of the occurrence of one of the events that constitute the composite outcome (MI, IS, RV, or cardiovascular death in 10 years), representing an absolute risk reduction projected over 10 years of 12.25%. When calculating the average costs for each of the outcomes, observing

Table 2 – Clinical and demographic characteristics of the population of patients with coronary artery disease and in the FOURIER trial

	SAMPLE	FOURIER
Age, mean (±SD)	63 (11)	63 (9)
Male, N. (%)	32 (52)	20,795 (75)
Cardiovascular risk factors, N. (%)		
Hypertension	51 (83)	22,040 (80)
Diabetes Mellitus	26 (42)	9,333 (34)
Smoking	19 (31)	7,770 (28)
Previous vascular disease, N. (%)		
MI	33 (54)	22,356 (71)
IS	0 (0)	5,330 (17)
Ezetimibe use, N. (%)	6 (10)	1,393 (5)
Lipid parameters		
LDL cholesterol, mean (±SD), mg/dL	111 (34)	97 (28)
LDL cholesterol 70-99 mg/dL, No. (%)	26 (43)	15,586 (57)
LDL cholesterol ≥ 100mg/dL, No. (%)	35 (57)	9,943 (36)
HDL cholesterol, mean (±SD), mg/dL	45 (13)	46 (13)
Triglycerides, mean (±SD), mg/dL	159 (97)	149 (70)

SD: standard deviation; MI: myocardial infarction; IS: ischemic stroke.

the proportion of their occurrence in the placebo group of the FOURIER[7] study, an average value of R$ 23,145.40 was obtained, if one of the outcomes occurred.

The cost of the drug for standard therapy with atorvastatin 80mg/day for 10 years would be R$ 7,300.00 per treated patient, while it would be R$ 223,686.40 per patient for 10 years for therapy with atorvastatin 80mg/day + evolocumab 140mg administered every 15 days. When considering the global cost per patient, which includes the probability of occurrence and the costs of negative outcomes, the global cost of treatment with atorvastatin monotherapy was R$ 46,522.44, *versus* R$ 236,141.85 for the combined therapy, with an overall effectiveness of 0.54 and 0.73, respectively.

When considering the average costs and effectiveness observed in the model, an incremental cost of R$ 189,619.41 and incremental effectiveness of 0.19 were obtained, which resulted in an ICER of R$ 1,011,188.07 for an avoided cardiovascular outcome. Figure 3 summarizes the comparison of the cost-effectiveness ratio between the two alternatives analyzed in the study.

Table 3 shows the results of the cost and effectiveness measures resulting from the economic model, with the respective sensitivity analysis obtained through the Monte Carlo simulation.

In the deterministic sensitivity analysis, with variation in the cost and effectiveness values of each of the strategies, a range of ICER variation was obtained, from R$ 864,498.95 to R$ 1,296,748.43 and through the analysis of the acceptability (Figure 4), it was possible to observe that the combined therapy with evolocumab was more likely to be more cost-effective only after an increase of R$ 1,000,000.00 in the availability to pay.

Discussion

In the present study, a cardiovascular risk reduction model demonstrated by the FOURIER clinical trial was extrapolated to 10 years and used to assess the cost-effectiveness of adding evolocumab to a sample monitored through SUS. The patients had proven CAD, with recent ACS and elevated LDL-cholesterol levels, despite optimized high-potency statin therapy. The cost-effectiveness analysis showed that adding evolocumab 140mg every 15 days to the standard therapy, considering the current purchase value of both drugs, would result in an incremental cost in 10 years of R$ 189,619.41 per patient. Thus, it would be necessary to invest R$ 1,011,188.07 with additional evolocumab therapy for each additional cardiovascular event (fatal or not) avoided in the sample.

PCSK9 inhibitors have emerged as a promising therapy in the secondary prevention for patients at high risk of cardiovascular events, and with high levels of LDL-cholesterol refractory to high-potency statin therapy, with a greater absolute risk reduction and a lower number needed treat (NNT) in patients with higher residual levels of LDL-cholesterol.[14] However, the importance of the economic analysis in health before deciding about the implementation of new technologies, including medications, in the public health system is increasingly understood, since new technologies are almost always accompanied by high financial increments to the system. This knowledge would allow the allocation of economic resources to be carried out in a more systematic than intuitive way by health managers.[15] Thus, concerning evolocumab, a humanized monoclonal antibody, studies like this are necessary to decide about its implementation in SUS.

Many countries, aiming to standardize a value to guide decisions about the incorporation of new technologies into health systems, have established a cost-effectiveness threshold. This is represented by a ratio, between the monetary cost in the numerator and the measure of health gain in the denominator, a measure that can vary, below which the technology is considered cost-effective. In Brazil, the Ministry of Health has not yet established a cost-effectiveness threshold.[16] The use of values established by other countries in national studies is questionable, since the definition of the threshold is context-specific depending on the local wealth, availability and ability to pay, characteristics of the health system, and social preferences.[17] Studies published in Brazil, however, have already used the cost-effectiveness threshold suggested by the World Health Organization (WHO) of three times the Gross Domestic Product (GDP) *per capita* for years of life using the quality-adjusted life year (QALY), even if not using the same measure of health gain.[18] So, if we compared the result of this study with the threshold suggested by the WHO (R$ 95,500.00/QALY, considering Brazil's GDP *per capita* in 2017), we would have a non-cost-effective result.

Despite this, there are similar experiences in the literature. A study carried out in the United States (2017) intending to evaluate the cost-effectiveness of evolocumab in patients with ASCVD concluded that adding PCSK9 inhibitor to the standard lipid-lowering therapy would result in an incremental cost of U$ 105,398.00 and an increase in QALY of 0.39. This would represent an ICER of U$ 268,637.00 per achieved QALY, which exceeds the threshold of U$ 150,000.00 per QALY used by the study.[9] Even though the health gain unit considered by the present analysis was distinct, since it deals with studies with similar population and methodological characteristics, if QALY were considered the measure of health gain, it is believed that evolocumab would not be cost-effective in SUS, as it exceeds the threshold of U$ 150,000.00.

In Spain, on the other hand, a study carried out in 2017 evaluated the cost-effectiveness of evolocumab in two subgroups: patients with familial hypercholesterolemia (FH) and patients undergoing secondary prevention for cardiovascular events. A threshold of € 30,000.00 to € 45,000.00 per achieved QALY was considered. The results of the study demonstrated an ICER of € 30,893.00 for the HF group and € 45,340.00 for the secondary prevention group, concluding that the addition of evolocumab to the standard statin therapy can be considered a cost-effective alternative for these subgroups in the context of the Spanish National Health System.[19] This favorable result for the implementation of evolocumab is probably explained by the high values attributed to hospitalizations resulting from cardiovascular outcomes. Compared with the list used by SUS for hospitalization reimbursement, the value considered by the Spanish study was 47 times the tabulated value for MI, 110 times the value for IS, and 8 times the value for RV.

A meta-analysis published in 2019 assessed the cost-effectiveness of PCSK9 inhibitors in cardiovascular disease, analyzing 16 studies carried out in different countries with estimated results for life.[20] The study found a wide variation in the considered cost-effectiveness thresholds and in the annual costs of therapy with PCSK9 inhibitors, with ICER values ranging from U$ 51,687 to U$ 1,336,221 and the need for a 20% to 88% reduction in the purchase values of PCSK9 inhibitors for the therapy to be considered cost-effective. Thus, as suggested in the present study, despite its proven efficacy, the high cost of therapy with PCSK9 inhibitors makes it non-cost-effective for the general

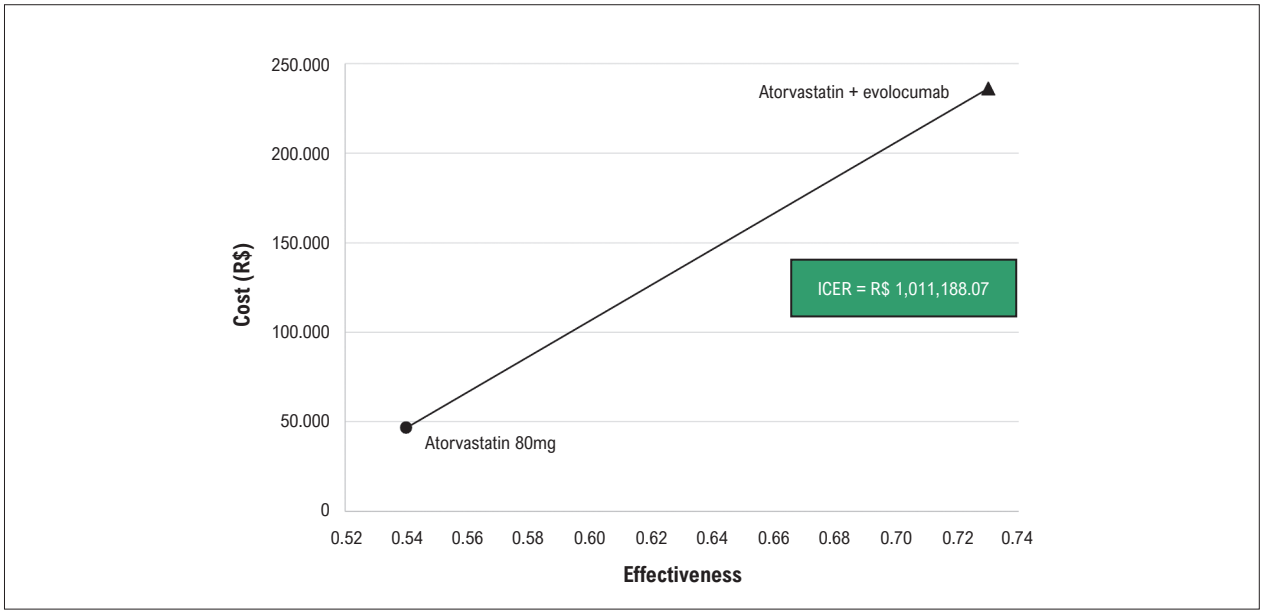

Figure 3 – *Cost-effectiveness comparison between Atorvastatin and Atorvastatin + Evolocumab in reducing cardiovascular outcomes. ICER: Incremental Cost-Effectiveness Ratio.*

Table 3 – Monte Carlo simulation in the cost-effectiveness assessment of the combined therapy of atorvastatin and evolocumab versus standard therapy with atorvastatin alone

		Therapy	
Attribute	**Measure**	**Atorvastatin**	**Atorvastatin + Evolocumab**
Cost (R$)			
	Mean	46,122.35	220,373.82
	Standard deviation	2,136.05	1,450.45
	Median	46,065.31	220,404.32
	2.5th Percentile	41,643.23	217,668.81
	10th Percentile	43,402.22	218,484.95
	90th Percentile	48,845.06	222.212.71
	97.5thPercentile	50,186.16	223,240.95
Effectiveness			
	Mean	0.55	0.73
	Standard deviation	0.01	0.01
	Median	0.55	0.73
	2.5th Percentile	0.53	0.72
	10th Percentile	0.54	0.72
	90th Percentile	0.56	0.74
	97.5th Percentile	0.56	0.75

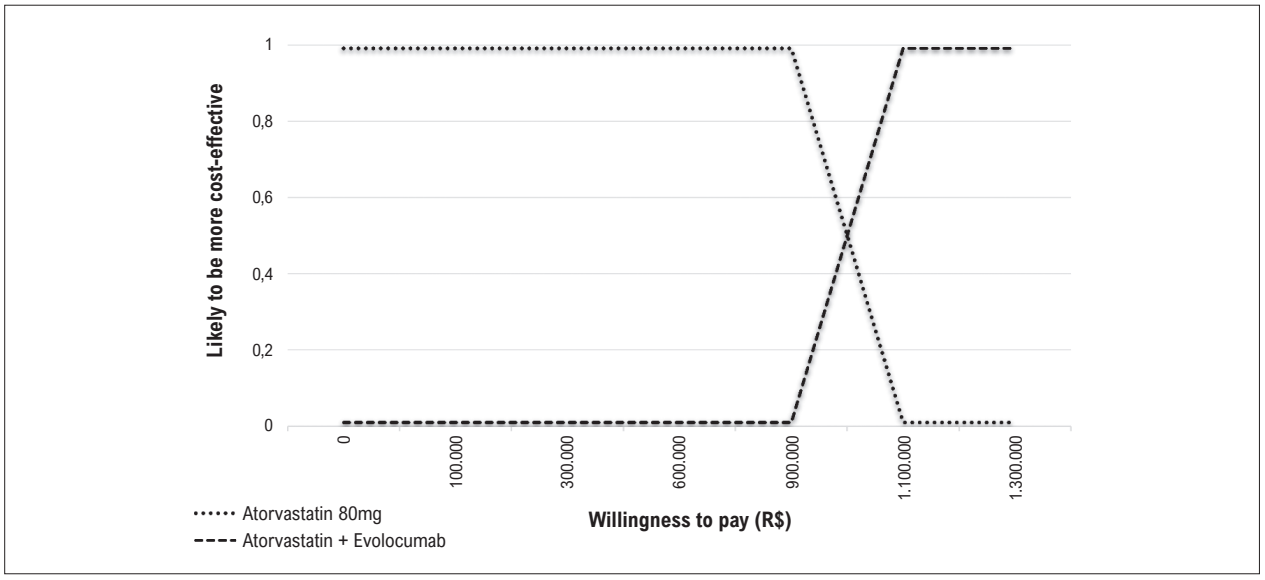

Figure 4 – *Acceptability curve according to the willingness to pay when comparing Atorvastatin versus Atorvastatin + Evolocumab in reducing cardiovascular outcomes.*

population. Reductions in the price of the drug have been implemented in some countries and it is necessary for further analysis to be carried out, considering the decrease in the cost of therapy.

In the national context, it is important to highlight the chronic underfunding of SUS, which can, at least in part, justify the observed results. A clear example is the underestimated values found in the SUS list: the reference standard for payment for services provided by establishments that provide service to the public health network. These pre-established values often do not cover the real costs of providing a service or carrying out a procedure,[21] which can be partly explained by the lag in the values in the SUS list that have not kept up with inflation rates in recent years. Therefore, the financial impact of reducing hospital admissions for MI, IS, and RV through the addition of evolocumab could be greater. Consequently, this would result in a lower incremental cost, since the high expense of adding evolocumab to the standard therapy would be offset by greater financial savings due to the prevention of cardiovascular outcomes.

Similarly, it should be considered that the costs of standard treatment with atorvastatin were estimated from their wholesale value, through the acquisition in our institution, which is financed by SUS. On the other hand, the costs related to evolocumab were obtained from its retail sales value. Taking this into account, we believe that variations in cost values are included in the performed sensitivity analysis, showing a lower ICER margin of R$ 864,498.95, which is still too high to demonstrate the cost-effectiveness of the therapy.

The study has other limitations. Initially, while the FOURIER study evaluated the prevention of cardiovascular outcomes during an average follow-up of 26 months, the values found were extrapolated here for a period of 10 years. During this period, if the benefits in preventing outcomes differed from the FOURIER study or if significant adverse effects occurred, the cost-effectiveness estimate could change. A progressive decrease in cardiovascular events was observed throughout the clinical trial, so the total benefit of evolocumab in reducing cardiovascular events may have been underestimated.

A potential limitation, since the amount related to early retirement was not considered in the calculation of the cost of the assessed outcomes, is not applicable. This happens, because the average age of the patient sample is older than the average retirement age by contribution time (55.6 years for men and 52.8 years for women), according to data from the Brazilian National Social Security Institute (INSS – *Instituto Nacional de Seguridade Social*) as of 2018. Thus, there is no financial impact in the case of evolution with incapacity for work or early death, in addition to those estimated by the reduction in GDP. The absence of a well-established Brazilian cost-effectiveness threshold with a health gain unit, like the one used in the present study, made it difficult to accurately conclude whether the strategy is cost-effective or not. Also, the economic analysis of evolocumab was based on a specific sample of patients undergoing secondary prevention and at high risk for cardiovascular events and should not be extrapolated to the primary prevention scenario or other populations at lower cardiovascular risk.

Conclusion

Although there are no national standards for acceptability in cost-effectiveness analyses, the observed data suggest that the strategy of associating evolocumab with statin therapy is not cost-effective at the moment. The reduction of treatment values and/or the selection of candidates for therapy with a higher risk profile would help to achieve better cost-effectiveness values. Therefore, future discussions on the topic should involve health professionals and SUS managers assessing groups of patients at higher cardiovascular risk,

allowing the availability of effective therapies to improve the population's health.

Author Contributions

Conception and design of the research, Writing of the manuscript and Critical revision of the manuscript for intellectual content: Braga LL, Melo RMV, Mistro S, Latado AL; Acquisition of data: Braga LL, Melo RMV, Lira YM, Oliveira NFC, Galindo YS, Viana T, Passos LCS; Analysis and interpretation of the data: Braga LL, Melo RMV, Mistro S; Statistical analysis: Braga LL, Melo RMV, Mistro S, Nascimento HF.

Potential Conflict of Interest

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

Sources of Funding

There were no external funding sources for this study.

Study Association

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

Erratum

November 2021 Issue, vol. 117(5), pages 988-996

In the Original Article "Cost-Effectiveness Analysis of Evolocumab Therapy in Patients at High Risk of Cardiovascular Events in the Context of the Brazilian Unified Health System", with DOI: https://doi.org/10.36660/abc.20200690, published in the journal Arquivos Brasileiros de Cardiologia, Arq Bras Cardiol. 2021; 117(5):988-996, on page 1, change the name of the author Luiza Latado to: Luisa Latado.

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The Challenge of Incorporating High-Cost Technologies: An Analysis of PCSK9 Inhibitors

Miriam Allein Zago Marcolino,[1,2] Sérgio Renato da Rosa Decker,[3,4] Eduardo Gehling Bertoldi,[1,3,5] Carisi A. Polanczyk[1,2,6,7]

Instituto de Avaliação de Tecnologia em Saúde - INCT/IATS, Universidade Federal do Rio Grande do Sul,[1] RS - Brasil
Programa de Pós-Graduação em Epidemiologia - Universidade Federal do Rio Grande do Sul (UFRGS),[2] Porto Alegre, RS - Brazil
Programa de Pós-Graduação em Cardiologia - Universidade Federal do Rio Grande do Sul (UFRGS),[3] Porto Alegre, RS - Brazil
Programa de Residência Médica em Medicina Interna - Hospital Nossa Senhora da Conceição,[4] Porto Alegre, RS - Brazil
Hospital Escola, Universidade Federal de Pelotas,[5] Pelotas, RS - Brazil
Hospital de Clínicas de Porto Alegre, Universidade Federal do Rio Grande do Sul,[6] Porto Alegre, RS - Brazil
Serviço de Cardiologia, Hospital Moinhos de Vento,[7] Porto Alegre, RS - Brazil

Short Editorial related to the article: Cost-Effectiveness Analysis of Evolocumab Therapy in Patients at High Risk of Cardiovascular Events in the Context of the Brazilian Unified Health System

Since the discovery, in 2003, that loss-of-function mutations in the gene that encodes proprotein convertase subtilisin/kexin type 9 (PCSK9) reduce LDL cholesterol levels, there has been growing interest in using PCSK9 pathways to treat patients with increased risk of cardiovascular disease and atherosclerosis.[1,2] In multiple randomized clinical trials, PCSK9 inhibitors reduced LDL levels, with a significant reduction in cardiovascular events, although the effect on mortality has been less consistent.[3] The FOURIER clinical trial was the largest randomized clinical trial with these medications, including 27,564 patients with high risks; it demonstrated a reduction in major cardiovascular events with the use of PCSK9 inhibitors, without any significant impact on cardiovascular mortality.[4]

Nevertheless, the high cost of therapy, with continuous lifelong treatment, is an important obstacle to its use. Costs directly impact the prescription of these medications by physicians, as well as patient compliance, and large-scale adoption by health systems.[5] This problem is not unique to low- and middle-income countries. Several international studies have indicated that, from an economic perspective, the prices of these drugs were not proportionate to the expected benefit.[6,7] There has been massive appeal from the international community for a reduction in the price of PCSK9 inhibitors, which has been taking place over the years.[7,8]

In Brazil, this scenario is also rather critical, given that this class of drugs has not been approved for incorporation into the Brazilian Unified Health System (SUS), nor is it included in private health insurance coverage. Accordingly, the cost-effectiveness analysis of evolocumab in patients with high cardiovascular risks in the context of SUS in Brazil[9] is very timely.

The authors used data from a cohort of patients treated at a public hospital in the Brazilian state of Bahia in combination with data from the FOURIER study, extrapolated for a period of 10 years, in a cardiovascular risk reduction model that simulates events in a Brazilian cohort. The population is the one most likely to benefit from the use of PCSK9 inhibitors in the context of non-familial dyslipidemia,[10] consisting of patients treated for acute coronary syndrome in the last year (57% with acute myocardial infarction) and LDL levels > 100 mg/dL, notwithstanding the use of atorvastatin and ezetimibe. The authors demonstrated an additional cost of 189,619 Brazilian reais (BRL) and an incremental cost-effectiveness ratio greater than 1 million BRL per cardiovascular outcome avoided.

Some methodological aspects of the study should be pointed out before interpreting the data. The reduction in cardiovascular events was extrapolated from the predicted reduction in cholesterol levels, resulting in nearly 35% relative reduction and 12% absolute reduction over 10 years. However, in the FOURIER study, in spite of a 59% reduction in LDL cholesterol, there was a 15% relative reduction in the primary outcome and an absolute reduction of only 1.5%.[4] Surely, the proposed model overestimates the benefit of therapy.

Regarding the applied costs, the authors used direct costs of acquiring the medications, and reimbursements tabulated by SUS for hospital admissions due to acute myocardial infarction, stroke, and myocardial revascularization, considering the frequency of events observed in FOURIER. However, the reimbursement values used by SUS for these procedures have not been updated, thus representing values that are frequently underestimated when compared to the actual costs of hospital admissions.[11]

Additionally, the cost of atorvastatin, based on the cost of acquisition by a local public reference hospital, is probably lower than the cost of direct acquisition by patients, which is a plausible scenario for an analysis from the societal perspective. The unit cost of treatment with evolocumab has not been described, but it is known that the consumer price has reduced over the past years. The authors opted to present the results in the form of cost per cardiovascular

Keywords

Health Expenditures; Cost-Bebefit Analysis; Proprotein Convertase/therapeutic use; Technology Assessment, Biomedical; Atherosclerosis;Unified Health System.

Mailing Address: Carisi A. Polanczyk •
Instituto de Avaliação de Tecnologia em Saúde - INCT/IATS - Ramiro Barcelos, 2350, sala 21507. Postal Code 90035-903, Porto Alegre, RS - Brazil
E-mail: cpolanczyk@hcpa.edu.br

DOI: https://doi.org/10.36660/abc.20210840

event avoided; although this decision holds some merit, measuirng the outcomes in cost per quality-adjusted life year is considered the gold standard, and it would allow comparison with other health therapies.[12]

These methodological issues demonstrate how complex and sensitive studies of this nature are. We need to join efforts to produce knowledge related to economic analysis in the Brazilian health scenario, and in this sense we congratulate the authors.

Regarding this topic, it is necessary to reflect on how we may offer our patients therapies with added clinical value, which are, however, very costly. Resources are finite, and we must prioritize cost-effective therapies, that is, those that offer the greatest benefit at a reasonable cost. To solve this equation, the path involves maximizing choices of patients with the highest risks and seeking to reduce prices for patients.[13]

We know that technological innovations are at the frontier of our practice, and we want to offer the best to those who need it. In order to do so, we need to rethink our healthcare system and model, reducing inefficiencies and cutting down on misspending. Incorporating high-cost technologies, especially to control cardiovascular diseases, depends on optimizing existing resources, suppressing actions that do not add value for patients, and agreeing on prices according to the expected benefits.[13]

The study[9] contemplates the cost-effectiveness of PCSK9 inhibitors, finding an unfavorable incremental cost-effectiveness ratio for incorporation, based on inputted parameters. The study represents a step toward expanding the role of economic analysis for decision-making in Brazilian health system. To offer the best interventions to our patients, we should aim for more economic studies, improving our understanding of the role of PCSK9 inhibitors and other high-cost therapies.

Acknowledgement

This study was financed in part by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior – Brasil (CAPES) – Finance Code 001.

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Cardiac Autonomic Nervous System Remodeling May Play a Role in Atrial Fibrillation: A Study of the Autonomic Nervous System and Myocardial Receptors

Ítalo Martins de Oliveira,[1,2] Evilásio Leobino da Silva Júnior,[1,2] Yasmin de Oliveira Martins,[3] Hermano Alexandre Lima Rocha,[4] Maurício Ibrahim Scanavacca,[1] Paulo Sampaio Gutierrez[1]

Instituto do Coração (InCor), Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo,[1] São Paulo, SP - Brazil
Hospital Messejana de Coração e Pulmão Dr. Carlos Alberto Studart Gomes,[2] Fortaleza, CE - Brazil
Hospital Geral de Fortaleza (HGF),[3] Fortaleza, CE - Brail
Harvard T.H. Chan School of Public Health,[4] Boston - USA

Abstract

Background: **The primary factors that originate and perpetuate atrial fibrillation (AF) are electrical and anatomical substrate alterations. However, the central mechanisms governing AF perpetuation have not been elucidated yet, which is reflected on the modest results of the treatment in patients with long persistent AF.**

Objective: **To evaluate if human intrinsic cardiac autonomic nervous system (ICANS) remodeling, including nervous system fibers and muscarinic and β-adrenergic receptors, play a role in permanent AF.**

Methods: **Heart necropsy samples from thirteen patients with heart disease and permanent AF and thirteen controls without AF were used. By using immunoperoxidase and histomorphometry quantification, we identified the following: the density of all fibers of the ICANS, sympathetic and parasympathetic fibers; and the percentage of myocardium positive for β-adrenergic receptors 1, 2 and 3; G protein-coupled receptor kinase-5 (GRK-5); and muscarinic receptors M1 to M5. The results were compared using ANOVA and nested ANOVA and were adjusted according to the left atrium volume for all variables, and β-blocker use to evaluate the expression of β-receptors and GRK-5.**

Results: **There was an overall increase in the density of fibers of the ICANS (p=0.006), especially in atrial sympathetic nerve fibers (p=0.017). Only M1 muscarinic receptors were increased (5.87 vs 2.35, p=0.032). For adrenergic receptors, the results were positive for increased expression of β-3 (37.41 vs 34.18, p=0.039) and GRK-5 (51.16 vs 47.66; p<0.001). β-blocker use had no impact on β-receptor expression.**

Conclusion: **Increased ICANS innervation and remodeling receptor expression in regions prone to triggering AF may play a role in permanent AF.**

Keywords: **Atrial Fibrillation/physiopathology; Autonomic Nervous System; Neurotransmitter Agents; Myocardium.**

Introduction

The primary factors that originate and perpetuate atrial fibrillation (AF) are electrical and anatomical substrate alterations, which involve many factors. In patients with AF without structural heart disease, ectopic foci in pulmonary veins have a well-defined role as triggers of paroxysmal AF.[1] In most cases, however, AF is a consequence of a structural disease, such as ischemic heart disease, valvular disease and others, presenting hemodynamic and anatomical consequences, such as left atrial enlargement, which are related to arrhythmia progression.[1]

Mailing Address: Paulo Sampaio Gutierrez •
Laboratório de Anatomia Patológica - Instituto do Coração, Hospital das Clínicas FMUSP - Av. Enéas Carvalho Aguiar, 44. Postal Code 05403-000, São Paulo, SP - Brazil
E-mail: paulo.gutierrez@incor.usp.br
Manuscript received June 29, 2020, revised manuscript September 29, 2020, accepted November 25, 2020

DOI: https://doi.org/10.36660/abc.20200725

Fibrosis is also widely regarded as an independent factor related to persistent AF in structurally altered hearts.[2] Nevertheless, this data does not fully explain arrhythmia, and myocardial fibrosis might be more closely related to the underlying heart disease, rather than persistent AF itself.[3]

Invasive electrophysiological assessment of the pulmonary veins (PVs) has demonstrated not only an effective heterogeneity if the refractory period, but also anisotropic conduction properties, both at the pulmonary veins and at the PV-left atrium ostia, which can provide a substrate for reentry.[4] However, the central mechanisms governing AF perpetuation have not been elucidated yet, which is reflected on the modest results of treatment in patients with long persistent AF.[5]

Basic and clinical studies have suggested a significant participation of the cardiac autonomic nervous system in triggering and maintaining AF.[6,7] The activation of the cardiac autonomic nervous system can cause important changes in the refractory period of the atria, including increased

dispersion of refractoriness, which is a major mechanism for the development of persistent AF.[1, 8-10]

Experimental studies show sympathetic hyperinnervation in dogs with AF, and increased sympathetic and parasympathetic innervation in areas related to this arrhythmia in animals with heart failure.[11] A relationship between the intrinsic cardiac autonomic nervous system (ICANS) and AF has also been reported in humans, but the comparison was made with healthy patients.[2,12] The possibility of alterations in fibers of the ICANS and receptors in human AF has therefore been poorly explored up to this point.

Thus, the aim of this study was to evaluate ICANS, including the sympathetic and parasympathetic fibers, and the atrial myocardial expression of the five types of muscarinic receptors, and of the three types of adrenergic receptors, as well as of G-protein-coupled receptor kinase-5 (GRK-5), which controls the expression of adrenergic receptors. We studied the hearts of patients with structural diseases and permanent AF and control cases that, importantly, were matched by the same diseases, but without AF.

Methods

This study was guided by the principles of the Declaration of Helsinki and approved by the Scientific and Ethics Committee of the Heart Institute (InCor), #SDC 3043/07/118, University of São Paulo, School of Medicine, São Paulo, Brazil.

Patients

We used the same samples from a previous study.[3] We analyzed thirteen hearts from adult patients (older than 18 years of age) with recorded permanent AF (for at least 2 years)[1] that underwent necropsy (performed less than 24 hours after death) in the Pathology Laboratory at this hospital. All the patients had underlying heart diseases: ischemic heart disease (4), valve disease (4), hypertensive cardiopathy (2), idiopathic dilated cardiomyopathy (2), or Chagas disease (1). To avoid confounding factors linked to the underlying diseases, hearts from thirteen other patients analyzed in the same laboratory were included as controls. The subjects were chosen by matching the heart diseases to those of the patients with permanent AF, but without any mention of atrial arrhythmia in their files. Patients who underwent any type of surgery or other procedures with the potential to modify cardiac structure were excluded, as were hearts from patients with congenital heart diseases.

