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Prognostic Value of Plasma NT-proBNP levels in Hospitalized Patients Older than 80 Years of Age in a Hospital in Beijing, China

Qiwei Zhu,[1,2] Peng Gao,[1,2] Shihui Fu,[1,2] Hao Wang,[1,2] Yongyi Bai,[1,2] Leiming Luo,[1,2] Ping Ye[1,2]

Chinese People's Liberation Army General Hospital,[1] Beijing - China
Department of Geriatric Cardiology, Chinese People's Liberation Army General Hospital,[2] Beijing - China

Abstract

Background: Despite growing evidence that N-terminal pro-brain natriuretic peptide (NT-proBNP) has an important prognostic value in older adults, there is limited data on its prognostic predictive value.

Objectives: The aim of this study is to evaluate the clinical significance of NT-proBNP in hospitalized patients older than 80 years of age in Beijing, China.

Methods: This prospective, observational study was conducted in 724 very elderly patients in a geriatric ward (age ≥80 years, range, 80100 years, mean, 86.6 3.0 years). Multivariate linear regression analysis was used to screen for factors independently associated with NT-proBNP, and the Cox proportional hazard regression model was used to screen for relationships between NT-proBNP levels and major endpoints. The major endpoints assessed were all-cause death and MACEs. P values < 0.05 were considered statistically significant.

Results: The prevalence rates of coronary heart disease, hypertension, and diabetes mellitus were 81.4%, 75.1%, and 41.2%, respectively. The mean NT-proBNP level was 770 ± 818 pg/mL. Using multivariate linear regression analyses, correlations were found between plasma NT-proBNP and body mass index, atrial fibrillation, estimated glomerular filtration rate, left atrial diameter, left ventricular ejection fraction, use of betablocker, levels of hemoglobin, plasma albumin, triglycerides, serum creatinine, and blood urea nitrogen. The risk of all-cause death (HR, 1.63; 95% CI, 1.0052.642; P = 0.04) and major adverse cardiovascular events (MACE; HR, 1.77; 95% CI, 1.2893.531; P = 0.04) in the group with the highest NT-proBNP level was significantly higher than that in the group with the lowest level, according to Cox regression models after adjusting for multiple factors. As expected, echocardiography parameters adjusted the prognostic value of NT-proBNP in the model.

Conclusions: NT-proBNP was identified as an independent predictor of all-cause death and MACE in hospitalized patients older than 80 years of age.

Keywords: Natriuretic Peptide Brain; Prognosis; Coronary Artery Disease; Hospitalization; Aging; Echocardiography/methods; Hypertension; Diabetes Mellitus; Aged 80 and over.

Introduction

Brain natriuretic peptide (BNP) was first described in 1988 after its isolation from porcine brain. The ventricular myocardium was soon found to be the major source of BNP synthesis and secretion. BNP is initially synthesized as a prehormone in response to myocyte stretch and then it is enzymatically cleaved into biologically active BNP and biologically inactive N-terminal pro-BNP (NT-proBNP), in equal proportions. Many studies have shown that BNP and NT-proBNP are important predictors of cardiovascular morbidity and mortality in middle-aged and older adults.[1-4] However, as there are limited data on individuals aged ≥80 years, the predictive value of BNP and NT-proBNP in such elderly individuals is unclear.[3,4]

China is the most populous country in the world. With improvements in living standards and medical facilities, the Chinese population aged 80 years and older has gradually increased. According to the results of the 2010 census, there are approximately 20 million people aged 80 years and older in China. As plasma NT-proBNP levels increase with age, even in the absence of heart failure or other cardiovascular diseases (CVD),[5,6] we hypothesized that an increase in plasma NT-proBNP levels reflects the risk of all-cause death and major adverse cardiovascular events (MACE) in those aged 80 years and older.

Methods

Study population

This prospective, observational study examined very elderly patients (age ≥ 80 years) who were hospitalized

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in the Department of Geriatric Internal Medicine at the Chinese People's Liberation Army (PLA) General Hospital, Beijing, China. Patients were excluded if they had severe systemic diseases, such as collagenosis, cachexia, severe infection, severe liver disease, acute heart failure, or acute coronary syndrome, or had undergone coronary artery bypass grafting or percutaneous transluminal coronary angioplasty in the previous 6 months. A total of 739 very elderly patients were enrolled between November 2007 and October 2010; 326 were hospitalized for stable coronary heart disease (CHD), 278 were hospitalized for poor blood pressure control (blood pressure was not controlled within the target range with unchanged drug treatment), 39 were admitted to the hospital for respiratory diseases (31 cases were upper respiratory tract infections), and 17 were admitted to the hospital for digestive diseases.

Questionnaire and physical examination

Information about patient age and disease history, including CHD, hypertension, atrial fibrillation (AF), diabetes mellitus (DM), and cancer, was collected by the physician upon admission to the hospital.

The physical examination included measurements of height and weight. After the patient had been seated for at least 5 minutes, blood pressure was measured using a calibrated desktop sphygmomanometer, which is consistent with current recommendations. The patient's blood pressure was measured three times consecutively with at least 1 minute between measurements, and the mean values were used for the analysis.

Biochemical assay

All patients underwent a complete laboratory evaluation. Blood samples were collected from patients between 6 am and 8 am after overnight fasting ($\geq$12 hours) to measure the following parameters: total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), serum creatinine (sCr), blood urea nitrogen (BUN), and NT-proBNP. Blood samples were sent to the Biochemical Laboratory of the General Hospital of the PLA. For each parameter, the same reagents, methods, and instruments were used to analyze all samples. Concentrations of sCr were determined using an enzymatic assay (Roche Diagnostics GmbH, Basel, Switzerland) and a Hitachi 7600 autoanalyzer (Hitachi, Tokyo, Japan). Plasma NT-proBNP levels were determined using an electrochemiluminescence immunoassay (Roche Diagnostics GmbH, Mannheim, Germany) and a Roche analyzer (Roche Diagnostics, Indianapolis, IN).

Echocardiography measurements

Echocardiography was performed within 3 days of admission by experienced ultrasonographists. Left ventricular ejection fraction (LVEF) was determined using the biplane Simpson's rule from apical four- and two-chamber images of the heart.[7] Left atrial diameter (LAD), left ventricular end-systolic diameter, left ventricular end-diastolic diameter (LVEDd), interventricular septal diameter (IVSd), and posterior wall thickness (PWT) were measured on three consecutive beats, and the results were averaged.

Variable definition

Estimated glomerular filtration rate (eGFR) was calculated using the Chinese version of the Modification of Diet in Renal Disease equation as follows:[8] eGFR (mL/min/1.73 m^2) = 175 $\times$ standard sCr (mg/dL)$^{-1.234}$ $\times$ age (year)$^{-0.179}$ $\times$ 0.79 (if female). Chronic kidney disease (CKD) was defined according to clinical practice guidelines.[9] Body mass index (BMI) was defined as weight (kg) divided by the square of the height (m). Left ventricular mass (LVM) was calculated as $\{0.8 [1.04 (LVEDd + PWT + IVSd)^3 - (LVEDd)^3]\} + 0.6$ g[7]. Body surface area (BSA) was calculated as 0.0061 $\times$ height$^{+0.0124}$ $\times$ weight$^{-0.0099}$.[10] LVM index (LVMI) was defined as LVM divided by BSA. Left ventricular hypertrophy (LVH) was defined according to the following criteria: (i) LVMI greater than 125 g/m^2 (male) and/or (ii) LVMI > 110 g/m^2 (female).[7,11] Hypertension was defined according to the following criteria: (i) systolic blood pressure greater than or equal to 140 mm Hg, (ii) diastolic blood pressure (DBP) greater than or equal to 90 mm Hg, and/or (iii) the use of antihypertensive drugs.[12] DM was defined according to the following criteria: (i) fasting glucose levels greater than or equal to 7.1 mmol/L, (ii) 2-h venous blood glucose levels greater than or equal to 11.1 mmol/L, and/or (iii) the use of hypoglycemic drugs or insulin.[13] Diagnoses of CHD, AF, and cancer were confirmed by the patient's medical history.

Follow-up and Endpoints

The follow-up visits were conducted from December 2015 to January 2016. During these visits to the Chinese PLA General Hospital, all patients received a questionnaire. The median follow-up interval was 5.3 years [Interquartile range (IQR), 2.7-6.6 years]. During the follow-up, 15 patients were lost and excluded from the analysis. Complete follow up data were obtained from 724 patients (follow-up rate, 98%).

The major endpoints assessed were all-cause death and MACEs. Death was ascertained from the death record (a legal document including time, site, and other information). The MACE included non-fatal myocardial infarction, coronary revascularization therapy, unstable angina pectoris, and hospitalization for heart failure or stroke. The incidence of MACE was the event that did not cause death, and only the first time was recorded when more than one occurred.

Statistical analyses

The Kolmogorov-Smirnov test employed to verify to the normality of the data. Continuous variables with a normal distribution were expressed as the mean ($\pm$ standard deviation), and those with a skewed distribution were expressed as the median and IQR. Categorical

variables were expressed as the number and percentage. Plasma NT-proBNP levels underwent natural logarithmic transformation because there was no Gaussian distribution. Plasma NT-proBNP levels at baseline were categorized as quartile 1 (≤124 pg/mL, n = 181), quartile 2 (124–271 pg/mL, n = 180), quartile 3 (271–668 pg/mL, n = 182), and quartile 4 (≥668 pg/mL, n = 181). Continuous variables between groups were compared using analysis of variance, whereas comparison between two independent samples was performed using Mann-Whitney U test. The categorical variables between groups were compared using the Chi-Square and Fisher's exact tests.

The correlations between continuous variables were assessed using linear regression and the assumptions of linearity for the continuous independent variables of the standardized residuals were assessed by plotting the residuals against a predictor variable, whereas collinearity between the independent variables was evaluated using the variance inflation factors. The multivariate linear regression analysis (entry criteria p ≤ 0.10) was used to screen the factors independently associated with NT-proBNP.

The relationships between NT-proBNP levels and major endpoints were evaluated using Cox proportional hazard regression model. Model 1 was adjusted for age and gender. Model 2 was adjusted for the variables in model 1 plus BMI, hypertension, AF, CHD, DM, hemoglobin, plasma albumin, eGFR, LDL-C, and HDL-C. Model 3 was adjusted for the variables in model 2 plus the use of cardiovascular drugs. Model 4 was adjusted for the variables in model 3 plus LVEF, LAD, and LVMI. A correction for competing risk was not used when evaluating the relationship between NT-proBNP and MACE. Cumulative mortality and MACE curves were generated using the Kaplan-Meier method. Receiver operating characteristic (ROC) curves were generated to evaluate the accuracy of NT-proBNP levels in the prediction of all-cause death and MACE.

All analyses were conducted using SPSS software for Windows (version 13.0; SPSS, Chicago, IL) and State software (version 11.0; Stata Corporation, College Station, TX). P values < 0.05 were considered statistically significant.

Results

Baseline characteristics of participants

A total of 724 very elderly patients were included in the analysis. Patients' ages ranged from 80 to 100 years (mean, 86.6 ± 3.0 years) and the majority of patients were males (93.3%). At baseline, the mean NT-proBNP level was 770 ± 818 pg/mL. Cardiovascular drugs, demographic characteristics, cardiovascular risk factors, and related laboratory tests in each group are shown in Table 1. Patients in the highest quartile of plasma NT-proBNP levels were significantly older, had a higher prevalence of CHD and AF, and had higher levels of sCr, LAD, and LVMI; these patients also had a lower BMI and lower levels of eGFR, TC, TG, LDL-C, hemoglobin, plasma albumin, LVEF, and DBP.

Association of plasma NT-proBNP levels with clinical variables

At baseline, older age, CHD, AF, sCr, BUN, LAD, and LVMI were positively associated with plasma NT-proBNP levels, whereas eGFR, TC, LDL-C, TG, hemoglobin, plasma albumin, LVEF, BMI, DBP, and mean blood pressure levels were inversely associated with plasma NT-proBNP levels, as shown by the results of the univariate analyses. Using the multivariate linear regression analysis, older age (p = 0.019), AF, sCr, BUN, LAD, and using a betablocker were positively associated with plasma NT-proBNP levels, whereas eGFR, TG, hemoglobin, plasma albumin, LVEF, and BMI were inversely associated with plasma NT-proBNP levels (Table 2).

Association of plasma NT-proBNP levels with all-cause mortality and MACE

During a median follow-up of 5.3 years (IQR 2.7–6.6 years), 353 patients (48.8%) died; 45 (12.7%) died from cardiac causes and 150 (42.5%) died from an infection. The all-cause mortality rate significantly increased from 28.7% in the lowest quartile of plasma NT-proBNP levels (<124 pg/mL) to 77.3% in the highest quartile of plasma NT-proBNP levels (≥668 pg/mL), according to results using an unadjusted model. A Kaplan-Meier survival analysis was performed to study the relationship between the subgroups and survival probability; patients with higher NT-proBNP levels had a significant lower survival probability (p = 0.008; Figure 1). All-cause death risk [hazard ratio (HR), 1.63; 95% confidence interval (CI), 1.005–2.642; p = 0.04)] for patients in the highest quartile of plasma NT-proBNP levels was significantly higher than that for patients in the lowest quartile of plasma NT-proBNP levels, according to results using the Cox proportional hazard regression model after adjusting for age, gender, BMI, presence of a comorbidity (HT, CHD, or AF), eGFR, pulse pressure, use of a cardiovascular drug (ACEI and betablocker), and levels of BUN, TG, hemoglobin, and plasma albumin (Model 3; Table 3).

There were 202 patients with MACE during the follow-up. The incidence of MACE significantly increased from 16.6% in the lowest quartile of plasma NT-proBNP levels to 45.3% in the highest quartile of plasma NT-proBNP levels. A Kaplan-Meier survival analysis revealed significant differences between the groups (log-rank test, p = 0.002; Figure 2). The risk of MACE (HR, 1.77; 95% CI, 1.29–3.53; p = 0.04) for patients in the highest quartile of plasma NT-proBNP levels was significantly higher than for patients in the lowest quartile of plasma NT-proBNP levels, after adjusting for multiple cardiovascular risk factors. Further subgroup analysis found that the highest incidence of MACE was nonfatal acute coronary syndrome (ACS)(67.8%). The risk of ACS (HR, 1.89; 95%CI, 1.14-4.08; p=0.04) for patients in the highest quartile of plasma NT-proBNP levels was significantly higher than for patients in the lowest quartile of plasma NT-proBNP levels after adjusting for multiple cardiovascular risk factors (Model 3). However, plasma NT-proBNP levels were not associated with the risk of death (HR, 1.47; 95% CI, 0.88–2.45; p = 0.14) , MACE (HR, 1.31; 95% CI, 0.62–2.78; p = 0.48) or ACS (HR, 1.54; 95%CI, 0.87-3.58; p=0.20), according to results using the Cox proportional hazard regression model after further adjusting for LVEF, LAD, and LVMI (Model 4; Table 3).

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Table 1 – Baseline characteristics of patients in each quartile of plasma NT-proBNP levels

Characteristics	All patients included	NT-proBNP (pg/mL)				p value
		<124	124-271	271-668	≥668	
n	724	181	180	182	181	
Age(years)	86.6±3.0	85.7±2.9	86.1±2.9	87.0±2.9	87.4±3.0	<0.001
Male(%)	680(93.9)	171(94.5)	169(93.9)	168(92.3)	172(95.0)	0.727
Female(%)	44(6.1)	10(5.5)	11(6.1)	14(7.7)	9(5.0)	
CHD(%)	589(81.4)	135(74.6)	144(80)	150(82.4)	160(88.4)	0.008
HT(%)	544(75.1)	124(68.5)	135(75)	144(79.1)	141(77.9)	0.088
DM(%)	298(41.2)	71(39.2)	69(38.3)	76(41.8)	82(45.3)	0.537
AF(%)	130(18.0)	15(8.3)	16(8.9)	27(14.8)	72(39.8)	<0.001
BMI(kg/m²)	23.8±2.6	24.7±2.3	23.7±2.3	23.5±2.7	23.3±2.9	<0.001
NT-proBNP(pg/mL)	770±818	70±27	190±37	420±93	2399±1618	<0.001
eGFR(ml/min.1.73m²)	75.7±20.4	82.8±17.2	77.8±19.7	75.6±20.7	66.6±22.1	<0.001
sCr(ug/mL)	99.6±29.4	85.1±16.6	92.4±21.2	98.1±28.3	122.5±50.3	<0.001
BUN(mmol/L)	7.61±2.50	6.48±1.63	6.83±1.64	7.59±2.41	9.55±3.88	<0.001
TC(mmol/L)	4.14±0.67	4.31±0.67	4.24±0.65	4.00±0.69	3.99±0.61	<0.001
TG(mmol/L)	1.45±0.57	1.62±0.60	1.41±0.54	1.42±0.62	1.34±0.50	0.023
LDL-C(mmol/L)	2.37±0.57	2.54±0.59	2.46±0.57	2.23±0.57	2.26±0.52	<0.001
HDL-C(mmol/L)	1.16±0.23	1.13±0.24	1.18±0.25	1.18±0.27	1.16±0.29	0.473
Hb(g/L)	124.6±13.9	131.6±12.5	125.3±11.8	122.1±13.6	119.2±15.4	<0.001
ALB(g/L)	39±2.8	40.0±2.6	39.8±2.7	38.4±2.7	37.7±2.8	<0.001
LVEF(%)	60.0±3.8	61.4±3.1	60.8±2.9	59.7±4.2	57.9±4.4	<0.001
LVEF<40%	3	0	0	1	2	
LVEF>50%	697	180	179	173	165	
LVEDD(mm)	48.5±2.8	48.2±2.5	47.9±2.3	48.8±2.7	49.3±3.4	0.002
LVESD(mm)	32.9±2.3	32.2±1.7	32.3±2.0	33.2±2.4	34.0±2.9	<0.001
LAD(mm)	37.2±3.1	36.3±2.7	36.0±2.8	37.4±2.6	39.3±3.9	<0.001
IVS(mm)	10.7±1.1	10.6±1.0	10.5±1.0	10.7±1.2	10.9±1.2	0.040
PLVW(mm)	10.1±0.7	10.0±0.6	10.0±0.6	10.2±0.8	10.2±0.9	0.203
LVMI(g/m²)	123.2±19.9	118.9±15.7	118.0±16.0	126.7±19.4	129.1±27.5	<0.001
Anti-platelet drugs(%)	493(68.1)	118(65.2)	129(71.7)	120(65.9)	126(69.6)	0.506
Statins(%)	311(43.0)	84(46.4)	70(38.9)	78(42.9)	79(43.6)	0.547
CCB(%)	361(49.9)	95(52.5)	93(51.7)	87(47.8)	86(47.5)	0.697
ACEI(%)	92(12.7)	21(11.6)	25(13.9)	14(7.7)	32(17.7)	0.035
ARB(%)	227(31.4)	55(30.4)	62(34.4)	68(37.4)	42(23.2)	0.023
ACEI/ARB(%)	307(42.4)	72(39.8)	85(47.2)	79(43.4)	71(39.2)	0.386
Betablocker(%)	291(40.2)	58(32.0)	56(31.1)	82(45.1)	95(52.5)	<0.001
Mean SBP(mmHg)	129.3±9.4	129.3±9.4	129.9±8.5	128.6±9.4	129.4±10.2	0.753
Mean DBP(mmHg)	67.3±5.8	68.2±5.7	68.1±5.2	66.9±5.9	66.2±6.1	0.027
MBP(mmHg)	88.0±6.0	88.6±6.2	88.7±5.2	87.5±5.9	87.3±6.4	0.152
PP(mmHg)	61.9±8.6	61.1±7.9	61.9±8.7	61.7±8.6	63.2±9.2	0.348

CHD: coronary heart disease; HT: hypertension; DM: diabetes mellitus; AF: atrial fibrillation; BMI: body mass index; NT-proBNP: N-terminal pro-brain natriuretic peptide; eGFR: estimated glomerular filtration rate; sCr: serum creatinine; BUN: blood urea nitrogen; UA: uric acid; TC: total cholesterols; TG: triglycerides; LDL-C: low density lipoprotein-cholesterol; HDL-C: high density lipoprotein-cholesterol; Hb: hemoglobin; ALB: plasma albumin; LVEF: left ventricular ejection fraction; LVEDD: left ventricular end-diastolic diameter; LVESD: left ventricular end-systolic diameter; LAD: left atrial diameter; IVS: interventricular septum; PLVM: posterior left ventricular wall; LVMI: left ventricular mass index; CCB: calcium channel blocker; ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor antagonists; SBP: systolic blood pressure; DBP: diastolic blood pressure; MBP: mean blood pressure; PP: pulse pressure.

Table 2 – Association of plasma NT-proBNP levels with clinical variables

Variables	Univariate		Multivariate		
	r value	p value	Standard β value	p value	95% CI
sex	0.003	0.926			
Age	0.178	<0.001	0.082	0.019	0.002 to 0.023
CHD	0.136	<0.001	-0.004	0.913	-0.104 to 0.093
HT	0.072	0.053	0.011	0.753	-0.075 to 0.104
AF	0.310	<0.001	0.218	0.000	0.213 to 0.414
DM	0.047	0.202			
eGFR	-0.240	<0.001	-0.131	0.003	-0.005 to 0.000
sCr	0.285	<0.001	0.192	0.001	0.001 to 0.003
BUN	0.325	<0.001	0.112	0.010	0.004 to 0.028
TC	-0.162	<0.001	0.058	0.485	-0.067 to 0.142
LDL-C	-0.173	<0.001	-0.050	0.535	-0.161 to 0.084
HDL-C	0.026	0.495			
TG	-0.111	0.004	-0.088	0.018	-0.107 to -0.010
Hb	-0.293	<0.001	-0.121	0.002	-0.006 to -0.001
ALB	-0.287	<0.001	-0.137	0.000	-0.033 to -0.009
LVEF	-0.261	<0.001	-0.179	0.000	-0.029 to -0.013
LAD	0.292	<0.001	0.179	0.000	0.015 to 0.036
LVMI	0.163	<0.001	0.006	0.865	-0.001 to 0.001
BMI	-0.170	<0.001	-0.111	0.005	-0.032 to -0.006
Antiplatelet drug	0.026	0.478			
statins	0.007	0.848			
CCB	-0.056	0.136			
ARB	-0.047	0.204			
ACEI	0.074	0.046	0.057	0.088	-0.014 to 0.205
ACEI/ARB	0.005	0.883			
Beta-blocker	0.172	<0.001	0.124	0.000	0.066 to 0.219
SBP	-0.007	0.860			
DBP	-0.110	0.003	0.000	0.992	-0.006 to 0.005
MBP	-0.075	0.042			
PP	0.065	0.080	0.065	0.064	0.000 to 0.007

CHD: coronary heart disease; HT: hypertension; DM: diabetes mellitus; AF: atrial fibrillation; BMI: body mass index; NT-proBNP: N-terminal pro-brain natriuretic peptide; eGFR: estimated glomerular filtration rate; sCr: serum creatinine; BUN: blood urea nitrogen; TC: total cholesterols; TG: triglyceride; LDL-C: low density lipoprotein cholesterol; HDL-C: high density lipoprotein cholesterol; Hb: hemoglobin; ALB: plasma albumin; LVEF: left ventricular ejection fraction; LAD: left atrial diameter; LVMI: left ventricular mass index; CCB: calcium channel blocker; ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor antagonists; SBP: systolic blood pressure; DBP: diastolic blood pressure; MBP: mean blood pressure; PP: pulse pressure.