Heart samples

Four heart samples containing epicardium, myocardium, and endocardium were taken from each heart: at the posterior wall of the right atrium (Figure 1A); at the junction of the left superior pulmonary vein with the left atrium (Figure 1B); at the middle of the route of the vein of Marshall (Figure 1C); around the superior left fat pad (Figure 1D). These areas were chosen because these structures (fat pads, the vein of Marshall) have been implicated in AF. These sampling areas are commonly analyzed in other studies.[3,12,13] The posterior wall of the right atrium was sampled to verify whether the alterations were diffuse in the atria. These locations are shown in Figure 1.

After conventional histological processing and embedding, four micrometer-thick sections of these samples were prepared to quantify autonomic innervation, adrenergic and muscarinic receptors and GRK-5 expression.

Quantification of autonomic receptors

Strong positivity for adrenergic, muscarinic receptors, GRK-5 and total myocardial area was measured by automatic color detection in 3 microscopic fields in each slide. To avoid selection bias in choosing the fields, we analyzed those more distant from the slide tag. Additional analyses to verify the effects of β-blocker use and β-receptor expression were also performed.

Quantification of autonomic nerve fibers, receptors and immunohistochemistry

Additionally, all samples of each heart were verified for the quantification of autonomic nerve fibers. The S-100 protein stains all nerves, whereas tyrosine hydroxylase (TH) only stains postganglionic adrenergic (sympathetic) fibers. Thus, like other authors,[14] we evaluated cost-effectiveness and considered the TH positive nerves as sympathetic nerves; and parasympathetic nerves were considered to be S-100 positive and TH negative. The area of the section, as well as the area and number of nerves positive for the antibody were quantified in each slide. The following variables were then calculated: mean percent positive area (positive area/section area); mean density of positive nerves (number of positive nerves/section area); and mean area of the nerves (positive area/number of nerves). We also calculated the total number of nerve fibers (S-100 positive); sympathetic nerve fibers (TH positive); and parasympathetic nerve fibers (S-100 positive and TH negative, difference between total and sympathetic nerve fibers).

To increase the contrast between weak and strong positivity, the dilutions for the receptors and GRK-5 were supraoptimal[15] when compared to those established in control tissues. As a control for the reactions, the primary antibody was omitted in 5 slides chosen at random. The sections were examined on an *Axiovision* 4.6 image analysis system, coupled to an *Axion imager* A1 *microscope* (both from *Carl Zeiss*, Germany), by an observer blinded to the group to which the slides belonged.

Antibody specification and dilution: muscarinic receptor 1 (AB5164) - 1:100; muscarinic receptor 2 (AB9452) - 1:800; muscarinic receptor 3 (AB9451) - 1:200; muscarinic receptor 4 (AB9219) - 1:400; muscarinic receptor 5 (AB9453) - 1:400; adrenergic receptor β1 (SC568) – 1:200; adrenergic receptor β2 (SC570) - 1:50; adrenergic receptor β3 (SC1473) - 1:20; receptor kinase GRK5 (SC 565) – 1:200; S-100 (Z0311) - 1:300; tyrosine hydroxylase (MAB318) - 1:50.

The antibody for S-100 was from *Dako*, Denmark. The antibodies for tyrosine hydroxylase and muscarinic

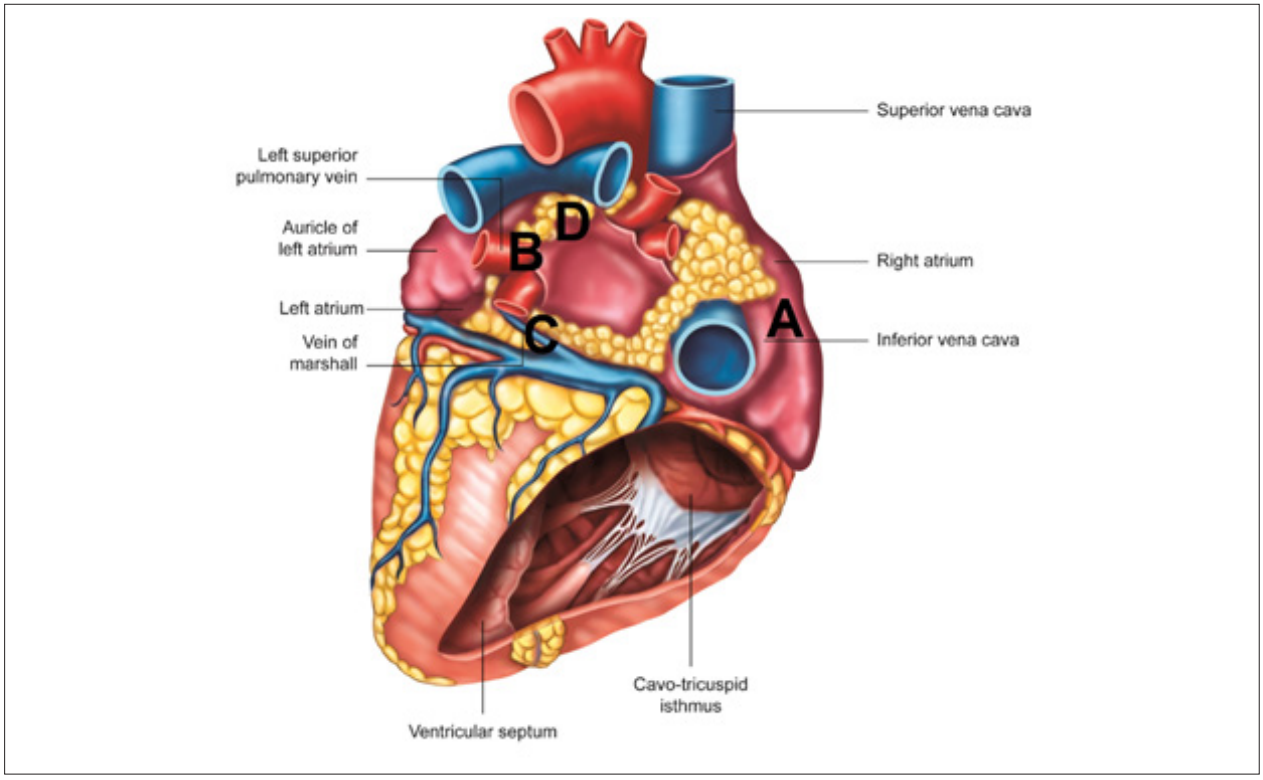

Figure 1 – *Photorealistic image of the posterior view of the human heart. Four heart samples were collected from the following locations: A) posterior wall of the right atrium; B) junction of the left superior pulmonary vein and left atrium; C) middle route of the Marshall vein; D) superior left fat-pad.*

receptors were from *Chemicon*, USA. The antibodies for the adrenergic receptors and GRK-5 were from *Santa Cruz* Biotechnology, USA.

Statistical analysis

Initially, absolute and relative frequencies were calculated for categorical variables, and measures of central tendency and dispersion for numeric ones. Chi square and Student's t test were used to compare cases and controls. Parametric tests were used after the Kolmogorov-Smirnov normality test was performed for all variables, and therefore robust error estimators were used in regressive models. An ANOVA One-Way was performed considering each set of equal samples to identify differences between them. Analysis of covariance was also performed for atrial dimensions and β-blocker use adjustment, when appropriate, while analyzing the individual sections. General linear models, also known as nested ANOVA, of all histological samples for each one of the individual participants, were applied to identify the impact of the principal determinant (namely, treatment, a between-subjects factor) on the various dependent variables. Finally, multiple general linear nested models were applied to all histological sections for each case. We considered significant p values to be lower than or equal to 0.05. In all models, Bonferroni adjustment in p values was performed. Analyses were done using SPSS v.23, IBM, Inc.

As in our previous study of fibrosis and histological features, since left atrial volume differs between patients with and without permanent AF, we performed a sensibility analysis with adjusted means considering the differences in left atrium size. Then, we predicted the results of each variable in hearts of any group with a given left atrium size to verify if potential differences between groups could be linked to this covariable. Additionally, β-blocker use was included for β-receptor and GRK-5 expression adjusted analysis.

Results

The clinical, morphological, and echocardiographic characteristics of patients with permanent AF and their controls are shown in Table 1.

Data concerning nerve fibers and considering each sample and all samples are presented in Table 2. When considering each location separately, we observed no difference regarding the density of intrinsic autonomic nerve fibers. The analysis considering all samples showed an increase in sympathetic nerves in patients with AF ($8.53 \pm 20.25/cm^2$ vs $2.67 \pm 4.57/cm^2$ and $p=0.04$). After adjusting for the size of the left atrium, both parasympathetic nerves and the total amount of nerve fibers were also increased. Figure 2 (A and B) shows the immunoexpression of nerve fibers in our samples.

Results regarding the expression of muscarinic and adrenergic receptors and GRK-5 are presented in Table 3. The results are divided by myocardial area for each location and atrial sample.

Table 1 – Clinical and echocardiographic data from patients with permanent AF and control cases

Variables	Cases with pAF (n=13)	Controls (n=13)	p
Male patients [n/(%)]	5 (38.5)	8 (61.5)	0.24†
Age (years) [mean/(sd)]	67.5 (15.4)	65.5 (11.4)	0.71¥
Underlying heart disease [n/(%)]			
Ischemic heart disease	4 (30.8)	4 (30.8)	
Valve disease, including RHD	4 (30.8)	4 (30.8)	
Hypertensive cardiopathy	2 (15.4)	2 (15.4)	
Idiopathic dilated cardiomyopathy	2 (15.4)	2 (15.4)	
Chagas' disease	1 (7.7)	1 (7.7)	
Weight (kg) [mean/(sd)]	66.5 (14.1)	63.8 (15.0)	0.67¥
Height (cm) [mean/(sd)]	162.4 (14.7)	160.8 (8.8)	0.78¥
BMI (kg/m^2) [mean/(sd)]	25.0 (2.9)	24.5 (4.2)	0.74¥
Diabetes *mellitus* [n/(%)]*	3 (23.1)	3 (25.0) (n=12)	0.99 †
Beta-blocker use	5 (38.4)	5 (38.4)	
Systemic arterial hypertension – [n/(%)]*	9 (69.2)	4 (33.3) (n=12)	0.07 †
Left atrium volume at echo (mL) [mean/(sd)]	83.2 (38.4)	47.9 (40.8)	0.03¥
LV septum thickness (mm) [mean/(sd)]	10.3 (2.4)	10.4 (1.6)	0.94¥
LV ejection fraction [mean/(sd)]	49.8 (20.1)	46.1 (19.8)	0.67¥
Collagen/collagen+myocardium ratio [mean +(sd)]	0.26 (0.09)	0.23 (0.06)	0.35¥

*pAF: permanent atrial fibrillation; n: number of cases; sd: standard deviation; RHD: rheumatic heart disease; BMI: body mass index; * no information regarding one control patient; echo: echocardiogram; LV: left ventricle. ¥ t test; † chi-square. Adapted from Oliveira IM et al.[3]*

Table 2 – Autonomic nerve fibers from hearts of patients with permanent AF and control cases

Fibers	All (S100) (units/cm^2)		Sympathetic nerve (TH+) (units/cm^2)		Parasympathetic nerve (TH-) (units/cm^2)	
Group	**pAF**	**Control**	**pAF**	**Control**	**pAF**	**Control**
RA - posterior wall	8.85±9.40	9.10±5.15	0.37±0.99	0.50±1.14	8.48±9.57	8.59±5.07
	p 0.935,	0.710¥	p 0.753,	0.905¥	p 0.971,	0.700¥
LA - junction of the left superior pulmonary vein	41.61±35.79	25.78±20.90	19.74±34.26	4.95±6.78	21.86±14.78	20.83±20.47
	p 0.181,	0.256¥	p 0.140,	0.158¥	p 0.884,	0.918¥
LA - middle of the route of the vein of Marshall	40.15±60.28	14.90±9.48	5.58±9.56	2.39±4.76	34.56±58.07	12.51±9.48
	p 0.149,	0.390¥	p 0.292,	0.230¥	p 0.189,	0.500¥
FP - superior left	38.05±55.72	19.25±11.95	8.42±16.07	2.85±2.82	29.62±40.56	17.47±10.53
	p 0.246,	0.637¥	p 0.248,	0.666¥	p 0.325,	0.681¥
Overall samples	32.16±45.76	17.26±14.20	8.53±20.25	2.67±4.57	23.63±36.77	14.80±13.27
	p 0.136&,	0.001†	p 0.044&,	0.017†	p 0.237&,	0.001†

Data presented as mean±standard deviation. Overall locations include all samples from each heart. pAF: permanent atrial fibrillation; LA: left atrium; RA: right atrium; FP: fat pad. p value ANOVA not adjusted, ¥ ANOVA adjusted by left atrium volume; & Nested ANOVA not adjusted; † Nested ANOVA adjusted by left atrium volume.

Immunostaining for muscarinic receptors is shown in Figure 2-C and D. There was no remarkable difference between the subepicardial and subendocardial regions. In hearts from patients with permanent AF, the expression of all types of muscarinic receptors (except type 5) was increased in at least one location. We observed more changes in the left superior fat pad and the oblique vein of the left atrium (vein of Marshall). Nevertheless, after adjusting for left atrial size, only the difference in M1 expression in the right atrium (and, consequently, the overall evaluation) and M2 near the fat pad remained significant.

Concerning β-adrenergic receptors and GRK-5, no difference was found in the overall analysis of the

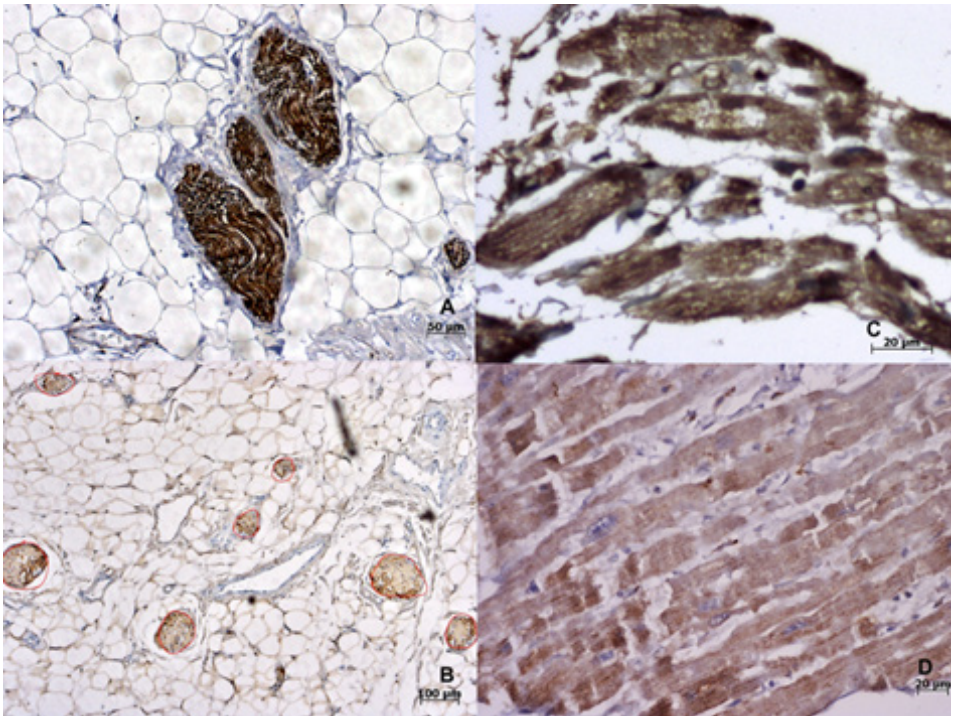

Figure 2 – *A) Nerve fibers strongly positive for tyrosine hydroxylase, thus considered to be sympathetic fibers; B) Photomicrograph of the image analysis system display showing nerves stained by S-100 protein; C and D) Negative (C) and positive (D) areas of myocardial sections with immunohistochemical reaction for muscarinic receptor 1.*

β-adrenergic subtypes 1 and 2 (only an increase in one sample each). However, β-3 and GRK-5 presented increased expression in all samples in the adjusted analysis. No difference was detected between patients who were taking β-blockers and those who were not (data not shown).

Discussion

The fibers of the ICANS in permanent AF

The ICANS is a neural network composed of nerve fibers and ganglia plexuses (GP) (sympathetic and parasympathetic) found in the heart and large adjacent veins.[16] ICANS plays an important role in the physiopathology of AF, as demonstrated by electrical stimulation or parasympathomimetic injections.[17] The current data reflects not only the activation of either a sympathetic or parasympathetic pathway, but also a change in the balance between their actions that is involved in the initiation of AF.[8,18]

In this study, we performed a comprehensive analysis of ICANS, focusing both on the nerves and on the muscarinic and beta-adrenergic receptors. We observed an increase in the amount of autonomic nerve fibers, especially atrial sympathetic nerves. However, when analyzing each location in isolation, these differences were not maintained. Moreover, when we adjusted for left atrium (LA) volume, the results remained the same. These last results also indicate that there is a significant change in nerve density in patients with permanent AF, even taking LA enlargement into consideration.

Several articles[12,14,19,20] have reported increased autonomic innervation in areas related to AF in terms of electrophysiology, such as the pulmonary veins, the coronary sinus, and the vein of Marshall. These studies only compared the nerve density (parasympathetic or sympathetic) in these regions, or in other areas, with the GP in the atrial myocardium. However, these regions, close to GP, are described as having higher nerve density, but they are not necessarily related to AF. Our results reveal a higher concentration of ICANS at these regions, especially sympathetic innervation. The greater sympathetic density of nerves may be a potential trigger of arrhythmia caused by innervation close to the GP, and the resulting activation of the autonomic nervous system that has already been demonstrated in experimental studies.[12-20]

Muscarinic receptors in permanent atrial fibrillation

The stimulation of the postganglionic parasympathetic neurons releases acetylcholine (cholinergic mediator), which acts on muscarinic receptors in the cell membrane in target organs (in the heart´s case, these would be the myocytes). Five types have been described.[21] The presence of all of these receptor types (M1 to M5) in the human heart was demonstrated by Wang et al.[22] in a descriptive study

Table 3 – Muscarinic and β-adrenergic receptor expression in hearts of patients with permanent AF and control cases

Receptor	Group	RA - posterior wall	p	p*	LA - midpoint of Marshall vein	p	p*	LA - junction of the left superior pulmonary vein	p	p*	LA - near the left superior fat pad	p	p*	Overall samples	p	p**
M1	pAF	6.47±3.39	0.001	0.002	5.56±4.64	0.021	0.131	6.32±5.33	0.286	0.270	5.15±4.89	0.038	0.220	5.87±4.52	<0.001	0.032
	Control	2.77±1.38			2.22±1.48			4.30±4.03			2.12±0.93			2.85±2.40		
M2	pAF	7.60±5.95	0.762	0.982	5.64±3.54	0.110	0.066	7.84±4.13	0.198	0.107	5.65±2.41	0.039	0.038	6.69±4.26	0.760	0.666
	Control	6.93±5.15			3.73±2.12			14.24±16.88			3.62±2.41			7.14±9.73		
M3	pAF	43.50±19.08	0.105	0.315	37.61±20.97	0.296	0.281	41.90±18.88	0.546	0.281	31.00±13.27	0.025	0.151	38.51±18.34	0.069	0.291
	Control	31.04±18.61			29.10±18.80			46.50±19.61			20.10±9.58			31.71±19.21		
M4	pAF	9.14±5.47	0.201	0.169	9.90±6.67	0.023	0.049	7.64±4.00	0.690	0.618	8.18±11.72	0.192	0.678	8.71±7.37	0.016	0.213
	Control	5.76±4.74			4.44±4.56			8.42±5.66			3.76±1.95			5.59±5.45		
M5	pAF	18.94±11.93	0.302	0.704	12.90±11.34	0.368	0.645	20.92±22.81	0.737	0.946	12.06±9.32	0.570	0.977	16.21±14.88	0.212	0.507
	Control	14.51±9.37			8.67±12.14			18.30±15.91			9.83±10.39			12.83±12.47		
β1	pAF	43.90±12.39	0.975	0.742	47.59±21.40	0.036	<0.001	37.48±21.90	0.438	0.288	40.23±22.37	0.552	0.214	42.05±19.75	0.295	0.520
	Control	44.10±17.81			28.98±19.34			43.60±17.42			34.89±22.83			37.89±19.93		
β2	pAF	23.81±11.96	0.785	0.445	32.42±19.20	0.180	0.589	20.57±13.48	0.323	0.257	23.47±16.69	0.037	<0.001	24.80±15.61	0.408	0.081
	Control	25.48±17.51			23.04±13.88			27.63±21.32			12.38±7.00			22.14±16.46		
β3	pAF	39.32±20.29	0.911	0.469	36.36±26.36	0.422	0.940	36.45±11.81	0.351	0.281	37.50±18.53	0.177	0.314	37.41±18.17	0.406	0.039
	Control	38.40±20.45			29.04±20.40			42.38±19.10			26.89±20.31			34.18±20.53		
GRK5	pAF	49.81±18.49	0.899	0.976	44.84±18.78	0.999	0.147	53.43±15.28	0.796	0.862	55.45±16.53	0.086	0.320	51.16±17.17	0.284	<0.001
	Control	50.53±7.61			44.85±19.75			52.95±13.26			43.29±18.00			47.66±15.39		

*Data presented as the mean proportion (%) ± standard deviation. pAF: permanent atrial fibrillation; LA; left atrium; RA: right atrium. p value ANOVA not adjusted. *Anova adjusted by left atrium volume for M1 to M5, and by left atrium volume and β-blocker use in β1 to β3 and GRK5.**Nested Anova adjusted by left atrium volume for M1 to M5 and by left atrium volume and β-blocker use in β1 to β3 and GRK-5.*

of right atrial samples from 4 patients undergoing coronary artery bypass surgery.[22] In the present study, the expression of all receptors (except M5) was increased in the hearts of patients with AF compared to the expression in the hearts of the controls. The expression of the M1 receptor was the most significantly altered, even in adjusted analyses, as shown in Table 3. All locations exhibited significant increase of this receptor, except at the junction of the left superior pulmonary vein. The increase in M1 in the myocardium of patients with permanent AF can be directly related to the permanent AF itself, which helps to explain the previously described increase in sympathetic tonus by the release of catecholamine in the sympathetic nerve endings, with a catecholamine-induced stimulatory effect.[23]

Receptor types 2, 3, and 4 were increased in patients with AF in only one location: 2 and 3 were increased near the superior left fat pad, and 4 was increased in the region of the vein of Marshall. In addition to the M1 and M2 receptors, M4 receptors have been found in the sympathetic ganglia and may be catecholamine-induced, similar to the M1 receptor. According to the study by Makino et al., the vein of Marshall has increased sympathetic nerve fibers and parasympathetic ganglia, and it may have an actual role linked to the enhanced expression of these receptors.[14] Thus, these affected areas are the ones that are actually more related to AF; only M1 seems to have a more diffuse alteration, reaching both the right and the left atria.

Changes in the expression of muscarinic receptors have been described in experimental models, which may suggest its role in the physiopathology, and perhaps int he treatment of AF. In an experimental study of canine heart failure models, the densities of the M2 and M4 receptors were reduced in atria with AF, and M3 receptors were increased compared to those in samples without AF.[24] It is noteworthy that M2 and M4 inhibit calcium channels, and M2 has inotropic and chronotropic actions.[21,22] Thus, one would expect for these receptors to be decreased, and not increased, in permanent AF. The same does not apply to M1 and M3 receptors, which have been documented in other organs as having stimulatory functions.[22] The M5 receptor and its action in the human heart are poorly understood, but the M5 receptor did not differ between the groups.

Our results suggest that the atrial myocardial tissue underlying a GP may be associated with increased muscarinic receptor expression, except in the case of M5. Increased muscarinic receptor expression occurred more often in the portion of the left atrium related to the vein of Marshall.

Despite the fact that we did not evaluate function, some considerations about the physiopathology of permanent AF in humans can be made based on our morphological observations. First, it is necessary to consider the possibility that the changes we found may not be the cause, but rather the effect of AF, by an unclear mechanism. In contrast, the imbalance of the ICANS, as demonstrated in experimental and electrophysiological studies, can be caused by lower activity of cardiac autonomic innervation (in which the reduction of the mean nerve area and the maintenance of the overall density of fibers could have an influence, although it must be mentioned that there was no alteration in the nerve area) with a disproportionate increase in sympathetic innervation. More importantly, increased myocardial expression of muscarinic receptors, especially those related to catecholamine-induced activity (M1, M2, and M4), and in specific regions related to AF (M1 and M3), indicates a possible imbalance in autonomic activity, which could perpetuate this arrhythmia in a permanent manner in human hearts by increasing the sensitivity to atrial stimulus caused by acetylcholine.

β-adrenergic receptors in permanent atrial fibrillation and the use of β-blockers

Despite the great importance of β-adrenergic control of heart rhythm, our data indicate there was no difference in the expression of these receptors or their kinase GRK-5 with the use of β-blockers.

No important differences were found in β-adrenergic types 1 or 2. However, the β3 receptors and GRK-5 kinase were strongly increased in the samples with permanent AF.

Methodological considerations and study limitations

Relatively few studies use pathological methods to study cardiac arrhythmias, mainly because most of the changes that underlie them are essentially electrophysiological, with few morphological repercussions, and because they frequently require laborious cardiac mapping. Once these challenges are faced, however, such methods have the potential to bring significant contributions to the understanding of these diseases. Our approach in this study was to verify types and areas of the autonomic nerve fibers, the expression of muscarinic and adrenergic receptors, and the kinase for adrenergic receptors (GRK-5) in human AF.

Our findings demonstrate that this method is useful to identify alterations when they are present (such as those observed with receptors). Clearly, one of the limitations of this kind of study is that the morphological expression of nerve fibers and receptors does not directly imply they are functional, but we can infer that changes in their myocardial concentration may reflect changes in their activity.

It is worth reinforcing the importance of choosing adequate controls for pathological studies: although AF usually occurs in patients with an underlying disease, most previous reports have used normal hearts as controls.[11] Thus, it is not possible to determine with enough precision which findings are actually related to the arrhythmia. To avoid such bias, our control patients had the same diseases as the patients with AF, as if we had "excluded" the disease both above and below the line in a fraction, leaving only the arrhythmia as an explanation for the differences. Additionally, we utilized samples from patients with permanent AF, with at least 2 years since the time of diagnosis, aiming to be certain that any potential alterations were established.

Conclusions

Increased ICANS innervation and receptors expression remodeling in regions prone to trigger AF may play a role in the condition of patients with permanent AF, secondary to structural heart disease.

Acknowledgments

The authors thank Solange Consorti and Ângela Santos for their technical support.

Author Contributions

Conception and design of the research: Oliveira IM, Silva Júnior EL, Scanavacca MI, Gutierrez PS; Acquisition of data: Oliveira IM, Silva Júnior EL, Martins YO; Analysis and interpretation of the data and Obtaining financing: Oliveira IM, Silva Júnior EL, Gutierrez PS; Statistical analysis: Oliveira IM, Rocha HAL; Writing of the manuscript: Oliveira IM, Silva Júnior EL, Martins YO, Rocha HAL, Scanavacca MI, Gutierrez PS; Critical revision of the manuscript for intellectual content: Oliveira IM, Martins YO, Scanavacca MI, Gutierrez PS.

Potential Conflict of Interest

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

Sources of Funding

This study was funded by FAPESP, process number 07/56648-8.

Study Association

This article is part of Doctoral theses submitted by Ítalo Martins de Oliveira from the Department of Cardiology of the School of Medicine of the University of São Paulo, Brazil, and by Evilásio Leobino da Silva Júnior from the same University in association with the State University of Ceará, Brazil.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Instituto do Coração under the protocol number 3043/07/118. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013.

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Role of the Autonomic Nervous System in Atrial Fibrillation

Enrique Indalécio Pachón Mateo[1]

Hospital do Coração,[1] São Paulo, SP – Brazil

Short Editorial related to the article: Cardiac Autonomic Nervous System Remodeling May Play a Role in Atrial Fibrillation: A Study of the Autonomic Nervous System and Myocardial Receptors

Since the late 1990s, we have been intensely studying the role of the autonomic nervous system in the genesis and maintenance of atrial fibrillation (AF) and neurocardiogenic syncope.[1]

AF can occur both in normal hearts and in those with significant structural changes.[2] Episodes of AF in young individuals with apparently normal heart have always caught our attention. The fact that these patients often have dysautonomic-like manifestations led us to think that purposeful denervation could be a way to treat these cases, and this technique was pioneered in 2004.[3] The effect of innervation seems to be not only due to neural stimulation but also by promoting disarray in the atrial syncytial architecture, in the sites of penetration of neurons, which detach the myocardial cells, disconnecting them. This disarrangement also promotes changes that can be detected in the endocardium by the local electrical signal, which we call AF Nests (AFN), and in the case of innervation, we call AFN type I.

The AFN are part of the AF substrate but to be sustained, it is necessary to have a maintainer that we call background tachycardia (BKT).[4] The AF elimination seems to depend on the elimination of substrate and sustaining factor, according to our observations and the findings of several more recent authors.[5] The vagal stimulation significantly reduces the refractory period of cardiac cells, facilitating the induction of AF.[6] The most interesting is that this alteration in the refractory period is not homogeneous, favoring arrhythmia.

Keywords

Autonomic Nervous System; Atrial Fibrillation; Cardioneuroablation; Cardiac Nervous System.

Mailing Address: Enrique Indalécio Pachón Mateo •
Hospital do Coração - Rua Cubatão, 86 Sala 508. Zip Code 04004-030, São Paulo, SP – Brazil
E-mail: epachon@gmail.com

DOI: https://doi.org/10.36660/abc.20210771

Another important fact is that the regions innervated by the right and left vagus, although partially overlapping, are not precisely the same.[7] Furthermore, the stimulation of the stellate ganglia or the infusion of sympathomimetics associated with vagal stimulation significantly reduces the AF threshold of the evaluated patients, showing that the balance between the sympathetic and parasympathetic system is primordial for the maintenance of regular cardiac rhythm. The authors of this study also found similar data when studying both the intrinsic cardiac innervation and its receptors.[8] The work is very well conducted, selecting two very similar groups with the same pathologies, in which the difference is that only one group had AF. The authors were careful to adjust the variables with statistical tools, the size of the left atrium, and the minimum diagnostic time to avoid interference in the results. The samples were also collected in regions close to the main paracardiac ganglia, and therefore sites more densely innervated and previously related to AF.[9] In addition, not only nerves but also the various receptors were evaluated. The increased sympathetic innervation in these regions in AF patients corroborates data from the literature, but there is still no adequate explanation to justify it. The unbalance of sympathetic/parasympathetic innervation is certainly arrhythmogenic, as already extensively described.[10] It is possible that this proves the efficiency of the use of beta-blockers in the treatment of many cases of AF, restoring the balance between the two systems, although the number of receptors was not modified by the use of this medication as observed in this paper.