ROC curves of plasma NT-proBNP levels for predicting all-cause death and MACEs

The data shown in the ROC curves show that NT-proBNP is a reasonably accurate predictor of all-cause death and MACE. The area under the ROC curve was 0.71 (95% CI, 0.677–0.752; p < 0.001) for all-cause death (Figure 3). The cut-off value for plasma NT-proBNP levels to predict all-cause death was 406 pg/mL and had a maximum Youden index of 0.36, with a sensitivity of 65% and a specificity of 81%. The area under the ROC curve

was 0.58 (95% CI, 0.537–0.626; p = 0.001) for MACE (Figure 4). The cut-off value for plasma NT-proBNP levels to predict MACE was 406 pg/mL and had a maximum Youden index of 0.23, with a sensitivity of 69% and a specificity of 54%.

Discussion

The main finding of this study is that NT-proBNP is an independent predictor of all-cause death and MACE in

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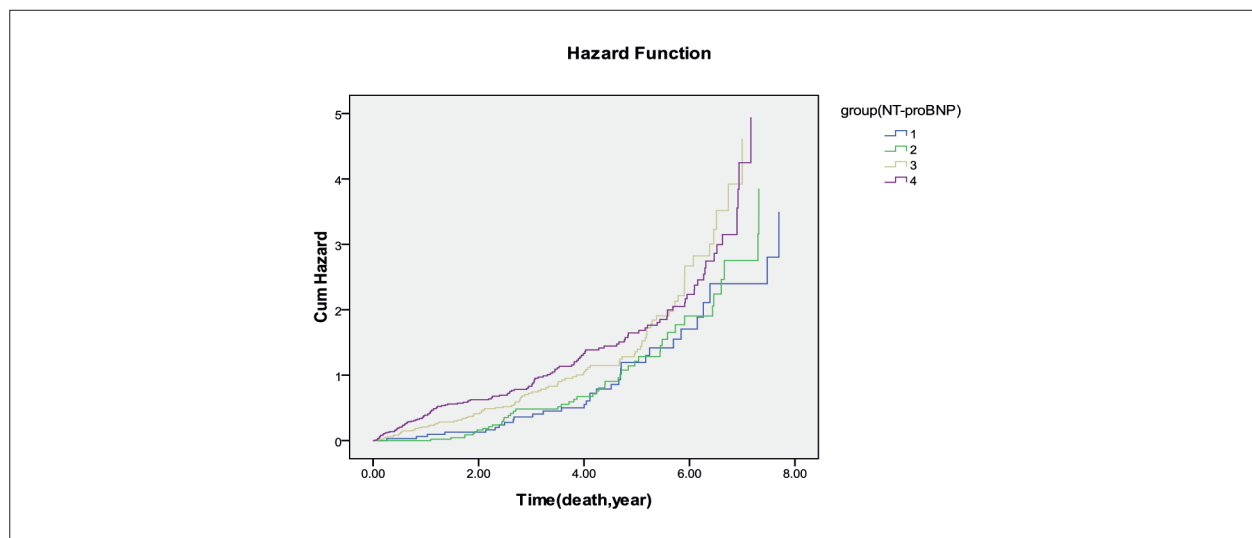
Figure 1 – *Kaplan-Meier curves demonstrating the cumulative incidence of all-cause death in the very elderly with different NT-proBNP levels (quartile 1: <124 pg/mL, quartile 2: 124-271 pg/mL, quartile 3: 271-668 pg/mL, and quartile 4: ≥668 pg/mL). The risk of all-cause mortality was significantly higher in quartile 4 (77.3%) than that in quartile 1 (28.7%) (HR=1.63; 95%CI, 1.005-2.642; p=0.04). Log-rank, p=0.008. Abbreviations: NT-proBNP: N-terminal pro-brain natriuretic peptide; HR: hazard ratio; CI: confidence interval.*

this very elderly population, although the parameters of echocardiography weakened its predictive value. In addition, the risk of 5-year death (77.3%) and 5-year MACE (45.3%) was particularly increased in individuals with plasma NT-proBNP levels ≥668 pg/mL in this study, suggesting that it is possible to have an independent risk assessment with NT-proBNP in the elderly patients.

Many studies have confirmed that NT-proBNP is an important predictive biomarker in different populations,[1] not only in patients with heart failure and other CVDs[14,15] but also in the general population.[2,16] However, in the very elderly, there are limited data on its prognostic predictive value. In the present study, NT-proBNP was an independent predictor of all-cause death and MACE in very elderly patients (≥80 years), which is consistent with results from previous studies.[4] Vaes et al.[4] first reported that NT-proBNP was an independent prognostic factor in the very elderly (≥85 years). However, for that study specific population, a history of CVD was based on different diagnostic standards; not all participants underwent an echocardiography examination.[4] These factors may affect the prognostic value of NT-proBNP.

In the present study, a history of hypertension, CHD, and AF were based on accepted diagnostic standards; all participants underwent an echocardiography examination. NT-proBNP was an independent predictor of all-cause death, MACE and ACS after adjusting for age, gender, and traditional cardiovascular risk factors. Since the prognostic value of NT-proBNP was no longer significantly present after adjusting for echocardiographic parameters (LVEF, LAD and LVMI), our hypothesis is that NT-proBNP measurement and echocardiography findings can complement each other. NT-proBNP measurement is a fast and inexpensive way of

possibly preventing the need for an echocardiogram in case of low values and, on the other hand, it is a better indication for an echocardiogram in cases of the higher NT-proBNP level.

Currently, few studies have discussed the prognostic value of NT-proBNP in the very elderly, and there are no studies about the optimal cut-off value for plasma NT-proBNP levels to predict death or MACE in this population.

In previous studies, the optimal cut-off values differed for different populations,[17,18] which were very high in patients with acute decompensated heart failure[19,20] and <90 pg/ mL in the general population.[16,18] Fu et al.[17] reported that the optimal cut-off value for NT-proBNP to predict death in older Chinese patients with coronary artery disease is 369.5 pg/mL in non-CKD patients and 2,584.1 pg/mL in CKD patients. In this study, the results from the ROC curves indicate that NT-proBNP is a reasonably accurate predictor of all-cause death and MACE. The areas under the ROC curves were 0.71 (95% CI, 0.677–0.752) for all-cause death and 0.58 (95% CI, 0.537–0.626) for MACE. The cut-off value for plasma NT-proBNP levels (406 pg/mL) had a sensitivity of 65% and a specificity of 81% to predict all-cause death, and a sensitivity of 69% and a specificity of 54% to predict MACE. But this value is not suitable as the optimal cut-off value to predict the all-cause death and MACE, because of low specificity and sensitivity. Simultaneously, it was also observed that the individuals at highest quartile (NT-proBNP level≥668pg/mL) had 77.3% risk of death and 45.3% risk of MACE during the follow-up period, significantly higher than the other three groups; this identifies high risk population and it is clinically relevant.

We think it is possible to have an independent risk assessment by assessing NT-proBNP levels in this elderly patients. It was very similar to an increased risk for

Table 3 – Association of plasma NT-proBNP levels with death, MACE, ACS and stroke

HR (95% CI)

	Group 1	Group2	Group 3	Group 4
	(n=181)	(n=180)	(n=182)	(n=181)
All-cause mortality	52(28.7%)	60(33.3%)	101(55.5%)	140(77.3%)
Unadjusted HR	1(control)	1.058(0.729-1.535)	1.301(0.928-1.822)	1.432(1.039-1.974)
Model 1	1(control)	1.073(0.686-1.680)	1.52(1.020-2.265)	1.668(1.137-2.449)
Model 2	1(control)	1.057(0.629-1.777)	1.414(0.864-2.312)	1.583(0.984-2.545)
Model 3	1(control)	0.993(0.583-1.687)	1.391(0.847-2.285)	1.629(1.005-2.642)
Model 4	1(control)	0.934(0.549-1.590)	1.354(0.819-2.236)	1.473(0.884-2.454)
MACE	30(16.6%)	41(22.8%)	49(26.9%)	82(45.3%)
Unadjusted HR	1(control)	0.512(0.309-0.849)	0.516(0.322-0.827)	0.568(0.370-0.874)
Model 1	1(control)	1.020(0.569-1.828)	1.025(0.591-1.778)	1.979(1.193-3.285)
Model 2	1(control)	1.021(0.492-2.118)	0.975(0.508-1.873)	1.748(0.893-3.425)
Model 3	1(control)	0.956(0.446-2.053)	1.071(0.545-2.102)	1.769(1.289-3.531)
Model 4	1(control)	0.799(0.362-1.762)	0.797(0.392-1.621)	1.313(0.621-2.780)
ACS	16(53.3%)	25(61%)	34(69.4%)	62(75.6%)
Unadjusted HR	1(control)	1.55(0.86-2.78)	1.74(0.97-3.10)	2.02(1.33-3.59)
Model 1	1(control)	1.53(0.85-2.76)	1.67(0.93-2.99)	2.01(1.25-3.58
Model 2	1(control)	2.04(0.99-4.17)	1.48(0.72-3.04)	2.12(1.18-4.45)
Model 3	1(control)	1.94(0.94-4.01)	1.39(0.66-2.92)	1.89(1.14-4.08)
Model 4	1(control)	1.67(0.81-3.47)	1.12(0.51-2.44)	1.54(0.87-3.58)
Stroke	12(40%)	11(26.8%)	7(14.3%)	6(7.3%)
Unadjusted HR	1(control)	0.66(0.31-1.37)	0.27(0.11-0.71)	0.39(0.15-1.01)
Model 1	1(control)	0.737(0.35-1.56)	0.25(0.10-0.64)	0.41(0.16-1.08)
Model 2	1(control)	1.36(0.48-3.77)	0.28(0.09-0.84)	0.59(0.17-2.03)
Model 3	1(control)	1.27(0.44-3.68)	0.32(0.12-1.01)	0.73(0.19-2.80)
Model 4	1(control)	1.28(0.40-4.10)	0.34(0.09-1.26)	0.93(0.21-4.23)

Model 1 was adjusted for age and gender. Model 2 was adjusted for the variables in model 1 plus hypertension, DM, AF, CHD, BMI, hemoglobin, plasma albumin, eGFR, LDL-C and HDL-C. Model 3 was adjusted for the variables in model 2 plus cardiovascular drugs. Model 4 was adjusted for the variables in model 3 plus LVEF, LAD and LVMI. NT-proBNP, N-terminal pro-brain natriuretic peptide; ACS: acute coronary syndrome; HR: hazard ratio; CI: confidence interval; CHD: coronary heart disease; HT: hypertension; DM: diabetes mellitus; AF: atrial fibrillation; BMI: body mass index; LDL-C: low density lipoprotein cholesterol; HDL-C: high density lipoprotein-cholesterol; eGFR: estimated glomerular filtration rate; LVEF: left ventricular ejection fraction; LAD: left atrial diameter; LVMI: left ventricular mass index; MACE: major adverse cardiovascular events.

cardiovascular morbidity and mortality observed by van Peet et al.[6] found at the higher tertiles of NT-proBNP levels for men (cut-off level 649pg/mL), as well as at the higher tertiles of NT-proBNP levels for women (cutoff level 519pg/mL). They stated that high levels of NT-proBNP may help clinicians to identify patients who will probably benefit the most from a proactive follow-up, and our results were consistent with theirs.

This study has several limitations. First, only 45 (12.7%) patients died of cardiac causes in this study; most died of multiple-organ failure. Therefore, the predictive value of NT-proBNP for cardiac death was not analyzed in this study. Second, although the results were adjusted for multiple covariates that may be associated with plasma NT-proBNP levels, it is possible that residual confounding factors, such as tumors, pacemaker implantation, and silent myocardial ischemia, may impact the findings. Third, because of the long follow-up period, the primary cardiovascular drugs used may have changed with time and, thus, may not be reflected in the results of this study. Fourth, this study was performed at a single center in China, the population consisted of almost exclusively men, and all patients were hospitalized and very elderly, so the results cannot be applied to a broader population. Fifth, frailty and other physical parameters were not assessed in this study, which may impact the results. Sixth, the analysis of incidences of MACE did not consider a competing risk model with noncardiac death as competing risk, which may have underestimated the prognostic value of NT-proBNP for predicting MACE.

Original Article
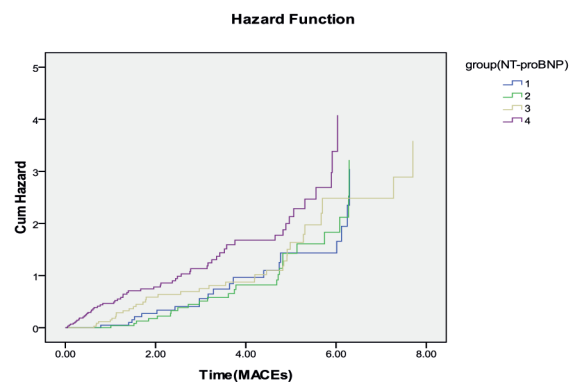
Figure 2 – Kaplan-Meier curves demonstrating the cumulative incidence of MACE in the very elderly with different NT-proBNP levels (quartile 1: <124 pg/mL, quartile 2: 124-271 pg/mL, quartile 3: 271-668 pg/mL, and quartile 4: ≥668 pg/mL). The risk of MACE was significantly higher in quartile 4 (45.3%) than in quartile 1 (16.6%) (HR=1.77; 95%CI, 1.289-3.531; p=0.04). Log-rank, p=0.002. NT-proBNP: N-terminal pro-brain natriuretic peptide; HR: hazard ratio; CI: confidence interval.
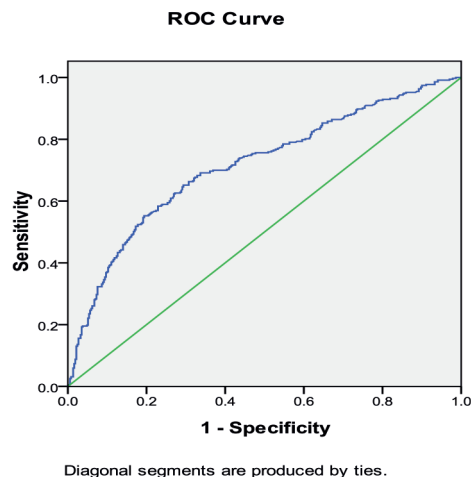
Figure 3 – A ROC curve of NT-proBNP to predict the all-cause death. The AUC was 0.71 (95% CI, 0.677-0.752), p<0.001. ROC: receiver operating characteristic; NT-proBNP: N-terminal pro-brain natriuretic peptide; AUC: area under curve; CI: confidence interval.
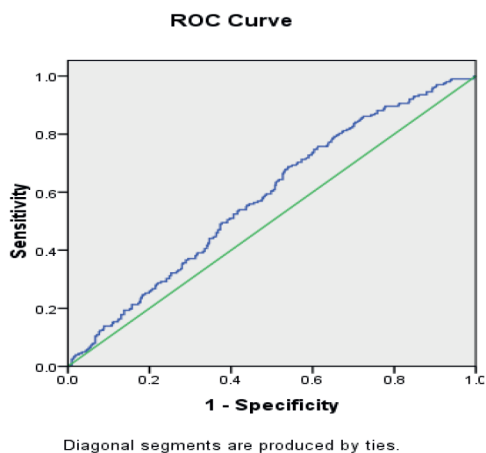
Figure 4 – A ROC curve of NT-proBNP to predict MACE. The AUC was 0.58 (95% CI, 0.537-0.626), p=0.001. ROC: receiver operating characteristic; NT-proBNP: N-terminal pro-brain natriuretic peptide; AUC: area under the curve; CI: confidence interval.

Conclusion

NT-proBNP was identified as an independent predictor of all-cause death and MACE in hospitalized patients older than 80 years of age.

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Author Contributions

Conception and design of the research and Analysis and interpretation of the data: Zhu Q, Gao P, Fu S, Wang H, Bai Y, Luo L, Ye P; Acquisition of data: Zhu Q, Gao P, Wang H; Statistical analysis: Zhu Q, Gao P, Fu S, Bai Y, Ye P; Writing of the manuscript: Zhu Q, Ye P; Critical revision of the manuscript for intellectual contente: Zhu Q, Fu S, Wang H, Bai Y, Luo L, Ye 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.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Chinese PLA General Hospital under the protocol number S2016-056-02. 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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What to Expect from Cardiovascular Life at 85?

Wouter Kok[1]
Amsterdam University Medical Center,[1] Amsterdam - Netherlands
Short Editorial related to the article: Prognostic Value of Plasma NT-proBNP levels in Hospitalized Patients Older than 80 Years of Age in a Hospital in Beijing, China

While there is plenty of literature for risk prediction of cardiovascular disease and preventive therapies,[1] risk estimates are less well known for patients aged > 80 years. There is a need to address this gap in knowledge, as the health status of very elderly people will increasingly impact on health care.[2]

A detailed study carried out in Beijing by Zhu et al., published in this journal, describes the 5-year risk of cardiovascular disease in 724 very elderly Chinese patients - all > 80 years old, most of them men.[3] They were admitted to the geriatric cardiology department, something that is an evolving field at the international level.[4] The reasons for hospital admission were mostly related to coronary artery disease and hypertension control; only a few were admitted for respiratory or digestive tract disease. After a median follow-up of 5.3 years and a follow-up rate of 98%, about 50% of the patients died, most of them from infections and only 1 in 16 patients from a cardiac cause. The study shows that cardiovascular morbidity and all-cause mortality risk in this population can be successfully predicted by the N-terminal pro-B-type natriuretic peptide levels (NT-proBNP).[3]

Predicting all-cause mortality and cardiovascular events with low levels of NT-proBNP has been done in the general population aged 50-89 years,[5] and in the geriatric population >80 years.[6,7] How should we interpret these low levels, and what do they predict? Based on other studies, it seems that lower levels of NT-proBNP not only predict cardiovascular but also non-cardiovascular death.[8] One interpretation may be that variations in NT-proBNP at such low levels are a measure of biological age, reflecting the various interactions with NT-proBNP.[8] There are other measures of vitality, such as frailty scores in elderly patients that also predict CV events, so this concept is not new.[9] Also, in heart failure with preserved ejection fractions we are starting to see that low values of NT-proBNP maintain their predictive value for all-cause mortality, although there is no certainty that the outcomes will be cardiovascular ones.[10] Contrarywise, the finding that much higher levels of NT-proBNP, for example in heart failure, do not always imply a very high or immediate all-cause mortality; this is exemplified in a study of elderly patients aged ≥85 years in whom a range of NT-proBNP levels of 1707- 9729 ng/L was still associated with a 1-year survival of almost 100%, while only patients with levels above this range showed increased mortality.[11] The final risk to be predicted therefore probably depends on distributions of additional risks. Thus, the finding in the study by Zhu et al.,[3] that low levels of NT-proBNP independently predict all-cause mortality is as expected, but it has the catch that most of the mortality was non-cardiovascular, and the documentation that shows that almost every patient had an echocardiogram with preserved ejection fraction.[3]

Therefore it is an interesting finding that also major adverse non-fatal cardiovascular events (MACEs), which have a much higher incidence than cardiovascular mortality, are well predicted by low NT-proBNP levels. In Table 3 the MACEs (n= 202) are shown with an incidence of about 1 in 4 patients (28%) after a median follow-up of 5 years; most events comprise acute coronary syndrome (19% incidence), and somewhat less frequent are cerebral stroke (5% incidence). These incidences of MACE are known to exponentially increase with old age, such as seen in a British population, where people aged > 80 years have a 10-year incidence risk of 50% of cardiovascular disease - a composite of coronary and cerebral events.[12] Because of the high incidence of MACE, identifying elderly patients with intermediate risks of these events would already have implications for prevention, and not only for those with the highest risk of MACE. It also may be interesting to know what the relationship is between cardiovascular morbidity (MACE) and all-cause mortality.

A tempting interpretation of NT-proBNP from Table 1 is that 4 NT-proBNP categories summarize the risks of previous coronary heart disease, hypertension, atrial fibrillation, and decreased renal function, all increasing with higher NT-proBNP levels. The NT-proBNP levels do not appear to reflect diabetes mellitus (equal distribution) or cholesterol levels (decreasing with higher NT-proBNP). However, a risk model would be needed for the actual risk estimates of these factors.

For those interested in preventive therapies, the MACEs in the study by Zhu et al. occurred despite protective medications (70% of patients received antiplatelet agents, 45% statins, 40% ACE inhibitors or ARBs). It would be interesting to assess medication interactions after considering the full range of the risk of CV events (not only in relation to NT-proBNP tertiles).

It can be inferred from the work of Zhu et al. that cardiovascular life at 85 may be predicted by low levels of NT-proBNP, but at the same time, we should acknowledge that this risk assessment should not depend on the cutoff levels of NT-proBNP alone.

Keywords

Cardiovascular Diseases; Risk Factors; Health Services for the Aged; Mortality; Natriuretic Peptide, B-Type.

Mailing Address: Wouter Kok •
Amsterdam Universitair Medisch Central – Cardiology - Meibergdreef 9 Duivendrecht 1115 ZJ - Amsterdam - Netherlands
E-mail: w.e.kok@amc.uva.nl

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Does Advanced Age Reduce the Typicality of Clinical Presentation in Patients with Acute Chest Pain Related to Coronary Artery Disease?

Pedro Henrique Correia Filgueiras,[1] Antônio Maurício Cerqueira Junior,[1] Gabriela Oliveira Bagano,[1] Vitor Calixto de Almeida Correia,[1] Fernanda Oliveira de Andrade Lopes,[1] Thiago Menezes Barbosa de Souza,[1] Leticia Lara Fonseca,[1] Lara Queiroz Kertzman,[1] Yasmin Falcon Lacerda,[1] Marcia Noya Rabelo,[2] Luis Claudio Lemos Correia[1]

Escola Bahiana de Medicina e Saúde Pública (EBMSP),[1] Salvador, BA - Brazil
Hospital São Rafael,[2] Salvador, BA - Brazil

Abstract

Background: According to traditional diagnosis thinking, very elderly individuals are more predisposed to develop atypical symptoms in acute coronary syndromes.

Objective: To test the hypothesis that very elderly individuals are more predisposed to atypical chest pain manifestations due to obstructive coronary artery disease (CAD).

Methods: The Registry of Thoracic Pain includes patients admitted with acute chest pain. Firstly, the typicality index of this clinical manifestation was constructed: the sum of 12 symptom characteristics (8 typical and 4 atypical symptoms). In the subgroup of patients with coronary etiology, the typicality index was compared between octogenarian and non-octogenarian individuals. Statistical significance was defined by $p < 0.05$.

Results: 958 patients were included in the registry, and 486 (51%) had a supposedly coronary etiology. In this group, 59 (12%) octogenarians (age 84 ± 3.5, 50% men) were compared to 427 patients aged <80 (60 ± 12 years, 71% men). The typicality index in octogenarians was 3.42 ± 1.92, which is similar to that of non-octogenarians (3.44 ± 1.74; $p = 0.92$ in univariate analysis and $p = 0.80$ after adjustment for sex by analysis of variance — ANOVA). There was also no statistically significant difference when the sample was divided into median age (62 years; 3.41 ± 1.77 vs. 3.49 ± 1.77; $p = 0.61$). There was no statistically significant linear association between age and typicality index ($r = -0.05$; $p = 0.24$). Logistic regression analysis for prediction of CAD in the general sample of 958 patients showed no interaction of typicality index with numeric age ($p = 0.94$), octogenarians ($p = 0.22$) or age above median ($p = 0.74$).