It was clear from the data obtained in this article that intrinsic cardiac innervation plays a crucial role in maintaining AF, regardless of structural heart disease. The treatment of this arrhythmia should include the approach of the autonomic nervous system, whether through the use of drugs or even through the ablation of these more densely innervated regions so that we can have more robust and lasting results. In this way, we consider it fundamental to insist deeply in the research of the autonomic nervous system of the heart as described in this article, for understanding the genesis of the diverse types of AF, as well as to identify different forms of treatment of this arrhythmia that is so prevalent today in the general population.

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Cardiac Arrhythmias in Patients with COVID-19

Mauricio Pimentel,[1] Ana Paula Arbo Magalhães,[1] Camila Valvassori Novak,[1] Bruna Miers May,[2] Luiz Gustavo Bravosi da Rosa,[1] Leandro Ioschpe Zimerman[1]

Hospital de Clinicas de Porto Alegre,[1] Porto Alegre, RS - Brazil

Programa de Pós-Graduação em Ciências da Saúde: Cardiologia e Ciências Cardiovasculares – Universidade Federal do Rio Grande do Sul,[2] Porto Alegre, RS – Brazil

Abstract

Background: The coronavirus disease 2019 (COVID-19) is associated with cardiovascular clinical manifestations, including cardiac arrhythmias.

Objective: To assess the incidence of cardiac arrhythmias (atrial tachyarrhythmia, bradyarrhythmia, and sustained ventricular tachycardia) and cardiac arrest (CA) in a cohort of patients hospitalized with COVID-19 in a tertiary university-affiliated hospital.

Methods: Cohort study with retrospective analysis of electronic medical records. For comparison between groups, a value of p <0.05 was considered statistically significant

Results: We included 241 consecutive patients diagnosed with COVID-19 (mean age, 57.8 ± 15.0 years; 51.5% men; 80.5% white), 35.3% of whom received invasive mechanical ventilation (MV). The overall mortality was 26.6%, being 58.8% among those on MV. Cardiac arrhythmias were identified in 8.7% of the patients, the most common being atrial tachyarrhythmia (76.2%). Patients with arrhythmias had higher mortality (52.4% *versus* 24.1%, p = 0.005). On multivariate analysis, only the presence of heart failure (HF) was associated with a higher risk of arrhythmias (hazard ratio, 11.9; 95% CI: 3.6-39.5; p <0.001). During hospitalization, 3.3% of the patients experienced CA, with a predominance of non-shockable rhythms. All patients experiencing CA died during hospitalization.

Conclusions: The incidence of cardiac arrhythmias in patients admitted with COVID-19 to a Brazilian tertiary hospital was 8.7%, and atrial tachyarrhythmia was the most common. Presence of HF was associated with an increased risk of arrhythmias. Patients with COVID-19 experiencing CA have high mortality.

Keywords: COVID-19; Cardiac Arrhythmias; Heart Arrest; Atrial Fibrillation.

Introduction

The first cases of the disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), named COVID-19, were reported in China. Since then, COVID-19 has spread fast across the globe, being declared a pandemic by the World Health Organization on March 11, 2020. In Brazil, the number of confirmed cases of COVID-19 exceeded 3 million by August 2020.[1]

In COVID-19 case series, cardiovascular complications, such as myocardial injury, arrhythmias, myocarditis, heart failure, and cardiogenic shock, have been reported.[2] The damage to the cardiovascular system might have a multifactorial cause, including direct viral myocardial injury, exaggerated systemic inflammatory response, and thromboembolic phenomena.[3] Viral action via the angiotensin-converting-enzyme 2 receptor and its down regulation effect are factors involved in the exaggerated inflammatory response.[4] In addition, regarding cardiac arrhythmias, the following possibilities can be considered: proarrhythmic effects of the drugs used for the treatment of COVID-19, hypoxia caused by viral lung involvement, myocardial ischemia, water-electrolyte imbalance, myocardial strain, and intravascular volume changes.[5] The unbalanced inflammatory response by type 1 and type 2 T helper cells is another mechanism proposed to explain inflammation and arrhythmogenesis in patients with COVID-19.[6] The first case series from China have shown an incidence of cardiac arrhythmias of 17%, which could reach 44% in patients admitted to the intensive care unit (ICU).[7] Those studies, however, have detailed neither the type nor the characteristics of the arrhythmias observed. More recent studies conducted in North American centers have reported an overall incidence of arrhythmias of 6% and of atrial tachyarrhythmias of 16%.[8-10]

This study aimed to assess the incidence of cardiac arrest and cardiac arrhythmias in a cohort of patients with COVID-19 admitted to a Brazilian tertiary university-affiliated hospital.

Mailing Address: Leandro Ioschpe Zimerman •
Hospital de Clinicas de Porto Alegre – Cardiologia - Ramiro Barcelos, 2350. CEP 90035-903, Porto Alegre, RS – Brasil
E-mail: lizimerman@gmail.com
Manuscript received August 31, 2020, revised manuscript November 17, 2020, accepted November 25, 2020

DOI: https://doi.org/10.36660/abc.20200963

Methods

Cohort study including consecutive patients diagnosed with COVID-19 admitted to the Hospital de Clínicas de Porto Alegre, Rio Grande do Sul state, from March 1st to July 20, 2020. The first 241 consecutive patients diagnosed with SARS-CoV-2 infection confirmed by use of reverse transcription polymerase chain reaction of nasal and oropharyngeal swabs were assessed.

All electronic medical records were reviewed for the collection of demographic data and comorbidities, hospital outcome (death or hospital discharge), need for invasive mechanical ventilation (MV), and occurrence of cardiac arrest and cardiac arrhythmias. Medical and nursing data, as well as electrocardiographic findings, when available in the electronic medical record system, were analyzed.

Regarding the cases of cardiac arrest, the initial rhythm was reviewed and classified as: ventricular fibrillation/ventricular tachycardia (VF/VT), asystole, bradyarrhythmia, and pulseless electric activity (PEA). The occurrence of cardiac arrhythmias was defined as the presence of sustained atrial tachyarrhythmias (atrial fibrillation, atrial flutter), bradyarrhythmias, and sustained ventricular tachycardia. Arrhythmias present on hospital admission were not included, only those occurring during hospitalization. The study protocol was approved by the Committee on Ethics and Research of the Group of Research and Postgraduation of the Hospital de Clínicas de Porto Alegre.

Statistical analysis

The continuous variables with normal distribution were described as mean and standard deviation. The length of hospital stay showed no normal distribution by the Shapiro-Wilk test, was presented as median and interquartile range, and compared by use of Mann-Whitney test. The demographic and clinical characteristics were compared between patients with and without cardiac arrhythmias by using nonpaired Student *t* test for continuous variables and chi-square test for categorical variables. The association between clinical variables and the occurrence of cardiac arrhythmias was assessed with univariate and Cox multivariate analysis models. A two-tailed p value < 0.05 was considered statistically significant. All analyses were performed using the SPSS software, version 14.0, for Windows.

Results

This cohort study included 241 consecutive patients hospitalized with COVID-19 and mean age of 57.8 ± 15.0 years, 51.5% of whom were men, and 80.5% were white. The median length of hospital stay was 9 (interquartile range: 5-17) days, and 35.3% of the patients required MV. The length of hospital stay was longer in patients who had cardiac arrhythmias. The overall mortality was 26.6%, being 58.8% among those on MV and 9% among those not requiring MV (p=0.001).

Cardiac arrhythmias, defined as the presence of sustained atrial tachyarrhythmias, bradyarrhythmias and sustained ventricular tachycardia, were observed in 21 patients (8.7%). Table 1 shows the demographic and clinicals characteristics of the patients with and without arrhythmias. Of those with arrhythmias, 16 (76.2%) had sustained atrial tachyarrhythmias, 3 (9.5%) had sustained ventricular tachycardia, and 2 (9.5%)

Table 1 – Clinical characteristics of patients with and without cardiac arrhythmias

	All patients (n = 241)	With arrhythmia (n = 21)	Without arrhythmia (n = 220)	p value
Age, years	57.8 ± 15.0	62.6 ± 13.4	57.3 ± 15.0	0.11
Men	124 (51.5)	15 (72.4)	109 (49.5)	0.05
BMI, kg/m^2	30.4 ± 6.3	29.3 ± 5.0	30.5 ± 6.4	0.43
White skin color	194 (80.5)	17 (81)	177 (80.5)	0.24
Mechanical ventilation	85 (35.3)	14 (66.7)	71 (32.2)	0.002
Hospital length of stay, days	9 (5-17)	25 (12-43)	9 (5-16)	0.001
Death	64 (26.6)	11 (52.4)	53 (24.1)	0.005
Comorbidities				
SAH	123 (51)	14 (66)	109 (49.5)	0.13
DM	64 (26.6)	7 (33.3)	57 (25.9)	0.46
HF	15 (6.2)	5 (23.8)	10 (4.5)	0.001
Pulmonary disease	52 (21.6)	7 (33.3)	45 (20.5)	0.17
Chronic kidney disease	29 (12)	-	29 (13.2)	0.07
Drugs				
Hydroxychloroquine	43 (17.8)	3 (14.3)	40 (18.2)	0.65
Anticoagulants	39 (16.2)	2 (9.5)	37 (16.8)	0.24

Data were expressed as mean ± standard deviation or absolute numbers (percentage). The hospital length of stay was expressed as median and interquartile range. BMI: body mass index; SAH: systemic arterial hypertension; DM: diabetes mellitus; HF: heart failure.

had bradyarrhythmias. Patients with arrhythmias had higher mortality, 52.4% *versus* 24.1% (p=0.005). Cardiac arrhythmias were more frequent in men, patients on MV, and those with history of heart failure. Table 2 shows the results of the univariate and Cox multivariate analysis for the occurrence of cardiac arrhythmias. In that model, only the presence of heart failure associated significantly with a higher risk for cardiac arrhythmias (hazard ratio: 11.9; 95% CI: 3.6-39.5; p<0.001). When adjusted for the presence of heart failure, the occurrence of cardiac arrhythmias was associated with a higher risk for total mortality (hazard ratio: 3.4; 95% CI: 1.8-6.7; p<0.05).

During hospitalization, 8 patients (3.3%), all of them admitted to the ICU, experienced cardiac arrest, and their clinical characteristics are shown in Table 3. Figure 1 shows the distribution of the cardiac arrest rhythms: VF/VT, 2 patients (25%); PEA, 3 patients (37.5%); and asystole, 3 patients (37.5%). All patients undergoing cardiac arrest died during hospitalization.

Discussion

In this cohort study including consecutive patients with COVID-19 admitted to a referral hospital, the overall mortality was 26.6%, and the incidence of arrhythmias, 8.7%, and of cardiac arrest, 3.3%. Atrial tachyarrhythmia was the most common arrhythmia, accounting for 76.2% of the arrhythmias. On multivariate analysis, the presence of heart failure was the only variable associated with a higher risk for cardiac arrhythmias. The length of hospital stay of patients with arrhythmias was longer than that of those without arrhythmia. This might be due to the need to treat the arrhythmia itself or represent the higher complexity and severity of patients developing arrhythmias.

The initial series have shown incidence of cardiac arrhythmias in patients with COVID-19 ranging from 7% to 17%, but have not specifically described their types.[7,10] In the New York State cohort, the incidence of arrhythmias was associated with different combinations of drugs used to treat COVID-19, and ranged from 10% to 20%, but the types of arrhythmia assessed were not defined.[11] In our study, we found no association of the use of hydroxychloroquine with higher risk for arrhythmias. The specific incidence of each type of arrhythmia has been described only recently. Data from an international registry including 1197 electrophysiology professionals have shown that atrial fibrillation was the most frequently described arrhythmia in patients with COVID-19.[12] A study with 115 patients has found an incidence of atrial tachyarrhythmias of 16.5%, which reached 27.5% in patients admitted to the ICU.[8] The largest study specific to arrhythmias published so far has assessed 700 patients hospitalized for 9 weeks.[9] During follow-up, 44 patients (6.3%) had cardiac arrhythmias, such as atrial fibrillation, bradyarrhythmias, and nonsustained ventricular tachycardia, and atrial fibrillation was the most frequent (57%). Presence of heart failure and ICU

Table 2 – Univariate and multivariate analysis for the outcome 'cardiac arrhythmias'

	Univariate analysis			Multivariate analysis		
	HR	95% CI	p	HR	95% CI	p
Men	2.04	0.79-5.32	0.14	1.65	0.62-4.40	0.31
Mechanical ventilation	2.13	0.75-6.04	0.15	2.57	0.88-7.49	0.08
Heart failure	11.10	3.48-35.3	0.01	11.91	3.59-39.46	0.01

HR: hazard ratio; CI: confidence interval.

Table 3 – Characteristics of the cardiac arrests of patients with COVID-19

Patient number	CA on hospitalization day	CA rhythm	Clinical description	Outcome
1	1	PEA	26 years, asthma, obesity, and schizophrenia	ROSC 20 minutes, anoxic encephalopathy, comfort measures, death
2	26	PEA	54 years, renal transplant patient	ROSC 2 minutes, progressed to refractory shock, death
3	25	VF/VT	58 years, dilated cardiomyopathy, ICD, ARDS and MV	ROSC 20 minutes, refractory shock, death
5	10	VF/VT	45 years, dilated cardiomyopathy	ROSC 12 minutes, refractory shock, death
6	43	Asystole	71 years, ischemic heart disease	Death
7	12	Asystole	63 years, SAH, DM	Death
8	01	PEA	76 years, ischemic heart disease	Death
9	25	Asystole	41 years, SAH, obesity	ROSC 35 min, multiple organ dysfunction, death

CA: cardiac arrest; PEA: pulseless electric activity; VF/VT: ventricular fibrillation/ventricular tachycardia; ROSC: return of spontaneous circulation; ICD: implantable cardioverter-defibrillator; ARDS: adult respiratory distress syndrome; SAH: systemic arterial hypertension; DM: diabetes mellitus; MV: mechanical ventilation.

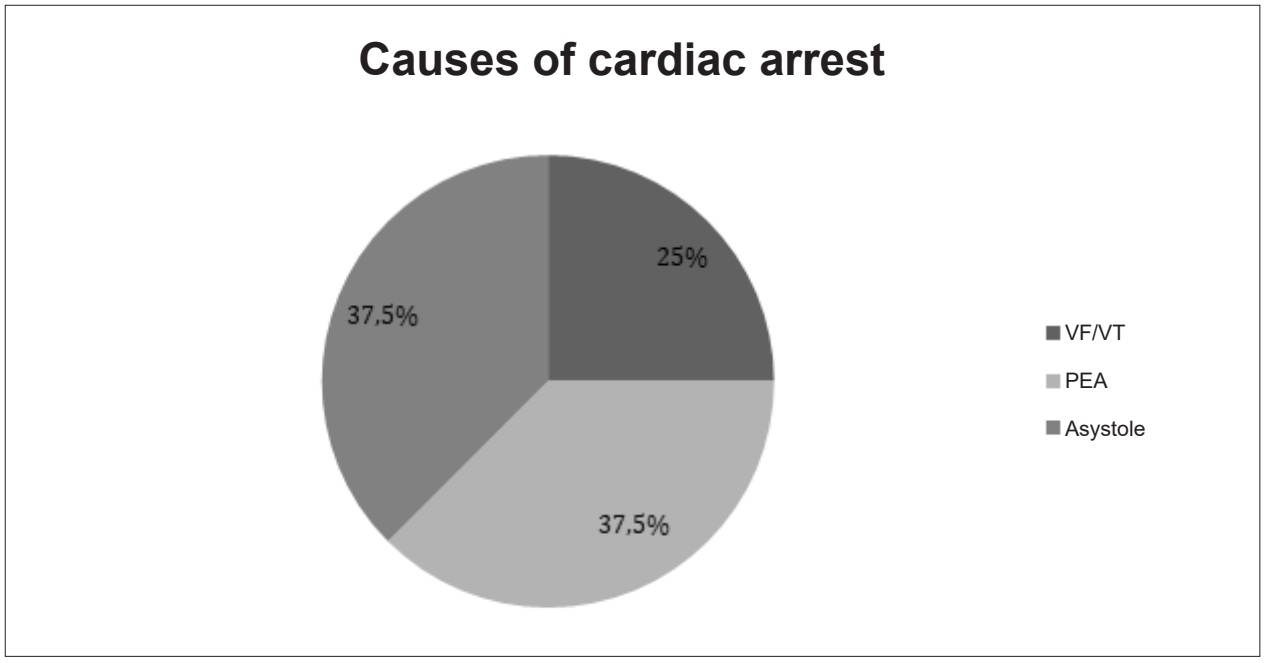

Figure 1 – *Rhythms of cardiac arrest of patients with COVID-19. VF/VT: ventricular fibrillation/ventricular tachycardia; PEA: pulseless electric activity.*

admission were significantly associated with a higher risk for arrhythmias. In that cohort, 11% of the patients were admitted to the ICU and overall mortality was 4%. Our incidence of arrhythmia of 8.7% can be considered close to that of that study, as well as the predominance of atrial arrhythmias and the association of heart failure with a higher risk of arrhythmia. However, our study included patients with more severe disease (35% required MV), and the presence of nonsustained ventricular tachycardia was not listed as an outcome. The use of MV was associated with a trend towards a higher risk for arrhythmia, although not statistically significant. The confirmation of the finding that patients with heart failure are at a higher risk for arrhythmias can indicate the need for more careful monitoring of such patients during hospitalization.

In the international survey with electrophysiology professionals, 4.8% reported cases of VF/VT and 5.6%, of PEA.[12] In the initial series from China, there was no specific mention to the occurrence of cardiac arrest and its rhythms.[2,7] In one of the studies, the incidence of VF/VT was 5.9%, and higher in patients with elevated troponin levels.[2] In the New York State cohort, the incidence of cardiac arrest ranged from 6% to 15%, depending on the different combinations of drugs used to treat COVID-19.[11] The rhythms of cardiac arrest were not described. In the study by Bhatla et al. described above, of the 9 cases of cardiac arrest (1.3%) reported, 6 were PEA, 2 were asystole, and 1, *torsades de pointes*.[9] In our study, the incidence of cardiac arrest was 3.3%, with predominance of non-shockable rhythms. The reduction in the occurrence of VF/VT cases as compared to that in the initial studies might be hypothetically attributed to changes in the COVID-19 treatment, with less use of drugs that can prolong the QT interval, in addition to the evolution of the learning curve of health professionals regarding the disease. Moreover, the predominance of non-shockable rhythms can be attributed to the systemic impairment and intense inflammatory response present in cases of severe COVID-19.

Our study has limitations that should be considered. The number of patients included is relatively small and reflects our initial experience. Patients admitted to the wards were not on continuous cardiac monitoring; thus, asymptomatic episodes of arrhythmia might not have been reported. The diagnosis of arrhythmia was obtained from review of medical records, and in some cases the arrhythmia described was only visualized on a monitor and no 12-lead electrocardiogram was recorded. The following data potentially associated with the occurrence of arrhythmias during hospitalization were not obtained: markers of myocardial injury and/or dysfunction, such as troponin and BNP; data on noninvasive ventilation modes; time of use and doses of vasoactive drugs; water-electrolyte imbalance; previous history of arrhythmias. This is a study with retrospective data collection in a single tertiary center. Therefore, our results cannot be generalized to other clinical settings.

Conclusions

In this cohort study of patients with COVID-19 admitted to a Brazilian referral hospital, the incidence of cardiac arrhythmias was 8.7%, and atrial tachyarrhythmia was the most common. The presence of heart failure was associated with a higher risk of cardiac arrhythmias. Patients with COVID-19 and experiencing cardiac arrest have high mortality.

Author Contributions

Conception and design of the research, Statistical analysis, Writing of the manuscript and Critical revision of the

manuscript for intellectual content: Pimentel M, Zimerman LI; Acquisition of data: Pimentel M, Magalhães APA, Novak CV, May BM, Rosa LGB, Zimerman LI; Analysis and interpretation of the data: Pimentel M, Magalhães APA, Zimerman LI.

Potential Conflict of Interest

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

Sources of Funding

There were no external funding sources for this study.

Study Association

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

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Hospital de Clínicas de Porto Alegre under the protocol number 12744919500005327. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013.

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Cardiac Arrhythmias and COVID-19: Side-By-Side in the Pandemic

Bruno Moreira dos Santos[1] and Luciana Sacilotto[1]

Instituto do Coração do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo,[1] São Paulo, SP – Brazil

Short Editorial related to the article: Cardiac Arrhythmias in Patients with COVID-19

The current pandemic caused by the new coronavirus (SARS-CoV-2), which was first detected in Wuhan, China, in December 2019, has changed healthcare services worldwide. According to recent reports of the World Health Organization, there are more than 224 million cases of COVID-19 in the world, with deaths surpassing 4.6 million.[1] The exponential increase in the number of cases has caused an impact on healthcare demand, and data on COVID-19 and its treatment have been constantly updated.

Although the respiratory system is the most affected by the SARS-CoV-2, other systems are commonly involved, including the cardiovascular system, leading to myocardial injury and arrythmias.[2,3]

In the first report of the 138 cases in China, cardiac arrhythmias were observed in 16.7% of total cases, and in 44.4% of intensive care unit (ICU) patients, with no distinction in the type of arrhythmias.[3] In another report from Italy, published in February 2020, the number of cases of out-of-hospital cardiac arrest increased by 58% as compared with the number of cases identified during the same period in the previous year. However, the study neither presented detailed information on heart rhythm nor confirmed SARS-CoV-2 infection. In this context, recent studies have been conducted aiming at better understanding the association between COVID-19 and cardiac arrhythmias.

The pathophysiological mechanisms of arrhythmia are still uncertain in COVID-19; hypotheses include internalization and reduction of angiotensin-converting enzyme 2 receptors, inflammatory and immune hyperactivation with increased cytokines, endothelial dysfunction, hypoxemia, sympathetic hyperactivation or dysautonomia, which altogether, cause changes in myocyte depolarization and repolarization, mainly in severe cases of the disease.[5,6] The presence of previous comorbidities and eventual arrhythmogenic substrate, combined with the frequent use of drugs that prolong the QT interval, may predispose to arrhythmia.[2,3,7]

Patients may present many types of arrhythmias, with occurrence of sinus bradycardia, atrioventricular block, and tachycardias (ventricular and supraventricular). In a study conducted in an American hospital with 700 patients with positive result for SARS-CoV-2, 11% received ICU care, there were 53 arrhythmia events, including 25 cases of atrial fibrillation, nine cases of bradycardia, 10 cases of nonsustained ventricular tachycardia, and nine cases of cardiorespiratory arrest, six of them pulseless electrical activity, two asystolic cardiac arrest and one case of torsades de pointes.[8] In another analysis of world data,[9] encompassing 4,526 patients hospitalized for COVID-19 in 12 countries, including Brazil and the current publication, 827 patients had arrhythmias during hospitalization; 81.8% of them had supraventricular tachycardia (mainly atrial fibrillation), 20.7% had ventricular tachycardia, and 22.6% had bradycardia, with an incidence of arrhythmia of 12.9%. In this study, the presence of arrhythmias was associated with a poor prognosis, with higher rate of morbidity and mortality.[9]

In the current scenario, data on Brazilian registries are relevant. Pimentel et al.[10] presented data of 241 patients admitted to a tertiary hospital with a diagnosis of COVID-19, confirmed by real-time PCR, based on medical record review. Mean age of participants was 57.8 years, 35.5% of the cases required intensive care therapy, 58.8% required mechanical ventilation, and mortality rate was 26,6%. The incidence of arrhythmias was 8,7%, of which 76,2% were supraventricular tachycardia, 14,3% were sustained ventricular tachycardia and 9,5% were bradycardia. There were eight cases of cardiorespiratory arrest in the ICU, only two with a shockable rhythm (ventricular fibrillation / pulseless ventricular tachycardia). Among the comorbidities analyzed, only previous heart failure was shown to be a significant risk factor for arrhythmia. Patients who had arrhythmias during hospitalization had greater odds of death (hazard ratio, 3.4. 95%CI 1.8-6.7; $p<0.05$), in accordance with results of studies conducted in other countries.[9]

Thus, despite its limited number of patients and single-center registry, the present study provides data on the association between SARS-CoV-2 infection and cardiac arrhythmias. Also, it is worth pointing out that most of the studies carried out in the world consist of medical chart reviews, in which diagnosis of arrhythmias was based on rhythm monitoring, sometimes without a 12-lead electrocardiogram, and a minor use of telemetry in the ward, which may underestimate the real incidence of arrhythmias. Multicentric studies with larger number of patients including different disease severity are needed for a better association between arrhythmias and mortality, so as to define measurements of prevention, surveillance and treatment.

Keywords

Arrhythmias, Cardiac; COVID-19; Pandemics.

Mailing Address: Luciana Sacilotto •
Instituto do Coração do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo - Unidade de Arritmia – Av. Dr. Enéas de Carvalho Aguiar, 44. Postal Code 01421-001, São Paulo, SP – Brazil
E-mail: luciana.sacilotto@incor.usp.br

DOI: https://doi.org/10.36660/abc.20210810

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C-reactive Protein as a Prognostic Marker of 1-Year Mortality after Transcatheter Aortic Valve Implantation in Aortic Stenosis

André Luiz Silveira Sousa,[1,2] Luiz Antônio Ferreira Carvalho,[2] Constantino González Salgado,[2] Rafael Lauria de Oliveira,[2] Luciana Cristina Correia Lima e Lima,[2] Nelson Durval Ferreira Gomes de Mattos,[2] Francisco Eduardo Sampaio Fagundes,[2] Alexandre Siciliano Colafranceschi,[2] Evandro Tinoco Mesquita[1]

Universidade Federal Fluminense - Hospital Antonio Pedro – Cardiologia,[1] Niterói, RJ – Brazil

Hospital Pró-Cardíaco – Hemodinâmica,[2] Rio de Janeiro, RJ – Brazil

Abstract

Background: C-reactive protein (CRP) is an inflammation biomarker that can be a predictor of adverse events in cardiovascular procedures. Its use in the assessment of long-term prognosis of transcatheter aortic valve implantation (TAVI) is still incipient.

Objective: To evaluate CRP as a prognostic marker in the first year after TAVI in aortic stenosis (AoS).

Methods: CRP was assessed on the first postoperative week in a retrospective cohort of patients with AoS. Pre- and post- CRP levels were correlated with mortality, and predictors of 1-year mortality were investigated. Multivariate Cox regression was performed to identify independent factors of 1-year mortality.

Results: This study evaluated 130 patients who underwent TAVI, with median age of 83 years, and 49% of women. High pre-TAVI CRP (> 0.5 mg/dL) was observed in 34.5% of the cases. Peak CRP was 7.0 (5.3-12.1) mg/dL no quarto dia. The rate of 1-year mortality was 14.5% (n = 19), being greater in the groups with high pre-TAVI CRP (68.8% vs 29.1%; p = 0,004) and with peak CRP ≥ 10.0 mg/dL (64.7% vs 30.8%; p = 0,009). Independent predictors of mortality were acute renal failure (ARF) (hazard ratio [HR] = 7.43; 95% confidence interval [95%CI], 2.1-24.7; p = 0,001), high pre-TAVI CRP (HR 4.15; 95%CI, 1.3-12.9; p = 0.01), and large blood transfusion [HR 4,68; 1,3-16,7; p = 0.02].

Conclusions: High pre-TAVI CRP showed to be an independent predictor of 1-year mortality, as well as the presence of ARF and large blood transfusions.

Keywords: C-Reactive Protein; Inflammation; Bomarkers; Heart Valve Prosthesis Implantation; Transcatheter Aortic Valve Replacement; Aortic Valve Stenosis.

Introduction

Fibrocalcic aortic stenosis (AoS) is a degenerative disease whose number of cases is estimated to triplicate in Brazil in the next 20 years, due to population aging.[1]

Transcatheter aortic valve implantation (TAVI) is a treatment that has been increasingly used in older adults, a group affected by chronic low-grade systemic inflammation (inflammaging),[2] whose presence is associated with greater: (1) organ dysfunction and frailty; (2) immune system compromise and risk of infections; and (3) rate of cardiovascular (CV) events and mortality.[3] This systemic inflammation is compounded by aortic valve inflammation in the process of valve degeneration from the initial stage of lipid infiltration[4] to the end-stage of calcification and neovascularization of leaflets.[5] Therefore, both systemic and valve inflammations are present before TAVI and have an increase, at different levels, after the procedure, depending on the adopted techniques and strategies.

However, few studies have used biomarkers to assess the role of systemic inflammation in mid- and long-term prognosis after TAVI. The present study evaluated the extent of systemic inflammation before and over 1 week after TAVI through serum C-reactive protein (CRP) levels and correlated them with 1-year prognosis.

Mailing Address: Andre Silveira Sousa •
Universidade Federal Fluminense - Hospital Antonio Pedro – Cardiologia - Av. Marquês do Paraná, 303. Postal Code 24033-900, Centro, Niterói, RJ – Brazil
E-mail: andreluizsousa@gmail.com
Manuscript received October 28, 2019, revised manuscript August 17, 2020, accepted December 02, 2020

DOI: https://doi.org/10.36660/abc.20190715

Methods

Population

This is a retrospective, cohort, observational study of symptomatic patients with severe AoS who underwent TAVI at a private hospital from June 2009 to May 2015. During this period, 137 TAVIs were performed on native valves, of

which the following were excluded from the present study: four cases of mechanical complications during the procedure resulting in death within 24 hours, and three procedures performed in critically-ill patients. We investigated 130 patients with severe AoS and symptoms of heart failure (HF), angina, or syncope who underwent TAVI with: (1) native aortic valve on transthoracic echocardiogram (TTE), with the presence of at least one of the following criteria: mean aortic transvalvular gradient > 40 mm Hg, or aortic jet velocity > 4 m/s, or aortic valve area (AVA) < 1 cm^2 (or AVA indexed by body surface < 0.6 cm^2/m^2);[6] (2) high risk for surgical aortic valve replacement (SAVR) as defined by the cardiologic team; (3) viable vascular access: transfemoral (TF), trans subclavian (TSC), and transaortic.

This study was conducted in compliance with the principles set forth in the Declaration of Helsinki and reviewed in 2000 (Scotland 2000) and was approved by the Research Ethics Committee of Hospital Pró-Cardíaco under no. 423. All patients signed an Informed Consent Form.

Investigation procedures

This study evaluated demographic variables and intervention and post-intervention variables correlated with clinical and laboratory parameters involved in inflammatory response after TAVI.

Laboratory tests included complete blood count, creatinine, and CRP. Convenience samples were sent to a clinical analysis laboratory, and results were immediately made available. Serum high-sensitive CRP concentrations were measured by turbidimetric immunoassay according to the hospital laboratory routine (reference value < 0.5 mg/dL) with the Dimension EXL 200 Clinical Chemistry System device (Siemens, German).

The procedures were performed under conscious sedation with TTE monitoring, or under general anesthesia with monitoring by three-dimensional transesophageal echocardiogram (TEE). Vascular access was obtained surgically. The following prostheses were used: self-expandable Medtronic CoreValve bioprosthesis (Medtronic, Minneapolis, USA) and balloon-expandable Edwards-Sapien XT valve (Edwards Lifesciences, Irvine, USA).

The study population was followed for 1 year after TAVI. Post-hospitalization adverse events were collected by systematic phone calls with the patients and/or their relatives and/or their treating physicians, as well as by test reports and records of subsequent hospitalizations and interventions. Phone calls and follow-up records were performed at 30 days, 180 days, and 1 year. However, only one patient was lost to follow-up at 1 year.

TAVI success and complications were defined according to the criteria proposed by the Valve Academic Research Consortium: TAVI success was considered the implantation of only one prosthesis, final mean aortic transvalvular gradient < 20 mm Hg, Indexed effective orifice area > 0.85 cm^2/m^2 (> 0.7 cm^2/m^2 in patients with body mass index > 30 kg/m^2), aortic regurgitation < 2+/4, and survival at 30 days. Systemic inflammatory response syndrome (SIRS) was diagnosed by the presence of at least two of the following criteria: fever (> 38ºC), tachycardia (> 90 beats/minute), tachypnea (> 20 breaths/minute), and leukocytosis (> 12000 leukocytes/mL).

CV events were defined as CV death or sudden undetermined death; hospitalization for any cause related to the CV system, such as arrhythmia, decompensated HF, coronary artery disease, percutaneous or surgical intervention; acute myocardial infarction; execution of coronary angioplasty; and ischemic or hemorrhagic stroke.

Statistical analysis

Descriptive analysis was presented in tables, and the observed data were expressed as median and interquartile range (Q1 and Q3) for numeric data, and frequency (n) and percentage (%) for categorical data, in addition to some illustrative graphs.

Inferential analysis consisted of the following methods: (1) the association of clinical and cardiologic data with 1-year survival was assessed in an univariate analysis using an individual Cox regression model; (2) the independent predictors of 1-year mortality were identified in a multivariate analysis using Cox regression with stepwise forward selection of variables; (3) the Kaplan-Meier curves were built to illustrate 1-year survival stratified by post-TAVI CPR subgroups and compared by log-rank statistics; (4) the association of clinical and cardiologic data with 1-year survival among survivors after hospital discharge was assessed in an univariate analysis using an individual Cox regression model; (5) the independent predictors of 1-year mortality among survivors after hospital discharge were identified in a multivariate analysis using Cox regression with stepwise forward selection of variables; (6) finally, an additional analysis was conducted, including only the patients who survived hospitalization, with a multivariate analysis to identify the independent predictors of 1-year mortality, using Cox regression with stepwise forward selection of variables.

Non-parametric methods were used, because all variables did not have a normal (Gaussian) distribution in at least one of the subgroups, leading to the rejection of the normality hypothesis according to the Shapiro-Wilks test. The level of significance was set at $p < 0.05$. Statistical analysis was conducted by the SAS System statistical software, version 6.11 (SAS Institute, Inc., Cary, USA).

Results

Population characteristics

From July 2009 to May 2015, 130 patients underwent TAVI on native valve at a single private hospital and were followed for 1 year.

Demographic and clinical characteristics of the study population are described in Table 1. Baseline serum creatinine was 1.1 (0.9-1.4) mg/dL, and creatinine clearance was estimated at 48.0 (21.8) mL/min by the Cockcroft-Gault formula. Baseline hemoglobin was 11.9 (10.4-13.1) mg/dL. Nine (6.9%) patients received blood transfusion before the procedure.

Table 1 – Demographic and clinical characteristics of the study population

Characteristics	N = 130 n (%)
Age (years) (median)	83.0 (80.0-87.0)
Male sex	67 (51.5)
BMI (median)	25.3 (22.5-29.4)
Clinical presentation	
Syncope	38 (29.2)
Angina pectoris	27 (20.8)
HF, NYHA functional class	
II	6 (4.8)
III	70 (53.8)
IV	54 (41.5)
Systemic arterial hypertension	94 (72.3)
Diabetes mellitus	48 (36.9)
Coronary arterial disease	70 (53.8)
Previous AMI	15 (11.5)
Previous MRS	30 (23.1)
Previous PCI	42 (32.3)
Previous stroke	7 (5.4)
Peripheral vascular disease	31 (23.8)
COPD	12 (9.2)
Chronic kidney disease*	101 (77.7)
Pulmonary arterial hypertension	40 (30.8)
Previous pacemaker	25 (19.2)
STS mortality (%)	8.6 (4.8-19.3)
STS morbidity (%)	34.6 (24.8-63.1)
Anemia	83 (63.8)
Atrial fibrillation	17 (13.1)
LV dysfunction (LVEF < 50%)	33 (25.4)

BMI: body mass index; HF: heart failure; NYHA: New York Heart Association; AMI: acute myocardial infarction; MRS: myocardial revascularization surgery; PCI: percutaneous coronary intervention; COPD: chronic obstructive pulmonary disease; STS: Surgeons Thoracic Society; LV: left ventricle LVEF: LV ejection fraction.
** Glomerular filtration rate estimated by the Cockcroft-Gault formula < 60 mL/min.*

On baseline TTE, AVA was 0.6 (0.6-0.8) cm^2, and mean left ventricle (LV)-aortic gradient was 45.5 (34.0-57.3) mm Hg. Associated moderate or severe aortic failure was present in 14 (10.8%) cases. LV ejection fraction (Simpson method) was 64.0% (48.0-73.0%).

Balloon aortic valvuloplasty and percutaneous coronary intervention (PCI) were performed days before TAVI in four (3.1%) and 13 (10.0%) patients, respectively.

Procedures were conducted under general anesthesia in 80.8% of the cases. Vascular access was TF in 123 (94.6%) patients, TSC in six (4.6%), and transaortic in one (0.8%). PCI was performed concomitantly with TAVI in eight (6.2%) cases. Valve pre-dilatation was performed in 107 (82.3%) patients. CoreValve prosthesis was implanted in 132 (97.0%) patients, and Edwards-Sapien XT prosthesis in four (3.0%). The number of rapid pacing runs was 1.0 (1.0-2.0). Maneuvers to correct paraprosthetic regurgitation were conducted in 43 patients, of which 38 (36.9%) underwent post-dilatation, four (3.1%) underwent implantation of a second valve, and one (0.8%) underwent bow traction.

Mean LV-aortic gradient on TTE was reduced from 45.5 (34.0-57.3) mm Hg at baseline to 7.0 (5.0-10) mm Hg ($p<0.001$) after the procedure. At the end, moderate paraprosthetic regurgitation was found in 7 (5.4%) patients.

Thirty (23.1%) cases required implantation of a new permanent pacemaker. There were vascular complications in seven (5.4%) patients. A total of 28 (21.5%) patients were subjected to blood transfusion: of which 10 (7.6%) received one red blood cell (RBC) unit, 9 (6.9%) received from 2 to 3 RBC units, and 9 (6.9%) received 4 RBC units or more.

Acute renal failure (ARF) was observed in 31 (23.8%) patients, of which 25 (19.5%), 4 (3.1%), and 2 (1.6%) were classified into stages I, II and III, respectively, in the first 72 hours. Hemodialysis was performed in 5 (3.9%) patients during hospitalization. Platelet count ranged from 194 (158-237) thousand/mm^3 to 135 (101-165) thousand/mm^3, with nadir at 72 hours ($p < 0.0001$).

Implantation success was obtained in 115 (88.5%) patients. Length of hospital stay after TAVI was 7 (6-7) days, ranging from 3-212 days.

Intra-hospital mortality occurred em 8 (6.2%) patients, with 1 death after 30 days for sepsis.

Inflammatory response before and after TAVI

SIRS was identified in 55 (42.6%) patients. Urinary or respiratory tract infections were treated with antibiotics in 13 (10.0%) patients. Blood or urine cultures were positive in 4 cases.

Leukocyte count ranged from 6675 (5535-8623) cells/mm^3 at baseline to 10520 (8570-13800) cells/mm^3, reaching its peak 24 hours after TAVI ($p < 0.001$).

Baseline CRP was 0.3 (0.2-1.0) mg/dL, and 41 (34.5%) patients showed high CRP levels (> 0.5 mg/dL). Peak CRP was 7.0 (5.3-12.1) mg/dL and occurred on the fourth day after TAVI (Figure 1).

Follow-up at 30 days and 1 year

At 30-day follow-up, there were 7 (5.4%) deaths. Ten (7.8%) patients were readmitted, 8 of which due to CV events.

Overall 1-year mortality was 14.6%. Deaths had a CV cause in 8 (42.0%) patients, and a non-CV cause in 11 (58.0%), with a predominance of sepsis (n = 9) in the last group.

An analysis was made to compare survivors and non-survivors at 1 year (Table 2). Independent predictors of

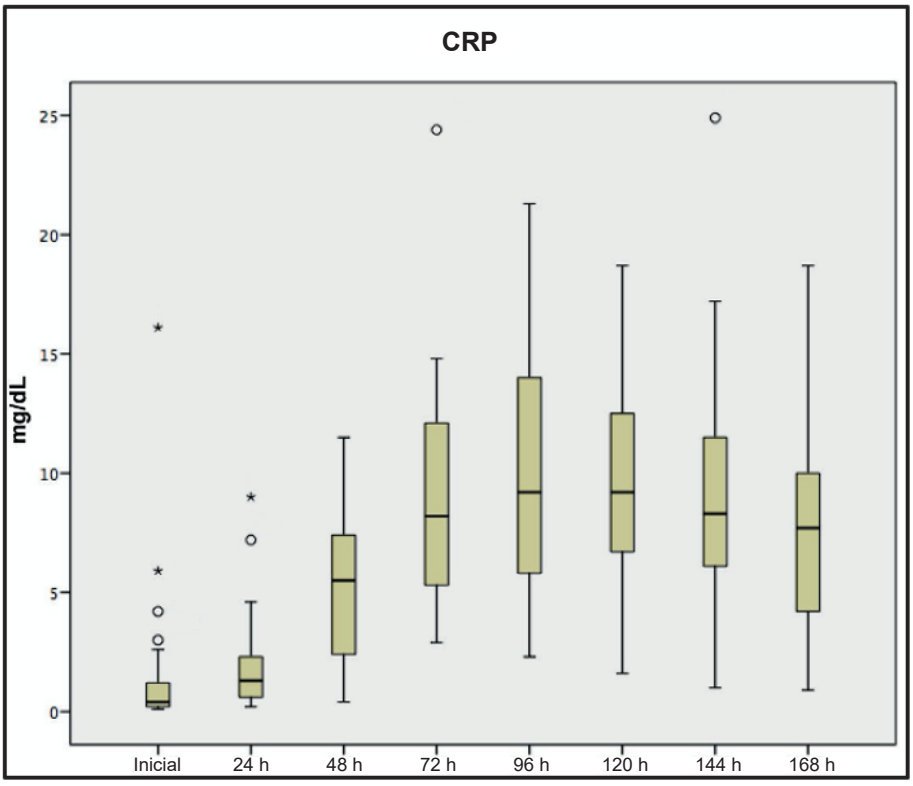

Figure 1 – *CRP concentration in the first week. CRP: C-reactive protein.*

1-year mortality were the presence of ARF, high baseline CRP, and blood transfusion ≥ 4 RBC units (Table 3), and 1-year survival curves stratified by these variables are shown in Figure 2. When we assessed patients only after hospital discharge, we observe that baseline CRP > 0.5 mg/dL remained as an independent predictor of 1-year mortality (Table 4).

The comparison between the groups with high (> 0.5 mg/dL) and normal baseline CPR is presented in Table 5.

Peak CRP ≥ 10.0 mg/dL had a sensitivity of 64.7% and specificity of 69.2% for 1-year mortality on the receiver operating characteristic curve, with area under the curve = 0.71 (95% confidence interval [CI], 0.57-0.86; p = 0.005). Peak CRP after TAVI was a predictor of 1-year mortality only in the univariate analysis, with hazard ratio (HR) = 1.14 (95%CI, 1.06-1.22; p < 0.0001).

Discussion

This study assessed the impact of inflammatory response on 1-year mortality after TAVI through CRP levels in the pre- and post-operative periods, with predominance of CoreValve placement via TF access. Low intensity chronic inflammation (CRP > 0.5 mg/dL) before TAVI occurred in one third of the patients and was an independent predictor of 1-year mortality (HR 4.1; p = 0.01). Peak CRP was observed from the third to the forth days, with peak CRP ≥ 10 mg/dL being associated with greater mortality, but this was influenced by the presence of ARF and large blood transfusions.

The assessment of prognosis through inflammatory biomarkers before-TAVI was also performed by Sinning et al.,[7] who reported that the inflammatory biomarker GDF-15 and the surgical risk score EuroSCORE II were the best predictors of 1-year mortality after TAVI. In their study, pre-TAVI CRP led to higher risk of mortality (HR 1.2; 95%CI 1.0-1.4; p = 0.012). Similarly, we found that median pre-TAVI CRP indicated higher risk of 1-year mortality (HR 1.2; 95%CI 1.0-1.3; p < 0.001). However, we believe that analysis of CRP as a categorical variable showed to be more useful, especially when adopting the cutoff value of > 0.5 mg/dL, based on publications that involved heart surgery[8] and, more recently, TAVI.[9,10]

High CRP in the preoperative period of heart operations was associated with higher mortality in the study by Cappabianca et al.,[8] who assessed preoperative CRP among 597 patients subjected to different types of heart surgery (SAVR in 15%) and observed that those with CRP > 0.5 mg/dL evolved to higher mortality at 3-years follow-up (odds ratio [OR], 1.93; p = 0.05). Reference values for CRP < 0.3 mg/dL were proposed based on an epidemiological study that assessed CV events without performing invasive procedures and may not represent the best cutoff value in the surgical context.

Table 2 – Characteristics of non-survivors and survivors at 1 year follow-up

Characteristics		Non-survivors n=19	Survivors n=111	HR (95%CI)	p-value
Age (years)		84 (81-87)	83 (80-87)	-	0,3
Male sex		36.8%	54.1%	-	0,2
BMI (kg/m^2)		26.2 (22.6-27.4)	25.2 (22.5-30.1)	-	0,8
NYHA FC IV heart failure		57.9%	38.7%	-	0,1
Diabetes mellitus		42.1%	36.0%	-	0,6
CAD		42.1%	36%	-	0,6
PVD		26.3%	23.4%	-	0,4
COPD		15.8%	8.1%	-	0,3
STS score (%)		17.9 (8.1-30.2)	8.1 (4.7-17.1)	1,03 (1,01-1,06)	0,02
Baseline creatinine (mg/dL)		1.3 (0.8-1.5)	1.1 (0.9-1.3)	-	0,8
LVEF (%)		55 (31-73)	64 (50.5-73.0)	0,98 (0,95-1,00)	0,04
Baseline hemoglobin (mg/dL)		11.2 (10.2-12.9)	12.0 (10.6-13.3)	-	0,4
Nadir hemoglobin (mg/dL)		8.1 (7.4-9.9)	9.8 (8.4-10.9)	0,68 (0,49-0,94)	0,01
Baseline CRP (mg/dL)		1.5 (0.2-2.8)	0,3 (0,2-0,9)	1,19 (1,06-1,34)	<0,0001
Baseline CRP > 0,5 mg/dL		68.8%	29.1%	4,70 (1,63-13,5)	0,004
Peak CRP (mg/dL)		14.3 (6.0-16.2)	7.8 (5.1-11.1)	1,14 (1,06-1,22)	<0,0001
SIRS		47.3%	41.8%	-	0,6
Post-TAVI aortic failure ≥ +2/4		5.3%	5.4%	-	0,99
Major vascular complication		10.5%	4.5%	-	0,2
Bleeding	Major	26.3%	20.7%	-	0,2
	Life-threatening	26.3%	4.5%	7,85 (2,62-23,5)	<0,001
Blood transfusion	2 to 3 RBC units	15.8%	5.5%	4,3 (1,20-15,5)	0,02
	≥ 4 RBC units	26.3%	3.6%	9,4 (3,24-27,2)	<0,001
ARF	Stage I	52.6%	58.2%	8,2 (3,0-23)	<0,001
	Stage II	10.5%	1.8%	14,4 (2,9-72)	0,001
	Stage III	5.3	0.9	14,7 (1,8-123)	0,013
New pacemaker		42.1%	19.8%	2,72 (1.09-6,8)	0,03
NYHA FC III heart failure at 30 days		38.5%	0.0%	66,8 (16-279)	<0,001

HR: hazard ratio; CI: confidence interval; BMI: body mass index; NYHA: New York Heart Association; FC: functional class; CAD: coronary artery disease; PVD: peripheral vascular disease; COPD: chronic obstructive pulmonary disease; STS: Society of Thoracic Surgeons; LVEF: left ventricle ejection fraction; CRP: high sensitive C-reactive protein; SIRS: systemic inflammatory response syndrome; TAVI: transcatheter aortic valve implantation; RBC: red blood cell; ARF: acute renal failure. The Mann-Whitney test (numeric variables) and the chi-square or Fisher exact tests (categorical variables) were used.

Table 3 – Cox regression multivariate analysis of 1-year mortality

Variables in the model	Coefficient	SE Coef	HR	95%CI	p-value
ARF	1,983	0,624	7,43	2,1-24-7	0,001
Baseline CRP > 0.5 mg/dL	1,422	0,577	4,15	1,3-12,9	0,01
Blood transfusion ≥ 4 RBC units	1,543	0,649	4,68	1,3-16,7	0,02

SE Coef: standard error of the coefficient; HR: hazard ratio; CI: confidence interval; ARF: acute renal failure; CRP–C: reactive protein; RBC: red blood cell. Method of variable selection: stepwise forward.

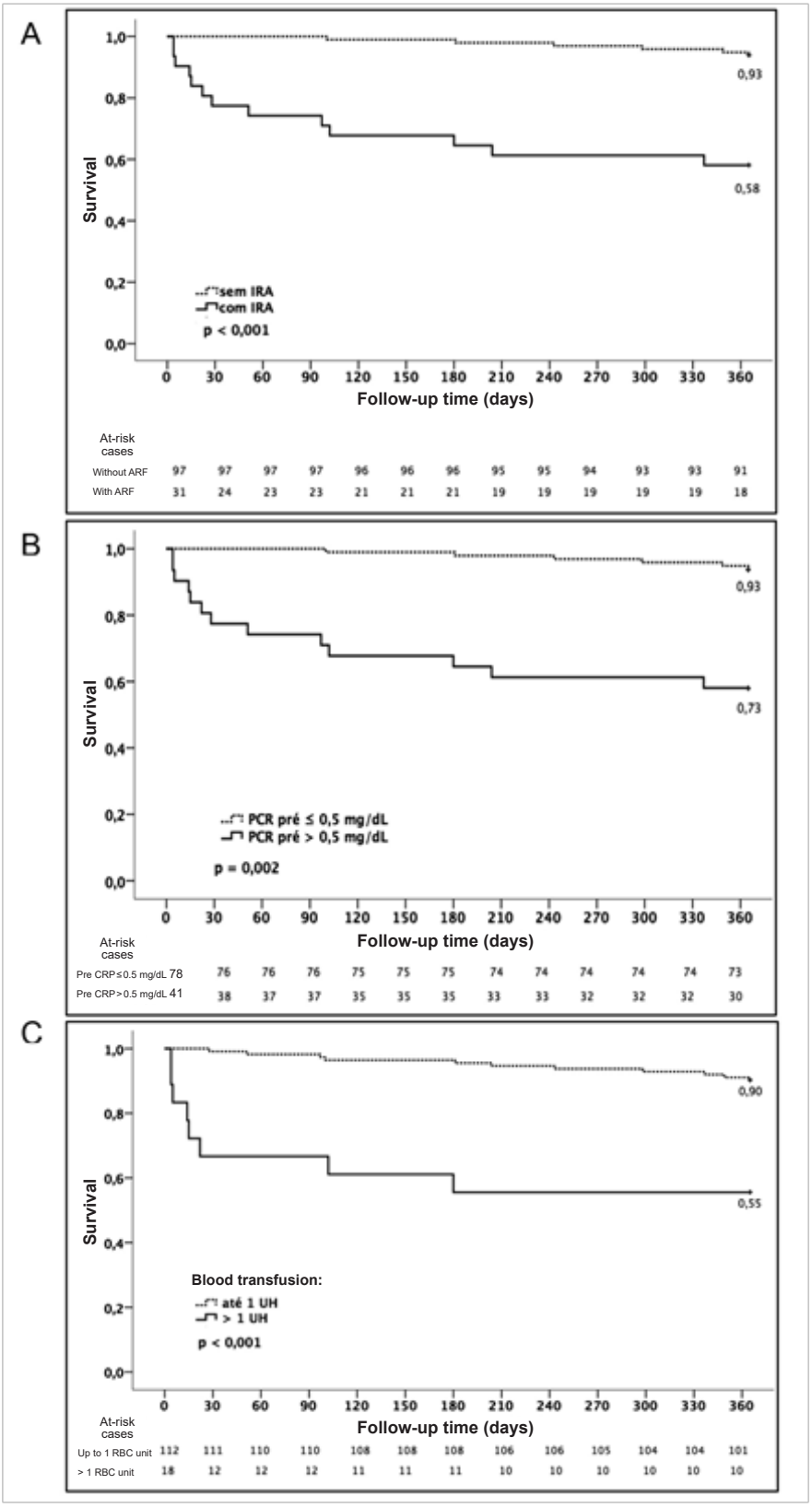

Figure 2 – *Rates of 1-year survival stratified by (A) presence of ARF, (B) baseline CRP > 0.5 mg/dL, and (C) blood transfusion > 1 RBC unit. CRP – C-reactive protein; ARF: acute renal failure; RBC: red blood cell.*

Table 4 – Cox regression multivariate analysis for 1-year mortality in hospital-discharged patients

Variables in the model	Coefficient	SE Coef	HR	95%CI	p-value
NYHA FC III heart failure at 30 days	3.3	1.0	27.5	3.8-199	0.001
Male sex	-4.1	1.3	0.02	0.001-0.23	0.002
New pacemaker	2.3	0.8	10.2	2.0-52.3	0.005
Baseline CRP > 0.5 mg/dL	2.1	0.8	8.9	1.6-48.0	0.01

SE Coef: standard error of the coefficient; HR: hazard ratio; CI: confidence interval; NYHA: New York Heart Association; FC: functional class; CRP–C: reactive protein; Method of variable selection: stepwise forward.

Table 5 – Characteristics of groups with baseline CRP > 0.5 mg/dL and ≤ 0.5 g/dL

Characteristics		Baseline CRP > 0.5 mg/dL n = 46	Baseline CRP ≤ 0.5 mg/dL n = 84	p-value
Age (years)		84 (80-88)	83 (80-87)	0.3
Male sex		53.7%	48.7%	0.6
BMI (kg/m^2)		25.5 (23.3-27.2)	25.3 (22.2-30.1)	0.7
NYHA FC IV heart failure		61.0%	29.5%	0.001
Diabetes mellitus		31.7%	38.5%	0.5
CAD		58.5%	51.3%	0.4
PVD		26.8%	23.1%	0.6
COPD		14.6%	5.1%	0.09
STS score (%)		18.8 (7.7-26.6)	6.9 (4.2-15.3)	0.001
LVEF (%)		60 (44-68)	66 (52-74)	0.3
Baseline creatinine (mg/dL)		1.3 (0.9-1.5)	1.1 (0.9-1,3)	0.06
Baseline hemoglobin (mg/dL)		11.8 (10.0-13.2)	12.1 (10,9-13.3)	0.2
Nadir hemoglobin (mg/dL)		9.3 (8.0-10.9)	9.9 (8.4-10.6)	0.5
Baseline platelets (x10^3/mm^3)		200 (145- 287)	194 (165-226)	0.4
Nadir platelets (x10^3/mm^3)		149 (101-192)	125 (102-152)	0.04
Peak CRP (mg/dL)		11.5 (6.5-14.8)	7.2 (4.6-10.3)	0.002
Aortic failure after TAVI ≥ +2/4		2.4%	6.4%	0.6
Bleeding	Major	14.6%	25.6%	0.2
	Life-threatening	9.8%	6.4%	
Blood transfusion	2 to 3 RBC units	9.8%	3.8%	0.4
	≥ 4 RBC units	7.3%	6.4%	
ARF	No ARF	66.7%	80.8%	0.04
	Stage I	25.6%	17.9%	
	Stage II	7.7%	0%	
	Stage III	0%	1.3%	
SIRS		47.5%	42.3%	0.6
New pacemaker		26.8%	21.8%	0.6

hs-CRP: high sensitive C-reactive protein; BMI: body mass index; NYHA: New York Heart Association; FC: functional class; CAD: coronary artery disease; PVD: peripheral vascular disease; COPD: chronic obstructive pulmonary disease; STS: Society of Thoracic Surgeons; LVEF: left ventricle ejection fraction; TAVI: transcatheter aortic valve implantation; RBC: red blood cell; ARF: acute renal failure; SIRS: systemic inflammatory response syndrome. The Mann-Whitney test (numeric variables) and the chi-square or Fisher exact tests (categorical variables) were used.

In this study, high baseline CRP was associated with decompensated HF, with greater proportion of patients in functional class IV and higher levels of brain natriuretic peptide (BNP). Villacorta et al.[11] showed that patients with LV systolic dysfunction and decompensated HF showed higher CRP levels on admission. Jensen et al. described the relationship between CRP and BNP in decompensated HF.[12] However, it is little likely that the worse prognosis related to CRP levels may be exclusively attributable to its relationship with HF, since more than a half of death had a non-CV cause.

Chronically high CRP has also been described among older adult, with growing evidence that chronic systemic inflammation has an impact on quality of life and on survival. The expression inflammaging was proposed to describe the many conditions related to the presence of inflammation in older adults.[13] A meta-analysis identified 20 circulating blood biomarkers that could be potentially used in the prognostic assessment of older adults, with CRP being a predictor of overall mortality (HR = 1.4; p < 0.001) and CV mortality (HR = 1.3; p = 0,03).[14] In the present study, no relationship was observed between CRP and advanced age, but higher STS scores were observed in the group with high baseline CRP (19% vs 7%; p = 0,001), which suggests that it may be correlated with patients' overall health. The group with pre-TAVI CRP > 0.5 mg/dL had intra-hospital outcomes with higher peak CRP and ARF, in addition to more severe thrombocytopenia.

After TAVI, CRP kinetics in response to the procedure during the first week reached its peak between 72-96 hours, with high values up to the seventh day, in line with other studies.[9,15] CRP kinetics in patients subjected to TAVI via TF is different from that found in SAVR.

Traditionally, the peak value of an inflammatory biomarker is considered the maximal inflammatory response obtained. In the short term, peak CRP was assessed by Krumsdorf et al.[9], who observed, in an univariate analysis, that CRP ≥ 10 mg/dL was associated with higher 30-day mortality. This short-term finding was not confirmed by Ruparelia et al.[15] In the long term, the prognostic value of high CRP values has not been described yet. In the present study, it was found that peak CRP ≥ 10mg/dL was able to predict 1-year mortality (HR = 3.74; p = 0.009); however, this variable was not an independent factor.

In the present sample, no association was found between some technical aspects and degree of inflammation, such as number of rapid pacing runs or direct implantation (without balloon pre-dilatation before TAVI). Sinning et al.[16] observed a correlation between SIRS e o number of rapid pacing runs and/or post-dilatation. Ruparelia et al.[15] found a higher peak CRP on the third day among patients who underwent pre-dilatation (11.0 [0.8] mg/dL vs 5.1 [0.3] mg/dL; p < 0.001).

In the present study, independent post-operative predictors of poor prognosis at 1 year were ARF and large blood transfusion (≥ 4 RBC units), confirmed by other authors.[17,18] CV deaths (42%) were almost as frequent as non-CV deaths (58%), which was consistent with the PARTNER trial.[19]

The assessment of prognostic factors related to TAVI has several implications that relate from surgical strategy to assessment of procedure futility. The contribution of this study may aid other studies in the comparison of techniques and valve prostheses. It is important to emphasize that the prostheses used in this study were soon replaced with new versions that require smaller introducer sheaths, which may reduce vascular complications. Therefore, this study may be used as a parameter for future comparisons.

The present study had limitations related to its observational, retrospective and non-consecutive design. Although its sample represents one of the largest unicentric national investigations, sample size was small compared with that of multicentric international studies, and the CV events were not assessed in an event adjudication center. Levels of CRP and BNP at post-discharge follow-up could clarify the relationship between HF and valve inflammation, as well as the potential inflammatory role of unresected valve leaflets that remained incarcerated by the implanted valve prosthesis.

Conclusions

Pre-TAVI CRP > 0.5 mg/dL is present in one third of the cases and showed to be an independent predictor of 1-year mortality, as well as the presence of ARF and large blood transfusions. Peak CRP occurs from the third to the fourth day after TAVI and, when reaching ≥ 10 mg/dL, it is correlated with higher 1-year mortality, although being dependent on other factors, such as ARF and blood transfusion.

Author Contributions

Conception and design of the research: Sousa ALS, Carvalho LAF, Salgado CG, Fagundes FES, Mesquita ET; Acquisition of data: Sousa ALS, Carvalho LAF, Salgado CG, Oliveira RL, Lima LCCL, Mattos NDFG, Fagundes FES, Colafranceschi AS; Analysis and interpretation of the data: Sousa ALS, Carvalho LAF, Fagundes FES, Colafranceschi AS, Mesquita ET; Statistical analysis: Sousa ALS, Oliveira RL; Obtaining financing: Sousa ALS; Writing of the manuscript and Critical revision of the manuscript for intellectual content: Sousa ALS, Mesquita ET.

Potential Conflict of Interest

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

Sources of Funding

There were no external funding sources for this study.

Study Association

This article is part of the thesis of master submitted by Andre Silveira Sousa, from Pós-graduação de Ciências Cardiovasculares da Universidade Federal Fluminense.