Conclusion: In patients with acute chest pain of coronary etiology, advanced age does not influence the typical clinical presentation.

Keywords: Elderly; Chest Pain; Acute Coronary Syndrome; Prognosis.

Introduction

Traditional clinical thinking indicates that elderly individuals are predisposed to atypical symptoms in acute coronary syndromes (ACS), a condition that may imply difficult diagnosis and delayed treatment.[1] The plausible mechanisms for atypicality would be cognitive limitations, compromised communication or reduction of pain perception.[2]

However, although this traditional clinical thinking has as a possible physiological basis nociceptive alteration caused by depression and diabetes, which are more prevalent in older individuals, the vast majority of the studies found in the literature are retrospective and with a fairly variable and subjective definition of "pain typicality". Therefore, it is still not clear whether, in fact, old age implies a different clinical presentation in the context of coronary syndromes.[3,4]

Thus, the present study proposes to test the hypothesis that very elderly individuals are more predisposed to atypical manifestations of chest pain of coronary etiology. As a primary analysis, the overall typicality of the clinical manifestation was compared between octogenarians and non-octogenarians in the subsample of patients with coronary etiology. This was followed by the analysis of the interaction between age and pain typicality in the prediction of coronary etiology in the sample of all etiologies of thoracic pain.

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Methods

Sample selection

The Registry of Chest Pain is a sample of patients consecutively admitted to the Coronary Unit of a tertiary hospital from September 2011 to December 2017, primarily for chest discomfort, regardless of electrocardiographic abnormalities, necrosis markers or any other complementary examination showing the cause of the symptom.

The selected sample aims to represent the target population of patients admitted to the coronary unit due to chest pain. Thus, all patients admitted during the study period were included in the study, with no subsample selection in this population. Admission to the coronary care unit was not influenced by the study protocol. The diagnostic probability was established at the discretion of the attending physicians.

The study is in accordance with the ethical standards of resolution 510/2016 from the Ministry of Health, was approved by the Committee of Ethics in Hospital Research, and all subjects signed a free and informed consent.

Characterization of thoracic discomfort

Upon admission, information about the clinical presentation of chest discomfort was collected through a parameterized interview. This interview was done in a systematized way by trained investigators to avoid inducing patients' responses and to focus on the reproducibility of the method. The interview was parameterized to require objective yes/no answers. When the patient expressed doubt, the symptom was considered absent.

Twelve symptom characteristics were evaluated, including 8 characteristics known as typical of angina (precordial pain, compressive aspect, irradiation to the left upper limb, irradiation to the neck, intensity classified by the patient as severe, discomfort on the previous days, presence of vagal symptoms, administration of sublingual medication followed by improvement of the symptom) and 4 characteristics considered atypical (change of pain according to the position, change with palpation of the site, change with movement of the arm and change with breathing).

Symptom typicality index

In order to quantify the overall typicality of the clinical manifestation, 1 point was assigned to each typical characteristic and 1 point was subtracted for each atypical characteristic (variation from -4 to +8, proportional to typicality).

Definition of symptom etiology

For the diagnostic evaluation, the patients were submitted to invasive coronary angiography or non-invasive provocative test (nuclear perfusion magnetic resonance imaging and single-photon emission computed tomography or dobutamine stress echocardiography), at the discretion of the attending cardiologist. For positive noninvasive tests, the patients had an angiography done for confirmation. Based on this diagnostic algorithm, obstructive coronary artery disease (OCAD) was defined as stenosis ≥70% at angiography. Coronary angiography without obstructive lesion or normal noninvasive test (ischemic defect size <5% of left ventricular myocardium) indicated the absence of OCAD.

Data analysis

Normality of numeric variables was tested by histogram, comparing mean and median, and mainly considering the level of kurtosis and skewness <3. Very elderly individuals were defined as age ≥80 years (octogenarians). Primary analysis was performed on the sample of patients with obstructive coronary disease, comparing the typicality index between octogenarians and non-octogenarians. In addition, each symptom characteristic was compared between the two groups. Numerical variables were expressed as mean and standard deviation, compared between the two groups by Student's unpaired t-test. Categorical variables were expressed in proportions and compared using Pearson's chi-squared test. Analysis of variance was done to compare the typicality index between groups after adjustment for gender. A linear association between typicality index and age was tested by Pearson's correlation coefficient, based on a normal distribution of both variables. Multiple comparison was adjusted using the Bonferroni method.

Then, the total sample of the registry (all patients admitted with acute chest pain, with and without coronary artery disease) was used and we evaluated the predictive capacity of the typicality index for obstructive coronary artery disease based on the area under the Receiver Operator Characteristic (ROC) curve. Next, we evaluated the age-modifying effect on the diagnostic accuracy (OCAD) of the overall pain typicality, in terms of interaction vs. age typicality in logistic regression, with age being inserted in three different ways: as a numerical variable, categorized into two groups (octogenarians or non-octogenarians) and categorized into two groups from the sample median. The software SPSS Version 23 was used. Statistical significance was defined as a two-tailed p value smaller than 0.05.

Sample size calculation

As for the sample size calculation, this was a study conducted on a previously existing sample as part of the Chest Pain Registry, a prospective collection of patients hospitalized for chest pain. This registry is used for various analyses and, in our methodology, before deciding to test any hypothesis, we evaluated the statistical power, which depends on the behavior of the variable in question. Thus, as the data had already been collected, we could use the standard deviation of the sample that would be used to evaluated whether the sample size was powered enough, an essential criterion to allow data analysis in our protocol.

Thus, sample size was defined first, based on the distribution of the typicality index in the coronary disease sample. Considering a standard deviation of 1.7, it would be necessary for 36 octogenarians and 109 non-octogenarians to offer 80% power in detecting a 30% difference in the typical index by the Student's t test.

Results

Sample characteristics

Between September 2011 and December 2017, 958 individuals were included in the registry, and 486 (51%) had a supposedly coronary etiology. In this group, 59 octogenarians were compared to 427 non-octogenarians. The mean age of the octogenarians was 85±3.4 years, including 56% men, compared to 60±12 years, including 71% men, in the non-octogenarian group (p<0.001). Octogenarian patients had a higher prevalence of clinically manifested left ventricular dysfunction (24% versus 8.7%, p<0.001), triple vessel disease or left main coronary artery (41% versus 26%, p=0.01) and a lower prevalence of ST segment elevation acute myocardial infarction (25% versus 30%, p<0.001). Mortality was higher in the older group (14% versus 2.1%, p<0.001). The variables compared between the two groups are described in Table 1.

Age and typicality of symptoms

The typicality index of very elderly patients was 3.42±1.92, which is similar to that observed in younger individuals (3.44±1.74; p=0.92). Comparison of the typicality index remained non-significant (p=0.80) after adjusting for the gender difference between the groups (Figure 1).

There was no difference in the typicality index when the sample was divided into median age (62 years), being 3.41±1.77 versus 3.49±1.77 (p=0.61). Likewise, there was no correlation between typical index and age (r=- 0.05, p=0.24) (Figure 2).

The comparison between the 12 pain characteristics between octogenarians and non-octogenarians showed no significant difference after Bonferroni adjustment (Table 2).

Age-modifying effect on predictive capacity of pain typicality

Analyzing the 958 patients in the registry, the typicality index presented an area under the ROC curve of 0.62 (95% CI = 0.58–0.65) for prediction of obstructive coronary artery disease. The logistic regression analysis showed no interaction of typicality index with numerical age (p=0.94), octogenarians (p=0.22) or age above the median of 62 years (p=0.74) (Figure 3).

Discussion

The present study demonstrates that advanced age has no influence on the clinical presentation typicality in the context of acute coronary syndromes. In addition, the diagnostic value of the clinical manifestation is not influenced by age. As shown, even analyzing "old age" from various perspectives (dividing the sample between octogenarians and non-octogenarians, median age, 62 years, and still placing age as a continuous variable), none of the analyses suggested influence.

The use of a "typicality index" allowed us to analyze overall pain typology, information complemented by the individual analysis of each characteristic. The so-called "index" is just the count of suggested symptoms minus unsuggested symptoms, a way to treat typicality as a numerical variable, avoiding the subjectivity of categorization in a typical or atypical clinical picture.

Another important point of this study is that, for the definition of OCAD, we used coronary angiography, the gold standard exam, which implies a low risk of calibration bias.

Previous studies that sought to study pain in older individuals with acute coronary syndrome showed controversial results.[2,3,5] It is found that in most of these studies the collection of pain characteristics was done retrospectively and from databases developed with other primary objectives.

Table 1 – Clinical characteristics and comorbidities

	Age <80 (n=427)	Age ≥80 (n=59)	p value
Age (years)	60±12	85±3.4	<0.001
Male	302 (71%)	33 (56%)	0.02
ECG ischemia	279 (67%)	37 (65%)	0.80
Positive troponin	274 (65%)	49 (83%)	0.005
ST-segment elevation infarction	127 (30%)	15 (25%)	<0.001
Diabetes mellitus	161 (38%)	27 (46%)	0.23
Creatinine (mg/dl)	1.0±0.69	1.1±0.43	0.12
Systolic blood pressure (mmHg)	154±31	153±36	0.08
Heart rate (bpm)	78±18	76±19	0.17
Previous coronary disease	139 (33%)	24 (41%)	0.22
Previous myocardial revascularization	37 (8.7%)	7 (12%)	0.40
Severe anatomical pattern*	80 (26%)	16 (41%)	0.01

Catheterism with obstruction ≥70%; ECG: electrocardiogram.

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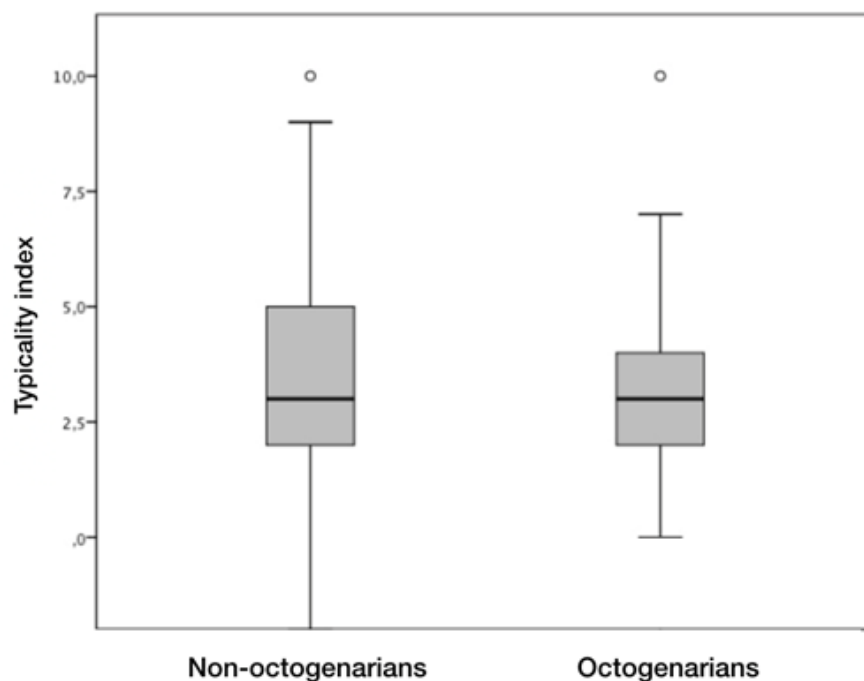
Figure 1 – *Boxplot of the typicality index for the octogenarian and non-octogenarian groups (p=0.92).*
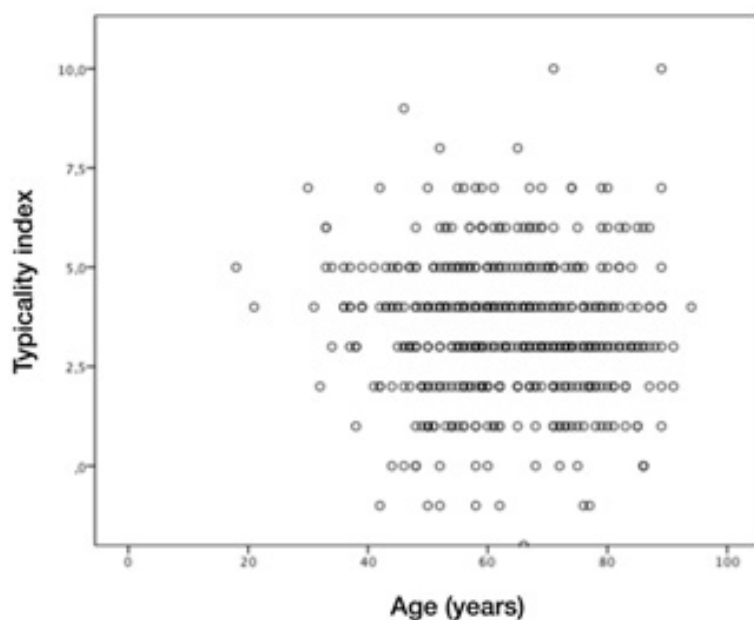
Figure 2 – *Scatter plot of typical index and age.*

In 2001, Mehta et al.,[1] through a registry of Medicare beneficiaries in the USA, selected patients diagnosed of acute myocardial infarction and stratified the sample on the basis of age.[1] In their study, the authors conclude that the initial presentation of chest pain decreased as the age increased. However, they do not show whether there is a statistical difference between the values, which makes this conclusion misleading.
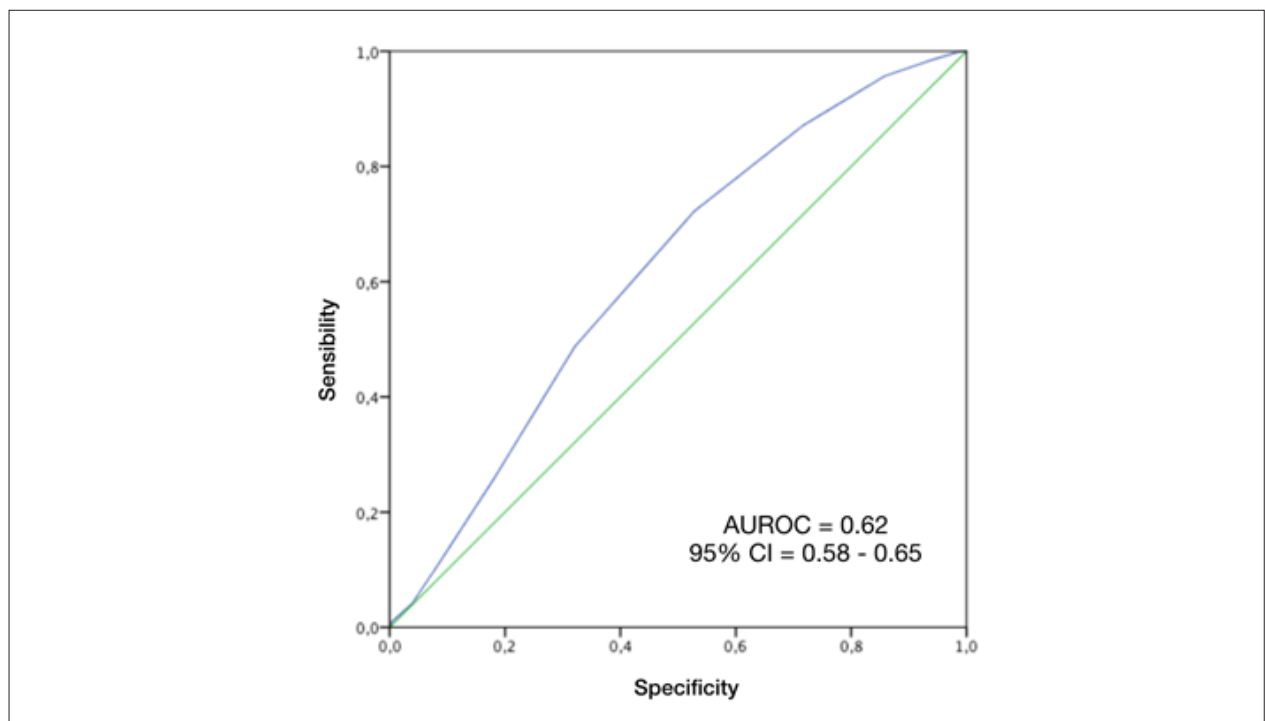
Figure 3 – *C-statistics of typicality index for prediction of obstructive coronary artery disease, considering all patients in the registry (958), ROC curve: 0.62 (95% CI = 0.58–0.65).*

Table 2 – Characteristics of thoracic pain

	Age ≥80	Age <80	p value	Adjusted p value (Bonferroni)
Precordial pain	348 (82%)	48 (81%)	0.98	--
Compressive	241 (56%)	28 (48%)	0.19	--
Irradiation to upper left limb	167 (39%)	19 (32%)	0.02	0.24
Irradiation to the neck	110 (26%)	8 (14%)	0.04	0.48
Severe intensity	253 (60%)	39 (66%)	0.33	--
Discomfort on previous days	67 (48%)	14 (67%)	0.10	--
Vagal symptoms	215 (50%)	32 (54%)	0.58	--
Improvement with nitrate	182 (43%)	18 (31%)	0.08	--
Changes with position	70 (16%)	7 (12%)	0.37	--
Changes with palpation	26 (6.1%)	2 (3.4%)	0.40	--
Changes with arm movement	29 (6.8%)	3 (5.1%)	0.62	--
Pleuritic pain	51 (12%)	5 (8.5%)	0.43	--

In a post-hoc analysis of the Internet Tracking Registry for Acute Coronary Syndromes (i*trACS), Han et al.[3] analyzed the clinical presentation in patients with ACS from two groups: age ≥75 years and <75 years. They classified "typical presentation" as thoracic pain in crushing, compression or pressure, and concluded that only in the group of younger patients (age <75 years) the typical presentation was associated with the diagnosis of ACS. In addition to the simplistic definition of "typical presentation," the authors did not compare the two age groups diagnosed with ACS.

In another post-hoc analysis, from the Gulf Registry of Acute Coronary Events (Gulf RACE), El-Menyar et al.[5] classified into three categories: typical, atypical and dyspnea, and found no age difference in the "typical" (55±12) and "atypical" (57 ± 13) presentation groups. However, the authors attribute rather broad characteristics as being "typical": "irradiation to the arm, shoulder, back, neck, jaw, epigastrium or other sites" which makes this classification subjective.

We must recognize that despite satisfying the sample size calculation, our population of very elderly patients

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was small. In addition, our study was carried out in only one center and in a selected population, thus, the development of new studies in this context is necessary. We also recognize that this study was carried out in a tertiary hospital environment, so we must be careful when extrapolating its results to the primary care environment. Our population of greatest interest is that of patients admitted to the coronary care unit, a population where the challenge of diagnostic discrimination is greater, because there is greater homogeneity of symptoms (gray zone of probability). This being our target population, there was no selection bias. Finally, there is a plethora of possibilities and combinations of symptoms to be included in an analysis such as this. But here, we are not trying to create a predictor score for the etiology of pain; we are just comparing the very elderly and not very elderly regarding the "typicality load." Regardless of whether we contemplate all possible symptoms, the hypothesis test for the "typicality load" is not compromised. We are just assessing whether there is a symptom gradient between these two groups.

Conclusion

In patients with chest pain of coronary etiology, advanced age does not seem to influence the typical clinical presentation, suggesting that symptoms should be interpreted regardless of age.

Author Contributions

Conception and design of the research: Filgueiras PHC, Cerqueira Junior AM, Lopes FOA, Correia LCL; Acquisition of data: Filgueiras PHC, Cerqueira Junior AM, Bagano GO, Correia VCA, Souza TMB, Fonseca LL, Kertzman LQ, Lacerda YF, Rabelo MN, Lopes FOA; Analysis and interpretation of the data: Filgueiras PHC, Cerqueira Junior AM, Bagano GO, Correia VCA, Souza TMB, Rabelo MN, Lopes FOA; Statistical analysis: Filgueiras PHC, Cerqueira Junior AM, Bagano GO, Correia VCA, Fonseca LL, Kertzman LQ, Lacerda YF, Correia LCL, Lopes FOA; Critical revision of the manuscript for intellectual contente: Filgueiras PHC, Cerqueira Junior AM, Bagano GO, Correia VCA, Souza TMB, Fonseca LL, Kertzman LQ, Lacerda YF, Rabelo MN, Correia LCL, Lopes FOA.

Potential Conflict of Interest

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

Sources of Funding

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Study Association

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Precordial Pain and Infarction in the Elderly. It´S no so Elementary, My Dear Watson!

Ricardo Wang,[1,2] *José Carlos da Costa Zanon,[3]* *Fernando Carvalho Neuschwander[1]*

Instituto Orizonti,[1] Belo Horizonte, MG - Brazil
Hospital UNIMEDBH,[2] Belo Horizonte, MG - Brazil
Universidade Federal de Ouro Preto,[3] Ouro Preto, MG - Brazil
Short Editorial related to the article: Does Advanced Age Reduce the Typicality of Clinical Presentation in Patients with Acute Chest Pain Related to Coronary Artery Disease?

In Medical School, we learn the traditional way to conduct the investigative process in order to reach a diagnosis. This process is traditionally based on the collection of anamnesis and clinical exams, clinical reasoning, the generation of a hypothesis, and tests with complementary exams. In general, we follow the the Occam's razor principle: "the simplest answer is usually the correct answer," or as William Osler's aphorism: "Where you hear hoofs, you don´t think of zebras". However, in this investigative process, the clinical reasoning is challenged in an elderly population over 80 years of age, and not always is the simplest answer the most correct. In this age group, the presence of comorbidities is quite common and can interfere, changing the perception of cardiovascular symptoms (depression, dementia, medications that interfere in the central nervous system, diabetes, analgesics, etc.), or even modify the symptomatology. The presence of atypical symptoms, such as dyspnea, sudoresis, vomiting, diarrhea, epigastric pain, and mental confusion can all mask the cardiovascular pathology.[1,2]

Many studies have shown the difficulty in diagnosing acute myocardial infarction (AMI) in this population, which clearly entails delays in or the lack of treatment. Even when the diagnosis and early treatment of AMI is established, the mortality rate remains high in this population. The under-treatment or lack of treatment contribute to the increase in mortality in this age group.[2-4] Understanding the factors that make the diagnosis difficult is of utmost importance in establishing protocols directed toward the older age elderly patient.

It is expected that doctors will apply the analytical method and methodology in the investigative process, but this not what happens in practice. There are other factors that influence the diagnostic process. Among these are cognitive factors, first described by Kahneman and Tversky[5] (winner of the Nobel Prize for economy), which are described as mental, intuitive shortcuts to reach the result (diagnosis)

quickly. This method is subjective, is highly influenced by emotional factors, and has a high risk for error.[6] For patients who receive medical care at emergency clinics complaining of precordial pain, it is even intuitive to discard AMI. Applying well-established protocols for patients with precordial pain, we can attain a high diagnostic accuracy for Acute Coronary Syndrome (ACS). However, the presence of atypical symptomatology opens the door to diagnostic possibilities,[7] and there is the need for a systematized care to reach the proper diagnosis. The application of these mental shortcuts, be they due to urgency, work overload (common in the emergency care sector), stress, or gaps in the formation and training in medical care embracement, often leads to a decline in diagnostic accuracy.