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The Role of Inflammation in Post-TAVI Outcomes

Pedro H. M. C. de Melo[1] and Rodrigo Modolo[2]

Departamento de Cardiologia Intervencionista - Hospital Sírio Libanês,[1] São Paulo, SP - Brazil

Departamento de Clínica Médica - Divisão de Cardiologia - Faculdade de Ciências Médicas - Universidade Estadual de Campinas (UNICAMP),[2] Campinas, SP - Brazil

Short Editorial related to the article: C-reactive Protein as a Prognostic Marker of 1-Year Mortality after Transcatheter Aortic Valve Implantation in Aortic Stenosis

In the early transcatheter aortic valve implantation (TAVI) experience with extreme/high risk for surgical aortic valve replacement (SAVR) patients, global mortality in one year was as high as 25% [1]. Since then, access to TAVI has been extended to intermediate and low-risk patients, and the annual volume of procedures has markedly increased. Post-discharge mortality rates have declined in parallel with the introduction of new devices and the adoption of broader indications. However, the one-year mortality after TAVI remains relevant, exceeding 15% in contemporary practice [2].

Over time, significant postprocedural paravalvular leak, acute renal failure, and comorbidities such as chronic obstructive pulmonary disease (COPD), heart failure, chronic kidney disease (CKD) and prior stroke were linked to higher rates of mortality [3,4]. Risk scores originally validated to estimate mortality after SAVR, and serum biomarkers related to congestive heart failure and others had their performance tested in patients who underwent TAVI [5]. Nonetheless, there is no specific, widely adopted tool to predict late mortality of post-TAVI patients.

In patients with degenerative aortic stenosis (AoS), inflammation is a crucial stage in the pathogenetic process that culminates with calcification and stenosis [6], and sufficient data on the impact of chronic inflammation on outcomes of post-TAVI patients is lacking. C-reactive protein (CRP) is a long-term predictor of cardiac events in the general population [7]. This biochemical parameter, which is related to chronic systemic inflammation, has also been extensively investigated in patients with coronary artery disease, in which increased CRP plasma levels were associated with worse clinical outcomes [8,9]. Thus, the prognostic value of this inflammatory biomarker, CRP, in TAVI patients was evaluated by Sousa et al. [10] in this issue of *Arquivos Brasileiros de Cardiologia*.

The authors have evaluated high-sensitive CRP as a prognostic marker in the first year after TAVI for aortic stenosis. Turbidimetric immunoassay was used to measure serum high-sensitive CRP concentrations before TAVI and along the first postoperative week. The investigators retrospectively analyzed 137 patients with symptomatic severe AoS who underwent TAVI from 2009 to 2015 in a single center. Critically-ill patients and procedures with mechanical complications were excluded, comprising a total population of 130 patients.

In the study, patients were mostly octogenarians (median age of 83.0 years), with a high SAVR risk (median Society of Thoracic Surgeons - STS - score of 8.6). General anesthesia was predominant (80.8% of the procedures), as well as the transfemoral route (94.6%). Almost all implanted devices were CoreValve (97%), with 3% of Edwards-Sapien XT.

The in-hospital mortality rate was 6.2%. Systemic inflammatory response syndrome (SIRS) criteria were met in 42.6% of the cases and 10% of the patients had infections treated with antibiotics during hospital stays. High-sensitive CRP (hs-CRP) peak was 7.0 (5.3-12.1) mg/dL and occurred more likely 96h after TAVI. A baseline hs-CRP level greater than 0.5 mg/dL, present in one-third of the patients, was an independent predictor of 1-year mortality (hazard ratio of 4.1). Other independent predictors of mortality were acute renal failure and blood transfusion ≥ 4 red blood cell (RBC) units. Post-TAVI peak CRP was a predictor of 1-year mortality only in the univariate analysis.

The study provided detailed information about CRP kinetics after TAVI. The authors have furnished some insight into questions not yet fully answered: Is chronic inflammation in AoS patients a reflection of the global health status and comorbidities or a consequence of aging? What is the mechanism for worse prognosis in patients with AoS and high pre-TAVI CRP levels?

The authors' finding of baseline hs-CRP ≥ 0.5 mg/dL as an independent predictor of 1-year mortality after TAVI is supported by previous retrospective studies using CRP or hs-CRP and different cutoffs [11-13]. The impact of high CRP on one one-year mortality could be due to more advanced disease at baseline (higher incidence of COPD, higher higher STS score and more advanced heart failure). Interestingly, more than half of all-cause deaths in the study had a non-cardiovascular cause. This could be related to the worse prognosis of infection and malignant disease in patients with elevated CRP levels [14].

It is worth mentioning that this observational and retrospective analysis could not allow the authors to establish a causal relationship between CRP levels and outcomes. This single-center investigation used a small sample size and cardiovascular events were not assessed by an event adjudication committee.

High-sensitive CRP may improve risk stratification in patients undergoing transcatheter aortic valve implantation.

Keywords

Implantation Transcatheter Aortic Valve/methods;Aortic Valve/surgery; Mortality; Comorbidity; Biomarkers; C-Reactive Protein; Inflammation.

Mailing Address: Rodrigo Modolo •
Departamento de Clínica Médica - Divisão de Cardiologia, Faculdade de Ciências Médicas. Universidade Estadual de Campinas – UNICAMP, 13084-971, Campinas, SP - Brazil
E-mail: modolo.rodrigo@gmail.com

DOI: https://doi.org/10.36660/abc.20210809

Sousa et al. have added valuable information to the body of data that supports inflammatory biomarkers as an arbiter of prognosis after TAVI in AoS patients. Nonetheless, further prospective studies are warranted to enlighten the impact of elevated serum CRP levels on mortality in TAVI patients.

Adding inflammatory serum biomarker levels to validated risk scores, echocardiographic parameters and frailty could support the identification of patients with poor outcomes after successful TAVI, and ultimately improve post-discharge management.

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Retention of Cardiopulmonary Resuscitation Skills in Medical Students

Miguel Antônio Moretti,[1] Adriana de Oliveira Camboim,[1] Caroline Awoki Ferrandez,[1] Isabela Corralo Ramos,[1] Iaggo Bemini Costa,[1] Juliana Seidler Canonaco,[1] Vanessa Lopes Mathia,[1] João Fernando Monteiro Ferreira,[1] Antonio Carlos Palandri Chagas[1]

Faculdade de Medicina da Fundação do ABC – Cardiologia,1 Santo André, SP – Brazil

Abstract

Background: **Reduction of mortality and sequelae of cardiac arrest depends on an effective and fast intervention, started as soon as possible. Basic life support involves a series of steps that may be initiated out of the hospital setting and taught to any person in specific courses. However, it is important that the rescuers retain the knowledge and skills to perform cardiopulmonary resuscitation (CPR), as one never knows when they will be required. Studies have shown that a loss of skills occurs as early as 30 days after the training course, with variations according to personal and professional characteristics.**

Objectives: **To assess whether medical students are able to retain skills acquired in a BLS course for more than six months.**

Methods: **Prospective, case-control, observational study. Medical students attended a 40-hour course on sudden death and cardiac arrest. Skills acquired during the course were evaluated immediately after and six months after the course. Students' individual scores were compared between these time points, the percentage of correct answers was evaluated, and overall performance was rated as excellent, good, and poor. Observers and evaluation criteria were the same immediately after the course and six months later. Data were analyzed using the paired t-test and the McNemar test. The 95% confidence interval was established, and a $p < 0.05$ was set as statistically significant.**

Results: **Fifty students (27 female) in the first year of medical school aged from 18 to 24 years (mean of 21 years) attended the course. The number of steps successfully completed by the students at six months was significantly lower than immediately after the course (10.8 vs 12.5 $p < 0.001$). Neither sex nor age affected the results. Overall performance of 78% of the students was considered excellent immediately after the course, and this percentage was significantly higher than six months later ($p < 0.01$). After six months, the steps that the students failed to complete at six months were those related to practical skills (such as a correct hand positioning).**

Conclusion: **A significant loss of skills was detected six months after the BLS course among medical students, compromising their overall performance.**

Keywords: **Cardiopulmonary Resuscitation; Mortality; Heart Arrest; Medical Students; Education; Learning; Hability.**

Introduction

Ischemic heart diseases are the main causes of death from cardiovascular disease,[1] sudden death (SD), and cardiorespiratory arrest (CRA)[2] in the Brazilian population.[1] CRA may be reversed by cardiopulmonary resuscitation (CPR) maneuvers, and reduction of mortality and sequelae of CRA depends on an effective and fast intervention, started as soon as possible, preferably at the scene.[2,3]

Basic life support (BLS) is a series of procedures that can be initiated outside the hospital seting.[4,5] A BLS course addresses CPR techniques that include early recognition of cardiac arrest and initiation of chest compression and ventilation maneuvers, and use of automated external defibrillator (AED), and is open to the lay public.[5-7] Since most of CRA occurs out of hospital, it is important that CPR techniques can be performed by the general population,[8-10] despite the common belief that only healthcare providers are able to act it properly in emergency situations.

However, an adequate training only is not enough. Rescuers should not only acquire but retain knowledge and skills for appropriate performance of CPR, as one never knows when they will have to be applied. Several studies have been conducted to assess the acquisition of these information and skills over time.[11,12] Nevertheless, there is no consensus on what causes knowledge reduction and when it occurs, which makes it difficult, for example, to establish the frequency of retraining.

Studies have suggested a loss of ability to perform CPR even among healthcare providers, and possible causes include insufficient training and/or poor skill retention.[13] Even these professionals may spend a long time without applying this knowledge. Smith et al.[11] have shown that CPR psychomotor

Mailing Address: Miguel Antônio Moretti •
Faculdade de Medicina da Fundação do ABC – Av. Príncipe de Gales, 821. Postal Code 09060-650, Santo André, SP – Brasil
E-mail: mamorett@uol.com.br
Manuscript received May 27, 2020, revised manuscript October 19, 2020, accept December 02, 2020

DOI: https://doi.org/10.36660/abc.20200546

skills degrade within 10 weeks in nursing undergraduate students, and other studies have pointed out that practical skills start to decay as early as 30 days and continue up to one year after an advanced life support (ALS) course.[14] A study published in 2014 reported a decrease in skill retention in undergraduate medical students, one and two years after a CPR course.[15,16]

As any person, medical students may witness SD or CRA events out of hospital settings, which would already warrant training on CPR maneuvers.[17,18] Since the first months of college, medical students are expected to act as physicians and to have the same skills as professional ones.[19,20] For this reason, we advocate that training on the management of CRA should be part of the medical school curriculum,[12] with the BLS offered in their first undergraduate year, and the ALS at the end of the medical course, when the student will have acquired more knowledge and skills, and will be soon provide care to people. In our opinion, the guidelines published by the American Heart Association for CPR (e.g. BLS and Heart Saver) and by the Brazilian Society of Cardiology for cardiovascular emergencies (TECA B) meet the needs of healthcare providers as well as the lay population. However, for first-year medical school students, the basic course should include not only the training of skills, but also provide a wider theoretical basis, to facilitate the learning process and retention of abilities.[12,17]

Our hypothesis is that loss of knowledge and skills to successfully perform CPR maneuvers already occurs at six months after a BLS training among medical students, even in case of more detailed and longer courses.

Methods

Fifty medical students (27 female) of the first year of college, aged between 18 and 24 years (mean of 21 years), attended the course entitled "Sudden death and cardiopulmonary resuscitation". This is an optional course of the undergraduate curriculum, with a duration of 32 hours (30% theoretical classes and 70% practical classes), and emphasis on the development of skills and simulations of SD and/or CRA.

In addition to a theoretical content of history, epidemiology and pathophysiology of SD, this course also includes a practical content, where the students are trained to respond to a CRA event. During practical classes, students are trained to recognize and to respond to the signs of CRA – to check the safety of the scene, to know who and how to call for help, to perform effective chest compression (strength, rate, depth, site, and hand positioning), to perform safe and effective ventilation using the appropriate device, to verify the need for an AED and to learn how to use it, and to decide to either continue or interrupt the intervention. This practical training is based on the AHA (BLS)[16] and the Brazilian Society of Cardiology (TECA B)[5] guidelines for standardization of the management of CRA.

After the course, the knowledge and skills acquired by the students were assessed in an out-of-hospital setting using a standard form containing a checklist of procedures (Chart 1).

Each step was considered as successfully performed or not (YES if performed correctly or NO if not performed or if performed incorrectly). Then, overall performance was rated as excellent, good, or poor. An excellent performance was considered when up to two mistakes were made (which would be more than 84% of correct responses recommended by the AHA[16]); a good performance was considered when three or four mistakes were made (more than 70% of correct responses); and a poor performance when more than four mistakes were made (less than 70% of correct responses). To be approved in the course, the student had to give more than 70% of correct responses. Six months later, the students were reassessed using a CPR simulation mannequin, with no previous scheduling, and the same checklist and criteria (including the same instructors and teachers) used in the first assessment. Overall performance was rated also.

All students signed an informed consent form and agreed to participate in the study. The study, approval by the ethics committee and the consent form were approved and registered on Brazilian national ethics platform (Plataforma Brasil; CAAE: 81721317.7.0000.0082).

Statistical analysis

This was a prospective study, where each patient was the control of him/herself. Results of the two assessments of the students' performance were compared by the McNemar test for categorical variables (presented as absolute numbers and percentages). Means and standard deviations of continuous variables with normal distribution (tested by the Shapiro-Wilk test) were compared by paired t test using Microsoft Excel (Office 365). A 95% confidence level was calculated and a p-value lower than 0.05 was set as statistically significant.

Results

All students were evaluated right after the course and six months thereafter. Of the 14 steps assessed, an average of 12.5 steps were correctly performed by the students immediately after the course, which was significantly higher than the average of 10.8 steps at six months ($p < 0.001$). Thus, there was a decay of knowledge and skills after six months of the course. In addition, although men had a higher mean age than women (21.7 years vs 20.2 years – $p = 0.006$), age and sex did not independently affect the results of the evaluations. The number of correct answers in the second evaluation was significantly lower as compared with the first evaluation in both men (10.9 vs. 12.8 correct answers; $p = 0.003$) and women (12.2 vs. 10.7 correct answers; $p = 0.013$). Regarding overall performance, the quality of care provided also decreased; while 39 (78%) students had an excellent performance in the first evaluation, performance of only 20 (40%) students was rated as excellent six months after ($p < 0.01$). The percentages of students who gave correct answers in each step of the checklist are described in Table 1 and Figure 1.

Discussion

Our study showed a significant reduction ($p < 0.01$) in skills related to the management of CRA. The students correctly completed a mean of 12.5 steps immediately after the course and 10.8 steps six months later. While 39 (78%) students successfully completed more than 12 of the 14 steps of the

simulated cardiac arrest event immediately after the course, only 20 (40%) achieved the same score six months later.

We evaluated the skills required for an adequate and correct intervention of CRA and observed that the students successfully acquired them at the end of the course. The first step (where students had to check safety before intervening) was the only step that was not correctly performed by most of the students (42%). When questioned about it, the students explained that, since simulation was carried out in a classroom, that is known to be safe, and using a mannequin, they have

Chart 1 – Checklist used to assess knowledge and skills acquired during the course "Sudden death and cardiopulmonary resuscitation" immediately after and six months after the course

PROCEDURES TO BE PERFORMED AFTER IDENTIFYING AN unconscious person WHO DOES NOT MOVE OR BREATHE
Check the safety of the scene and safety for intervention
Ask help to another person and state what must be done in a clear and objective way
Call 192 or 193
Request an automated external defibrillator (AED)
Position the victim correctly to check pulse and breathing
Initiate chest compressions immediately
Position the hands on the sternum
Perform chest compression with an adequate depth (4-5 cm)
Compress the chest at an adequate rate (100 per minute)
Perform ventilation only with a protection device
Perform five cycles of 30 compressions and two rescue breaths before reassessing the victim
Do not interrupt cardiopulmonary resuscitation (CPR) when an AED arrives
Use the AED following manufacturer's instructions
Resume CPR after defibrillation if necessary

Table 1 – Results of the assessment of students' knowledge and skills acquired in the "Sudden death and cardiopulmonary resuscitation" course by numbers and percentages of students who successfully completed each step, immediately after and six months after the course

Step	Percentage of students who successfully completed the step		P*
	Immediate after (N)	At six months (N)	
1- Check the safety	42 (21)	54 (27)	0.307
2- Ask for help	88 (44)	84 (42)	0.683
3- Decide who to call	94 (47)	68 (34)	**0.002**
4- Request an automated external defibrillator	92 (46)	80 (40)	0.181
5- Check pulse and breathing	96 (48)	92 (46)	0.683
6 - Initiate chest compressions	100 (50)	94 (47)	0.248
7 - Position the hands correctly	90 (45)	66 (33)	**0.010**
8 - Correct depth of compression	96 (48)	88 (44)	0.289
9- Compression at an adequate rate	82 (41)	70 (35)	0.264
10- Perform ventilation with a protection device	88 (44)	62 (31)	**0.010**
11-Use the 30:2 compression-ventilation ratio	100 (50)	76 (38)	**0.002**
12-Do not interrupt cardiopulmonary resuscitation when the AED arrives	100 (50)	88 (44)	**0.041**
13-Use AED following manufacturer's instructions	88(44)	80 (40)	0.387
14-Resume CPR after defibrillation if necessary	92(46)	84 (42)	0.387

** McNemar test (two-tailed); CPR: cardiopulmonary resuscitation; AED: automated external defibrillator.*

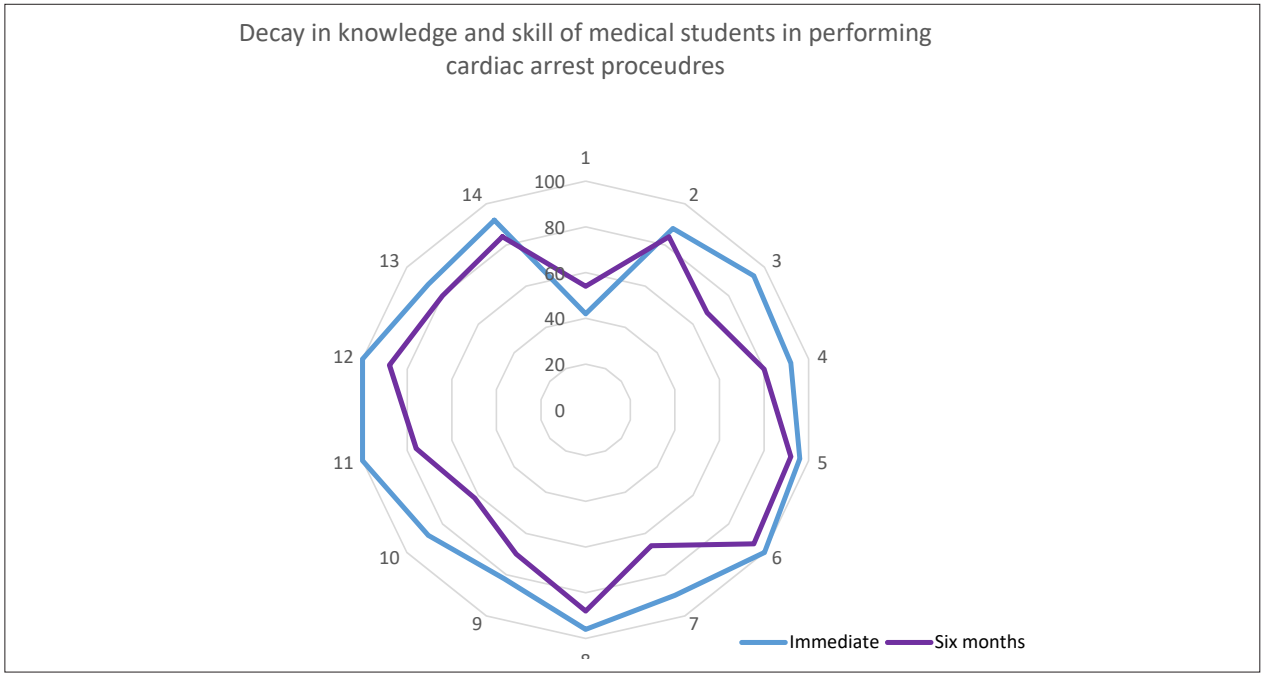

Figure 1 – *Percentage of students that successfully completed the cardiac arrest procedures immediately after and six months after the course and six. Numbers correspond to those used in Table 1.*

forgotten to check safety. Another explanation was the eager to rapidly initiate the intervention. Despite that, the outcome of the course was considered satisfactory, according to the AHA recommendations of a minimum of 84% of correct answers.[16] We also found that neither age nor sex influenced the students' score in the end of the course, reinforcing the importance of the course in knowledge acquisition.

One common problem related to teaching the management of CRA events is how to retain knowledge. A meta-analysis[14] on the theme made it clear that skills become lost when they are not practiced, initiating within few weeks, achieving a maximum at approximately nine months to one year. These studies have shown that the time elapsed from the last training is directly proportional to the degree of loss of the skills and knowledge needed to deliver CPR effectively.[14]

In our study, such decay in skills and knowledge was also observed in first-year medical students, with a loss of approximately 15% in the test of skills, which caused a loss of nearly 50% in overall performance. We did not expect that the loss of knowledge retention was different among medical students, since previous studies have already shown that with healthcare professionals and students.[13] Also, we do know that students do not frequently practice managing CRA events. In fact, a study comparing knowledge loss between medical students and other students is warranted.

In our sample, there was a clear loss of skills, especially in the practical steps that require more attention and promptness. This is corroborated by previous studies reporting that these steps were more frequently forgotten or inadequately performed.[21,22] When these practical steps are not properly performed (decide who to call; position and place hands correctly, perform ventilation with protection device, continue performing the five cycles and the maneuvers when an AED arrives) the risk for adverse events or complications increases, such as rib fractures and ineffective compressions, resulting in ineffective circulation.[23]

Also, neither age nor sex affected retention of knowledge and skills by our students, and time seems to be the only factor responsible for retention loss. This is reinforced by the fact that none of the students responded to CRA events or helped teaching CPR courses.

One strategy to retain skills, proposed in previous studies,[17,24] is to participate in continuous training, such as the e-learning. However, one question still unanswered is how often and what type of training would be recommended and who is the training for (healthcare professionals or lay people, who work in different settings where CRA events are relatively common). Another question is whether the course should be more comprehensive or maybe simpler, particularly for medical students, which would be answered by a comparative study between the two methods.

One limitation of the study is the small number of students evaluated and the fact that, despite its prospective design, the study was conducted in a single center, and after one training course. Ruijter et al.[15] also demonstrated a reduction in retention of skills after one and two years of BLS training in 120 medical students, similar to our findings. Therefore, although the aim of the study was to assess skill retention, our results were in accordance with previous studies, and this limitation does not affect the importance of our study. Another limitation for a more in-depth discussion about skill retention and of what is the most appropriate type

of course is the fact that we did not evaluate the theoretical knowledge of students. Some studies, however, have already shown that more important losses have occurred in practical skills.[11] Although the students knew that they would be reevaluated at some point after the course, this seemed not to have affected the results; many of them have forgotten this reevaluation as they had already been approved in the course. However, this fact does not undermine the need for more frequent training courses to try to reduce the loss of skills.

Conclusion

Six months after a BLS course in simulated SD or CRA events, we observed a significant loss of skills in first-year medical students, similarly to what is observed in the lay population (outside the healthcare filed). This loss was associated with the period during which the students did not practice or review the techniques to correct perform CPR, which affects treatment efficacy. A more robust course may improve learning, but not the retention of skills. Finally, the assessment of learning and knowledge retention could be complemented by studies including retraining and clinical outcomes, i.e., aiming to demonstrate that training and retraining may not only improve skills but also save lives.

Author contributions

Conception and design of the research: Moretti MA, Camboim AO, Ferrandez CA, Ramos IC, Costa IB, Canonaco JS, Mathia VL, Ferreira JFM. Acquisition of data: Moretti MA, Camboim AO, Ferrandez CA, Ramos IC, Costa IB, Canonaco JS, Mathia VL. Analysis and interpretation of the data: Moretti MA, Camboim AO, Ferrandez CA, Ramos IC. Costa IB, Canonaco JS, Mathia VL. Statistical analysis: Moretti MA. Writing of the manuscript: Moretti MA, Camboim AO, Ferrandez CA, Ramos IC, Costa IB. Canonaco JS, Mathia VL, Ferreira JFM, Chagas ACP. Critical revision of the manuscript for intellectual content: Moretti MA, Ferreira JFM, Chagas ACP.

Potential Conflict of Interest

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

Sources of Funding

There were no external funding sources for this study.

Study Association

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

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Faculdade de Medicina do ABC under the protocol number CAAE 81721317.0000.0082, parecer 2.559.797. 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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Retention of Cardiopulmonary Resuscitation Skills in Medical Students: What Can Be Done to Improve Them?

Sergio Timerman[1] *and Thatiane Facholi Polatri*[1]

Instituto do Coração (InCor) do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo,[1] *São Paulo, SP – Brazil*

Short Editorial related to the article: Retention of Cardiopulmonary Resuscitation Skills in Medical Students

Since the beginning, great researchers have been working on estimating the best technique for maintaining the body blood flow of a victim undergoing CPA. Several techniques were applied, such as the Trotting method and rolling over a barrel.[1] The technique of external chest compressions was conceived in 1960, based on the observation made by Kouwenhoven, Jude, and Knickerbocker[2] that adequate compression on the lower third of the sternum provided sufficient artificial circulation to sustain life in animals and humans with cardiac arrest. Since then, many studies have been carried out to improve the depth and frequency of appropriate compressions to maintain coronary perfusion at an adequate level, contributing to the return of spontaneous circulation.

According to the 2020[3] worldwide guidelines publications, performing high-quality compressions refers to performing compressions at a frequency of 100 -120 per minute, depth of 5-6cm, returning the chest to the normal position between compression minimize interruptions in compressions avoiding excessive ventilation. In this sense, a big question arises: do we understand the parameters for performing good compressions, which significantly increase the survival of CPA victims? However, how to ensure that health professionals and the general public can learn the technique and retain this learning to the point of reproducing it in an actual emergency?

The technology and simulation to educate resuscitation have gained increasing importance, promoting changes in the way training is conducted, as training in simulators enables the student that the same technique be repeated several times, thus developing the necessary competence.[4,5]

In this issue of the Brazilian Archives of Cardiology, Moretti et al.[6] presented a prospective case-control study, where 50 medical students were evaluated in basic life support skills. They were assessed on skill performance immediately after the course and 06 months later. The number of steps correctly completed after six months was significantly lower than right after the course (10.8 vc 12.5 $p<0.001$).

When reading this article, the main question for reflection is: how to maintain the retention of learning CPR skills? According to the resuscitation education guidelines of the European Resuscitation Council,[4] BLS skills decay within 3 to 12 months after initial CPR education. Still, resuscitation skills are better maintained if training and retraining are distributed throughout the period between two and twelve months.

In this sense, the current trend in emergency training is based on the new concept of "low-dose and high frequency" – low dose and high frequency, which uses an approach of developing and promoting maximum retention of clinical knowledge, skills and attitudes. The training relies on learning activities based on short, specific simulations over time and is reinforced with structured and continuous practical sessions in the workplace.[7]

Another proposal is the use of feedback devices during resuscitation training. These devices are provided with audiovisual resources, which allow the monitoring of performance in performing CPR, in relation to several parameters, such as: frequency and depth of compressions, compression fraction, frequency and volume of ventilations, among others.[8]

A systematic review published in 2021,[9] on improving the quality of CPR using feedback devices concluded that these devices improve CPR skill acquisition and performance during the training of healthcare professionals.

Thus, reading this study brings us a reflection on the present and future of resuscitation training. Furthermore, health services and universities can implement better educational practices that lead to better patient outcomes after cardiac arrest. This is our top priority: saving lives!

Keywords

Medicine; Students, Health Occupational; Health Occupations/education; Cardiopulmonary Resuscitation/methods; Clinical Competence; Professional Training.

Mailing Address: Sergio Timerman •
Instituto do Coração (InCor) do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo - Av. Dr. Enéas Carvalho de Aguiar, 44. Postal Code 05403-900, Cerqueira César, São Paulo, SP – Brazil
E-mail: sergio.timerman@hc.fm.usp.br, timerman@cardiol.br

DOI: https://doi.org/10.36660/abc.20210856

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Review Article

Amiodarone-Induced Thyrotoxicosis - Literature Review & Clinical Update

Luciana Vergara Ferraz de Souza,[1] Maria Thereza Campagnolo,[2] Luiz Claudio Behrmann Martins,[3] Maurício Ibrahim Scanavacca[3]

Faculdade de Medicina de Jundiaí,[1] Jundiaí, SP – Brazil

Centro Universitário Lusiada Faculdade de Ciências Médicas de Santos,[2] Santos, SP – Brazil

Universidade de São Paulo Instituto do Coração - Arrritmia e Marcapasso,[3] São Paulo, SP – Brazil

Abstract

Amiodarone is widely used in treating atrial and ventricular arrhythmias; however, due to its high iodine concentration, the chronic use of the drug can induce thyroid disorders. Amiodarone-induced thyrotoxicosis (AIT) can decompensate and exacerbate underlying cardiac abnormalities, leading to increased morbidity and mortality, especially in patients with left ventricular ejection fraction <30%.

AIT cases are classified into two subtypes that guide therapeutic management. The risks and benefits of maintaining the amiodarone must be evaluated individually, and the therapeutic decision should be taken jointly by cardiologists and endocrinologists.

Type 1 AIT treatment is similar to that of spontaneous hyperthyroidism, using antithyroid drugs (methimazole and propylthiouracil) at high doses. Type 1 AIT is more complicated since it has proportionally higher recurrences or even non-remission, and definitive treatment is recommended (total thyroidectomy or radioiodine).

Type 2 AIT is generally self-limited, yet due to the high mortality associated with thyrotoxicosis in cardiac patients, the treatment should be implemented for faster achievement of euthyroidism. Furthermore, in well-defined cases of type 2 AIT, the treatment with corticosteroids is more effective than treatment with antithyroid drugs.

In severe cases, regardless of subtype, immediate restoration of euthyroidism through total thyroidectomy should be considered before the patient progresses to excessive clinical deterioration, as delayed surgery indication is associated with increased mortality.

Introduction

Amiodarone is a class III antiarrhythmic drug frequently used to treat atrial and ventricular arrhythmias,[1] especially when refractory to other antiarrhythmic drug.[2] It is also used for prophylaxis of sudden cardiac death in high-risk patients, mainly in patients without access to the implantable cardioverter-defibrillator, showing a reduction in mortality when compared to placebo and other antiarrhythmic drugs.[3]

Due to its high iodine concentration, amiodarone can induce thyroid dysfunction (hyperthyroidism or hypothyroidism) in up to 36% of patients who take this medication chronically.[4,5] The incidence of hyperthyroidism ranges from 2% to 18%,[4-12] and hypothyroidism from 5% to 22% (Table 1).[4-10,12] The influence of iodine on the development of these thyroid disorders is so evident that, according to its regional dietary intake, there is a change in the way the amiodarone alters the behavior of the thyroid. Proportionally, in areas with high iodine intake, there is a predominance of amiodarone-induced hypothyroidism cases, while in places with low intake, there is a higher incidence of amiodarone-induced thyrotoxicosis (AIT).[4,6,8]

Amiodarone-induced hypothyroidism is less severe than hyperthyroidism and has a simpler treatment. In hypothyroidism cases, amiodarone withdrawal is unnecessary, and treatment can be done just by introducing levothyroxine. In some subclinical cases, the dose adjustment (reduction) may be enough for the thyroid function to return to normal. Therefore, there is no need for hormone replacement in subclinical patients, only regular thyroid function assessment to evaluate progression to hypothyroidism.[13,14]

Clinically, AIT cases pose greater complications risks; moreover, the diagnosis and treatment are far more complex. Prolonged exposure to high levels of thyroid hormones may lead to the onset of arrhythmias and rapid deterioration of cardiac function.[5,15] An observational study analyzed 354 patients in chronic use of amiodarone demonstrated a significant increase in major cardiovascular events in the group that developed AIT, comparing to the group that remained euthyroid (31,6% vs. 10.7%, p<0.01), mainly due to the high incidence of ventricular arrhythmias leading to hospital admission (7% vs. 1.3%, p=0.03).[5] Another study reported a 10% mortality rate before thyrotoxicosis control, associated with left ventricular ejection fraction (LVEF) <30%.[15]

AIT's main diagnosis and treatment issues were revised and summarized practically based on recent studies and guidelines. Likewise, we emphasize the importance of therapeutic decisions to be taken jointly by cardiologists and endocrinologists.

Methods

A literary review through MEDLINE search using the combinations of the MeSH terms: "Amiodarone","Thyrotoxicosis",

Keywords

Amiodarone/therapeutic use; Arrhythmias,Cardiaca; Iosine; Hyperthyroidism; Thyrotoxicosis; Hypothyroidis; Thyrotoxicosis; Thyroiditis.

Mailing Address: Luciana Vergara Ferraz de Souza •
Faculdade de Medicina de Jundiaí - R. Francisco Teles, 250. Postal Code 13202-550, Vila Arens, II Jundiaí, SP – Brazil
E-mail: luciv.f@gmail.com
Manuscript received November 06, 2019, revised manuscript September 16, 2020, accepted November 04, 2020

DOI: https://doi.org/10.36660/abc.20190757

Table 1 – Studies showing the incidence of thyroid disorders induced by amiodarone use

First Author, Year	Country	Number of patients	Amiodarone-induced hypothyroidism	Amiodarone-induced thyrotoxicosis	Study design
Martino E,8 1984	Italy U.S.A.	Italy: 188 U.S.A.: 41	Italy: 10 (5%) U.S.A.: 9 (22%)	Italy: 18 (9.6%) U.S.A.: 1 (2%)	Not described
Trip MD,[4] 1991	The Netherlands	58	10 (17,2%)	11 (18,9%)	Prospective
Yiu KH,[5] 2009	Hong Kong	354	73 (20.6%)	57 (16.1%) AIT 1: 5/57 AIT 2: 13/57 Mixed/uncertain: 35/57	Retrospective 2000-2005
Stan MN,[25] 2013	U.S.A.	169	Not studied	23 (13,6%) AIT 1: 7/23 AIT 2: 13/23 Mixed/Undefined: 3/23	Retrospective 1987-2009 Adults with congenital heart disease
Huang C-J,[12] 2014	Taiwan	527	69 (13.1%)	21 (4%)	Retrospective 2008-2009
Uchida T,[11] 2014	Japan	225	Not studied	13 (5.8%) AIT 2	Retrospective 2008-2012
Lee KF,[9] 2010	Hong Kong	390	87 (22%)	24 (6%)	Retrospective 2005-2007
Benjamens S,[6] 2017	The Netherlands	303	33 (10,8%)	AIT: 44 (15,5%)	Retrospective 1984-2007
Barrett B,[10] 2019	U.S.A.	Total: 190	26 (13.7%)	4 (2.1%) 25% spontaneous resolution	Retrospective 2007-2018 Pediatric and young adults

and "Thyroid" was conducted. Also, manual and electronic searches were performed based on references cited in the studies evaluated. Clinical studies that address thyroid changes secondary to amiodarone use, focusing on the incidence and the clinical and surgical treatment, were included. Were excluded studies that addressed other organs disorders caused by amiodarone and case reports with less than ten patients. In the compiled data were also analyzed the most current consensus of the Brazilian Society of Endocrinology and Metabology (SBEM), American Thyroid Association (ATA) and European Thyroid Association (ETA).

Amiodarone: mechanism of action on the thyroid

In many ways, amiodarone can act by influencing the thyroid gland. Structurally, amiodarone is a diiodinated medication, with 37% of its molecular weight referring to iodine; thus, each 200mg of amiodarone (daily maintenance dose) contains about 75mg of iodine. The daily dose of iodine recommended by the World Health Organization is 0.15mg (adults),[16] and with the use of amiodarone, about 7.5mg of free iodine are released in the body daily, exceeding the recommended dose by 50 times.[17]

The medication also has extreme similarity with the hormones triiodothyronine (T3) and thyroxine (T4),[18] and its long half-life ensures that the substance stays in the body for up to 100 days, which enhances its toxicity and allows the side effects to occur during its use and even after the drug withdrawal.[19-21]

Despite the recognition that medication influences the thyroid itself and the metabolism of its hormones in the body, there is still little information about its mechanism of action. Inhibition of the enzyme 5'-deiodinase is one of the theories about how amiodarone acts on thyroid hormone metabolism. This interaction results in a serum increase of the reverse T3 and T4 substrates of the enzyme in question, concurrently with the decrease of T3, a product of the conversion performed by the inhibited molecule. Iodine overload and drug-induced cytotoxicity also corroborate the explanation of the onset of thyroid disorders as side effects of chronic medication use.[18,22]

Amiodarone-induced Thyrotoxicosis (AIT)

AIT is associated with high rates of major cardiovascular events and increased mortality, principally cardiovascular death. The appearance and recurrence of ventricular arrhythmias and severe left ventricular dysfunction (LVEF <30%) are the main factors related to this increase.[5,14,15] Therefore, restoration of euthyroidism should be established as soon as possible, and in emergency cases, the thyroidectomy can be indicated for a rapid resolution of the thyrotoxicosis.[14,19,23,24]

AIT cases are divided into two subtypes due to differences in pathophysiology and the need for directed treatment. Type 1 AIT (AIT 1) occurs through autonomous production of thyroid hormones due to iodine overload, particularly with concomitant previous thyroid abnormalities (thyroid nodules or latent Graves' disease). Type 2 AIT (AIT 2) is the most frequent and occurs in patients with a previously

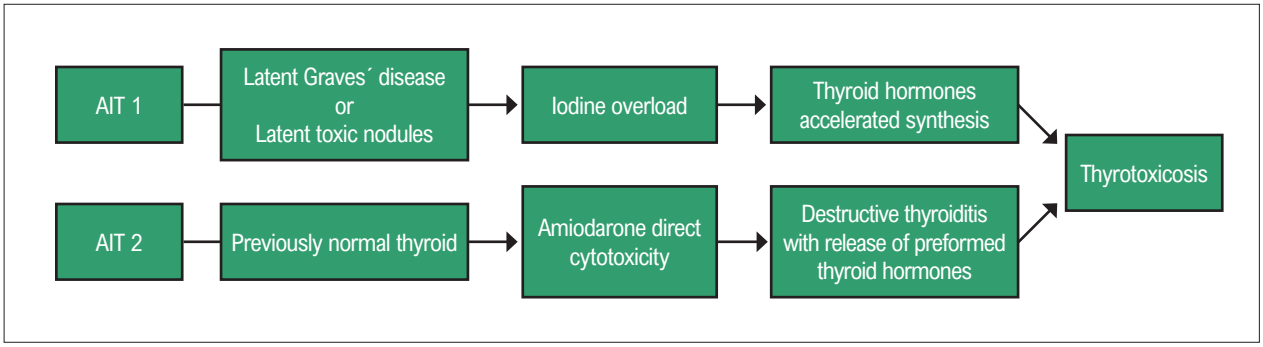

Figure 1 – *Pathophysiology of the main forms of AIT. AIT: amiodarone-induced thyrotoxicosis.*

healthy thyroid, corresponding to destructive thyroiditis due to direct amiodarone cytotoxicity in the follicular cells, with consequent release in the hormonal reserves preformed and the thyrotoxicosis induction.[11,14,19,24,25] Figure 1 illustrates the differences in pathophysiology of the two subtypes. Occasionally, this distinction is complicated, and there is an overlap between the two subtypes; these cases are denominated as mixed or undefined forms.[13,14,19]

Diagnosis

Means to identify patients at higher risk of developing thyroid dysfunction secondary to amiodarone use have not yet been defined.[14,26] The American Thyroid Association recommends thyroid function evaluation through serum dosage of thyrotropin (TSH) and free T4 evaluation before starting amiodarone and every three to six months during the medication use. The thyroid function should be evaluated before starting amiodarone, within the first three months after its initiation, and then every three to six months.[24]

Initially, patients treated with amiodarone present thyroid function changes; however, the majority return to normal without the need for treatment or drug discontinuation. In the first three months of treatment with amiodarone, there is a rise in the serum levels of TSH, T4 and reverse T3, and a concomitantly decrease of T3. After that, the levels of TSH, T4 and T3 normalize, and T4 may remain at the upper limit of normality or slightly elevated, and the reverse T3 remains elevated.[14]

TSH measurement is the most sensitive and specific method for diagnosing hyperthyroidism, as small changes in free T4 levels cause significant changes in TSH concentrations. In subclinical hyperthyroidism, TSH levels are low or even undetectable, and free T4 and T3 values are norma.[24] In thyrotoxicosis, TSH is very low or undetectable, and free T4 and/or T3 levels are elevated.[19,24]

The patients with AIT may be asymptomatic or have the typical clinical picture of hyperthyroidism, with symptoms such as palpitations, tremors, sweating, heat intolerance, nervousness and weight loss. Amiodarone beta-adrenergic blockade in the heart may justify the absence of palpitations, which makes AIT clinical presentation even more insidious.[17] The diagnosis of thyrotoxicosis is confirmed by suppressed serum TSH levels and elevated levels of free T3 and free T4 thyroid hormones.[14,19]

The differentiation between the two AIT subtypes can be difficult, although some laboratory parameters associated with thyroid ultrasound with Dopplerfluxometry may be used for the proper distinction.[13,14,19,24] The characteristics of AIT subtypes are summarized in Table 2.

It was believed that the serum interleukin-6 level was highly elevated in AIT 2 and, therefore, valuable for differentiating AIT subtypes; however, there is an overlap between AIT subtypes; thus, it can not be used for this distinction.[24,27] Radioiodine uptake (^{131}I or ^{123}I) is helpful in this differentiation in areas of low iodine intake, as in these regions, patients with AIT 2 present suppressed radioiodine uptake. In AIT 1, the uptake may be low, normal or even high. However, in areas with sufficient iodine intake, as in most metropolitan regions of Brazil, radioiodine uptake is always suppressed, making the investigation useless.[14,24,28]

The detection of thyroid peroxidase antibodies (anti-TPO)[14,24] and the presence of diffuse or nodular goiters on thyroid ultrasound point to AIT 1,[21,23] nevertheless due to their high prevalence in the population, these findings also do not exclude AIT 2.[13,14,24] Several recent studies indicate that the absence of hyperflow on Dopplerfluxometry is suggestive of AIT 2.[19,24,27,28] However, these findings should not be used alone due to the possibility of mixed forms.[14]

Maintain or discontinue amiodarone?

The need for amiodarone withdrawal is still controversial. In many cases, it is the only medication capable of controlling cardiac arrhythmia, and due to its prolonged half-life, the removal would not bring immediate benefits.[14] In addition, it is important to note that some patients have a recurrence of thyroid disorders, even months after amiodarone interruption. Furthermore, the drug has T3 antagonist properties and inhibits the conversion of T4 to T3 in the heart, so its removal could aggravate the clinical manifestations.[20,21,24]

AIT 2 is generally self-limited, and amiodarone may be maintained in these patients.[14,29-32] Observational studies with AIT 2 patients have shown that patients return to euthyroidism even when maintaining the amiodarone.[29,30,31] However, studies show a variation of 8% to 73% of thyrotoxicosis recurrence in patients that continued using the medication.[29,31,33,34] A 10-year follow-up study involving 50 patients who maintained amiodarone reported only three

Table 2 – Main characteristics of AIT subtypes[14]

Characteristics	Type 1 AIT	Type 2 AIT
Previous thyroid changes	Yes	Usually no
Dopplerfluxometry	Increased vascularity	No hypervascularity
Radioactive iodine uptake	Low, normal or high	Supressed
Antithyroid Antibodies	Present if related to Graves' disease	Usually absent
Onset time after starting amiodarone	Short (median 3 months)	Long (median 30 months)
Spontaneous remission	No	Possible
Subsequent hypothyroidism	No	Possible
First-line treatment	Antithyroid Drugs	Oral glucocorticoids
Subsequent definitive treatment	Generally yes	No

Modified from Bartalena L et al.[14] AIT: amiodarone-induced thyrotoxicosis.

cases of thyrotoxicosis recurrence, much milder than in the first episode.[32]

The decision to withdraw amiodarone should be individualized and made jointly by the cardiologist and the endocrinologist, considering the risks and benefits of the drug withdrawal.[14,19,24] Continuing the medication is widely accepted in critically ill patients with life-threatening arrhythmias who have a good cardiac response to the drug.[14,24,32] If the cardiac conditions are stable and there is another safe alternative, amiodarone may be discontinued.[13,14]

Treatment

Clinically stable patients with evidence that differentiates the treatment's subtypes must be established according to the subtype in which the patient fits.[14,19,24] In cases of mild thyrotoxicosis with impaired cardiac function, the American Thyroid Association recommends initiating combination therapy with antithyroid drugs and corticosteroids.[24]

If the patient presents with fast deterioration of cardiac function, emergency thyroidectomy should be performed regardless of AIT subtype.[14,24] Figure 2 shows the algorithm for AIT management as proposed by the European Thyroid Association.[14] Since the thyroid is loaded with iodine in AIT cases, radioactive iodine treatment is not feasible for at least six to nine months after the drugwithdrawal.[13,19,20]

Treatment: AIT 1

AIT 1 treatment is done with antithyroid drugs (ATD), but these are less effective due to the high iodine concentration, and it is necessary to use higher doses (40-60mg/day) methimazole or equivalent doses of propylthiouracil).[14,24] If the patient remains stable, the ATD should be maintained until euthyroidism restoration,[14,19,20,35] usually between three to six months.[24]

Potassium perchlorate may be associated in the first weeks to decrease thyroid uptake of iodine and make the thyroid more sensitive to the ATD.[1,14,19,35,36] Due to its toxicity, it should not exceed 1g/day and should not be maintained for more than 4-6 weeks.[1,14]

The thyrotoxicosis may recur or may even not go into remission, and in these cases, the definitive treatment is recommended.[14,19,36] If amiodarone is discontinued, definitive radioiodine treatment can be done after six to nine months. Thyroidectomy should be considered if amiodarone withdrawal is not possible.[14,19] Overall, the definitive treatment of AIT 1 is similar to spontaneous hyperthyroidism.[14]

Treatment: AIT 2

AIT 2 is usually self-limited, yet due to the increased mortality associated with thyrotoxicosis in cardiac patients, the treatment should be instituted to achieve euthyroidism more rapidly.[14,19,36] The decision to treat mild or subclinical cases should be made considering the patient's cardiac alterations.[14]

It has been suggested that, in well-defined AIT 2 cases, corticosteroid treatment is more effective than ATD treatment.[29,37] The doses used are 30-40mg/day of prednisone or equivalent dose of another glucocorticoid for two to three months, with subsequent gradual withdrawal based on clinical response.[14,24] In severe cases, as well as in AIT 1 and mixed/undefined AIT cases, radical thyroidectomy should be considered.[8,14,38]

Treatment: TIA mixed or undefined

Mixed or undefined forms are not yet fully characterized. However, it is believed that these cases involve mixed pathogenic mechanisms of both subtypes, such as increased hormones production and destructive thyroiditis.[14,36]

The treatment of undefined forms should begin with ATD, and oral corticosteroids may be associated at the beginning of the treatment or after 4-6 weeks if the response is small.[14,19,35] In more severe cases, combination therapy with ATD and corticosteroids should be promptly initiated.[24]

Treatment: Thyroidectomy

Total thyroidectomy is the best option in patients whose clinical treatment is flawed or those with delayed therapeutic response associated with depressed ventricular function, which is currently the best alternative for immediate euthyroidism restoration.[14,39,40] Despite the risks associated with thyroidectomy, it should be considered before the patient progresses with severe clinical worsening, as the delay in

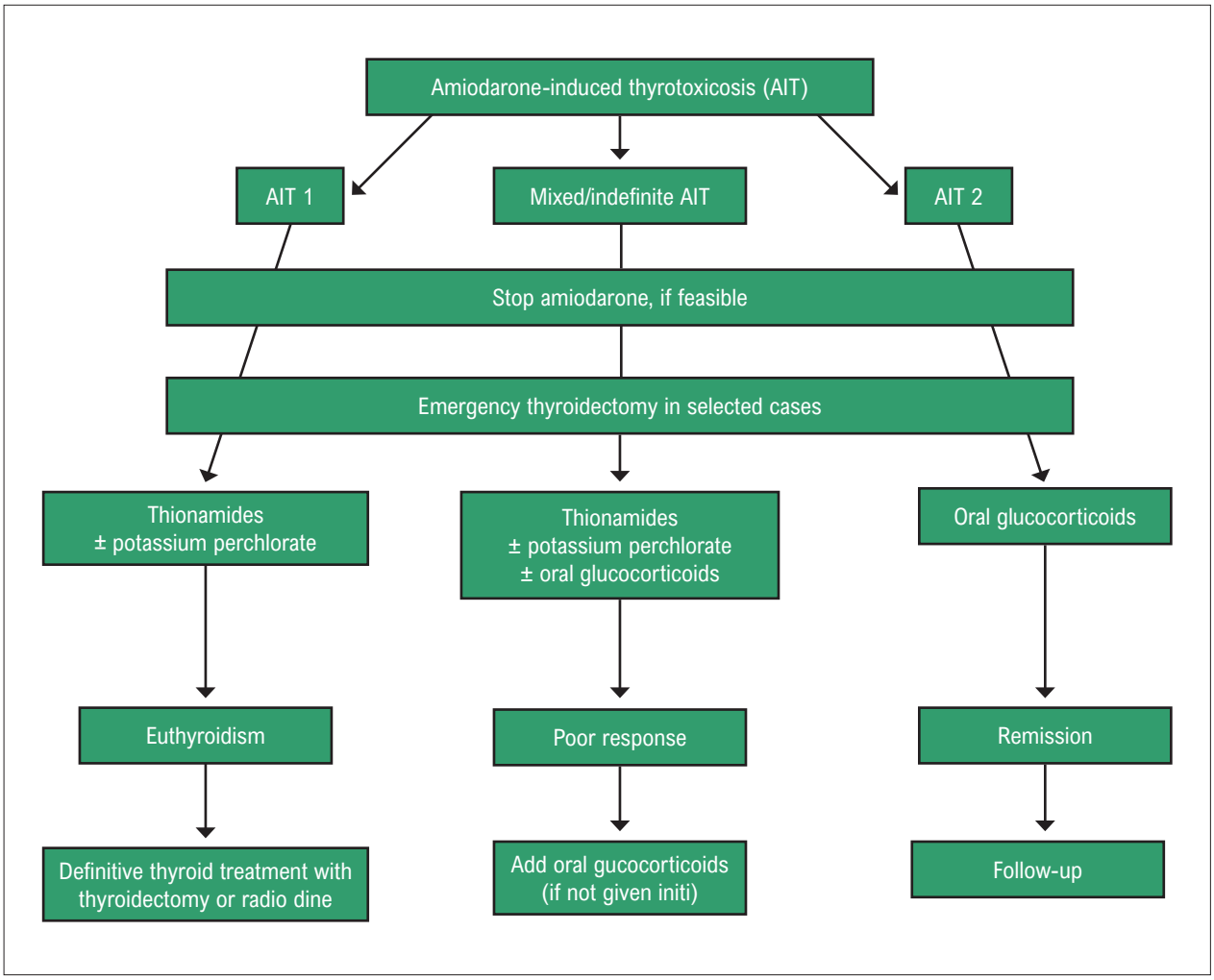

Figure 2 – *Algorithm for the management of amiodarone-induced thyrotoxicosis (AIT). Modified from Bartalena L, et al.*[14]

surgery indication is associated with increased mortality.[24,39-42] Several studies evaluating AIT patients submitted to thyroidectomy reported low morbidity associated with the procedure, showing a 0% to 1.9% mortality rate.[40-44]

In a recent observational study, 207 AIT patients submitted to thyroidectomy (57 thyroidectomized, 156 clinical treatment) evidenced lower mortality in patients who underwent thyroidectomy than those who were only treated clinically, particularly in LVEF <40% patients. This same study demonstrated a significant improvement of LVEF after euthyroidism restoration, being more evident in LVEF <40% patients.[42] Other three studies also reported significant improvement of cardiac function after thyroidectomy, being three patients removed from the cardiac transplant list after euthyroidism restoration.[40,41,43]

If total thyroidectomy is considered, individualized risk and benefit assessment should be made, and the decision should be multidisciplinary, involving cardiologists, endocrinologists, surgeons, and anesthesiologists. It is essential that a surgeon with high operative volume and experience with thyroidectomies is responsible for the procedure.[14]

Total thyroidectomy should be considered when:[14,24,39,43]

- Insufficient response to drug treatment with ATD and corticosteroids;

- Rapid deterioration of cardiac function;

- Advanced heart disease, right ventricular arrhythmogenic dysplasia, and malignant arrhythmias;

- Definitive treatment alternative to radioiodine (I^{131});

Conclusion

Given the consequences caused by TIA, the importance of diagnosing and treating TIA subtypes together is highlighted. Furthermore, it emphasizes the importance of therapeutic decisions being taken jointly by cardiologists and endocrinologists and that in more severe cases, thyroidectomy should be considered before exaggerated clinical worsening occurs.

Clinical studies involving patients with AIT are still limited and insufficient, particularly multicenter randomized controlled trials. Since amiodarone is a widely used drug,

and due to AIT consequences, the need for new clinical trials to improve the management of these patients is highlighted.

Author Contributions

Conception and design of the research, Writing of the manuscript and Critical revision of the manuscript for intellectual content: Souza LVF, Campagnolo MT, Martins LCB, Scanavacca MI; Acquisition of data and Analysis and interpretation of the data: Souza LVF, Campagnolo MT, Martins LCB.

Potential Conflict of Interest

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

Sources of Funding

There were no external funding sources for this study.

Study Association

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

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Aortic and Renal Artery Thrombosis as the First Clinical Manifestation of COVID-19 in a Heart Transplant Recipient

Deborah de Sá Pereira Belfort,[1] Fabiana G. Marcondes-Braga,[1] Sandrigo Mangini,[1] Caio Rebouças Fonseca Cafezeiro,[1] Diógenes Amauri Gonçalves Furlan,[1] Fernando Bacal[1]

Instituto do Coração (InCor), Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo,[1] São Paulo, SP – Brazil

Introduction

The novel coronavirus infection emerged in Wuhan, China, in the end of 2019 and is now a pandemic.[1] The relation between COVID-19 and thrombotic events is well established, even for patients under prophylactic anticoagulation. Although venous and arterial thromboembolic events have been described, usually stroke and acute myocardial infarction (AMI),[2,3] there are few reports of arterial thrombosis in unusual sites.[4] Almost all reports of thrombotic events are of intensive care unit (ICU) patients, and the incidence of thromboembolism in mild cases of COVID-19 is still not clear.

We report a case of a male heart transplant recipient admitted to emergency department with thrombosis of right renal artery and thoracic descending aorta associated with COVID-19.

Case presentation

A 28-year-old male heart transplant recipient since 2018, with previous familial dilated cardiomyopathy was admitted to the emergency department with acute right flank pain for three days associated with fever, chills, nausea, and vomiting. He denied respiratory symptoms, myalgia, headache or other symptoms which could suggest viral infection. Apart from diabetes mellitus and dyslipidemia, he had had no other comorbidity. The patient was on regular use of tacrolimus, mycophenolate and prednisone.

Physical exam revealed blood pressure of 150/100 mmHg, heart rate of 100 beats per minute, respiratory rate of 20 cycles per minute and blood oxygen saturation of 96% in ambient air. No rales were detected in lung evaluation and abdominal exam showed right costovertebral angle tenderness. Blood tests showed C-reactive protein of 317mg/dL, lactate dehydrogenase of 1,827U/L, D-dimer of 4,126ng/mL, ferritin of 651ng/mL, leukocytosis of 16,100/mm^3 and no other alterations.

An abdominal and thoracic computed tomography scan (CT scan) was performed and, surprisingly, revealed sparse luminal peripheral thrombi in the descending thoracic aorta (Figure 1). One of the thrombi extended to the right renal artery ostium and caused partial occlusion of its proximal segment (Figures 2 and 3). Right kidney presented multiple hypodense areas compatible with renal infarcts (Figure 3). No other artery was affected. Besides those findings, ground-glass opacities were found in 25% of pulmonary parenchyma (Figure 4), and for this reason COVID-19 was suspected. Nasopharynx real-time fluorescence polymerase chain reaction result for SARS-CoV-2 was positive. Coagulopathy tests were performed before starting anticoagulation. Protein C, protein S, antithrombin III levels were normal, prothrombin mutation test was negative, anticardiolipin (acL) antibody (IgG and IgM) tests were negative, but lupus anticoagulant (LAC) test was positive.

Hydration, antibiotics (ceftriaxone and azithromycin) and anticoagulation with enoxaparin were prescribed. Tacrolimus and mycophenolate were discontinued and prednisone was switched to hydrocortisone 150mg/day at admission. The patient improved and became asymptomatic. Inflammatory markers went down the following days. Immunosuppression was restarted after five days of admission and warfarin was prescribed. The patient was discharged on the 15th hospitalization day after adjustment of warfarin dose.

Discussion

Since the outbreak of COVID-19, a wide range of clinical presentations have been described. Most patients have mild symptoms, but up to 14% of infected patients develop interstitial pneumonia and 5% require mechanical ventilation.[1] Thromboembolic events in critically ill patients have been associated with COVID-19 in several studies.[2-4]

The mechanisms of the prothrombotic state and coagulopathy are not totally clear. COVID-19 is associated with a marked proinflammatory state, and the cytokine storm described in COVID-19 contributes to thrombosis by activating monocytes, neutrophils, and endothelium.[4] These cells activate platelets and increase levels of von Willebrand factor and factor VIII, all contributing to thrombin generation and fibrin clot formation. Thrombin, on the other hand, amplifies pro-inflammatory pathways.[5] The virus may also cause endotheliitis through the angiotensin-converting enzyme 2 receptor, leading to thrombotic microangiopathy.[6]

Although severe illness itself is known to provoke a hypercoagulable state, thromboembolic events may happen in outpatient settings, highlighting that critical illness is not the only factor involved. Overstad et al. reported venous thromboembolism (VTE) in four patients in isolation at home,[7] and a study in Italy showed that 50% of the reported thromboembolic events were diagnosed within 24h of hospital admission.[8]

Keywords

COVID-19; Thromboembolism; Heart Transplantation.

Mailing Address: Fabiana G. Marcondes-Braga •
Universidade de São Paulo Faculdade de Medicina Hospital das Clínicas Instituto do Coração - Avenida Dr. Enéas Carvalho de Aguiar, 44. Postal Code 05410-020, São Paulo, SP - Brazil
E-mail: fgmarcondes@yahoo.com.br, fgmarcondes@gmail.com
Manuscript received November 12, 2020, revised manuscript January 27, 2021, accepted March 24, 2021

DOI: https://doi.org/10.36660/abc.20201210

Research Letter

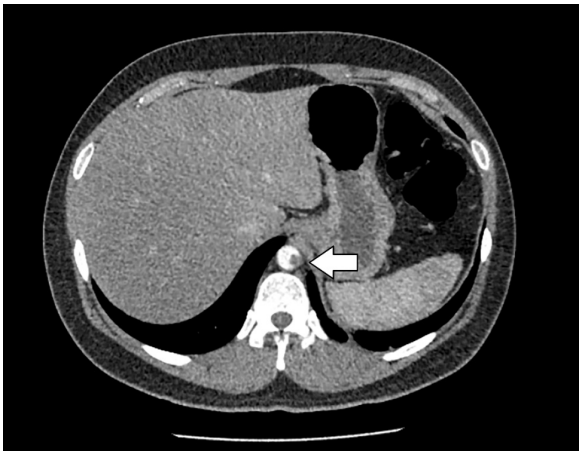

Figure 1 – *Abdominal computed tomography scan revealing sparse luminal peripheral thrombi in the descending thoracic aorta (arrow).*

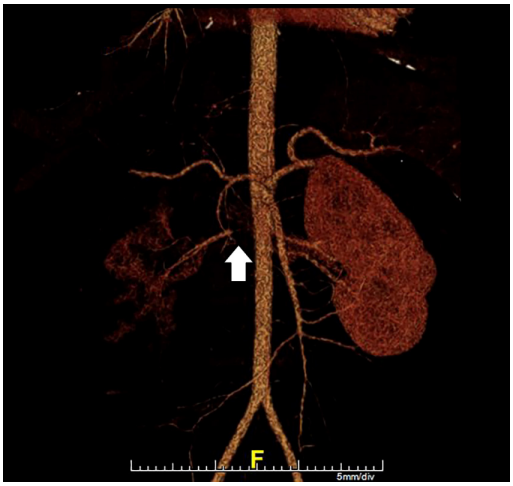

Figure 2 – *Tridimensional reconstruction of abdominal aorta showing partial occlusion of the proximal segment of right renal artery.*

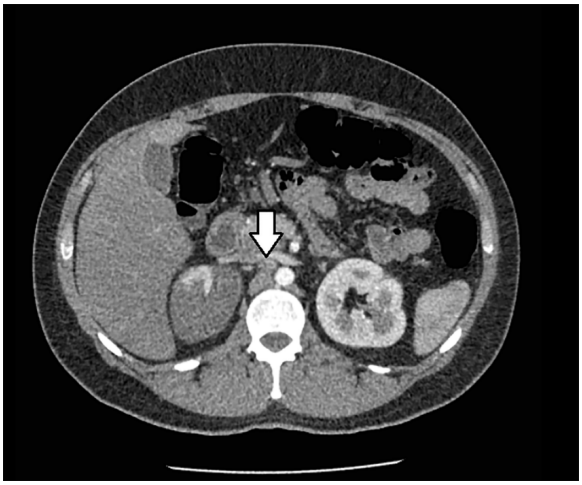

Figure 3 – *Abdominal computed tomography scan showing one of the thrombi extending to right renal artery ostium and causing partial occlusion of the proximal segment of this artery (arrow). Right kidney presents hypodense areas compatible with renal infarcts.*

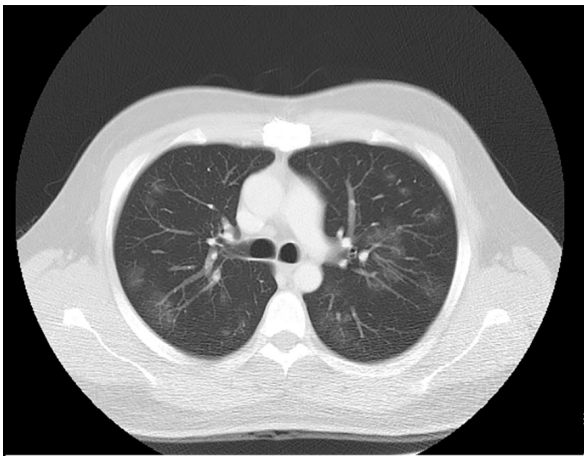

Figure 4 – *Thoracic computed tomography scan revealing ground-glass opacities in 25% of pulmonary parenchyma.*

Arterial thromboembolic events, although less common than VTE, occur in up to 10.5% of hospitalized patients.[2] Stroke was described in 1.6% and 3.8% of patients with COVID-19,[2,4] while the incidence of acute myocardial infarction (AMI) varies from 1.1%[4] in Italy to 8.9% in different centers of New York City.[2] Unusual sites of arterial thrombosis are also reported. Limb or acral ischemia was described in a case associated with multiple brain infarcts.[9] Bowel ischemia was detected in a woman presenting acute respiratory failure and right portal vein and upper mesenteric thrombosis on admission.[10] Two cases of renal infarction were reported by Post et al.,[11] one of them in a kidney transplant recipient, and both patients were in ICU.