In the impressive study conducted by Filgueiras et al.,[8] what stands out is the need for a 6-year data collection to obtain an adequate sample of elderly patients over 80 years of age (which shows the difficulty to study this population subgroup). Their study was conducted at a tertiary center (Coronary Care Unit - CCU), where the patients had been previously triaged in the emergency departament, the sector where most incorrect diagnoses occur. It was possible to observe, from the data presented, that 83% of the elderly population presented positive troponin, while 41% presented obstructive lesions observed in the coronarography, suggesting that the elderly patients with typical symptoms, and associated with markers of myocardial necrosis, had a higher chance of being admitted to the CU. In this sample, the selection bias can constitute a problem for the external validity of the obtained data.

It is important to note that the description of the comorbidities was missing, as was another a highly relevant theme, the degree of fragility of the studied population. It is very common for doctors not to apply the complete treatment for AMI, be it due to the low life expectancy or to the risk of complications, such as bleeding. Therefore, this group has a lower chance of being referred to the CU.

In this study, although the very elderly patients presented typical symptoms, when compared to younger patients (typicality index 3.41 ± 1.77 x 3.49 ± 1,77; p=0.61),the result runs in direct contrast with findings from Brieger,[4] in which the prevalence of atypical symptoms was of 14% in patients over 75, and only 5% if < 65 years of age. Of the patients with atypical symptoms, only 60% received the proper diagnosis of ACS.[4] Moreover, the analysis of the atypical symptoms would be essential in order to understand factors that contribute to the diagnostic

Palavras-chave

Chest Pain; Angina Pectoris; Aged; Aging; Myocardial Infarction/diagnosis; Acute Coronary Syndrome/diagnosis.

Mailing Address: Ricardo Wang •
Avenida José Patrocínio Pontes, 1355. Postal Code 30210-090, Mangabeiras, Belo Horizonte, MG - Brazil
E-mail: rwang@terra.com.br

difficulty and the keys to the diagnosis. In addition to the study of the symptoms, another essential aspect is the analysis of the medical investigative process: the manner in which the information is collected, the collection of information with caregiver, the time spent, the manner in which the information is processed, and the complementary methods used.

In sum, although most of the patients presented typical symptoms, associated with an increase in myocardial necrosis markers, very elderly patients with atypical symptoms still represent a challenge for doctors and, under these conditions, the investigative and systematic medical art must be applied. Furthermore, there is still a lack of specific protocols for this population.

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Original Article

Kidney Injury Molecule-1 Is Associated with Contrast-Induced Nephropathy in Elderly Patients with Non-STEMI

Mustafa Ahmet Huyut[1]

Yeni Yuzyil University, Faculty of Medicine, Department of Cardiology,[1] Istanbul - Turkey

Abstract

Background: Contrast-induced nephropathy (CIN) is associated with an increased risk of major adverse cardiovascular events (MACE), and the association between CIN and oxidative mechanisms is well documented.

Objective: This study aimed to evaluate the relationship between serum levels of kidney injury molecule-1 (KIM-1) and CIN in elderly patients with non-ST-segment elevation myocardial infarction (NSTEMI).

Methods: This study included a total of 758 patients with NSTEMI, who underwent percutaneous coronary intervention (PCI); 15 developed CIN after PCI, and another 104 were the control group, matched for age > 65 years. Baseline to 48-to-72-hour laboratory values and clinical outcomes were recorded. Patients were followed during one year. P values of < 0.05 were considered significant.

Results: CIN was observed in 12.60% of the patients. Serum KIM-1 was significantly higher in the CIN group than in the non-CIN group (14.02 [9.53 – 19.90] vs. 5.41 [3.41 – 9.03], p < 0.001). The Mehran score was significantly higher in the CIN group than in the non-CIN group (14 [5 – 22] vs. 5 [2 – 7], p = 0.001). MACE were significantly higher in the CIN group than in the non-CIN group (7 [46.70%] vs. 12 [11.50%], p = 0.001). Multivariate logistic regression analysis showed that baseline KIM-1 level (OR = 1.652, 95% CI: 1.20 – 2.27, p = 0.002) and Mehran score (OR = 1.457, 95% CI: 1.01 – 2.08, p = 0.039) were independent predictors of CIN in elderly patients with NSTEMI.

Conclusion: Baseline serum KIM-1 concentration and Mehran score are independent predictors of CIN in elderly patients with NSTEMI. Additionally, all-cause mortality, cardiovascular death, myocardial reinfarction, stroke, and MACE were significantly higher in the CIN group at one-year follow-up.

Keywords: Kidney Diseases/chemically Induced; Myocardial Infarction SST; Percutaneos Coronary Intervention.

Introduction

Contrast-induced nephropathy (CIN) is associated with increased morbidity, mortality, and increased hospitalizations, due to the application of intravenous or intra-arterial contrast media (CM) during diagnostic or therapeutic vascular procedures.[1] The incidence of CIN often varies depending on the populations studied and their related comorbidities.[2] The underlying mechanisms of CIN include endothelial dysfunction, inflammation, vasoconstriction, tubular cell toxicity, free radical injury, reactive oxygen species and oxidative stress, and activation of neutrophils and platelets, which cause the release of oxygen-free radicals, proteolytic enzymes, and proinflammatory mediators that can cause tissue and endothelial damage, particularly in critically injured

myocytes.[3,4] Uric acid, red cell distribution width, the platelet-to-lymphocyte ratio, and the neutrophil-to-lymphocyte ratio have been correlated with CIN in previous studies.[5,6] Kidney injury molecule-1 (KIM-1) has been related to both the occurrence and severity of acute kidney injury and chronic kidney disease.[7] KIM-1 is a type-1 transmembrane protein, expressed according to the injury in the proximal tubule of the apical membrane.[8] Cardiovascular disease has a strong link with acute kidney injury and chronic kidney disease, and cardiovascular events have been reported to be associated with acute kidney injury.[9] KIM-1 serves as a pro-inflammatory agent with cell-adhesive functions.[7] In the literature, there are some published studies regarding the relationship between KIM-1[10,11] and Mehran scores[12,13] in the development of CIN, but previous studies did not mention which one is the best predictor. Additionally, the previous studies did not make a comparison between KIM-1 and Mehran score for predicting the development of CIN among elderly patients.

We hypothesized that KIM-1 expression is induced in elderly patients with non-ST-segment elevation myocardial infarction (NSTEMI) and is related to CIN due to the pro-inflammatory response and that proximal tubular endothelial damage occurs in this manner. The association between KIM-1 protein levels and CIN in elderly patients with NSTEMI has

not yet been addressed in the literature. Understanding which biologic pathways and markers are associated with CIN may allow for the design of future studies to explore the mechanistic link between these pathways and to evaluate the efficacy of interventions designed to reduce the burden of cardiovascular disease and CIN in these patients. For this reason, this study aimed to evaluate the relationship between baseline serum KIM-1 protein levels and CIN in elderly patients with NSTEMI.

Methods

This study was prospectively conducted between July 2016 and July 2018 at Bezmialem Vakif University Hospital. We enrolled 758 patients who were diagnosed with NSTEMI and who underwent early PCI within 24 hours of the onset of symptoms (Figure 1). Patients with < 65 years (n = 474), coronary artery bypass graft (n = 47), signs of acute left ventricular dysfunction (n = 20), cardiogenic shock (n = 5), pulmonary edema (n = 8), stent thrombosis (n = 4), acute or chronic infective or neoplastic disease (n = 6), moderate to severe chronic kidney disease (n = 36), and chronic liver disease (n = 2) were excluded from this study (n = 602). During the follow-up we could not reach 37 patients. Finally, we concluded with 119 eligible patients; 15 patients

developed CIN after PCI, and 104 patients served as the control group, matched for age > 65 years (Figure 1). CIN was characterized as an absolute increase of 0.50 mg/dL in the level of serum creatinine above baseline or ≥ 25% relative increase in the levels of basal serum creatinine within 48 to 72 hours of CM exposure.[14] The study patients, who were ≥ 65 years old, were divided into two groups, the CIN group (n = 15) and the non-CIN group (n = 104). For all patients, medical history, hospital records, baseline to 48-to-72-hour laboratory values, and clinical findings were reviewed by the same two interventional cardiologists. Cardiovascular risk factors were identified, including age, sex, diabetes mellitus, hypertension, hyperlipidemia, and smoking status. Patients with prior antihypertensive therapy or blood pressure of approximately 140/90 mmHg, measured at least twice, were accepted as having hypertension.[15] Patients previously treated with oral antidiabetic and/or insulin therapy and patients whose fasting blood glucose was at least twice as high as 125 mg/dL were accepted as having diabetes mellitus.[16] The presence of hyperlipidemia was considered when a measure of total cholesterol > 200 mg/dL or low-density lipoprotein cholesterol > 100 mg/dL was obtained, or when the patient used a lipid-lowering medication by the provisions of the Adult Treatment Panel III.[17] Patients who were using tobacco
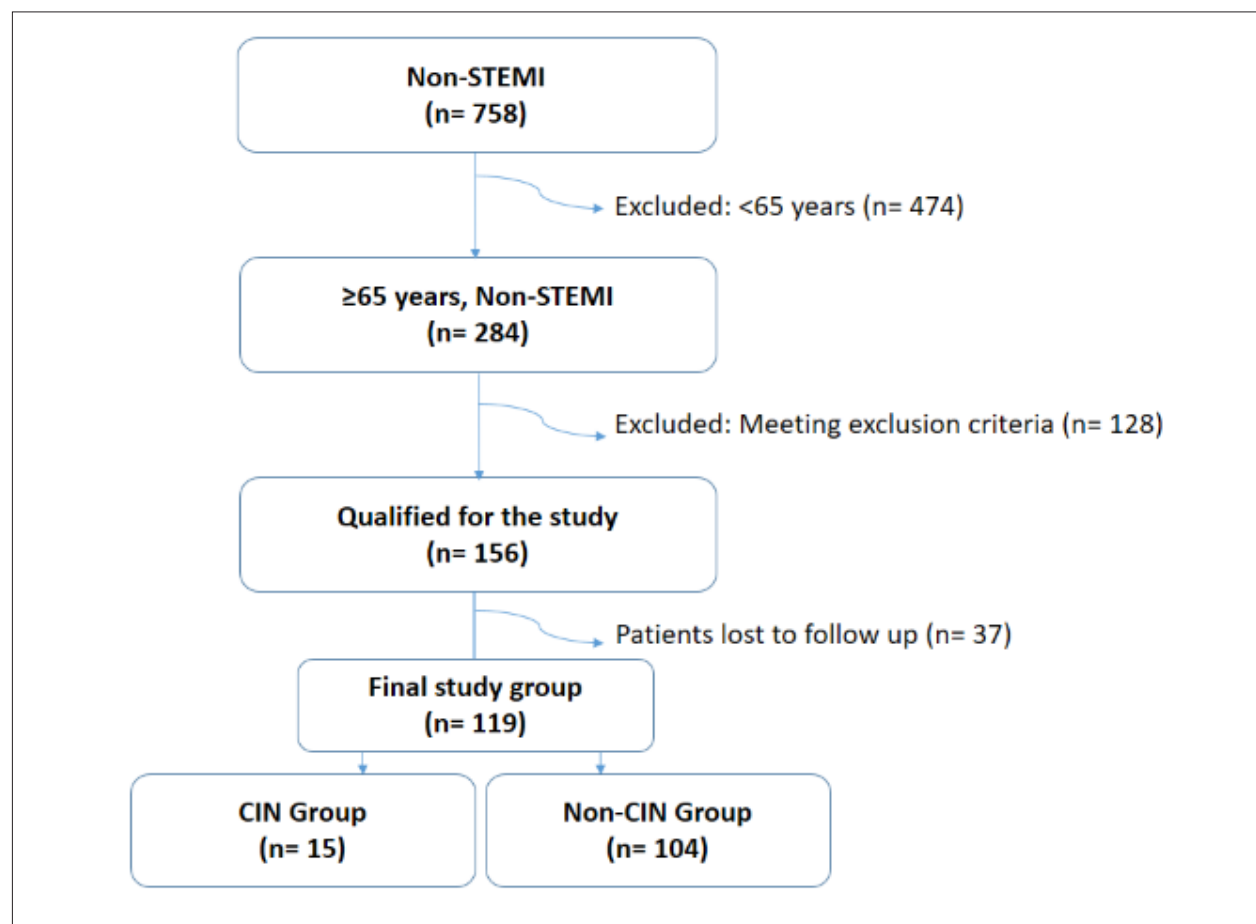
Figure 1 – *Selection of the study groups.*

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on admission to the emergency service and those who had been ex-smokers in the past month were considered smokers. The Mehran score, which was reported by Mehran et al.[1] in 2004, includes hypotension (5 points, if systolic blood pressure is < 80 mmHg for at least 1 hour, requiring inotropic support), use of intra-aortic balloon pump (5 points), congestive heart failure (5 points, if New York Heart Association [NYHA] class III/IV or history of pulmonary edema), age (4 points, if > 75 years), anemia (3 points if hematocrit < 39% for men and < 36% for women), diabetes mellitus (3 points), CM volume (1 point per 100 mL), and estimated glomerular filtration rate (eGFR) (2 points if GFR 60 to 40, 4 points if GFR 40 to 20, 6 points if GFR < 20). Scores of ≤ 5, 6 to 10, 11 to 15, and >15 indicate 7.5%, 14%, 26%, and 57% risk for CIN, respectively.

Venous blood samples from the antecubital vein were taken immediately after admission to the hospital, before PCI. A 12-lead electrocardiogram and blood pressure were obtained at the time of admission to the emergency department. The eGFR of each patient was calculated using the Cockcroft-Gault equation.[18] Body mass index was calculated with the formula weight (kg)/ height² (m²). Routine blood chemistry, lipid parameters, and peak cardiac troponin-I were measured with a standard auto-analyzer. Blood counts were measured with a Sysmex K-1000 (Block Scientific, Bohemia, NY, USA) auto-analyzer. Samples were centrifuged at 3000 rpm for 10 minutes, and the supernatant and serum were separated from the samples. Subsequently, they were frozen at −80 °C until further analysis. Serum creatinine levels measurement was repeated at 48 to 72 hours after CM administration.

The diagnosis of NSTEMI was made in the presence of the following characteristics based on definitions from clinical practice guidelines.[19] NSTEMI patients had typical chest pain or discomfort occurring at rest or minimal exertion for at least 10 minutes and the initial electrocardiogram showed normal or ischemic changes such as ST depressions or T-wave inversions, with elevated cardiac troponin-I level, with at least 1 value above the 99th percentile upper reference limit.

Coronary angiography procedures were conducted via the femoral approach using the Philips (Optimus 200 DCA and Integris Allura 9, Philips Medical Systems, Eindhoven, Netherlands) angiography system. A total of 300 mg acetylsalicylic acid and a loading dose of clopidogrel (600 mg) and UF heparin (100 mg/kg) were administered during PCI in all patients. Coronary angiography and PCI were conducted using nonionic, iso-osmolar CM (iodixanol, Visipaque 320 mg/100 mL, GE Healthcare, Cork, Ireland) according to standard clinical practice. PCI of the infarct-related artery was performed and CM volume was noted. At least two expert cardiologists examined coronary anatomy. A hydration protocol was used with 1,000 mL of intravenous (IV) isotonic saline infusion starting 12 hours before the procedure, and after the procedure, all patients received IV hydration with isotonic saline (1 mL/kg/h) for at least 12 hours.

Before discharge, each patient underwent transthoracic echocardiographic examination with a 3.5-MHz transducer (Vivid 7 GE Medical System, Horten, Norway), and left ventricular ejection fraction (LVEF) was calculated by two-dimensional echocardiography with the M-mode measurements of left ventricular end-diastolic and end-systolic diameters. Follow-up information was obtained from hospital records; admission to the hospital; and 1, 3, 6, and 12 months of patient visit data, by the same investigators.

The endpoints of this analysis were derived through hospital records and death certificates, or communication with patient families by telephone. Major adverse cardiovascular events (MACE) were defined as all-cause mortality, cardiovascular death, stroke, and myocardial re-infarction. All participants gave written informed consent before participation, and the study was approved by the local ethics committee (Number:7/71-04/04/17). Furthermore, the study was conducted in accordance with the provisions of the Helsinki Declaration.

Statistical Analysis

Data analyses were performed using SPSS version 22.0 statistical software package (SPSS Inc., Chicago, IL, USA). The normal distribution of a continuous variable was assessed using the Kolmogorov-Smirnov test. The independent samples t test or the Mann-Whitney U test was used to compare continuous variables depending on whether statistical assumptions were fulfilled or not. Continuous variables were expressed as mean and standard deviation if normally distributed, or median and 25th and 75th percentiles if they did not satisfy the normal assumption. Categorical variables were expressed as number (percentage). The chi-square test was used to compare categorical variables. The correlation between variables was performed using Spearman's rank-order correlation analysis. The Kaplan-Meier method was used to estimate event-free survival rates. Univariate logistic regression analysis was performed, and the variables that were found to be statistically significant ($p < 0.1$) were analyzed with multivariate logistic regression analysis. The odds ratio and 95% confidence interval of each independent variable were calculated. Receiver operating characteristic curve analysis was performed to determine the predictive value of KIM-1 and Mehran score for CIN. Two-tailed p values of < 0.05 were considered significant.

Results

In this study, we initially included 758 patients with NSTEMI, and we concluded with 119 eligible patients (79 male; mean age: 69.96 ± 5.67 years). In this study, CIN was observed in 12.60% (n = 15). Demographic and laboratory findings are described in Table 1. Clinical follow-up findings are described in Table 2. Hematocrit, LVEF, creatinine, uric acid, and Mehran score were significantly associated with eGFR ($p < 0.05$) (Table 3). We did not identify any patients with hemorrhagic stroke or patients requiring dialysis during follow-up. Kaplan-Meier estimates for MACE (Figure 2A), all-cause mortality (Figure 2B), myocardial reinfarction (Figure 2C), and stroke rates (Figure 2D) are described in Figure 2. Multivariate logistic regression analysis showed that baseline KIM-1 level (OR = 1.652, 95% CI: 1.20 – 2.27, p = 0.002) and Mehran score (OR = 1.457, 95% CI: 1.01 – 2.08, p = 0.039) were independent predictors of CIN in elderly patients with NSTEMI.

Table 1 – Baseline and laboratory characteristics of the patients

Variable, n (%)	CIN, n=15 (12.60)	Non-CIN, n=104 (87.40)	p value
Age, years	70.13±6.68	69.93±5.55	0.613
Male sex, n (%)	13 (86.70)	66 (63.50)	0.075
BMI, kg/m²	29.67±4.75	28.66±4.80	0.347
HT, n (%)	12 (80)	65 (62.50)	0.185
DM, n (%)	11 (73.30)	38 (36.50)	0.007
HL, n (%)	11 (73.30)	36 (34.60)	0.004
Smoking, n (%)	11 (73.30)	57 (54.80)	0.175
Family history, n (%)	4 (26.70)	38 (36.50)	0.455
LVEF, %	45±7.07	52.29±7.11	0.001
KIM-1, ng/mL	14.02 (9.53-19.90)	5.41 (3.41-9.03)	<0.001
Glucose, mg/dl	145 (108-252)	113.50 (96-163.75)	0.011
Uric acid, mg/dl	8 (6.70-8.70)	5.45 (4.20-6.65)	<0.001
Creatinine, mg/dl	1.20 (0.80-1.50)	0.87 (0.72-1.06)	0.003
eGFR, mL/min	57.79 (43.56-97)	82.85 (67.25-97.87)	0.017
Mehran score	14 (5-22)	5 (2-7)	0.001
HTC, %	37.53±5.49	40.38±4.36	0.017
Platelets 10³/uL	210 (190-275)	225 (190-267)	0.895
Length of hospital stay, days	4.53±1.95	3.11±0.33	<0.001
Triglycerides, mg/dL	147 (92-165)	158 (120.25-183.75)	0.247
LDL, mg/dL	113.87±46.42	127.73±31.17	0.135
Systolic BP, mmHg	110 (90-130)	130 (110-140)	0.020
Diastolic BP, mmHg	64 (60-70)	70 (65-80)	0.104
Peak troponin-I, pg/mL	178 (124-5762)	915 (162.75-6171.75)	0.291
NYHA FC	2.33±0.48	2.07±0.46	0.043
EuroSCORE II, %	2.11 (1.60-6.35)	1.58 (1.01-2.65)	0.053
Medications			
ACEI, n (%)	6 (40)	62 (59.60)	0.151
ARB, n (%)	6 (40)	34 (32.70)	0.575
Beta blockers, n (%)	15 (100)	97 (93.30)	0.300
CCB, n (%)	6 (40)	24 (23.10)	0.158
Statin, n (%)	14 (93.30)	93 (89.40)	0.638
Nitrate, n (%)	1 (6.70)	44 (42.30)	0.008
OAD, n (%)	10 (66.70)	37 (35.60)	0.021
Diuretic, n (%)	**8 (53.30)**	**37 (35.60)**	**0.185**

Values are mean ± SD, numbers and percentages or median and 25th and 75th percentiles. The p value is for categorical data from Chi-square. The p value for independent samples t test or the Mann-Whitney U test was used to compare continuous variables. ACEI: angiotensin-converting enzyme inhibitors; ARB: angiotensin receptor blockers; BMI: body mass index; BP: blood pressure; CCB: calcium channel blockers; CIN: contrast-induced nephropathy; DM: diabetes mellitus type 2; eGFR: estimated glomerular filtration rate; EuroSCORE: European System for Cardiac Operative Risk Evaluation; HL: hyperlipidemia; HT hypertension; HTC: hematocrit; KIM-1: Kidney injury molecule-1; LVEF: left ventricular ejection fraction; LDL: low-density lipoprotein; NYHA FC: New York Heart Association functional class; OAD: oral antihyperglycemic drugs.

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Table 2 – One-year clinical follow-up findings

Variable, n (%)	CIN, n=15 (12.60)	Non-CIN, n=104 (87.40)	p value
All-cause mortality, n (%)	6 (40)	8 (7.70)	<0.001
Cardiovascular death, n (%)	5 (33.30)	6 (5.80)	0.001
Stroke, n (%)	3 (20)	3 (2.90)	0.005
Myocardial reinfarction, n (%)	3 (20)	4 (3.80)	0.013
MACE, n (%)	**7 (46.70)**	**12 (11.50)**	**0.001**

Values are numbers and percentages. The p value is for categorical data from chi-square. CIN: contrast-induced nephropathy; MACE: major adverse cardiovascular events.

Table 3 – Baseline characteristics significantly associated with eGFR

Variable	r	p value
HTC	0.422	<0.001
LVEF	0.518	<0.001
Creatinine	−0.831	<0.001
Uric acid	−0.464	<0.001
Mehran score	**−0.664**	**<0.001**

eGFR: estimated glomerular filtration rate; HTC: hematocrit; LVEF: left ventricular ejection fraction; r: Spearman's rank correlation coefficient.

In receiver operating characteristic analysis, KIM-1 above 9.49 ng/mL predicted the presence of CIN with 80% sensitivity and 81.70% specificity in elderly patients with NSTEMI. The area under the curve was 0.887 (95% CI: 0.796 – 0.979, p < 0.001) (Figure 3A). Moreover, Mehran score above 7.5 predicted the presence of CIN with 60% sensitivity and 76% specificity in elderly patients with NSTEMI. The area under the curve was 0.772 (95% CI: 0.625 – 0.919, p = 0.001) (Figure 3B).