There are few reports of COVID-19 cases among heart transplant recipients. A series of case in New York reported mortality of 25%, but no cases of arterial thromboembolic events have been described.[8] We report here, the first case of arterial thrombosis in a heart transplant patient.

Because of the atypical presentation, we searched for an underlying thrombophilia, and we found a positive LAC. It has been reported association of COVID-19 with positivity of

antiphospholipid antibodies (AA). Zhang et al.[9] described three cases of thrombosis associated with AA represented by aCL and anti–β2-glycoprotein I (aβ2GPI), but no LAC was detected in any of the patients.[9] On the other hand, Harzallah et al.[12] reported positivity of LAC in 45% of 56 patients, and only 10% positive for aCL or aβ2GPI, most of them associated with LAC.[12] However, acute infections are known to be sometimes associated with transient AA.[13] For those reasons, the relevance of AA positivity in COVID-19 is yet to be determined.

Conclusions

This case report illustrates the heterogeneity of clinical presentation of COVID-19 and reinforces the existence of a prothrombotic state, even in the outpatient setting. Moreover, it adds information to the recent reports regarding the presence of AA in COVID-19, although their importance in the pathophysiology of thromboembolic events in this setting is still not defined. The implication of these findings in transplant patients is even less clear, and this case report highlights the need for further research.

Author Contributions

Conception and design of the research: Belfort DSP, Marcondes-Braga FG, Mangini S, Cafezeiro CRF, Furlan DAG, Bacal F; Acquisition of data: Belfort DSP, Cafezeiro CRF, Furlan DAG; Writing of the manuscript: Belfort DSP, Marcondes-Braga FG, Cafezeiro CRF, Furlan DAG; Critical revision of the manuscript for intellectual content: Belfort DSP, Marcondes-Braga FG, Mangini S, Bacal F.

Potential Conflict of Interest

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

Sources of Funding

There were no external funding sources for this study.

Study Association

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

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Impact of COVID-19 on the Life of Brazilian Cardiologists and Cardiovascular Surgeons

Andre Luiz Cerqueira Almeida,[1,2] Marcelo Melo,[3] Rodrigo Elton Ferreira Rodrigues,[3] Luis Fábio Botelho,[3] Paulo André Abreu Almeida,[4] Silvio Henrique Barberato[5,6]

Santa Casa de Misericórdia de Feira de Santana – Cardiologia,[1] Feira de Santana, BA - Brazil
Sociedade Brasileira de Cardiologia Departamento de Imagem Cardiovascular,[2] São Paulo, SP - Brazil
Universidade Federal da Paraíba,[3] João Pessoa, PB - Brazil
UNIFACS Curso de Medicina,[4] Salvador, BA - Brazil
Sociedade Brasileira de Cardiologia - Diretoria de Qualidade Assistencial,[5] Rio de Janeiro, RJ - Brazil
CardioEco - Centro de Diagnóstico Cardiovascular,[6] Curitiba, PR - Brazil

Introduction

The COVID-19 (from the English coronavirus disease) pandemic has had a strong impact on cardiology services. The number of visits and cardiac interventions has decreased in many parts of the world in recent months.[1,2] However, despite increasing pressure and burden on the healthcare system, the provision of care has continued, particularly because patients with pre-existing cardiovascular disease are at high risk of COVID-19 infection, complications, and primary cardiac manifestations.[3]

In addition, effects of the COVID-19 have affected the society and in particularly healthcare professionals in terms of physical and mental health consequences, financial disturbances, and changes in quality of life.[3-5] Therefore, the COVID-19 pandemic has affected many aspects of the work and life of health care providers.[1,2,5]

Our study aimed at assessing the impact of the COVID-19 pandemic on the life of cardiologists and cardiac surgeons in Brazil, regarding professional practice, income, health and life style.

Methods

The authors released an online form on two websites, the Brazilian Society of Cardiology (SBC) website and on the SBC quality of care board website, to invite cardiologists to participate in the research. In addition, an invitation was sent by a freeware, cross-platform centralized instant messaging service to groups of cardiologists and local societies, departments and study groups, members of the SBC. Participation was voluntary and necessarily anonymous.

Keywords

COVID-19; Coronavirus-19; Pandemics; Cardiologists; Surgeons; Cardiovascular Diseases; Risk Factors; Health Systems; Infection/complications; Health Personnel; Sedentary Behavior; Epidemiology.

Mailing Address: Andre Luiz Cerqueira Almeida •
Santa Casa de Misericordia de Feira de Santana – Cardiologia - Rua Edelvira de Oliveira, 192. Postal Code 44001-032, Feira de Santana, BA – Brazil
E-mail: andrealmeida@cardiol.br, andrealmeida@uefs.br
Manuscript received November 16, 2020,
revised manuscript May 09, 2021, accepted June 09, 2021

DOI: https://doi.org/10.36660/abc.20201231

Participants did not receive any financial or material compensation. Data were collected from 10 July to 22 July 2020. The online form was composed of 28 questions of mandatory completion about healthcare practices and the quality of life of Brazilian cardiologists during the COVID-19 pandemic. Most questions were multiple-choice questions, and many of them had more than one possible answers.

Ethical aspects

A descriptive analysis of data was performed – nominal or categorical variables were expressed as absolute values, percentages or proportions. Numerical variables were expressed as mean and standard deviation or median and interquartile range, according to the data distribution. The Fisher's exact test was used to assess possible associations between categorical variables, at a level of significance of 5%. The Microsoft 365 Excel software was used for data analysis and construction of graphs. The inferential analysis of data was performed using Stata/SE 16.1 (StataCorp).

Results

General aspects

A total of 1,224 cardiologists accessed the questionnaire; two declined to participate and 1,222 answered the instrument, corresponding to 9.4% of current members of the SBC. Mean age of the study population was 47.9 ± 11.5 years, 711 (58.2%) were men. Figure 1 shows the distribution of respondents by Brazilian geographical region (1-A), workplace (1B), monthly income before and during the pandemic (1C) and changes in work routines of the cardiologists (1D).

There was a significant association between male sex and higher income ranges ($p<0.001$) (Table 1). Cardiologists who work in the private sector or in teaching activities experienced greater changes in income during the pandemic ($p<0.001$).

Aspects of work and income

The number of cardiologists who started to work at three or more shifts per week during the pandemic increased by 37.5%. On the other hand, 64% reduced their work hours at the office, 22% canceled their office lease, 18% had to dismiss employees, and 9% canceled investments in marketing (Figure 1D).

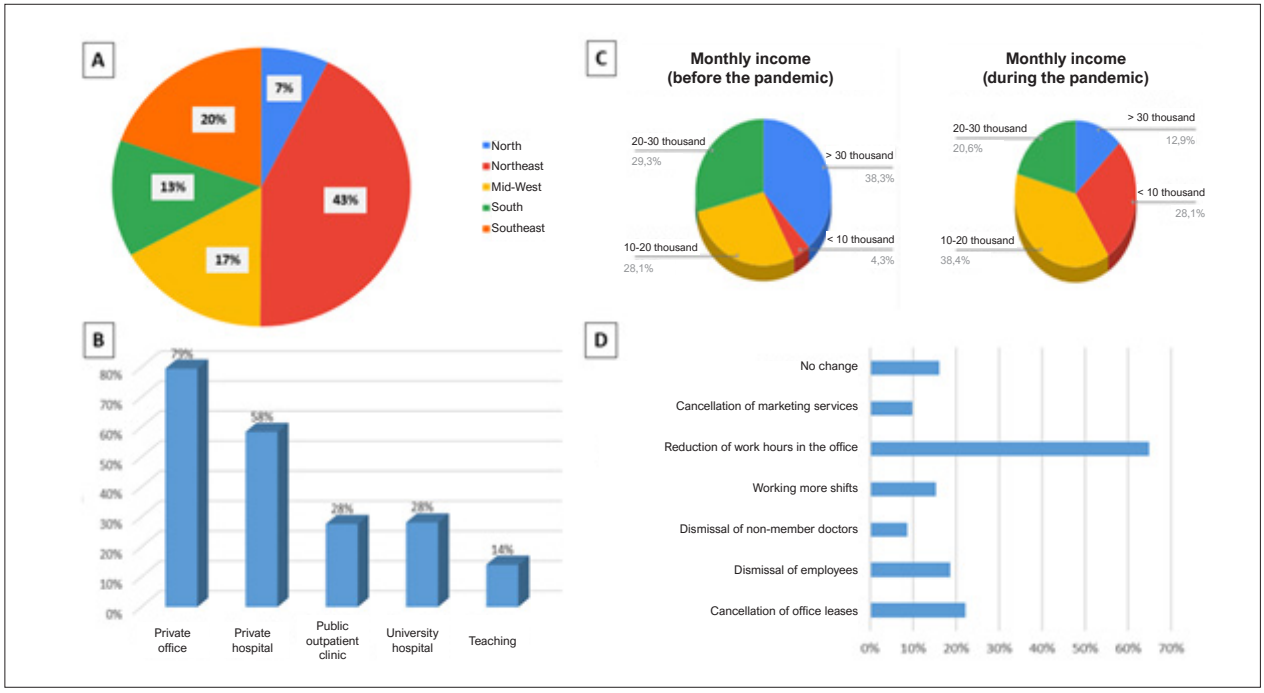

Figure 1 – *Distribution of Brazilian cardiologists participating in the study (n=1,222) by geographical area (A) place of work (B), monthly income before and during the COVID-19 pandemic (in Brazilian reals) (C), and changes in work routines / structure due to the pandemic.*

Table 1 – Table 1 Associations between the variables analyzed in the assessment of the COVID-19 pandemic on the life of Brazilian cardiologists (n=1,222)

Variable 01	Variable 02	Association (p-value)
Female sex	Reduction in sexual activity	< 0.001
Male sex	Higher income ranges	< 0.001
Work in the private sector	Greater changes in income	< 0.001
Teachinig activities	Greater changes in income	< 0.001
Age < 50 years	Working more shifts	< 0.001
Work as an echocardiography sonographer	Decrease in physical activity	< 0.001
Monthly income	Decrease in physical activity	> 0.05
Weight gain	Decrease in physical activity	> 0.05
Sex	Decrease in physical activity	> 0.05
Sex	Changes in work routines	> 0.05
Age range	Measures to reduce costs	> 0.05

As a consequence of the income reduction, 15% of cardiologists stopped paying medical councils of which they were members. Other measures for cost reduction are described in Figure 2A.

When we analyzed the impact of the pandemic by age range, considering 50 years of age as the cutoff, considering the valid responses, 56% of respondents were younger than 50 years and 44% aged 50 years or more. In these two groups, we found a significant increase ($p<0.001$) in the number of work shifts per week among the younger group, with no significant impact on the monthly income in none of the groups.

Forty-two percent of our sample were clinical cardiologists, 39% echocardiographists, 2% cardiovascular surgeons (Figure 3A). Among the echocardiographists, 54.5% reported a reduction greater than 50% in the volume of tests performed per month during the pandemic (Figure 3B). In the field of hemodynamics, 62.8% of respondents reported a reduction greater than 50% in the volume of tests or procedures in the same period (Figure 3C). Among cardiovascular surgeons,77.3% reported a reduction greater than 50% in the number of surgeries (Figure 3D). A significant association was found between working in the field of echocardiography and a reduction in physical activity by professionals ($p<0.001$).

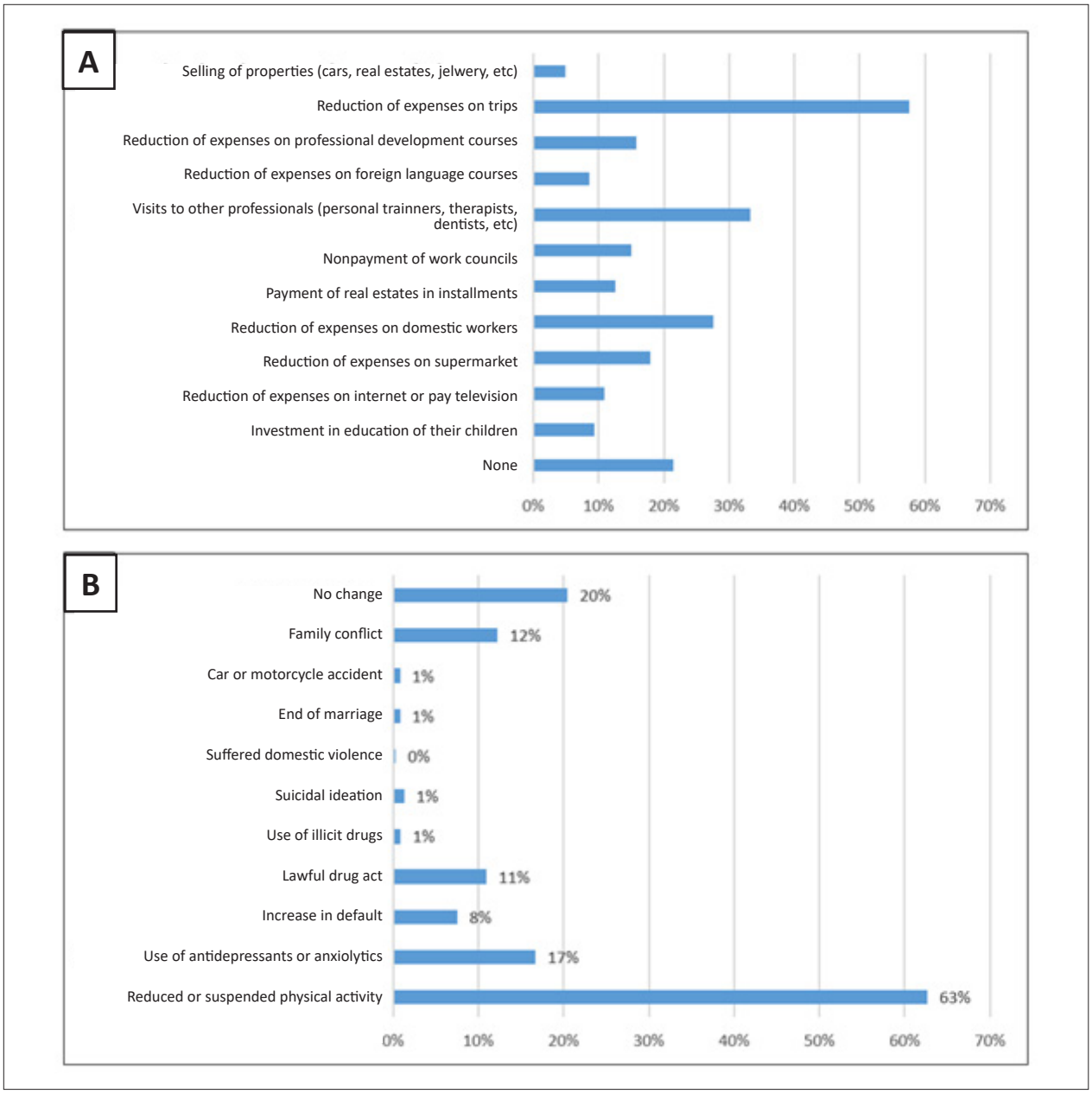

Figure 2 – *Measures for cost reduction (A) and changes in lifestyle (B) during the COVID-19 pandemic reported by Brazilian cardiologists (n=1,222).*

Telemedicine videoconferencing has been recently approved in Brazil. This modality of consultation was used by 30% of respondents in our study; however, 36% of these were fully reimbursed for the service (Figure 4). Before the pandemic, 48.8% of the women gained more than R$20,000 thousand a month and, during the pandemic, there was a reduction of 63%, and only 18% maintained the same income. Among men, 81.2% and 44.6% gained more than R$20,000 thousand a month before and during the pandemic, i.e., a reduction of 45% (Figure 5). Only 7.6% of women and 1.8% of men gained less than R$10,000 a month before the pandemic, and this percentage increased to 38.2% and 20.8%, respectively, during the pandemic (Figure 5).

No association was found between measures for cost reductions adopted during the pandemic and age ranges (Figure 6).

Changes in work routines and lifestyle

Among the respondents, 69% reported being physically active before the pandemic, and 63% of them reduced or stopped physical activities during the pandemic. Twelve percent of participants experienced family conflicts (four reported domestic violence); 17% started using antidepressants

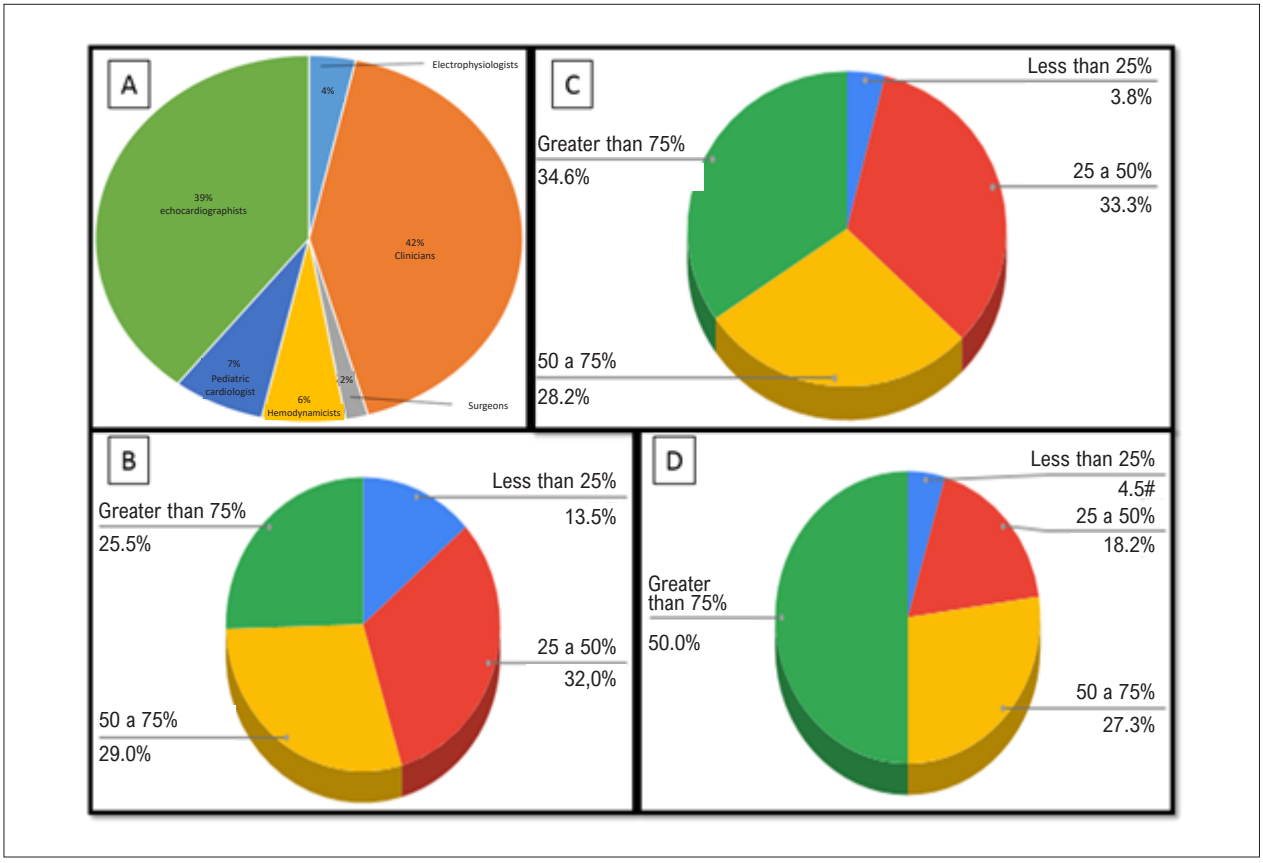

Figure 3 – *Distribution of cardiologists participating in the study by subspecialties (A) and percentages of professionals that reported a reduction in echocardiographic procedures (B); hemodynamic procedures (C) and cardiac surgeries (D).*

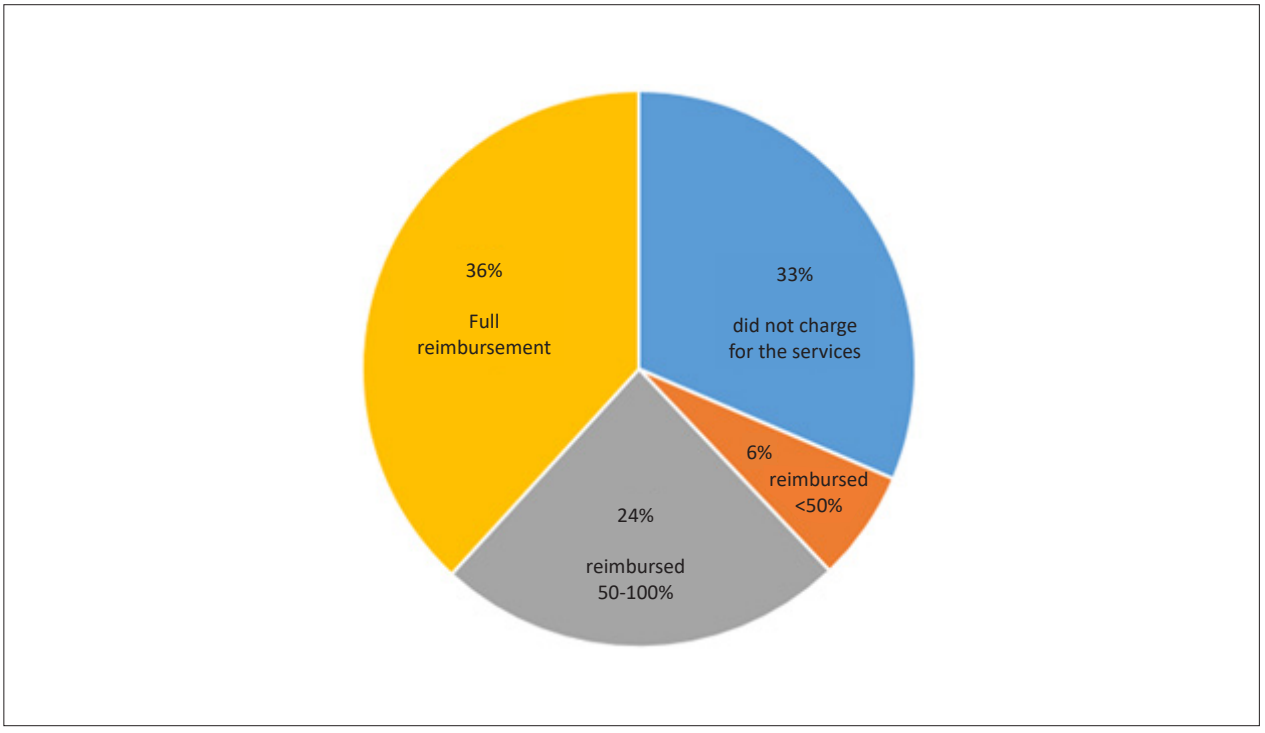

Figure 4 – *Reimbursement of consultations by video technology made during the COVID-19 pandemic, reported by Brazilian cardiologists (n=1,222).*

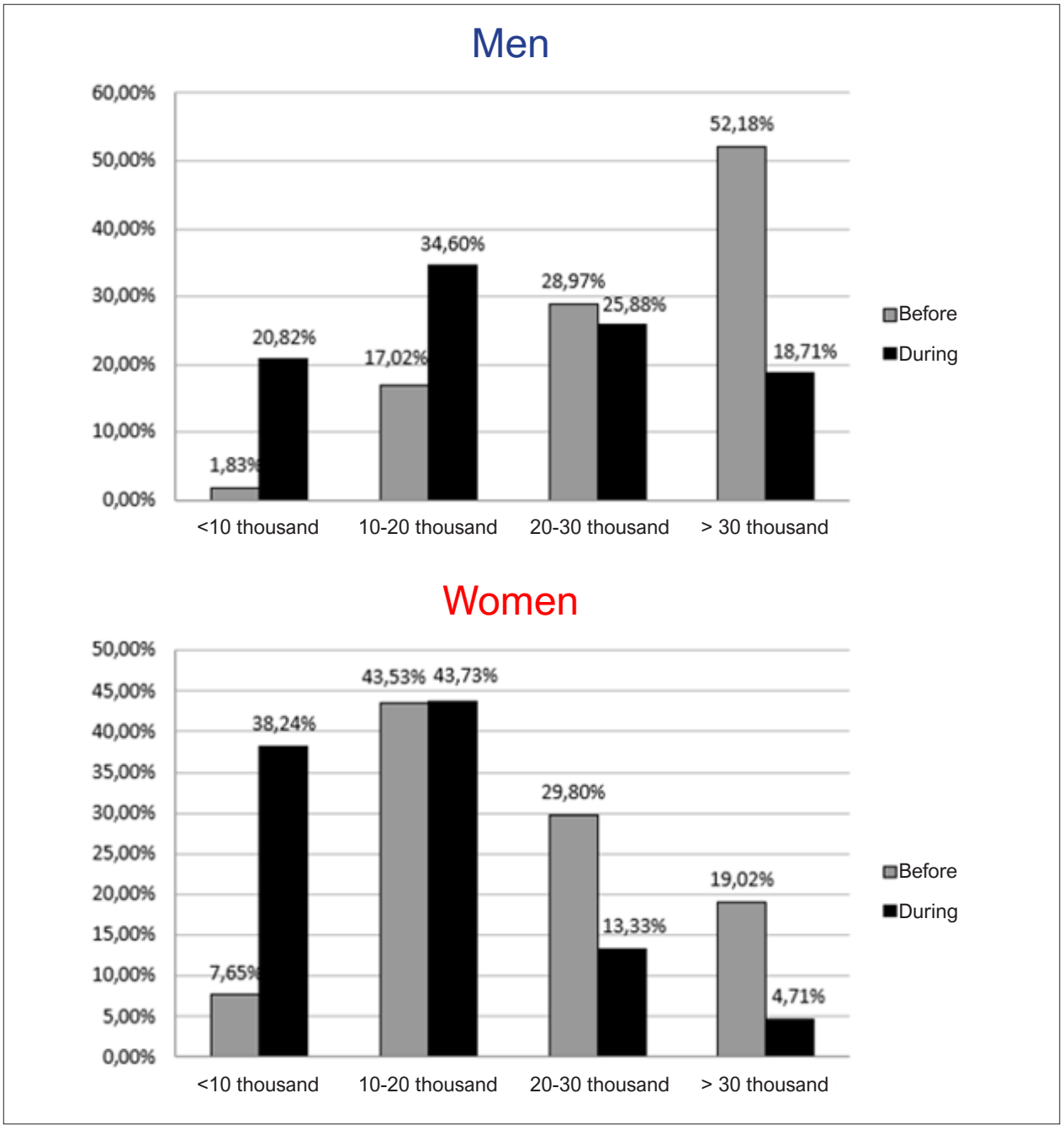

Figure 5 – *Distribution of Brazilian cardiologists (n=1,222) by monthly income (in Brazilian reals) and sex before and during the COVID-19 pandemic.*

or anxiolytics, and 11% increased the use of illicit drugs (Figure 2B). No association was found between reduction in physical activity with sex or income ($p>0.05$).

Considering the last four weeks of the pandemic, 44% of respondents reported weight gain, and 13% reported gaining more than three kilograms; weight was stable in 35% of respondents. In the same period of analysis, 26% of respondents reported increased alcohol consumption and 30% reported a stable consumption. There was no association between weight gain and change in physical activity ($p>0.05$).

In addition, for 40.2% and 41.6% of respondents, the frequency of sexual intercourse was reduced or unchanged, respectively, during the pandemic, and only 7.4% reported an increase in this frequency (Figure 7). The reduction in the frequency of sexual activity was more pronounced in women than men ($p<0.001$).