Discussion

The key finding of this study was that increased KIM-1 level and Mehran score were two determinants of CIN in elderly patients with NSTEMI. Additionally, in elderly patients with NSTEMI, CIN was significantly associated with poor outcomes. We have shown that values of KIM-1 above 9.49 ng/mL suggest the presence of CIN in elderly patients. Moreover, Mehran score above 7.5 suggests the presence of CIN in elderly patients. To the best of our knowledge, this is the first report in the literature demonstrating the relationship between CIN and KIM-1 in elderly patients with NSTEMI. In our study, the results of one-year clinical follow-up showed that MACE, all-cause mortality, myocardial reinfarction, and stroke were significantly higher in the CIN group.

Although the pathogenesis of CIN is controversial in elderly patients, oxidative reactions are generally accepted in the pathogenesis. CIN is a multifactorial disease and baseline renal insufficiency, heart failure, diabetes mellitus, and myocardial infarction have been proposed to explain the development of CIN.[20] There is an increased risk of hospitalization, morbidity, and mortality rates in patients with CIN.[21] Despite the development of less nephrotoxic contrast agents, the possibility of CIN remains high.[22] The incidence of CIN is > 2% in the general population, but it can exceed 20% to 30% in elderly patients with diabetes mellitus or congestive heart failure.[23] In this study, CIN was observed in 12.60% (n = 15) of elderly patients.

Moreover, Marenzi et al.[24] found that lower LVEF is associated with CIN.[24] Kaya et al.[25] found that patients who developed CIN had a markedly extended hospitalization when compared with the non-CIN group.[25] In this study consistent with the literature, we have seen significantly lower LVEF, eGFR, hematocrit, and systolic BP in the CIN group. Moreover in this study, we have seen significantly higher Mehran score, serum KIM-1 level, glucose, uric acid, extended hospitalization, and creatinine level in the CIN group. Extended hospitalization is associated with an increased total cost, which has important clinical and health care implications. Physicians need to be aware of this potential risk.

Additionally, Iakovou et al.[13] found that the female sex and higher NYHA score are independent predictors of CIN development.[13] Also, Zaytseva et al.[26] found that patients who have higher NYHA scores have increased risk of developing CIN.[26] In this study consistent with the literature, we have found higher NYHA scores in the CIN group, but we did not find any correlation between sex and the development of CIN in elderly patients with NSTEMI.

In general, proximal renal tubules express very low KIM-1 levels. However, KIM-1 expression is significantly increased in ischemic kidneys.[27] Studies have suggested that KIM-1 interacts with the proliferation of T cells and other pro-inflammatory proteins.[7,27] Macrophages and T lymphocytes are the main sources of numerous cytokines and molecules interfering with endothelial cells, contributing to an aggravation of inflammatory pathways. The key responsibilities for the pathophysiological pathways on tubular injury are endothelial dysfunction, inflammation, and unexplained elevated production of vasoactive compounds, such as endothelin-1 and angiotensin molecules.[7,27] The protein structure of KIM-1 acts as an adhesion molecule for the cell surface.[27] Therefore, we speculate that KIM-1 might alter cellular adhesion and modulate interactions between injured epithelial cells and the
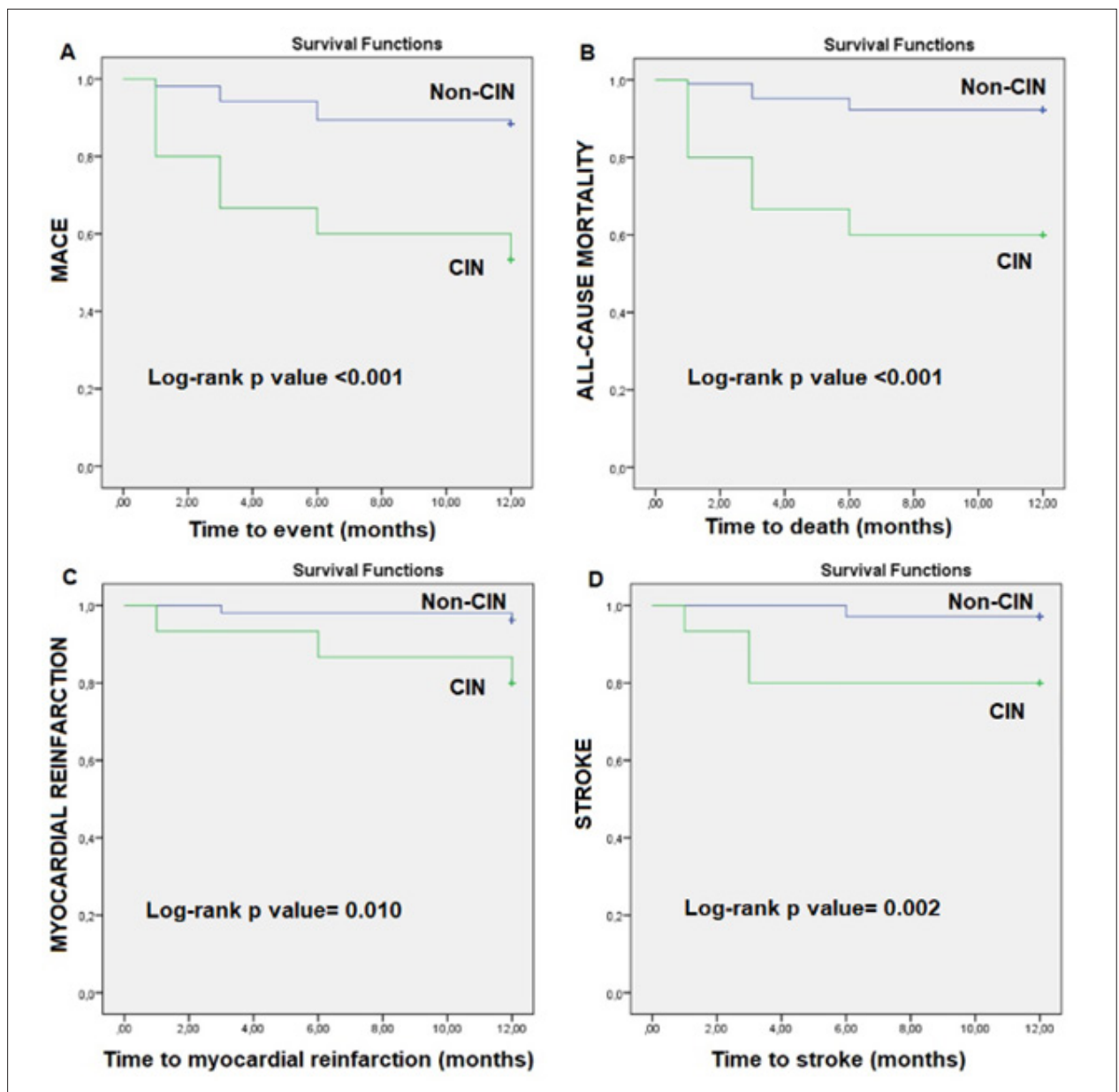
Figure 2 – A) Kaplan-Meier estimates for MACE. B) Kaplan-Meier estimates for all-cause mortality. C) Kaplan-Meier estimates for myocardial reinfarction. D) Kaplan-Meier estimates for stroke. CIN: contrast-induced nephropathy; MACE: major adverse cardiac events.

luminal contents that include casts, debris, and viable epithelial cells that have become dislodged from the intimal endothelium of the proximal renal tubules and might lead to CIN in elderly patients with NSTEMI. Inflammation plays an important role in establishing and promoting CIN. Therefore, combinations of these pro-inflammatory processes appear plausible to clarify the underlying mechanisms of CIN in elderly patients. KIM-1 not only helps in the proliferation of macrophages and T lymphocytes, but also enhances the production of oxidative cytokines.[9] The results of this study show that serum KIM-1 concentrations are positively associated with CIN in elderly patients with NSTEMI. We propose that inflammation,

atherothrombotic microembolization, and activation of neutrophils and platelets, which cause the release of oxygen-free radicals, proteolytic enzymes, and proinflammatory mediators that can cause tissue and endothelial damage, particularly in critically injured myocytes during NSTEMI, were the initial mechanisms of CIN in elderly patients. These common mechanisms also work on every ischemic-sensitive organ, particularly on the heart and kidneys. Thus, we can use KIM-1 as an early prognostic marker of CIN in elderly patients with NSTEMI.

Regarding this knowledge, KIM-1 continues to be released as a result of damage; it also causing damage, in itself, and

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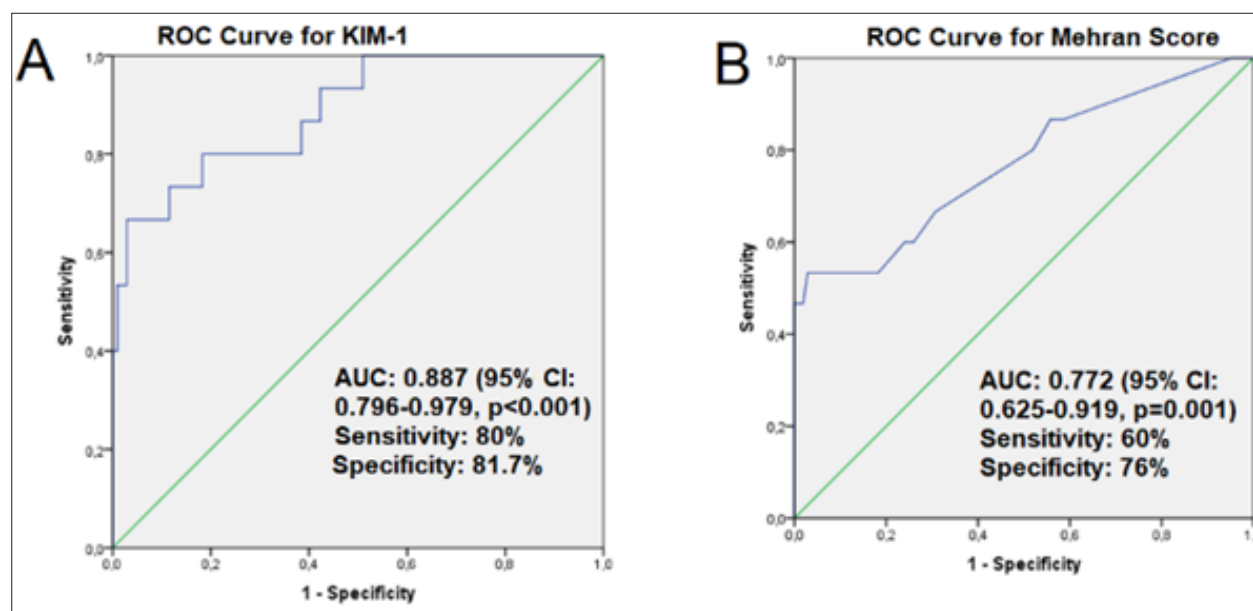
Figure 3 – A) ROC curve for the specificity and sensitivity of KIM-1. B) ROC curve for the specificity and sensitivity of the Mehran score. AUC: area under the curve; CI: confidence interval; KIM-1: kidney injury molecule-1; ROC: receiver operating characteristic curve.

the kidneys are vulnerable to direct damage. Moreover, we have found that KIM-1 is more sensitive and specific than the Mehran score (KIM-1: 80% sensitivity and 81.70% specificity vs. Mehran score: 60% sensitivity and 76% specificity). To the best of our knowledge, this is the first report in the literature demonstrating the relationship between KIM-1 concentrations and CIN in elderly patients with NSTEMI. We hypothesized that, by measuring the KIM-1 level, we would be able to predict the risk of CIN in elderly patients better than the with the Mehran score. However, the exact mechanism of KIM-1 in the pathogenesis of CIN has not been determined.

Also, CIN is an important predictor of poor cardiac outcomes in elderly patients with NSTEMI.[28] Shacham et al.[29] demonstrated that some older patients were more likely to develop CIN and have higher all-cause mortality, with worse renal function, and history of heart failure.[29] Maioli et al.[30] found that patients with CIN had a higher rate of death compared to the non-CIN group at five years of follow-up.[30] In this study, one-year clinical follow-up findings demonstrated that MACE, all-cause mortality, cardiovascular death, myocardial reinfarction, and stroke outcomes were significantly higher in the CIN group. In elderly patients with NSTEMI, we have found a 5.2-fold increase in the risk of all-cause mortality, a 5.7-fold in the risk of cardiovascular death, a 6.9-fold in the risk of stroke, a 5.3-fold in the risk of myocardial reinfarction, and a 4.1-fold in the risk of MACE in the CIN group with respect to the group of patients without CIN. With these results, we have shown that CIN worsens the outcomes of elderly patients with NSTEMI.

The accepted strategies for preventing CIN are monitoring the contrast volume, reducing the use of CM as much as possible, and hydrating the patient with saline solution 12 hours before and after catheterization at a speed of 1 mL/ kg/h, according to the guidelines. Saline hydration and volume expansion could speed up CM excretion, decrease direct renal toxicity, decrease vasoconstriction, and decrease reactive oxygen species.

Limitations

First, the main limitation of the present study is that it was conducted with a fairly small sample size. Although a multivariate model was conducted to adjust confounding variables, a bias was inevitable, given that this was a single-center analysis. Multicenter trials with more patients could provide better results and more data. Second, renal function was only assessed by creatinine levels. Direct measurement of GFR through 24-hour urine collection is the best method for assessing kidney function, but it is time-consuming and onerous for the patient. Third, to assess long-term clinical results, a follow-up period of one year may not be adequate. These are limiting factors in our study.

Conclusion

Baseline serum KIM-1 concentration and Mehran score are independent predictors of CIN in elderly patients with NSTEMI. Additionally, all-cause mortality, cardiovascular death, myocardial reinfarction, stroke, and MACE were significantly higher in the CIN group at one-year follow-up.

Author Contributions

Conception and design of the research; Data acquisition; Analysis and interpretation of the data; Statistical analysis; Obtaining financing; Writing of the manuscript; Critical revision of the manuscript for intellectual content: Huyut MA.

Potential Conflict of Interest

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

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Study Association

This study is not associated with any thesis or dissertation.

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What Is the Role of Kidney Injury Biomarkers in Contrast-Induced Nephropaty?

Pedro Pimenta de Mello Spineti[1,2] 🔵

Hospital Universitário Pedro Ernesto,[1] Rio de Janeiro, RJ - Brazil
Hospital Unimed-Rio,[2] Rio de Janeiro, RJ - Brazil
Short Editorial related to the article: Kidney Injury Molecule-1 Is Associated with Contrast-Induced Nephropathy in Elderly Patients with Non-STEMI

Contrast-induced acute kidney injury (CI-AKI) is a potential severe complication in the use of iodinated radiological contrast media and is associated with higher rates of morbidity and mortality and increased length of hospital stay in patients undergoing cardiac catheterization.[1] Its incidence is variable in the literature according to the criteria used for its diagnosis. The CI-AKI definition most often used in clinical trials is an increase in serum creatinine (Cr) levels of 0.5 mg/dl or 25% over baseline within 72 h after exposure to contrast medium.[1]

However, Cr has a number of limitations as a marker of renal function. Its serum level is influenced by external factors such as sex, age, skin color, weight and muscle mass. It underestimates renal function in women, in the elderly or in underweight individuals. Its variation overestimates renal damage in individuals with previous kidney failure. Another important limitation is the fact that Cr rises only after 24 h of an acute kidney injury, being considered a "slow marker" of acute kidney injury.[1,2]

New biomarkers have been evaluated to help diagnose CI-AKI. These include cystatin C (CysC), the lipocalin associated with neutrophil gelatinase (NGAL) and kidney injury molecule 1 (KIM-1).

CysC is a peptide of 122 amino acids with low molecular weight (13.36 Kda), from the family of cysteine protease inhibitors. It is produced steadily by most nucleated cells and its synthesis is not influenced by inflammatory processes, muscle mass or sex of the individual. Due to its low molecular weight and positive charge, it is freely filtered by the renal glomerulus and then reabsorbed and metabolized in the proximal renal tubule, with no renal or extra-renal secretion. Therefore, its serum determination reflects exclusively glomerular filtration and its increase in serum means a reduction in this rate.[2] CysC

reaches its peak 24 h after exposure to contrast in patients with CI-AKI and remains high for up to 48 h.[3]

NGAL is a 178 amino acid glycoprotein that belongs to the superfamily of lipocalins. It is expressed by neutrophils and certain epithelia, such as renal tubules. It is freely filtered by the glomerulus and later reabsorbed by the cells of the proximal tubule. Its basal serum and urinary levels are very low, rising in different clinical settings such as systemic inflammation, cancer and atherosclerosis.[2] Its levels rise sharply 4 h after exposure to contrast in cases of CI-AKI and return to baseline levels in 48h.[3]

A recent systematic review of the role of NGAL and CysC analyzed 37 studies and concluded that both can serve as early diagnostic indicators of CI-AKI, and that cystatin C may perform better than NGAL. There was no difference in the performance of serum NGAL compared to urine NGAL.[4]

Human KIM-1 is a type one transmembrane glycoprotein, with an immunoglobulin and mucin domain that is not detectable in normal renal tissue or in the urine, but it is expressed at very high levels in dedifferentiated cells of the renal proximal tubular epithelium after ischemic or toxic injury. There are numerous characteristics that could make it an attractive biomarker of kidney injury, such as: absence in normal kidney, increased expression after an acute ischemic insult and its persistence in the tubular epithelium cells until its complete recovery.[2]

In this edition of Arquivos Brasileiros de Cardiologia, Dr. Huyut[5] evaluated the association between serum levels of KIM-1 and CI-AKI in elderly patients with ST-segment elevation myocardial infarction. Despite the small size of the study population, he shows that this molecule was independently associated with CI-AKI with a good area under the ROC curve. CI-AKI, as expected, has been associated with increased morbidity and mortality.

Although this is an interesting finding, two recent studies comparing NGAL and KIM-1 demonstrated that it appears to have a worse performance in predicting CI-AKI.[6,7] These inconsistent results can be attributed to the different definitions of CI-AKI used by the studies, as well as different cutoff points for the biomarkers.

In conclusion, the new biomarkers have advantages on creatinine for the evaluation of CI-AKI, but there is still uncertainty about the best of them for this indication. Further studies are needed to assess not only the association between CI-AKI biomarkers, but also the cost-effectiveness of incorporating them into daily clinical practice.

Keywords

Acute Kidney Injury; Kidney Diseases; Contrast Media; Biomarkers; Cardiac Catheterization; Creatinine; Lipocalin 2.

Mailing Address: Pedro Pimenta de Mello Spineti •
Hospital Universitário Pedro Ernesto - Boulevard 28 de setembro, 77.
Postal Code 20551-030, Vila Isabel, RJ – Brazil
E-mail: pedrospineti@yahoo.com.br

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Relationship between Mitral Regurgitation and Transcatheter Aortic Valve Implantation: a Multi-Institutional Follow-up Study

Luciana de Cerjat Bernardes P. da Cunha,[1] Enio Eduardo Guerios,[1] Claudio Leinig Pereira da Cunha,[1] Luiz A. Carvalho,[2] Pedro Lemos Neto,[3] Rogério Sarmento-Leite,[4] Alexandre A. Abizaid,[3] José Antonio Mangione,[5] Adriano Dourado Oliveira,[6] Alexandre Siciliano,[3] Vinicius Esteves,[7] Fábio Sândoli de Brito Jr.[8,9]

Universidade Federal do Paraná - Hospital de Clínicas - UFPR,[1] Curitiba, PR - Brazil

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

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

Instituto de Cardiologia,[4] Porto Alegre, RS - Brazil

Hospital Beneficência Portuguesa de São Paulo,[5] São Paulo, SP - Brazil

Hospital Santa Izabel,[6] Salvador, BA - Brazil

Rede D'Or São Luiz,[7] São Paulo, SP - Brazil

Universidade de São Paulo Instituto do Coração,[8] São Paulo, SP - Brazil

Hospital Sírio-Libanês,[9] São Paulo, SP - Brazil

Abstract

Background: Mitral regurgitation (MR) is prevalent in patients undergoing transcatheter aortic valve implantation (TAVI). There are some controversies about the prognostic impact of MR in survival of TAVI patients.

Objective: To examine the relationship between TAVI and MR in a patient population from the Brazilian TAVI Registry.

Methods: Seven hundred and ninety-five patients from the Brazilian TAVI Registry were divided at baseline, discharge, and follow-up according to their MR grade as follows: absent/mild (AMMR) or moderate/severe (MSMR). They were subsequently regrouped according to their immediate and late changes in MR severity after TAVI as follows: no change, improved, or worsened MR. Predictors and prognostic impact on baseline as well as changes in MR severity were analyzed. Statistical significance was set at p < 0.05.

Results: Baseline MSMR was present in 19.3% of patients and was a predictor of increased late mortality. Immediately after TAVI, 47.4 % of cases improved to AMMR, predicted by a higher Society of Thoracic Surgeons score and a higher grade of baseline aortic regurgitation. Upon follow-up, 9.2% of cases of AMMR worsened to MSMR, whereas 36.8% of cases of MSMR improved to AMMR. Lower baseline left ventricular ejection fraction (LVEF) and improvement in LVEF at follow-up were predictors of MR improvement. Progressive worsening of MR upon follow-up was an independent predictor of higher late mortality after TAVI (p = 0.005).

Conclusions: Baseline MSMR predicts late mortality after TAVI. Lower LVEF and improved LVEF at follow-up predict MR improvement after TAVI. Progressive worsening of MR severity at follow-up is an independent predictor of late mortality, which is a rare finding in the literature.

Keywords: Aortic Valve Insuffciency; Mitral Valve Insufficiency; Aortic Valve Transcatheter Implantation; Epidemiology; Survival Analysis; Echocardiography/methods.

Introduction

Approximately two thirds of patients with severe symptomatic aortic stenosis (AS) and indication for surgical valve replacement present with some degree of mitral regurgitation (MR)[1] and, in some cases, an indication for double valve replacement surgery.[2] For patients undergoing isolated aortic valve replacement, moderate or severe MR may be associated with higher mortality rates, congestive heart failure, and subsequent mitral valve surgery.[3]

For patients with severe AS and MR for whom surgery is not the ideal therapeutic choice, transcatheter aortic valve implantation (TAVI) may be a suitable option.[1,2] Since, in some patients, a grade reduction may be expected, or subsequent transcatheter mitral valve intervention may be indicated, MR is generally not treated in this scenario.[1,4] However, in the case of isolated aortic surgery, MR severity may decrease, remain unchanged, or even increase after TAVI.[1,5] Although many studies consistently demonstrate that important MR at baseline is associated with poorer outcomes,[4,6] information regarding the prognostic implications of changes in MR severity after TAVI is scarce.[7]

Original Article

The aim of this study was to examine the relationship between TAVI and MR in a patient population from the Brazilian TAVI Registry.[8] We hypothesized that moderate/severe MR (MSMR) at baseline and progressive deterioration of MR influences the prognosis of TAVI.

Methods

Patients

The multicenter Brazilian TAVI Registry is a voluntary participation registry, conducted since 2008 by the Brazilian Society of Interventional Cardiology, which aggregates the results of TAVI performed in 22 centers across Brazil. Patients have been retrospectively and prospectively included in the registry since the first TAVI was performed in Brazil. The registry was approved by the Ethics Committee of the Albert Einstein Hospital, São Paulo, on November 10, 2010, and inserted in the "*Plataforma Brasil*" (a national and unified database of research records involving human beings). All prospectively included patients provided informed written consent.

Indication for TAVI was limited to groups of inoperable or high-surgical-risk patients with severe symptomatic AS or degenerated surgical bioprosthesis. The surgical mortality risk was estimated using the EuroScore[9] and the Society of Thoracic Surgeons (STS) risk score.[10] Details, definitions, and partial registry results have been previously published.[8]

This study included patients treated between January 2008 and January 2015. Patients who had previously undergone mitral valve surgery or patients who did not have adequate pre- and post-intervention echocardiographic records were excluded from the analysis. Follow-up was performed at medical visits with echocardiographic studies; the last follow-up echocardiogram was used to compare with baseline and discharge studies.

TAVI procedure

TAVI was performed using CoreValve prostheses (Medtronic, Minneapolis, MN, USA) by transfemoral and transubclavian access, Sapien XT (Edwards Lifesciences, Irvine, CA, USA) by transfemoral and transapical access, and Inovare (Braile Biomédica, São José do Rio Preto, SP, Brazil) implanted only by the transapical route. The procedure was performed according to standard techniques, previously described in detail.[11-13] The choice of access, type of anesthesia (general or sedation), and the use of intraoperative transesophageal echocardiography was left to the operator's discretion. After the intervention, aspirin (100 mg once daily) and clopidogrel (300 mg as a loading dose and 75 mg once daily thereafter) were administered to the patients for a minimum of 30 days. A complete transthoracic echocardiogram of the patients was performed in the pre-, peri-, and post-intervention periods (if there were several echocardiograms, the last one was included). MR severity was defined as absent, mild, moderate, or severe according to the recommendations of the American Society of Echocardiography, integrating structural, Doppler, and quantitative parameters.[14]

Patients' clinical data and echocardiograms were analyzed at baseline, hospital discharge, and late follow-up (mean follow-up time of 16.6 months). In each of these periods, the patients were separated into two groups, according to their MR grade. One group included patients with absent or mild MR (AMMR), and the other included those with MSMR, as described in prior studies.[2,15] Subsequently, patients were regrouped according to the change in MR severity after TAVI when comparing baseline, discharge, and follow-up periods, as follows: patients who showed no change in MR grade, those with worsened MR (from AMMR to MSMR), and those with improved MR severity (from MSMR to AMMR). Clinical and echocardiographic predictors of MR improvement/worsening were identified, and the relationship between changes in MR grade and mortality rates was analyzed.

Statistical analysis

Statistical analyses were performed with the IBM SPSS Statistics for Windows, Version 20.0 (IBM Corp, Armonk, NY, USA). Continuous variables were expressed as mean and standard deviation or median and range, while categorical variables were expressed as frequencies and percentages. Kolmogorov-Smirnov test was used to verify the normality of the data; normality of data distribution was accepted for most of the variables, without compromising other analyses. Associations in categorical variables between groups were assessed using Pearson's chi-square test. Continuous variables were analyzed using Student's t test for independent samples or non-parametric Mann-Whitney test to compare groups defined by baseline MR grade (AMMR or MSMR). One-way analysis of variance (ANOVA) or non-parametric Kruskal-Wallis test was used to compare the groups defined by MR changes (no change, worsened, or improved). Survival probability was estimated by Kaplan-Meier curves. To analyze the effect of MR changes on survival time, non-adjusted and adjusted Cox proportional hazard regression models were adapted by including covariates with $p < 0.05$ in the non-adjusted models. Final models were assessed by stepwise backward likelihood ratio method considering a p value < 0.05 for inclusion and exclusion criteria. Hazard ratios (HR) and 95% confidence intervals (CI) were presented for the final models. Statistical significance was set at $p < 0.05$.

Results

Baseline characteristics of the patients

Of the 819 patients included in the Brazilian TAVI Registry, 795 patients were included in this analysis. A patient flow diagram is shown in Figure 1, and Table 1 details patients' baseline clinical characteristics according to their baseline MR grade. Prior to the procedure, MR was absent/mild in 642 patients (80.7%) and moderate/severe in 153 patients (19.3%). Patients with MSMR were older, and they presented with more comorbidities (renal failure, lower hemoglobin levels, pulmonary hypertension, atrial fibrillation, previous pacemaker implantation, more advanced heart failure grades), higher surgical risk scores, lower ejection fractions, larger LV diastolic diameters, more severe aortic regurgitation, smaller aortic valve areas, and lower aortic gradients.
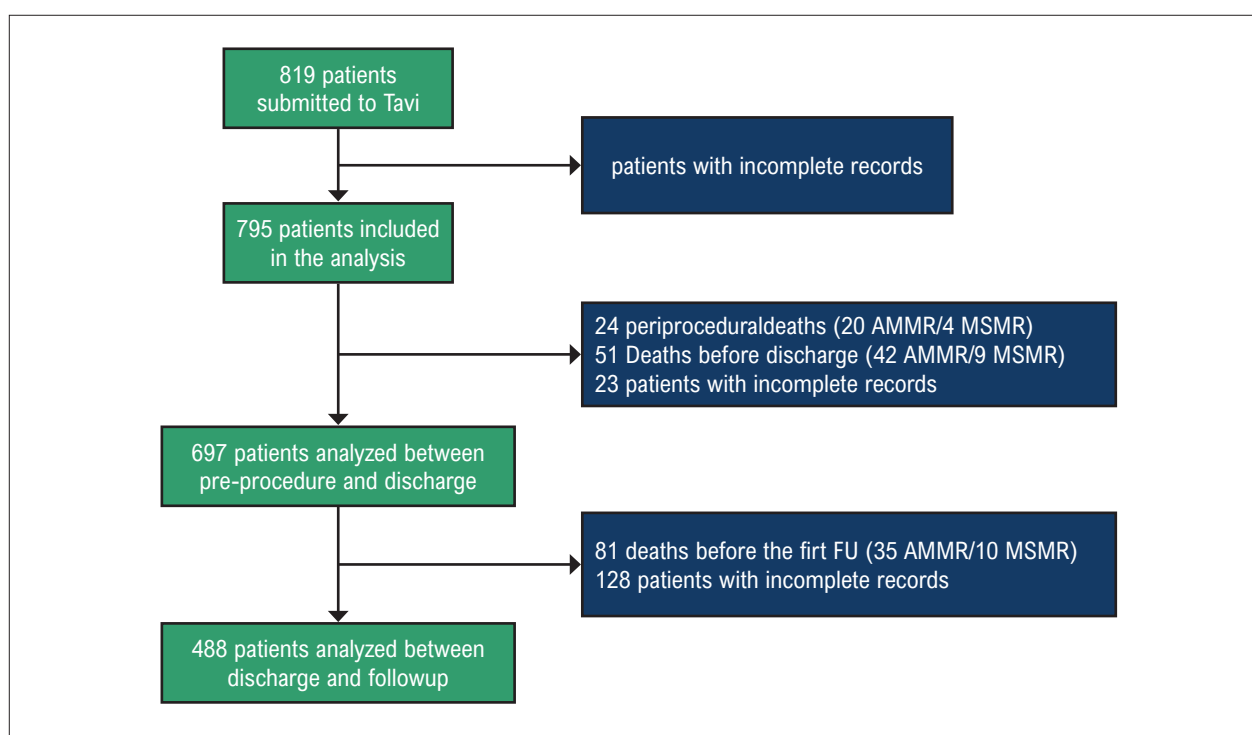
Figure 1 - *Patient flow diagram. This flow chart specifies the mortality rate in the AMMR and MSMR groups. Note that the mortality rate before discharge includes the peri-procedural mortality. "Incomplete records" are related to the absence of good echocardiograms for analysis. AMMR: absent/mild mitral regurgitation; MSMR: moderate/severe mitral regurgitation; FU: follow-up.*

CoreValve prostheses were implanted in 597 patients (73%) by transarterial accesses, Sapien XT in 200 patients (24%) (3 by transapical and 197 by transarterial approaches), and Inovare in 22 patients (3%) by transapical access. In total, there were 770 patients who received the prostheses by transarterial accesses, while 25 were by transapical access. Seven hundred and seventy nine patients (98%) had prostheses for native severe AS, and 16 (2%) had valve-in-valve prosthesis for degenerated surgical bioprostheses.

Predictors for late mortality

According to the adjusted Cox regression model, peripheral vascular disease (HR 1.6; 95% CI, 1.11-2.32; p = 0.012), previous balloon aortic valvuloplasty (HR 1.97; 95% CI, 1.25-3.11; p = 0.004), and baseline MSMR (HR 1.50; 95% CI, 1.05-2.14; p = 0.027) were independent baseline predictors of late mortality, with mean follow-up time of 16.6 months and median follow-up of 12.4 months (first quartile: 2.6 months and third quartile: 24.7 months) in this population

Changes in MR severity: pre-intervention versus discharge

After intervention, MR grade was compared between baseline and discharge in a total of 697 patients. TAVI did not change MR grade in comparison with baseline in 83.8% (n = 584) of patients. MR severity worsened after TAVI in 8.7% (n = 49) of patients with baseline AMMR,

but it improved in 47.8% (n = 64) of those with baseline MSMR (Figure 2).

There was a higher prevalence of renal failure in patients whose MR grade worsened after TAVI (p = 0.022). Upon univariate analysis, a higher STS score (p = 0.013) and a more severe baseline aortic regurgitation (p = 0.010) were predictors of an improvement in MR severity. Other baseline echocardiographic data, as well as changes in parameters, such as the left ventricular ejection fraction (LVEF) and aortic gradient between baseline and discharge, were not associated with MR severity improvement or worsening after TAVI (Table 2).

Changes in MR severity: discharge versus follow-up

After discharge, clinical and echocardiographic follow-up was performed in 488 patients, with a mean follow-up time of 16.6 ± 14.1 months (median follow-up: 12.4 months, first quartile: 2.6 months and third quartile: 24.7 months). Compared with discharge, there were no changes in MR severity in 86.4% (n = 422) of patients. Only 9.2% (n = 38) of patients with AMMR at discharge presented with worse MR severity grades, whereas 36.8% (n = 28) of patients with MSMR at discharge presented with an improvement to AMMR at follow-up (Figure 2).

Lower baseline LVEF (p = 0.015) was a predictor of late improvement of MR severity in the univariate analysis. In addition, a strong trend towards late improvement of MR severity was observed in patients with LVEF improvement

Table 1 – Baseline characteristics of patients and comparison of groups defined by baseline MR dysfunction (n = 795)

Characteristic	Whole population (n = 795)	According to baseline MR dysfunction		p value*
		Absent/mild (n = 642)	Moderate/severe (n = 153)	
Age (years)	81.5 ± 7.3	81.2 ± 7.5	83.1 ± 6.6	0.002
Male	389 (48.9)	313 (48.8)	76 (49.7)	0.838
Coronary artery disease	465 (58.4)	375 (58.4)	90 (58.8)	0.926
Previous myocardial infarction	117 (14.7)	99 (15.4)	18 (11.8)	0.251
Peripheral vascular disease	136 (17.1)	118 (18.4)	18 (11.8)	0.051
Stroke/TIA	63 (7.9)	50 (7.8)	13 (8.5)	0.771
Diabetes	253 (31.8)	206 (32.1)	47 (30.7)	0.744
Systemic arterial hypertension	601 (75.5)	484 (75.4)	117 (76.5)	0.780
Renal failure	615 (77,3)	485 (75.5)	130 (85.0)	0.012
Preprocedural pacemaker	81 (10.2)	57 (8.8)	24 (15.6)	0.012
Hemoglobin (mg/dl)	11.8 ± 1.7	11.8 ± 1.8	11.5 ± 1.6	0.045
Pulmonary hypertension	176 (22.1)	133 (20.7)	43 (28.1)	0.048
NYHA functional class III or IV	648 (81.5)	511 (79.6)	137 (89.5)	0.004
Atrial fibrillation	106 (13.3)	78 (12.3)	28 (18.5)	0.044
EuroScore mortality	16 (17.6)	15.2 (16.6)	21.1 (17.5)	0.001
STS score mortality	7.2 (10.5)	6.6 (9.9)	10.9 (12)	<0.001
Moderate/severe baseline aortic regurgitation	95 (11.9)	60(10,9)	35(23.0)	<0,001
Previous balloon aortic valvuloplasty	50 (6,2)	36 (5,6)	14 (9,2)	0,105
Baseline EF (%)	58.7 ± 14.9	60.1 ± 14.4	53.2 ± 16.0	<0.001
Baseline LV diastolic diameter (mm)	50.8 ± 9.4	50.2 ± 8.8	53.4 ± 10.3	0.001
Baseline aortic valve area (cm²)	0.66 ± 0.19	0.67 ± 0.19	0.63 ± 0.19	0.016
Baseline mean aortic gradient (mmHg)	49.3 ± 16.0	50.1 ± 15.7	46.3 ± 16.5	0.010
Baseline peak aortic gradient (mmHg)	81.0 ± 24.8	82.3 ± 24.6	76.0 ± 25.0	0.005

*Results described by frequency (percentage), mean ± standard deviation or median (interquartile range). *Student t test for independent samples, non-parametric Mann-Whitney test (quantitative variables), or chi-square test (categorical variables), p < 0.05. EF: ejection fraction, LV: left ventricle, MR: mitral regurgitation, NYHA: New York Heart Association, STS: Society of Thoracic Surgeons, TIA: transient ischemic attack.*

upon follow-up (p = 0.052, Table 3). No predictive factors of late worsening of MR severity were identified.

Mortality

Changes in MR severity at baseline versus discharge (both improvement [HR 1.17; 95% CI, 0.69–1.98; p = 0.56] or worsening [HR 1.28; 95% CI, 0.70–2.32; p = 0.43]) were not significant predictors of late mortality after TAVI, even when adjusted for survival determining factors such as baseline hemoglobin level (HR 0.89; 95% CI, 0.81-0.98; p = 0.013), NYHA functional class III/IV congestive heart failure (HR 1.95; 95% CI, 1.14-3.34; p = 0.015), and previous balloon aortic valvuloplasty (HR 2.19; 95% CI, 1.29-3.72; p = 0.004). In a non-adjusted analysis, late changes in MR severity also did not impact mortality rates. However, when adjusted for factors that increased mortality in this period, such as NYHA functional class III/IV congestive heart failure (HR 2.6; 95% CI, 1.11-6.05; p = 0.026) and previous balloon aortic valvuloplasty (HR 2.5; 95% CI, 1.31-4.83; p = 0.005), the worsening of MR between

discharge and follow-up periods, compared to unchanged MR, was strongly associated with an increased mortality risk (HR 2.74; 95% CI, 1.36-5.48; p = 0.005) (Table 4). Kaplan-Meier curves demonstrating survival probabilities for each group from discharge to follow-up are shown in Figure 3.

Discussion

In the present study, we observed the following: 1) baseline MSMR in patients undergoing TAVI was associated with age, the presence of comorbidities, and the severity of aortic stenosis; 2) baseline MSMR was a predictor of late mortality after TAVI; 3) approximately half of the patients with baseline MSMR presented with improved MR severity immediately after TAVI, and, in addition, 37% of patients with MSMR upon discharge presented with improved MR at the late follow-up; 4) baseline moderate/severe aortic regurgitation was a predictor of immediate improvement of MSMR after TAVI; 5) patients who showed a progressive improvement in MR at the late follow-up after TAVI were those who presented with
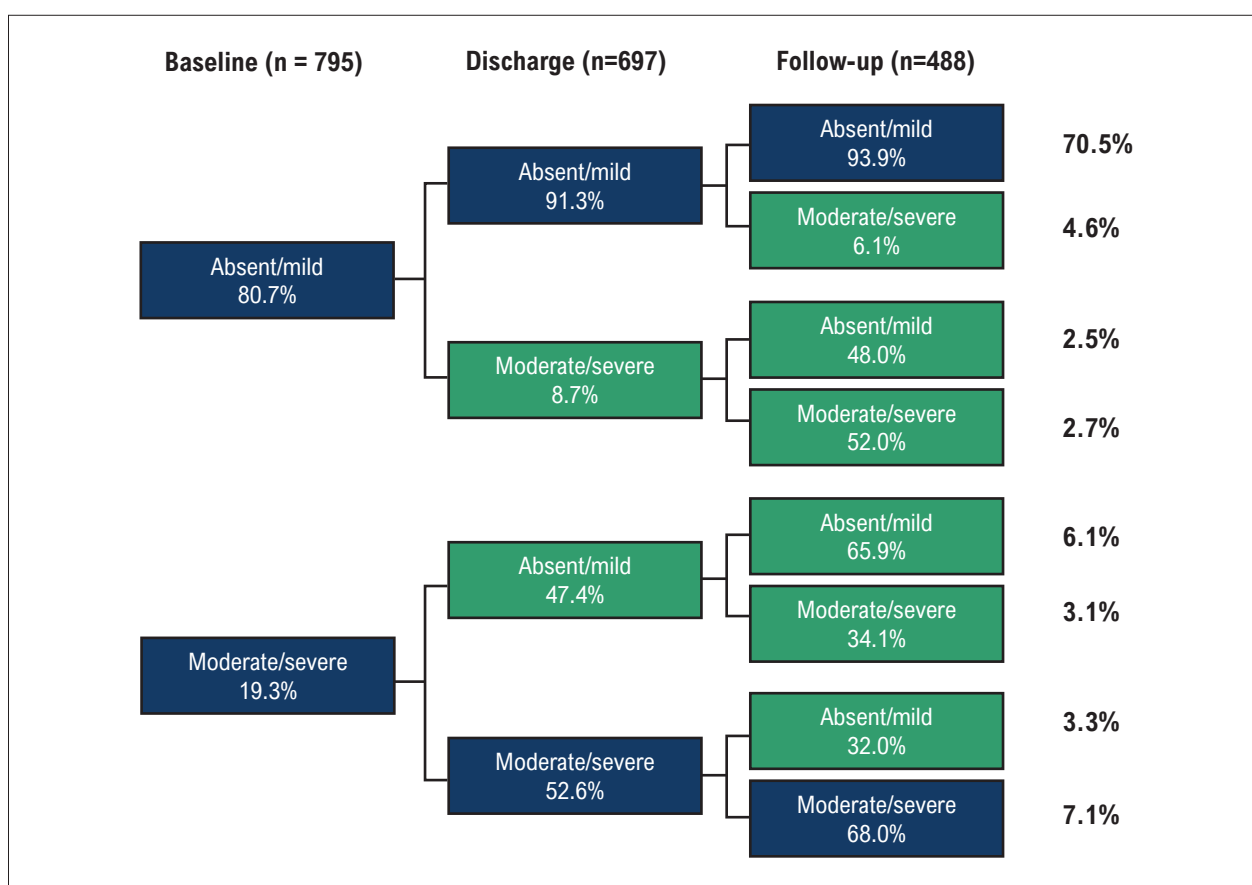
Figure 2 – *Changes in mitral regurgitation (MR) severity: baseline, discharge, and follow-up periods. This includes patients with complete echocardiography data in all three periods. Baseline: n = 795; discharge: n = 697; follow-up: n = 488. **Variation of MR grade when comparing baseline to the last follow-up for the whole population, excluding deaths and incomplete records.*

a lower baseline LVEF and improved LVEF after intervention; and, finally, 6) progressive worsening of MR severity at the late follow-up post-TAVI was an independent predictor of mortality; however, no predictor of this worsening was identified.

In corroboration with other studies, 20% of patients in the Brazilian TAVI Registry presented with baseline MSMR, and these patients had more serious comorbidities than those with less severe MR.[11,15-19] However, there is some controversy in the literature concerning the prognostic value of baseline MSMR on patient mortality after TAVI. Some studies showed no correlation,[15,18,20] whereas other publications demonstrated the influence of significant MR on early and/ or late mortality,[2,5,16,19-23] in particular an analysis of the US Transcatheter Valve Therapy Registry comprising more than 4,000 patients.[22] Similar to these later studies, our results also demonstrated that the presence of MSMR at baseline leads to increased late mortality rate after TAVI.

According to the severity of MR, there were four groups and they were analyzed together in absent/mild MR and moderate/severe MR groups. This was done due to the small number of patients with severe MR (n = 20 patients, 2.4%). In the literature, all the studies related to MR in TAVI patients have analyzed moderate and severe MR in only one group (moderate/severe MR) as we did.[2,3,5,7,15,20]

The etiology of MR (organic/degenerative versus functional) could not be defined based on our registry data. Vollenbroich et al.[7] studied the influence of functional versus degenerative MR on clinical outcome after TAVI. They found 36% functional and 64% degenerative MR among the patients with MSMR. Degenerative MR presented increased risk during long-term follow-up after TAVI, in relation to functional MR. Muratori et al.[3] also found organic MR more prevalent among patients with MSMR who underwent TAVI. They showed a greater reduction of MR degree after TAVI in functional MR and a negative impact on long-term follow-up for organic MR. Thus, the etiology of MR may influence prognosis after TAVI but we could not study this topic in our population of patients.

Little information is available regarding the frequency and prognostic value of changes in MR severity after TAVI. As depicted in Figure 2, and, in agreement with the findings of Boerlage-van Dijk et al.,[24] more than 80% of our patients presented with no change in their baseline MR grade at the late follow-up after TAVI. However, almost half of the patients with baseline MSMR presented with an improved MR grade immediately after TAVI. Among those without immediate improvement, almost

Table 2 – Comparison of groups defined by changes in MR severity: baseline versus discharge after TAVI (n = 697)

Characteristic	Changes in MR severity at baseline versus discharge			p value*
	Unchanged n = 584	Worsened n = 49	Improved n = 64	
Age (years)	81.3 ± 7.5	82.4 ± 5.5	81.9 ± 6.7	0.559
Male	294 (50.3)	21 (42.9)	31 (48.4)	0.590
Coronary artery disease	332 (56.8)	35 (71.4)	38 (59.4)	0.136
Previous myocardial infarction	90 (15.4)	7 (14.3)	7 (10.9)	0.629
Peripheral vascular disease	106 (18.2)	10 (20.4)	6 (9.4)	0.184
Stroke/TIA	49 (8.4)	4 (8.2)	5 (7.8)	0.986
Diabetes	187 (32.0)	13 (26.5)	20 (31.2)	0.728
Systemic arterial hypertension	429 (73.5)	40 (81.6)	51 (79.7)	0.279
Renal failure	444 (76.0)	44 (89.8)	55 (85.9)	0.022
Hemoglobin (mg/dl)	11.8 ±1.8	12.0±1.7	11.5±1.5	0.374
Pulmonary hypertension	130 (22.3)	8 (16.3)	17 (26.6)	0.431
NYHA functional class III or IV	471 (80.7)	39 (79.6)	55 (85.9)	0.570
Atrial fibrillation	73 (12.7)	8 (16.3)	10 (15.6)	0.642
EuroScore mortality	15.6 (17)	17.4 (15.7)	21.1 (17.9)	0.124
STS score mortality	6.9 (10.2)	9.5 (14.5)	11.5 (12.1)	0.013
Moderate/severe baseline aortic regurgitation	69 (11.9)	5 (10.9)	16 (25.4)	0.010
Previous balloon aortic valvuloplasty	33 (5,7)	3 (6,1)	7 (10,9)	0,309
Baseline EF (%)	59.2 ± 15.0	55.3 ± 15.5	57.3 ± 14.7	0.160
Baseline LV diastolic diameter (mm)	50.8 ± 9.0	51.2 ± 11.0	52.4 ± 10.0	0.430
Baseline aortic valve area (cm²)	0.67 ± 0.19	0.67 ± 0.17	0.63 ± 0.20	0.360
Baseline mean aortic gradient (mmHg)	49.5 ± 16.0	46.3 ± 12.6	49.5 ± 19.2	0.434
Baseline peak aortic gradient (mmHg)	80 (33)	75 (34.5)	78 (37.5)	0.324
Difference baseline-discharge EF (%)	1 (10)	1 (16.3)	3 (10)	0.314
Difference baseline-discharge aortic mean gradient (mmHg)	-39.6 ± 16.1	-39.7 ± 12.9	-37.5 ± 23.0	0.686
Difference baseline-discharge peak aortic gradient (mmHg)	-63.1 ± 24.9	-60.3 ± 22.3	-56.6 ± 34.2	0.174

*Results described by frequency (percentage), mean ± standard deviation, or median (interquatile range). *One-way ANOVA, non-parametric Kruskal-Wallis test (quantitative variables), or chi-square test (categorical variables), p < 0.05*
EF: ejection fraction, LV: left ventricle, MR: mitral regurgitation, NYHA: New York Heart Association, STS: Society of Thoracic Surgeons, TAVI: transcatheter aortic valve implantation, TIA: transient ischemic attack .