Aspects of the COVID-19 infection

In our sample, 54.9% of cardiologists reported to be moderately or very concerned about being on the frontline

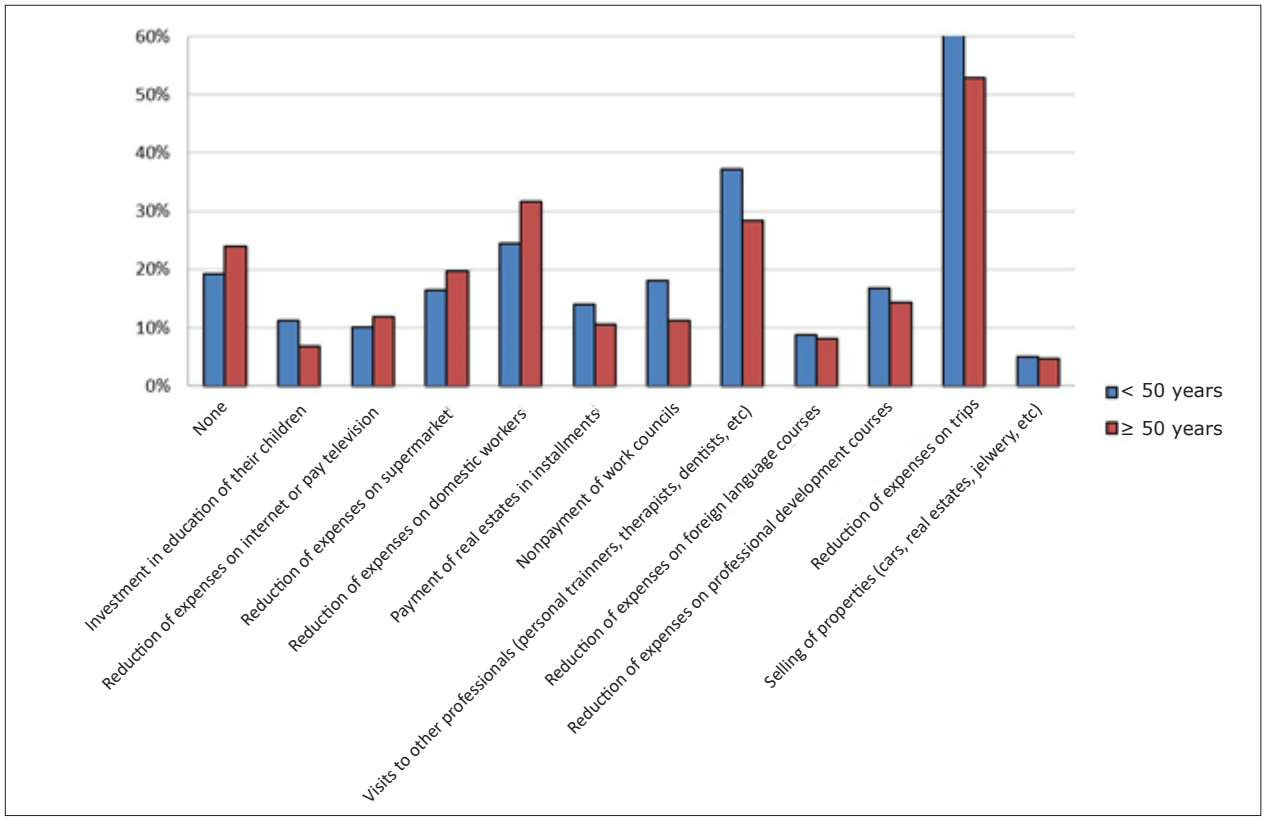

Figure 6 – *Relationship between age range and measures of cost reduction during the pandemic (n=1,222).*

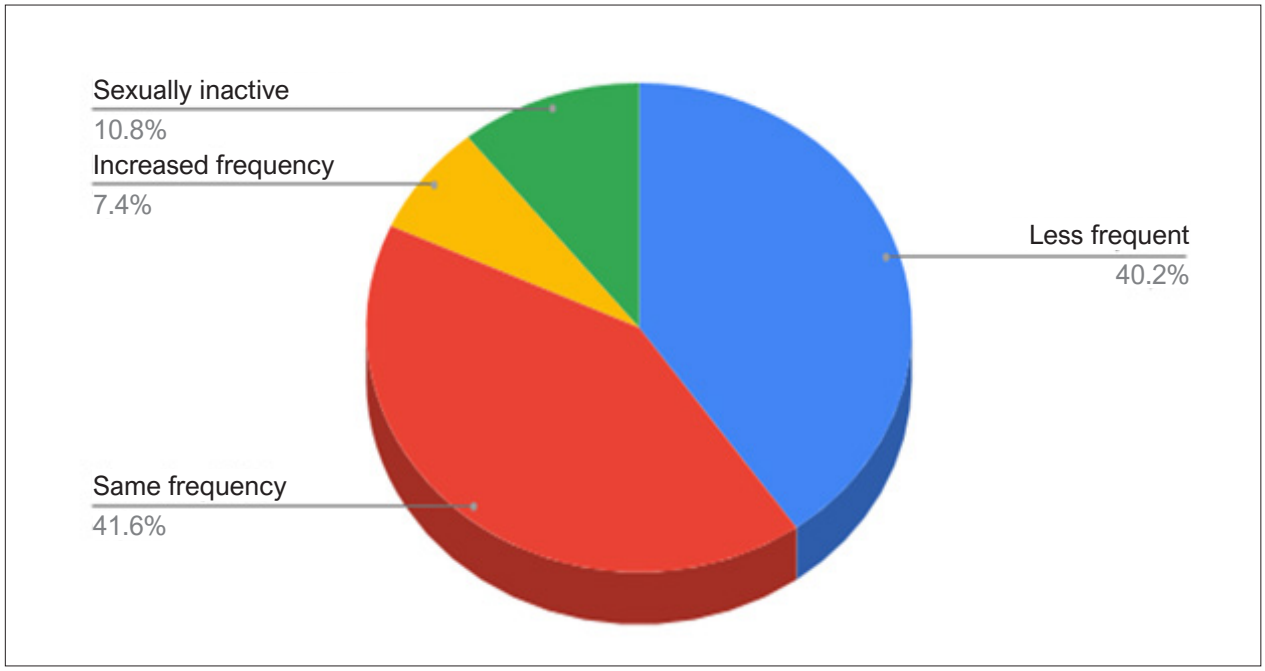

Figure 7 – *Frequency of sexual activity during the pandemic reported by Brazilian cardiologists (n=1,222).*

against COVID-19. Until the end of the study period (07/22/2020), 20% of respondents had a symptomatic COVID-19 infection; 1.8% of them had severe symptoms and required hospitalization, and 15% of respondents had mild symptoms and did not require hospitalization. Three percent of the cases had a confirmed infection, with an asymptomatic course though.

Discussion

The present study describes the results of the first nationwide survey that assessed the impact of the COVID-19 pandemic on professional and financial lives, health (physical and mental), and lifestyle of Brazilian cardiologists. The responses from 1,222 cardiologists from all geographical regions of the country demonstrated a strong impact of the pandemic on all these aspects. The findings reviewed a marked decrease in financial gain, associated with a reduction in working hours at the office, and an increase in the number of shifts per week. Consequently, payment of some expenses was affected, including payment of medical councils, attendance in professional development courses, and payment of school fees of their children. In addition, there was an important reduction in the practice of physical activities, frequency of sexual intercourse, and an increase in family conflicts and use of antidepressant and anxiolytics. Almost half of cardiologists reported weight gain and 25% reported an increase in alcohol consumption.

Similar to the results obtained here, a study published by the British Medical Association in July 2020 showed that 39.5% of British doctors reported a reduction in financial earnings, and 30.7% reported mental health conditions relating to or made worse by work during the COVID-19 pandemic, such as depression, anxiety, stress, burnout, and emotional distress.[4] In a recent study conducted with 766 Brazilian urologists, 54.8% reported a reduction greater than 50% in the income during the pandemic, 32.9% reported weight gain, 60.0% reported a reduction in physical activity, 39.9% increased alcohol consumption, and 34.9% reported a reduction in sexual activity.[5]

Several lines of evidence have suggested that physical inactivity may have important repercussions in cardiovascular physiology.[6] Physical activity was reduced or stopped by 63% of respondents, which may have contributed to the weight gain greater than three kilograms reported by 44% of participants. A recent publication established a relationship of physical activity reduction and weight gain with increased risk of cardiovascular diseases and drew attention to other obesity-related health problems.[7]

Our data showed that 26% of respondents increased alcohol consumption, and 40% reported a reduction in sexual activity during the pandemic as compared with before the pandemic. It is plausible to associate the increased alcohol consumption and exacerbation of family conflicts with the psychological impact caused by prolonged social isolation. An increase in family conflicts was reported by 12% of respondents, including four professionals who experienced domestic violence. It is of note that this number may be much higher, considering that the number of domestic violence incidents has drastically increased in other countries during the period of social isolation, including China (where the number of cases has tripled),[8] the United Kingdom, the United States and France (reaching a 36% increase).[9] In Brazil, the incidence increased by 17% according to the Brazilian Ministry of Women.[10]

The Brazilian government has regulated and temporarily authorized the remote consultation of patients by telemedicine in Brazil.[11] Precipitated by the social isolation imposed by the COVID-19 pandemic, and still in its early stages, 30% of the cardiologists reported using teleconsultation, although only 36% of them were fully reimbursed for the service. This differs from the results of another study that showed that 38.7% of the Brazilian urologists participating in the study reported evaluating their patients by teleconsultation, and 50% of them were fully reimbursed for the service.[5]

In 2017, a questionnaire was sent by e-mail to all 13,462 cardiologists, active members of the SBC; 2,101 (15.6%) responded to the questionnaire, 1509 (71.8%) men and 592 (28.2%) women.[12] In our study, of 1,222 (9.1% of the SBC active members) of respondents, 711 (58.2%) were men. Age range of respondents was similar between the two surveys, but 51.3% of respondents to the first survey were older than 50 years, versus 44% in the current study. Regarding the geographical distribution, 54% of active members of the SBC live in the southeast region of Brazil, 19% live in the northeast, 15% in the south, 8% in the middle-west, and 3% in the north region of Brazil. Among respondents, 43% live in the northeast region, 17% in the middle-west, 13% in the south. 20% in the southeast and 7% in the north.

The present study has some limitations inherent to cross-sectional studies based on questionnaire responses. The number of respondents represent slightly less than 10% of the number of cardiologists members of the SBC. The geographical distribution of respondents is markedly different from that of the members of the SBC. Also, it was impossible to prove or elucidate the questionnaire responses; however, although the truthfulness of the responses could not be checked, the study was consistent with literature published in Brazil and in other countries. In addition, although we have found some interesting and even statistically significant associations, our results should be considered exploratory, and the possibility of false-positive results cannot be disregarded due to the number of hypothesis tests performed.

Conclusion

This study reinforces the negative impact of the COVID-19 pandemic on the work, income, health, and lifestyle of Brazilian cardiologists. We present extremely relevant data that will help in planning in future scenarios of chaos, like the current challenge of the COVID-19 pandemic.

Author Contributions

Conception and design of the research: Almeida ALC, Melo M, Barberato SH; Acquisition of data: Almeida ALC, Melo M, Rodrigues REF, Almeida PAA, Barberato SH; Analysis and interpretation of the data, Writing of the manuscript and Critical revision of the manuscript for intellectual content: Almeida ALC, Melo M, Rodrigues REF, Botelho LF, Almeida PAA, Barberato SH; Statistical analysis: Botelho LF.

Potential Conflict of Interest

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

Sources of Funding

There were no external funding sources for this study.

Study Association

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

Ethics approval and consent to participate

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

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Left Ventricular Hypertrophy: One Phenotype, Two Hypotheses, Three Lessons

Patrícia Rodrigues,[1] *Ana Rita Soares,*[1] *Ricardo Taipa,*[1] *Sofia Ferreira,*[1] *Hipólito Reis*[1]

Centro Hospitalar Universitário do Porto EPE,[1] *Porto – Portugal*

Past medical history

A 58-year-old woman with familial amyloid polyneuropathy caused by the Val30Met (p.Val50Met) mutation in the transthyretin (TTR) gene started showing neuropathic symptoms by the age of 37 and a salivary gland biopsy confirmed TTR amyloid deposition. She was submitted to liver transplantation 7 years after symptom onset and was under immunosuppressive drugs, with stable neurological changes since then. She also had chronic kidney failure (stage 3b) and a pacemaker implanted due to sick sinus syndrome.

History of presentation

The patient was referred to the Cardiology outpatient clinic 14 years after liver transplantation, due to progressive dyspnea and bipedal edema. On physical examination, she had signs of peripheral and pulmonary congestion.

The ECG results and pacemaker interrogation revealed atrial fibrillation and ventricular pacing with controlled heart rate.

A transthoracic echocardiogram showed significant left ventricular hypertrophy (LVH), preserved systolic function and diastolic dysfunction – Figure 1.

She was started on oral anticoagulation and diuretics, with clinical improvement.

Differential diagnosis

In the presence of heart failure with LVH, we should first consider loading conditions such as hypertension or valvular disease, that were not observed in this patient.

Sarcomeric hypertrophic cardiomyopathy (HCM) was a possible diagnosis, which can present with different LVH patterns, being the most common genetic cause of LVH. Fabry disease could be another possibility, although rarer.

However, in this patient with a known mutation, the most likely diagnosis was Transthyretin Amyloid Cardiomyopathy (ATTR-CM).Patients without significant cardiomyopathy at the time of liver transplantation, particularly if their mutation was not Val30Met, can subsequently progress, due to enhanced deposition of wild-type protein.[1]

Investigations

Surprisingly, the technetium-99m 3,3-diphosphono-1,2-propanodicarboxylic acid (^{99m}Tc-DPD) scintigraphy was negative (Perugini grade of zero) – Figure 2.

AL amyloidosis was excluded after analyzing immunofixation (24h urine and serum) and free light chains in serum.

Cardiovascular magnetic resonance (CMR) was not performed, since the pacemaker leads and generator were not CMR conditional and the patient was claustrophobic.

An endomyocardial biopsy was requested, which was negative for amyloid and did not show significant changes. At this point, other diagnoses for LVH were reconsidered.

A genetic study with an HCM panel (including Fabry disease) was requested and a probably pathogenic variant in heterozygosity in the MYH7 gene (p.Arg783Leu) was found. This made us wonder if the phenotype could be attributed to HCM.

However, the patient needed high doses of diuretics (at least 120 mg of furosemide daily to remain euvolemic), even though no left ventricular outflow tract obstruction was seen, and she was pacemaker-dependent. Reviewing the echocardiogram (Figure 1), she had a restrictive transmitral flow pattern, low tissue Doppler S' velocities and very mild pericardial effusion. All these findings are not typical of HCM.

A review of the endomyocardial biopsy by a more experienced pathologist was requested, and it actually showed severe amyloid infiltration (Figure 3).

Discussion

Universally accepted criteria for diagnosing amyloid cardiomyopathy have been missing, specifically for ATTR-CM, and the algorithm proposed by Gillmore et al.[2] helps to determine the type of amyloidosis, but starts from findings "suggesting cardiac amyloid", which is quite broad. A recent European position statement proposes a more clear algorithm for the suspicion and diagnosis of cardiac amyloidosis.[3]

Usually, the diagnosis requires increased ventricular wall thickness (usually > 12 mm), combined with the results of hematologic tests, bone scintigraphy and sometimes a biopsy.

^{99m}Tc-DPD scintigraphy has shown an excellent sensitivity and specificity for detecting ATTR-CM, often precluding histological confirmation,[2] particularly when a Perugini grade of 2 or 3 (moderate or intense cardiac uptake) is noted.[4,5] However, more recently, false negative findings in radionuclide imaging have been

Keywords

Hypertrophy, Left Ventricular; Heart Failure; Cardiomyopathy, Hypertrophic; Amyloidosis; Amyloid Neuropathies, Familial/diagnostic imaging.

Mailing Address: Patrícia Rodrigues •
Centro Hospitalar Universitário do Porto EPE - Largo Professor Abel Salazar
Porto 4099-001 – Portugal
E-mail: pfdrodrigues@gmail.com
Manuscript received February 09, 2021, revised manuscript April 19, 2021, accepted June 09, 2021

DOI: https://doi.org/10.36660/abc.20210103

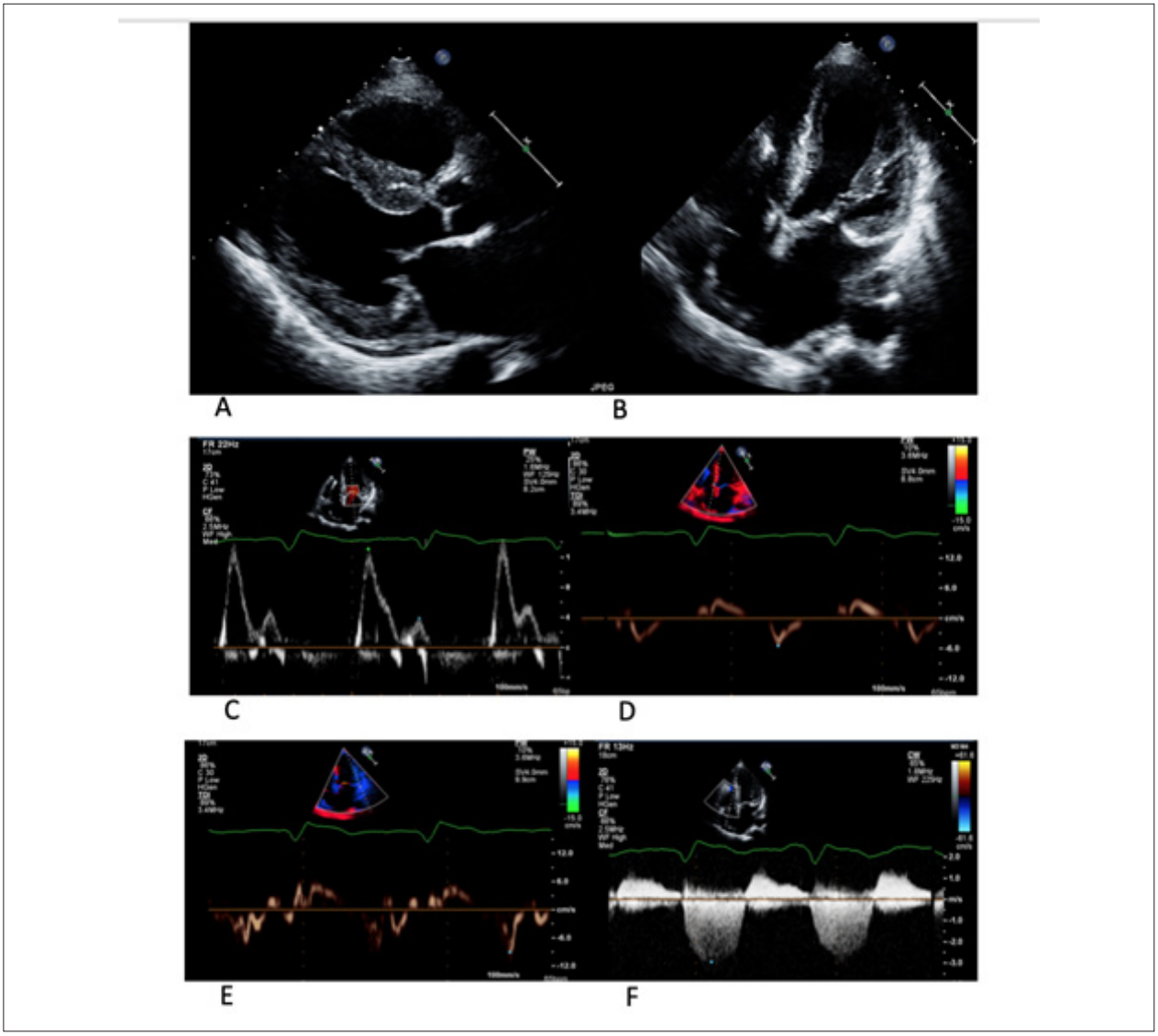

Figure 1 – *Transthoracic echocardiogram findings. Panel A (parasternal long axis view) and B (apical 4-chamber view) show increased wall thickness (maximum 15 mm in the basal interventricular septum) and mildly dilated left atrium (body-surface indexed volume of 40 mL/m²). Panel C shows increased E/A ratio of 3,4. Panel D shows a lateral e' velocity of 9 cm/s and panel E a septal e' of 5 cm/s, giving an average E/e' of 15. In panel F, tricuspid regurgitation velocity is estimated at 2,9 m/s with Cw Doppler. Therefore, the patient met the criteria for diastolic dysfunction.*

found in patients with TTR Val30Met mutation and early-onset of neurological symptoms.[6] The cause seems to be related to the fact that these patients have exclusively type B (full length) fibrils, with low avidity for ^{99m}Tc-DPD, unlike patients with late-onset or other mutations, who also have type A fibrils (truncated).[7] In the former cases, further investigation, including endomyocardial biopsy, may be needed.

Interestingly, in this patient, the endomyocardial biopsy was initially negative, making us explore other diagnoses, namely HCM (since the biopsies were very small and from the right ventricle, cardiomyocyte hypertrophy could be missed). However, we should acknowledge that a pathologist with experience in diagnosing amyloidosis is crucial.

Our group and several others have described the development of ATTR-CM years after liver transplantation, not only in patients with late-onset or non-Val30Met mutations as initially reported, but also in early-onset Val30Met patients. This phenomenon has been attributed to *seeding* mechanisms: small deposits of amyloid fibrils with a mutated TTR precursor may promote late accumulation of wild-type fibrils. However, we still don't understand why these patients do not have a positive score on ^{99m}Tc-DPD scintigraphy more often, similar to patients with wild-type disease.

Finally, genetic testing has been increasingly helpful in the investigation of cardiomyopathies, but the results need to be carefully discussed, since they can have implications for the diagnosis and for family screening. The cumulative knowledge

Research Letter

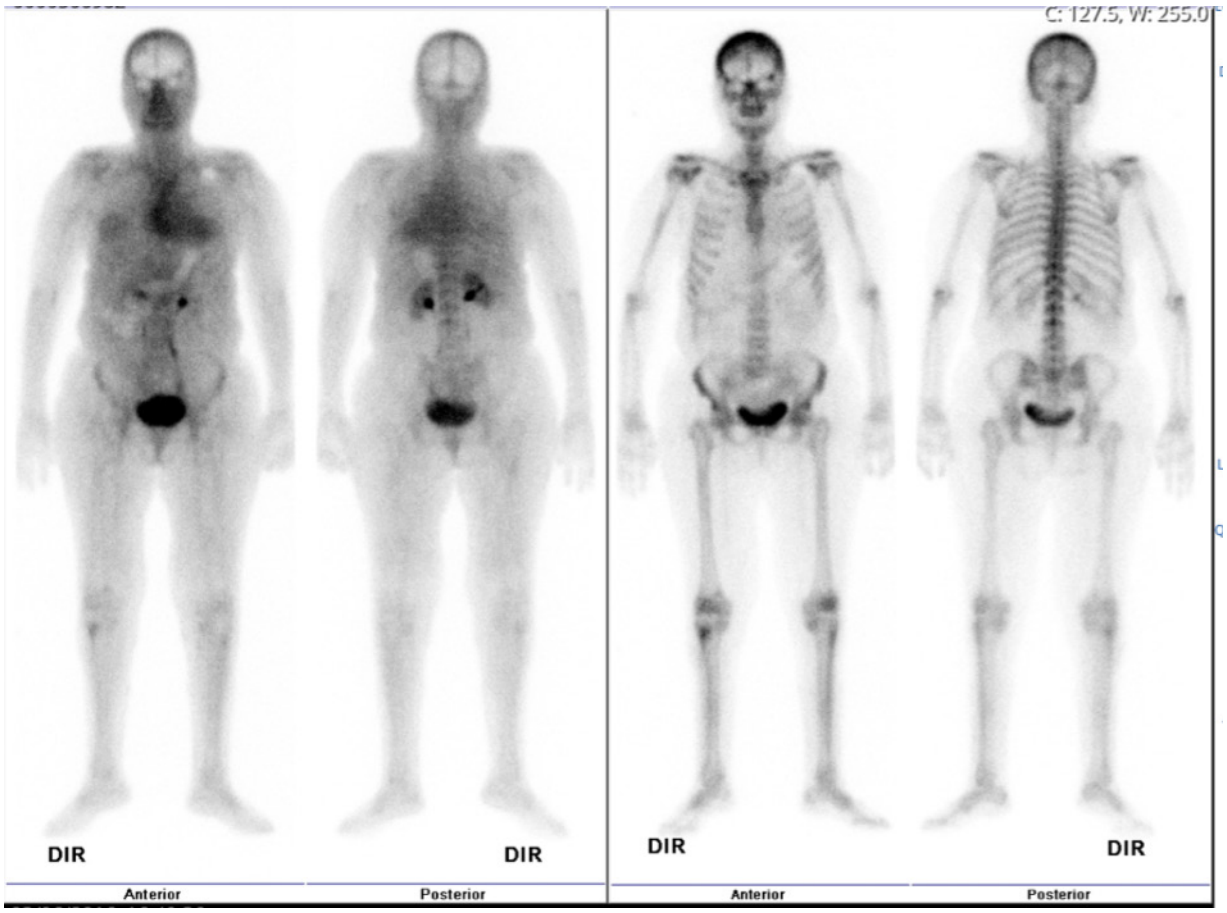

Figure 2 – *Technetium-99m 3,3-diphosphono-1,2-propanodicarboxylic acid (^{99m}Tc-DPD) scintigraphy images. The pictures on the left were obtained 10 minutes after ^{99m}Tc-DPD administration and the images on the right were obtained 2 hours after. The Perugini grading score was zero, meaning no cardiac uptake and normal bone uptake.*

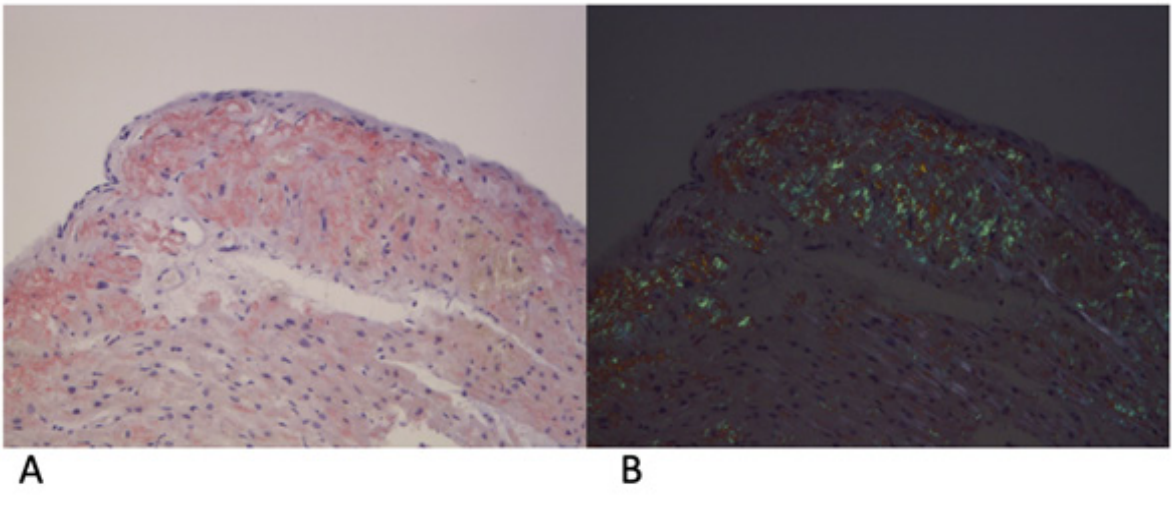

Figure 3 – *Endomyocardial biopsy, showing amyloid infiltration in the myocardial interstitium and particularly in the endocardium. Congo Red staining (A) and Congo Red staining under polarized light (B); amplification 200x.*

about cardiogenetics will enlighten the classification of some variants. When a pathogenic or likely pathogenic variant is found, genetic screening is usually offered to family members.

Conclusions

Our final diagnosis was ATTR-CM, even though the first exams seemed to rule out this hypothesis, highlighting the fact that endomyocardial biopsies are highly pathologist-dependent and that ^{99m}Tc-DPD scintigraphy can have false negative results. Moreover, the results of genetic testing in HCM need to be interpreted in the clinical context, since the finding of a mutation, particularly if it is not a clearly pathogenic one, does not mean it is causing the phenotype.

Unfortunately, there are currently no drugs approved for treating amyloid cardiomyopathy in transplanted patients; however, we hope this will change in a near future.

What is already known about this topic? What does this study add?

This case provides 3 take-home messages:

- identifying the cause of LVH is often overlooked, but pursuing different possibilities and identifying the etiology has clinical implications for the patient and the family;

- we should be aware of the pitfalls of amyloid identification in biopsies, particularly the importance of an experienced pathologist;

- ^{99m}Tc-DPD scintigraphy also has limitations, particularly in early-onset Val30Met patients; combining the medical history with the results from different exams is crucial for the diagnosis of cardiac amyloidosis.

Author Contributions

Conception and design of the research and Acquisition of data: Rodrigues P; Analysis and interpretation of the data and Writing of the manuscript: Rodrigues P, Soares AR, Taipa R; Critical revision of the manuscript for intellectual content: Rodrigues P, Soares AR, Taipa R, Ferreira S, Reis H.

Potential Conflict of Interest

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

Sources of Funding

There were no external funding sources for this study.

Study Association

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

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Centro Hospitalar do Porto under the protocol number 2017.219 (189-DEFI/181-CES). 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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Erratum

Arq Bras Cardiol. 2021; [online].ahead print, PP.0-0,

In Original Article “Training Non-Cardiologists Could Improve the Treatment Results of ST Elevation Myocardial Infarction”, with DOI number: https://doi.org/10.36660/abc.20200180, published in ahead of print in the Journal Arquivos Brasileiros de Cardiologia, Arq Bras Cardiol. 2021; [online].ahead print, PP.0-0, include the authors Bruno Mahler Mioto and Pedro Silvio Farsky and their respective institutions: InCor - Instituto do Coração do Hospital das Clínicas da FMUSP, São Paulo, SP - Brazil and Secretaria da Saúde do Estado de São Paulo, São Paulo, SP - Brazil. The author Bruno Mahler Mioto insert after the author João Fernando Monteiro Ferreira and the author Pedro Silvio Farsky insert after the author Naide Aparecida de Oliveira.

January 2021 Issue, vol. 116 (1), pages 119-126

In the Original Article “Catheter Ablation of Focal Atrial Tachycardia with Early Activation Close to the His-Bundle from the Non Coronary Aortic Cusp”, with DOI: https://doi.org/10.36660/abc.20180449, published in the journal Arquivos Brasileiros de Cardiologia, 116(1):119-126, in page 119, correct the author’s name Vera Aiello to Vera Demarchi Aiello.

DOI: https://doi.org/10.36660/abc.20210905