40% improved at the late follow-up. Recent literature has suggested that pre-procedure MR severity improves after TAVI in 29% to 70% of patients, and, in most cases, it is sustained at follow-up, having a favorable impact on late mortality and re-hospitalization rates after TAVI.[16,19,22-26] The absence of mitral annular calcification,[17,27] functional (rather than degenerative) MR,[6,21,27] absence of pulmonary hypertension,[17,21,27] absence of atrial fibrillation,[21,24,27] persistent left bundle branch block,[27] higher initial transaortic gradients,[17] absence of concomitant coronary artery disease,[26] and the implantation of an Edwards-Sapien rather than CoreValve prosthesis[28] were identified as predictors of this improvement. We identified lower LVEF at baseline and an improvement in LVEF after the intervention as predictors of MR improvement. These predictors have also been identified by other authors,[16,29,30] and they can be explained by reverse left ventricular remodeling and the

consequent reduction in the mitral valve complex stretching forces after TAVI. This explanation is supported by the previous demonstration that patients with improved MR severity after TAVI show a significant reduction in LV end-diastolic volume and favorable mitral annular geometric changes after aortic intervention.[31] The influence of reduced LV end-diastolic volume on the improvement of MR was also demonstrated by the association of moderate/severe baseline aortic regurgitation with early improvement of MR severity after TAVI that we demonstrated.

The Brazilian TAVI Registry was planned to include most of the TAVI procedures performed in Brazil, and, as a real-world sample, we included both severe AS in native valve, which constituted the vast majority (98%) and patients with degenerated surgical aortic bioprostheses (n = 16, 2% of patients). This could be considered a flaw in our patient

Table 3 – Comparison of groups defined by changes in MR severity: discharge after TAVI versus follow-up periods (n = 488)

Characteristic	Changes in MR severity at discharge versus follow-up (mean = 16.6 months)			p value*
	Unchanged n = 422	**Worsened n = 38**	**Improved n = 28**	
Age (years)	81.1 ± 7.3	81.7 ± 6.4	83.9 ± 6.6	0.119
Male	216 (51.2)	15 (39.5)	13 (46.4)	0.356
Coronary artery disease	238 (56.4)	25 (65.8)	19 (67.9)	0.287
Previous myocardial infarction	61 (14.5)	7 (18.4)	6 (21.4)	0.538
Peripheral vascular disease	73 (17.3)	6 (15.8)	6 (21.4)	0.830
Stroke/TIA	27 (6.4)	4 (10.5)	2 (7.1)	0.659
Diabetes	128 (30.3)	13 (34.2)	10 (35.7)	0.755
Systemic arterial hypertension	306 (72.5)	27 (71.1)	21 (75.0)	0.938
Renal failure	323 (76.5)	30 (78.9)	26 (92.9)	0.131
Hemoglobin (mg/dl)	11.8 ± 1.7	11.8 ± 1.7	11.8 ± 2.0	0.968
Pulmonary hypertension	85 (20.1)	9 (23.7)	11 (39.3)	0.055
NYHA functional class III or IV	347 (82.2)	28 (73.7)	24 (85.7)	0.365
Atrial fibrillation	50 (12.0)	7 (18.4)	5 (17.9)	0.407
EuroScore mortality	15.2 (15.8)	19.8 (20)	18.4 (21.2)	0.077
STS score mortality	7 (10.7)	10.9 (13.2)	10.6 (8.2)	0.254
Moderate/severe baseline aortic regurgitation	54 (13.1)	6 (16.2)	3 (11.1)	0.825
Previous balloon aortic valvuloplasty	28 (6,6)	3 (7,9)	1 (3,6)	0,744
Baseline EF (%)	58.6 ± 15.3	59.0 ± 14.5	49.8 ± 16.5	0.015
Baseline LV diastolic diameter (mm)	50,6 ± 8,0	51.4 ± 9.0	51.8 ± 8.0	0.569
Baseline aortic valve area (cm²)	0.66 ± 0.19	0.70 ± 0.14	0.62 ± 0.23	0.317
Baseline mean aortic gradient (mmHg)	50.5 ± 16.3	46.0 ± 14.4	45.7 ± 14.4	0.104
Discharge EF (%)	60.4 ± 13.4	61.4 ± 12.7	55.3 ± 15.3	0.117
Discharge LV diastolic diameter (mm)	50.4 ± 9.0	51.8 ± 9.0	51.6 ± 8.0	0.642
Discharge mean aortic gradient (mmHg)	10.2 ± 6.1	9.2 ± 7.9	7.6 ± 3.7	0.131
Discharge peak aortic gradient (mmHg)	18 (11)	15.5 (12.5)	15 (8.5)	0.068
Difference baseline-follow-up EF (%)	0 (11)	-2 (14)	2 (16)	0.052
Difference baseline-follow-up mean aortic gradient (mmHg)	0 (5)	0 (7)	2 (5)	0.212
Difference baseline-follow-up peak aortic gradient (mmHg)	0 (9)	-2 (9.8)	1 (9)	0.170
Moderate/severe residual aortic regurgitation	34 (8.0)	2 (5.4)	1 (3.5)	0.540

*Results described by frequency (percentage), mean ± standard deviation, or median (interquatile range). *One-way ANOVA, non-parametric Kruskal-Wallis test (quantitative variables), or chi-square test (categorical variables), p < 0.05*
EF: ejection fraction, LV: left ventricle, MR: mitral regurgitation, NYHA: New York Heart Association, STS: Society of Thoracic Surgeons, TAVI: transcatheter aortic valve implantation, TIA: transient ischemic attack.

selection, but a recent study by Akodad et al. has shown that valve-in-valve TAVI is as safe and feasible as TAVI in native AS, with no significant influence in the follow-up of such patients.[32] This finding indicates that the inclusion of a small number of degenerated surgical bioprostheses should not affect our results and conclusions.

One of the most important findings in the present study was that progressive deterioration of MR has a negative impact on late mortality in patients undergoing TAVI. It is known that a significant portion of the patients who show an initial improvement in MR severity, both after surgical aortic valve replacement and after TAVI, regress to baseline status if followed for more than 1 year.[33,34] However, the finding that this MR worsening is an independent predictor of higher late mortality rates has seldom been reported in the literature.[25] This finding could play an important role

Table 4 – Impact of groups defined by changes in MR severity: baseline to discharge, discharge to follow-up, and general mortality

	Mean time (months	Deaths (%)	Non-adjusted		Adjusted**	
			HR (95% CI)	p value*	HR (95% CI)	p value*
MR from baseline to discharge						
Unchanged (reference)	54.6	24,5	1		1	
Worsening	44.0	28.6	1.21 (0.68 – 2.14)	0.512	1.28 (0.70–2.32)	0.426
Improvement	35.1	25.0	1.03 (0.61 – 1.73)	0.912	1.17 (0.69–1.98)	0.561
MR from discharge to follow-up						
Unchanged (reference)	68.1	16.9	1		1	
Worsening	51.3	28.2	1.61 (0.85 – 3.04)	0.141	2.74 (1.36 – 5.48)	0.005
Improvement	50.5	18.8	1.42 (0.62 – 3.29)	0.408	1.48 (0.62 – 3.50)	0.377

*Cox regression model (stepwise backward likelihood ratio) and Wald test, p < 0.05. **Baseline-to-discharge mitral dysfunction: adjusted for baseline hemoglobin level, NYHA functional class and previous balloon aortic valvuloplasty; **Discharge-to-follow-up mitral dysfunction: adjusted for NYHA functional class and previous balloon aortic valvuloplasty. CI: confidence interval, HR: hazard ratio, MR: mitral regurgitation.*
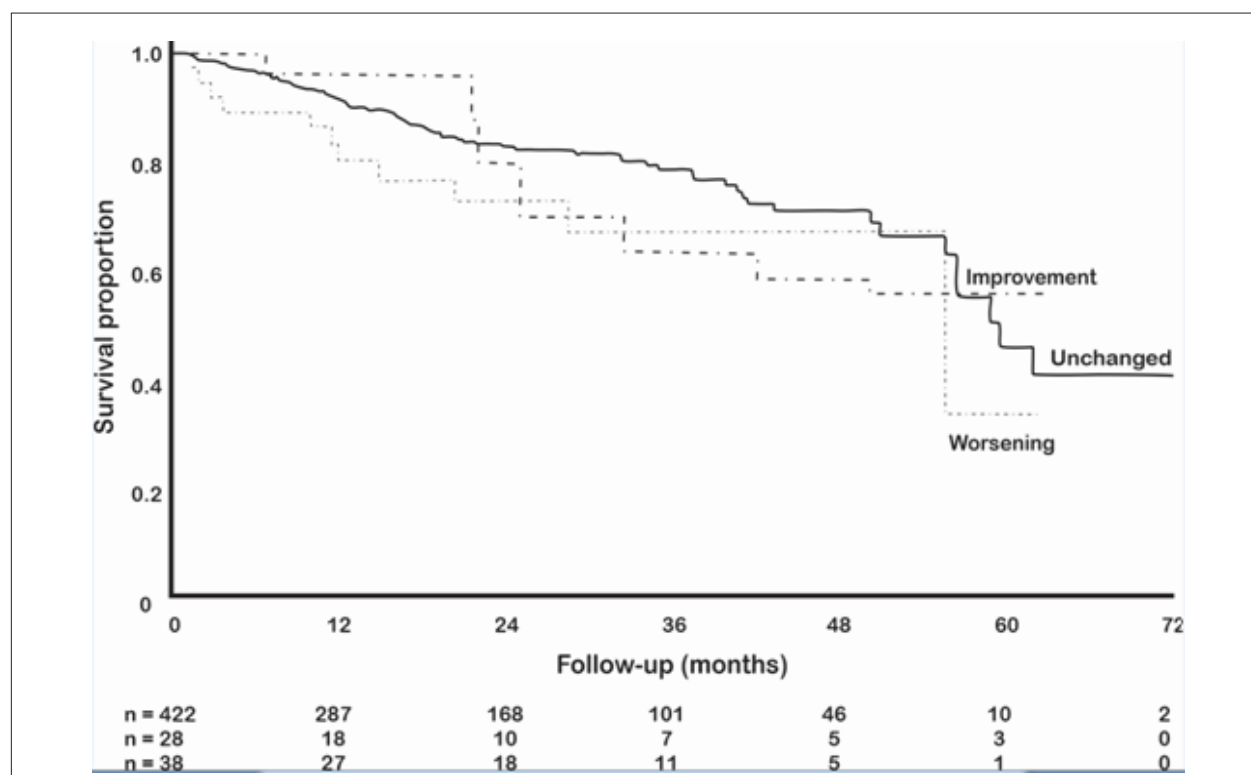
Figure 3 – *Kaplan-Meier curves with survival probabilities from discharge to follow-up periods for groups with improvement, no change and worsening of mitral regurgitation (MR) after TAVI (n = 488). Cox Regression Models comparing Unchanged MR to worsening of MR: p = 0.005; comparing unchanged MR to improvement of MR: p = 0.377.*

in future therapeutic strategies during TAVI follow-up. The association between MR worsening and increased mortality after TAVI does not indicate that MR treatment would lead to improved evolution after TAVI, since it can only be an indication of heart failure progression. However, associated percutaneous MR treatment has already been used for TAVI patients with good results,[35] and this combined therapy could be an option in the future.

Limitations

The present study has some limitations. Due to the non-randomized nature of the study, there was no control group, and, as the study design was observational, flaws in patient selection are possible. However, the TAVI Registry reflects the real-world practice in the Brazilian environment. The analysis was partially based on retrospective data and also included prospective data collection in most patients. Although echocardiographic criteria

for MR quantification were defined by current guidelines, there is no core lab for echocardiographic evaluation, and it may, therefore, be subject to inter-observer variation. The MR cases were separated according to severity, but their etiology (organic versus functional) could not be defined based on the registry data. The duration of late follow-up had a large variation, since patients were continuously included from 2008 to 2015; thus, some patients took longer to experience remodeling changes after TAVI. Finally, a non-negligible portion of patients was lost during echocardiographic follow-up.

Conclusions

The Brazilian TAVI Registry is the greatest series of TAVI in South America. It includes the first procedure carried out in Brazil, and it has the longest follow-up of such patients. The TAVI Registry reflects the real-world practice in the Brazilian environment. From our study, it is evident that baseline MSMR was a predictor of a higher late mortality rate after intervention. Most of the patients with baseline MSMR, especially those with a lower baseline LVEF and those who showed progressive improvement in LVEF, showed an improved MR grade at the follow-up. Progressive worsening of MR severity after TAVI resulted in a higher late mortality rate, and it should be considered in the future care of these patients.

Author contributions

Conception and design of the research and Analysis and interpretation of the data: Cunha LCBP, Guerios EE, Brito Jr. FS; Data acquisition: Guerios EE, Brito Jr. FS, Carvalho LA, Lemos Neto P, Sarmento-Leite R, Abizaid AA, Mangione JA, Oliveira AD, Siciliano A, Esteves V; Statistical analysis and Writing of the manuscript: Cunha LCBP; Critical revision of the manuscript for intellectual content: Guerios EE, Brito Jr. FS, Cunha CLP.

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*Supplemental Materials

For additional information, please click here.

Short Editorial

Mitral Regurgitation and Transcatheter Aortic Valve Replacement: Are There Any Other Prognostic Implications?

Antonio de Santis[1]

Universidade de São Paulo Instituto do Coração - Unidade Clinica de Valvopatia,[1] São Paulo, SP - Brazil

Short Editorial related to the article: Relationship between Mitral Regurgitation and Transcatheter Aortic Valve Implantation: a Multi-Institutional Follow-up Study

There is a variable prevalence of moderate to severe mitral regurgitation (13 to 74%) in patients with severe degenerative aortic stenosis.[1-6] In elderly and frail patients, this association can generate clinical dilemmas in cardiological practice: should I submit my patient to combined valve surgery, exposing him to higher morbidity and mortality, or contemplate only the severe aortic stenosis with a less aggressive treatment represented by the transcatheter aortic valve replacement (TAVR)? The variable degrees of severity associated with the commonly functional etiology (up to 80%) of the associated mitral regurgitation, places aortic valve stenosis in a high prominent position at this clinical hierarchy, with a resultant predilection for performing TAVR in these scenarios. In fact, some studies showed an improvement in the mitral regurgitation severity after TAVR, especially in patients with functional etiology and without pulmonary hypertension or atrial fibrillation.[5-7]

The impact of baseline mitral regurgitation on patients undergoing TAVR is still controversial. Toggweiler et al.[7] found that moderate to severe baseline mitral regurgitation in patients undergoing TAVR was associated with higher early mortality rates (first 30 days), with no difference in late mortality.[7] Conversely, Barbanti et al.,[8] using data from the randomized Placement of Aortic Transcatheter Valve (PARTNER) trial cohort A, found that moderate to severe baseline mitral regurgitation was associated with higher late mortality only in the surgical aortic valve replacement group, with no prognostic implication in the TAVR group.[8]

A very relevant and still little explored aspect is the prognostic value of changes in the degree of mitral regurgitation severity after TAVR. In this context, the present study conducted by Cunha et al.[9] consolidates the role of mitral regurgitation as a prognostic marker after TAVR, emphasizing that the prospective worsening of mitral regurgitation is an independent mortality predictor in the post-TAVR period.[9] By using the Brazilian TAVR registry, the authors had access to data from 22 national centers, allowing the inclusion of 795 patients for the analysis. Among those selected, 19.3% had moderate to severe baseline mitral regurgitation associated with severe aortic stenosis. The reported independent predictors of late mortality (mean follow-up period of 16.6 months) were: peripheral vascular disease, previous aortic balloon valvuloplasty and moderate to severe baseline mitral regurgitation, as demonstrated in previous studies.

Mitral regurgitation improvement was observed in almost 50% of the patients with moderate to severe reflux, while a small portion of patients showed mitral regurgitation worsening (8.7%). This finding, as well as the previous evidence, reinforces that TAVR, by reducing ventricular filling pressures and restoring an appropriate flow in the left ventricular outflow tract, can determine a reduction in the mitral regurgitant volume.[6-8] Interestingly, the authors found that patients with mitral regurgitation improvement in the post-TAVR period had a lower baseline ejection fraction. In these cases, the influence of TAVR in the reduction of the final diastolic volume and in the reverse ventricular remodeling may favor the geometry of the mitral valve annulus, especially in functional etiologies. Unfortunately, it was not possible to determine the mitral regurgitation etiology in the studied population. Furthermore, one of the most revealing findings of the present study was the negative impact of the worsening of the mitral regurgitation severity in the late follow-up of these patients, leading to higher mortality represented by the specific Kaplan-Meier curves.

The mitral regurgitation worsening in the post-TAVR period could be another potential outcome predictor, reinforcing the importance of periodic echocardiographic monitoring during the clinical follow-up of these patients. This progression also suggests that the usual lenient approaches, such as pharmacological therapies, may not be enough to prevent negative outcomes. Possibly, the use of percutaneous correction strategies for severe mitral regurgitation in the post-TAVR period could be further explored, always based on collegial decisions through institutional heart teams.

Keywords

Mailing Adress: Antonio de Santis •
Universidade de São Paulo Instituto do Coração - Unidade Clinica de Valvopatia – Av. Dr. Eneas Carvalho de Aguiar, 44. Postal Code 05403-000, São Paulo, SP - Brazil
E-mail: antonio.santis@einstein.br

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Original Article

Association between Serum Uric Acid and Pre-hypertension and Hypertension among Chinese Adults

Lijun Zhu,[1]* Xiaoyu Zhang,[2]* Zhengmei Fang,[1] Yuelong Jin,[1] Weiwei Chang,[1] Yan Chen,[1] Yingshui Yao[1,3]

Department of Epidemiology and Biostatistics, School of Public Health, Wannan Medical College/ Institute of Chronic Disease Prevention and Control,[1] Wuhu - China
Department of Clinical Nutrition, Hefei BOE Hospital,[2] Hufei - China
Department of Medicine, Anhui College of Traditional Chinese Medicine,[3] Wuhu - China
*The authors Lijun Zhu and Xiaoyu Zhang have contributed equally to the manuscript

Abstract

Background: Uric acid (UA), the end product of purine nucleotide metabolism, participates in the processes of metabolic and cardiovascular diseases. Experimental evidence suggests it is an important mediator in the physiological response to blood pressure increase.

Objective: To evaluate the association between serum UA levels and pre-hypertension and hypertension in a Chinese population.

Methods: A cross-sectional study was conducted from March to September 2017, and 1,138 participants aged 35 to 75 were enrolled in this study, where 223 normotensive, 316 pre-hypertensive, and 599 hypertensive subjects were selected to evaluate the association between serum UA levels and hypertension. A p-value <0.05 was considered statistically significant.

Results: Serum UA levels were significantly higher in the pre-hypertension and hypertension group compared to the control group in the entire population (p<0.05 for all). Quantitative trait analysis indicated that serum UA levels were (2.92±0.81, 3.06±0.85, 3.22±0.98 mg/d) linearly increased in normotensive, pre-hypertensive and hypertensive females, with a p value of 0.008. Serum UA levels in the quartiles were positively correlated with DBP (p<0.05), particularly in females. After adjusting for age, gender, body mass index (BMI), glucose (GLU), total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-c), the odds ratios (ORs) and 95% confidence intervals (CIs) of pre-hypertension from the lowest (referent) to the highest levels of serum UA were 1.718 (1.028–2.872), 1.018 (0.627–1.654) and 1.738 (1.003–3.010). Additionally, the second quartile of serum UA levels were significantly associated with hypertension, with an OR (95% CI) of 2.036 (1.256–3.298).

Conclusions: This study suggests that higher serum UA levels are positively associated with pre-hypertension and hypertension among Chinese adults.

Keywords: Cardiovascular Diseases/epidemiology; Blood Arterial; Hypertension; Risk Factors; Uric Acid; Hyperuricemia.

Introduction

The prevalence of cardiovascular diseases (CVD) is increasing rapidly in the world communities. The overall age-standardized prevalence rate of cardiovascular diseases increased significantly from 1990 to 2016 — by 14.7% — and the annual number of deaths from CVD increased from 2.51 million to 3.97 million in China.[1] High blood pressure (BP) has a major public health burden worldwide due to its high prevalence and it is a major risk factor for a series of CVD including stroke, myocardial infarction, heart failure and renal failure.[2] According to the "Summary of report on cardiovascular diseases in China (2018)", the number of hypertensive patients in China is about

245 million and the prevalence rate of males is higher than that of females.[3] Hypertension, a highly heterogeneous disorder, is influenced by the interaction between many factors such as sodium intake, alcohol, smoking, overweight, and genetic factors.[4] In recent years, many studies have shown that high serum uric acid (UA) levels are associated with increased incidence of hypertension.[5,6]

UA is the end product of purine nucleotide metabolism, and the disorder of purine metabolism or abnormal excretion of UA can lead to increased serum UA levels. Furthermore, increased serum UA concentration in the body results in hyperuricemia, ultimately leading to gout.[7] A screened cohort study has shown that hyperuricemia is a predictor of hypertension in both men and women.[8] Animal research has revealed that mild hyperuricemia causes hypertension and renal injury in rats via stimulation of the renin-angiotensin system and inhibition of neuronal nitric oxide (NO) synthase.[9] As an endothelial-derived relaxing factor, NO is crucial to the maintenance of blood pressure (BP).[10] A systematic review and meta-analysis reported that for a 60 umol/L increase in serum UA levels, the relative risk of hypertension increased

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by 13%, and this risk appears more pronounced in younger individuals and women.[11]

Hyperuricemia is commonly associated with pre-hypertension in adults.[12] Serum UA has also been shown to be an independent risk factor for a non-dipper circadian pattern of hypertension.[13] The higher the level of serum UA, the more difficult it is to control nighttime ambulatory blood pressure, nighttime diastolic blood pressure and morning blood pressure peak.[14] In an early study, hyperuricemia was reported in 25–40% of untreated hypertensive and 75% of malignant hypertensive subjects.[15] However, no independent association between serum UA levels and risk of incident hypertension was found among older men.[16]

When hypertension is complicated with hyperuricemia, both of them cause and affect each other, which aggravates the development of the disease. Therefore, despite an association between serum UA and hypertension, its mechanism remains unclear. Thus, in our study, we explored the association between high serum UA levels and hypertension among Chinese adults in Northern Anhui Province.

Methods

Study design

This study was conducted from March to September 2017 at the Physical Examination Center of a People's Hospital in Northern Anhui Province. A total of 1,191 participants aged 35 to 75 were enrolled in this study, including 643 hypertension cases and 548 normotensive subjects. Individuals with missing serum UA (n=53) value were excluded. Ultimately, 1,138 adults, including 223 normotensive, 316 pre-hypertensive, and 599 hypertensive subjects, were selected to evaluate the association between serum UA levels and hypertension. The study protocol was approved by the Ethics Committee of Wannan Medical College.

Data collection and measurement

Each participant completed a face-to-face interview and a standard questionnaire including demographic characteristics, medical history, and lifestyle characteristics. All information was collected by trained research staff. On physical examinations, all subjects were measured for height, weight, and blood pressure (BP). Body mass index (BMI) was calculated as body weight (kg) divided by height squared (m²). A well-trained research staff measured BP once using electronic sphygmomanometer with the participant in the sitting position after at least 5 minutes of rest. All the subjects fasted overnight for at least 10 hours before blood sampling. Venous blood samples of 5 ml were taken for measuring plasma total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-C) levels, glucose (GLU), and serum UA levels. Smokers were defined as cigarette consumers who had smoked at least 20 cigarettes per week or at least 3 months per year. Drinking alcohol at least 2 times per week or at least 6 months per year was considered as alcohol consumption.

Definition

Hypertension was defined as SBP≥140 mmHg and/or DBP≥90 mmHg, or use of antihypertensive drugs, and pre-hypertension was considered SBP 120–139 mmHg and/or DBP 80–89 mmHg.[17] Hyperuricemia was defined as serum UA levels >4.75 mg/dL in males and >4.04 mg/dL in females.[18] Serum UA levels were categorized by quartiles as ≤2.65, 2.66–3.24, 3.25–3.98, and ≥3.99 mg/dL.

Data analyses

Data normality was determined using the Kolmogorov-Smirnov test. Quantitative data are summarized as mean and standard deviation (mean±SD) with normal distribution; qualitative data as proportions. Gender differences in general characteristics were analyzed using Student's unpaired t-test for continuous variables and the Chi-square ($\chi2$) test for categorical variables. The differences for variables among the groups were determined by one-way analysis of variance (ANOVA) or $\chi2$ test, and Bonferroni corrections were used for multiple comparisons. Additionally, multiple unconditional logistic regression analysis was applied to estimate the relationship between UA and hypertension. Pearson's correlation coefficient test was performed to assess the interrelationships between baseline variables and serum UA levels. Epidata 3.1 (The Epidata Association, Odense, Denmark) was used to establish databases. All statistical analyses were performed with SPSS version 18.0 (SPSS, Chicago, IL). A 2-tailed p<0.05 was defined as statistically significant.

Results

Participant characteristics

This study included 1,138 individuals (223 controls, 316 pre-hypertensives, and 599 hypertensive subjects) aged 35 to 75. The demographic and clinical characteristics of the participants are presented in Table 1. The characteristics of LDL-C, creatinine, smoking, and drinking were not significantly different between the groups, whereas age, body mass index (BMI), glucose (GLU), total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), and UA did exhibit significantly differences. Serum UA levels (mg/dL) were significantly higher in the prehypertension (3.5±1.1) and hypertension (3.4±1.1) group compared to the control group (3.2±1.0) in the entire population (p<0.05 for all). Moreover, the prevalence of hyperuricemia was 10.3%, 17.1% and 17.0% in normotensives, pre-hypertensives and hypertensives, respectively.

By gender subgroup, of the 1,138 subjects, 568 were males, and 570 were females. The mean level of serum UA was 3.67 mg/dL in males and 3.11 mg/dL in females (p<0.05). Serum UA levels showed no difference between the groups in males. Further quantitative trait analysis of the serum UA (mg/dL) indicated that those for serum UA (2.92±0.81, 3.06±0.85, 3.22±0.98) increased linearly in normotension, pre-hypertension and hypertension in females, with a p value of 0.008 (Figure 1).

Levels of demographic and clinical variables in the serum UA quartiles

Baseline information of the subjects in each serum UA quartile is presented in Table 2. Mean BMI, DBP, TG, LDL-C, and creatinine were found to be increased with high levels of serum UA in the quartiles (p< 0.01 for trend).

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Table 1 – Demographic characteristics of normotension, pre-hypertension and hypertension

Characteristic	Normotension (n =223)	Pre-hypertension (n=316)	Hypertension (n=599)	p
Age (year)	56.1±11.3	58.2±11.2	61.2±9.8#*	0.000
BMI(kg/m²)	22.3±2.8	23.3±2.9#	24.1±2.9#*	0.000
SBP (mmHg)	108.3±7.8	126.2±7.4#	148.2±19.2#*	0.000
DBP (mmHg)	69.7±5.9	79.5±6.5#	89.1±13.0#*	0.000
GLU (mmol/L)	5.6±1.6	5.6±1.6	6.0±2.2#*	0.002
TC (mmol/L)	4.4±0.9	4.5±0.9	4.7±1.1#	0.003
TG (mmol/L)	1.2±0.8	1.3±0.8	1.7±1.2#*	0.000
HDL-C (mmol/L)	1.4±0.4	1.3±0.4	1.2±0.4#*	0.000
LDL-C (mmol/L)	2.6±0.8	2.7±0.8	2.6±0.8	0.235
Creatinine (umol/L)	82.5±61.8	80.4±13.5	86.1±39.2	0.110
UA (mg/dL)	3.2±1.0	3.5±1.1#	3.4±1.1#	0.013
Current smoker (n=362)	65 (29.1%)	95 (30.1)	202 (33.7%)	0.336
Current drinker (n=415)	68 (30.5%)	118 (37.3%)	229 (38.2%)	0.114
Prevalence of hyperuricemia (n=179)	23(10.3%)	54(17.1%)	102(17.0%)	0.046

*SBP: Systolic blood pressure; DBP: Diastolic blood pressure; GLU: Glucose; TC: Total cholesterol; TG: Triglycerides; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; UA: Uric acid. p: All participants from the normotension, pre-hypertension and hypertension groups had the variables analyzed by one-way ANOVA or Chi- square test. #: p<0.05 vs. Normotension. *: p<0.05 vs. Pre-hypertension.*
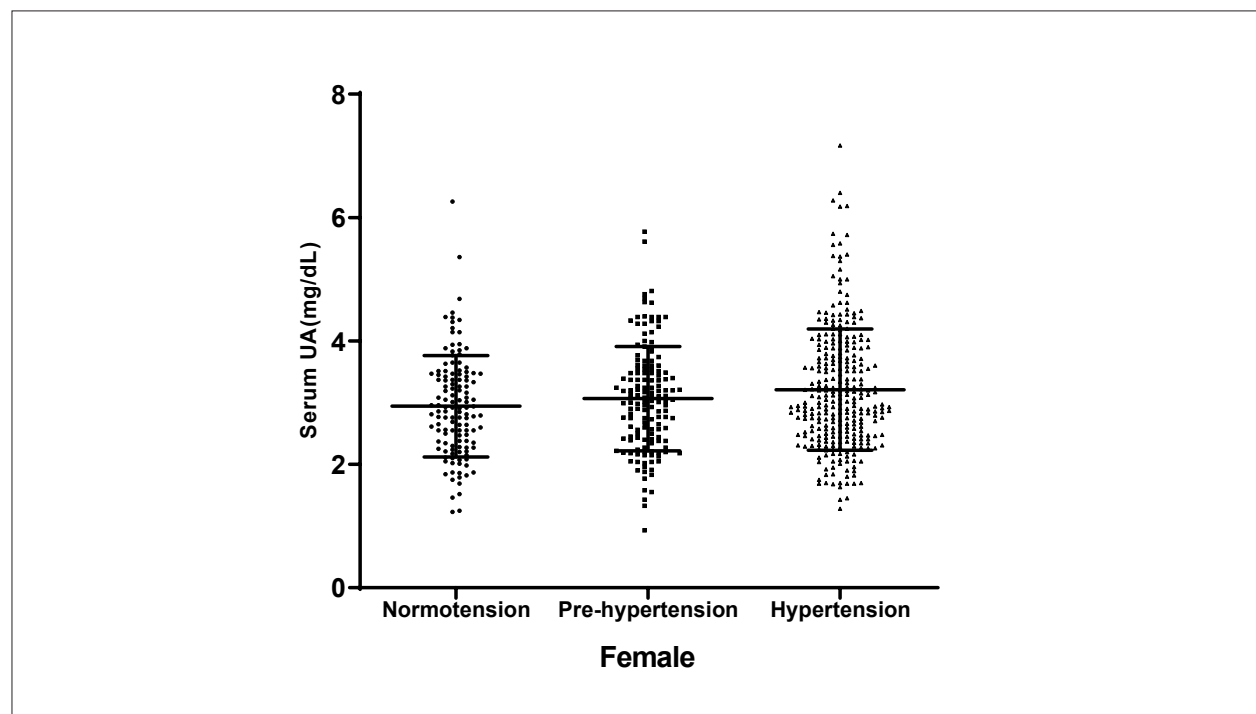
Figure 1 – *Comparison of serum UA levels in normotension, pre-hypertension and hypertension in females.*

Correlation of serum UA levels and clinical characteristics by gender

Serum UA levels were positively correlated with BMI, diastolic blood pressure (DBP), TC, TG, LDL-C, and creatinine in both genders. Serum UA levels were negatively correlated with age, and were positively correlated with BMI, TC, TG, LDL-C, and creatinine in males. In females, serum UA levels were positively associated with BMI, DBP, TG, LDL-C, and creatinine (Table 3).

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Table 2 – Baseline characteristics of the study participants according to serum UA quartiles

Characteristic	Serum UA (mg/dL)				p-values for trend
	Q1(≤2.65)	Q2 (2.66-3.24)	Q3(3.25-3.98)	Q4(≥3.99)	
Age (year)	60.2±10.5	59.2±10.5	58.7±10.7	59.4±11.1	0.305
BMI (kg/m²)	23.1±2.8	23.1±2.8	23.5±2.9	24.3±3.2	0.000
SBP (mmHg)	133.2±23.0	136.9±21.4	132.7±22.4	134.4±20.0	0.914
DBP (mmHg)	80.5±13.2	83.4±12.3	83.0±12.7	83.7±12.8	0.005
GLU (mmol/L)	6.0±2.4	5.8±2.2	5.6±1.5	5.8±1.5	0.120
TC (mmol/L)	4.5±1.0	4.5±1.0	4.5±0.9	4.7±1.00	0.098
TG (mmol/L)	1.2±0.7	1.3±0.9	1.5±1.1	1.8±1.3	0.000
HDL-C (mmol/L)	1.3±0.4	1.3±0.5	1.2±0.4	1.2±0.4	0.266
LDL-C (mmol/L)	2.5±0.8	2.6±0.8	2.7±0.9	2.9±0.8	0.000
Creatinine (umol/L)	73.7±14.3	81.9±53.5	83.1±14.1	96.6±54.4	0.000

SBP: Systolic blood pressure; DBP: Diastolic blood pressure; GLU: Glucose; TC: Total cholesterol; TG: Triglycerides; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; UA: Uric acid. p: All participants from the normotension, pre-hypertension and hypertension groups had the variables analyzed by one-way ANOVA for linear trend.

Table 3 – Correlation of serum UA levels and clinical characteristics of the study participants by gender

Characteristics	Male		Female		Total	
	r	p	r	p	r	p
Age (year)	-0.091	0.030	-0.042	0.314	-0.012	0.679
BMI (kg/m²)	0.167	<0.001	0.138	0.001	0.177	<0.001
SBP (mmHg)	-0.063	0.133	0.0.63	0.133	0.007	0.821
DBP (mmHg)	0.055	0.187	0.116	0.006	0.099	0.001
GLU (mmol/L)	-0.069	0.101	0.022	0.593	-0.017	0.570
TC (mmol/L)	0.152	<0.001	0.065	0.123	0.080	0.007
TG (mmol/L)	0.230	<0.001	0.205	<0.001	0.22	<0.001
HDL-C (mmol/L)	0.011	0.786	0.001	0.998	-0.041	0.163
LDL-C (mmol/L)	0.250	<0.001	0.148	<0.001	0.187	<0.001
Creatinine	0.143	0.001	0.443	<0.001	0.230	<0.001

SBP: Systolic blood pressure; DBP: Diastolic blood pressure; GLU: Glucose; TC: Total cholesterol; TG: Triglycerides; HDL-C; High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; UA: Uric acid.

Association between serum UA quartiles and pre-hypertension and hypertension

In logistic regression analysis, Table 4 presents the odd ratios of pre-hypertension and hypertension by increasing serum UA quartiles. After adjusting for age and sex in pre-hypertension, the odd ratios (ORs) (95% CI) were 1.686 (1.024–2.775), and 2.064 (1.220–3.492), respectively in Q2 and Q4 compared to Q1. After additionally adjusting BMI, GLU, TC, TG, HDL-C, the association was still statistically significant. The second quartile of serum UA levels was significantly associated with hypertension, with an OR (95% CI) of 2.061 (1.313–3.235), and 2.036 (1.256–3.298), for models 1 and 2, respectively.

Discussion

Abnormal UA levels have been involved in vascular remodeling and endothelial dysfunction, which may be the cause of cardiovascular disorders.[19,20] UA can be regarded as an important antioxidant, which doe not only stabilize endothelial nitric oxide synthase (eNOS) activity but also increases fat storage and triglycerides.[21] Epidemiological studies have demonstrated a strong association between UA and coronary artery disease, atherosclerosis and hypertension.[22] In our study, we report that higher serum UA levels were found to be positively associated with pre-hypertension and hypertension in middle-aged and old-age population, and high serum UA levels causes a corresponding increase in DBP. The overall risk for pre-hypertension has increased by 73.8% for the highest vs. lowest quartile of serum UA levels, even after adjusting for potential confounding variables. Furthermore, we found that the association was more robust in the female participants.

Previous studies have examined the association between serum UA levels and hypertension, and the results were in agreement with our findings. Sundstrom et al.[23] revealed that

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Table 4 – Association between serum UA quartiles and pre-hypertension and hypertension

Serum UA (mg/dL)	Pre-hypertension		Hypertension	
	Age, sex-adjusted	Multivariate	Age, sex-adjusted	Multivariate
Q1 (≤2,65)	1	1	1	1
Q2 (2.66–3.24)	1.686 (1.024–2.775)*	1.718 (1.028–2.872)*	2.061 (1.313–3.235)*	2.036 (1.256–3.298)*
Q3 (3.25–3.98)	1.091 (0.683–1.742)	1.018 (0.627–1.654)	1.105 (0.723–1.689)	0.912 (0.576–1.444)
Q4 (≥3.99)	2.064 (1.220–3.492)*	1.738 (1.003–3.010)*	2.236 (1.387–3.606)	1.613 (0.967–2.690)

*Multivariate was adjusted for age, gender, BMI, GLU, TC, TG, HDL-C; * Compared to Q1, p<0.05.*

increased serum UA levels were an independent predictor of hypertension development after a short-term follow-up. High LDL-c and serum UA levels are risk factors for endothelial dysfunction and vascular ageing. The contemporary presence of suboptimal LDL-c and serum UA values is associated with an increased risk of hypertension in an overall healthy population sample.[24] A 5-year retrospective cohort study found that increased UA is a strong risk marker for hypertension developed from pre-hypertension in Japanese adults.[25] Moreover, pilot clinical studies suggest lowering serum UA levels has been reported to lower blood pressure in pre-hypertensive adolescents.[26] Currently, pre-hypertension is common in China. Approximately 20–50% of adults were affected by pre-hypertension worldwide, and this increases the risk of incident hypertension.[27] The prevalence of pre-hypertension is rapidly increasing in China, but its causes and associated factors have not been well studied.

We observed that serum UA levels were increased linearly in normotension, pre-hypertension and hypertension in females, and this association between serum UA and blood pressure was stronger among females than in males. Besides, serum UA levels were positively associated with DBP, particularly in females. Some previous studies have demonstrated that the association between serum UA levels and hypertension was more pronounced in women. Peng et al.[28] also found that hyperuricemia was associated with pre-hypertension among 1,773 Chinese women aged ≥30. Similar results were presented in a follow-up study, in which Strasak et al.[29] demonstrated that serum UA is an independent predictor of all major forms of cardiovascular death in elderly women. The changing levels of serum UA in women at menopause suggests an interaction with sex hormones.[30] Research has reported that the gender difference of blood pressure began to appear in adolescence, and pubertal growth spurt occurs earlier for girls than for boys.[31] SBP increased significantly more in boys than in girls, while DBP increased more in girls than in boys.[32] Other complex physiological and hormonal changes may contribute to hypertension.

Several limitations must be considered. First, the cross-sectional design used to evaluate the relationship between serum UA and pre-hypertension and hypertension limits our ability to establish a causal relationship. This problem may be solved by longitudinal studies in the future. Secondly, the interaction mechanism between hypertension and increased uric acid has not been explored. Further studies are still needed to examine the potential gender difference of the association between serum UA levels and hypertension in different populations.

Conclusions

Our findings suggest that serum UA is significantly associated with pre-hypertension and hypertension, and the association was more robust in the female participants. Therefore, proper early management of UA levels in adults may be important to prevent the development of hypertension.

Author Contributions

Conception and design of the research: Zhang X, Yao Y, Chen Y; Acquisition of data: Zhang X, Fang Z, Jin Y; Analysis and interpretation of the dat and Writing of the manuscript a: Zhu L; Statistical analysis: Fang Z, Chang W; Obtaining financing: Zhu L, Jin Y, Chang W, Yao Y, Chen Y.

Potential Conflict of Interest

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

Study Association

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

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Still Trying to Understand the Role of Uric Acid in Cardiovascular Diseases

Gilson Soares Feitosa[1,2] ®

Escola Bahiana de Medicina,[1] Salvador, BA - Brazil
Hospital Santa Izabel da Santa Casa da Bahia, Salvador, BA - Brazil
Short Editorial related to the article: Association between Serum Uric Acid and Pre-hypertension and Hypertension among Chinese Adults

In this issue of *Arquivos Brasileiros de Cardiologia*, Zhu et al.[1] report an association between uric acid and the presence of pre-hypertension or hypertension in a cross-sectional study done in a population in North China, bringing about, once more, a possible role of uric acid in the determination of cardiovascular disease. In the study, the authors call our attention to the possibility of a relationship even though the measured uric acid serum level is relatively low as compared to what is referred to as normal in several Western populations, which presents a cutoff value of ≥7.0 mg/dL for men and ≥6.3 mg/dL for women[2] in the United States and also so considered, a cutoff value of ≥7.0 mg/dL for men and ≥ 6.0 mg/dL for women in a Brazilian population of healthy

Keywords

Cardiovascular Diseases; Uric Acid; Hyperurisemia; Oxidative Stress; Obesity; Endothelium; Risk Factors.

Mailing Address: Gilson Soares Feitosa •
Hospital Santa Izabel - Rua Florida, 211/302. Postal Code 40050-410,
Salvador, BA – Brazil
E-mail: gfeitosa@cardiol.br, gilson-feitosa@uol.com.br

individuals aged 20 to 55, in Rio de Janeiro,[3] whereas in their the cut off values were ≥4.75 mg/dL and ≥4.04 mg/dL for men and women, respectively.

In workers from the Company of Generation and Distribution of Energy in Rio de Janeiro, Brazil, from both sexes, aged predominantly between 50 and 59, the mean uric acid level was 4.7±1.3 mg/dL.[4]

In another study in Brazil, in a cross-sectional study named PROCARDIO-UFV, the mean serum uric acid levels were 4.4±1.6 mg/dL and 5.4±1.4 mg/dL in low and intermediate Framingham risk score, respectively.[5]

Similar studies that come from Asia display lesser uric acid values in the general population, and eating habits or genetic factors are speculated as its cause.[6-8]

In the study the values of 3.5±1.1 mg/dL in pre-hypertensives and 3.4±1.1 mg/dL in hypertensives were significantly higher than 3.2±1.0 mg/dL in the control group, regardless of the adjustments made for confounding factors such as age, sex, body mass index, glucose, and lipid levels.

A question that arises is whether such a minuscule difference of values would justify the conjectured changes in endothelial function as a cause of cardiovascular disease in such individuals,[9-11] in addition to its potential therapeutic target.

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Original Article

Clinical Profile and Outcome of Patients with Cardiac Implantable Electronic Device-Related Infection

Alessandra de Souza Maciel[1] and Rose Mary Ferreira Lisboa da Silva[2]

Universidade Federal de Minas Gerais - Hospital das Clínicas,[1] Belo Horizonte, MG - Brazil
Universidade Federal de Minas Gerais - Departamento de Clínica Médica,[2] Belo Horizonte, MG - Brazil

Abstract

Background: In recent years, the incidence of infections related to cardiac implantable electronic devices (CIED) has increased sharply, impacting mortality.

Objective: To verify the proportion of patients with CIED infection; to analyze their clinical profile and the variables related to the infection and its progression.

Methods: Retrospective and longitudinal observational study including 123 patients with CIED infection among 6406 procedures. Parametric tests and a level of significance of 5% were used in the statistical analyses

Results: The mean age of patients was 60.1 years and mean length of stay in hospital was 35.3 days; most (71) patients were male, and the system was completely removed in 105 cases. Infectious endocarditis (IE) and sepsis were observed in 71 and 23 patients, respectively. Intra-hospital mortality was 19.5%. IE was associated with extrusion of the generator (17.0% vs 19.5% with and without IE, respectively, p = 0.04, inverse association) and sepsis (15.4% vs 3.2%, p = 0.01). Intra-hospital death was associated with IE (83.3% vs 52.0% with and without intra-hospital death, respectively, p = 0.005) and sepsis (62.5% vs 8.1%, p < 0.0001). Ninety-nine patients were discharged. During a mean follow-up of 43.8 months, mortality rate was 43%; among patients with sepsis, it was 65.2% (p < 0.0001). By applying a Kaplan-Meier survival curve, we did not indicate significant associations with sex, etiologic agent, ejection fraction, IE, or treatment modality. The death rate was 32.8% for patients subjected to endocardial electrode reimplantation and 52.2% for epicardial reimplantation (p = 0.04). Chagasic etiology (44.7% of the baseline heart diseases) did not influence clinical and laboratory variables or disease progression.

Conclusion: The infection rate was 1.9%, mostly in men. We observed an association of intra-hospital mortality with IE and sepsis. After discharge, the annual mortality rate was 11.8%, influenced by sepsis during hospitalization and epicardial implantation.

Keywords: Cardiac Pacemaker Implantation; Cardiovascular Surgical Procedures; Bacteria; Endocarditis; Outcome; infection.

Introduction

The use of cardiac implantable electronic devices (CIED) has grown exponentially in the las 10 years owing to technology advancements, broadening indications, and increasing life expectancy. On the other hand, during this period, an important and disproportionate 210% increase in the incidence of CIED-related infections has brought this number to 19.9%.[1-4] These infections are related to the type of device and number of interventions.[5] After device replacement, the risk of infection is around 5%, which indicates a 2–4-fold increased risk when compared to a primary implant.[5,6] Other factors are also associated with increased infection rates, such as sex, age, comorbidities, and lack of prophylaxis.[7,8]

This type of infection causes significant morbidity, and intra-hospital mortality varies from 6% to 14% with a total mortality of approximately 20% in one year.[1,6,9] Some variables are also associated with unfavorable outcomes and mortality predictors, such as the patient's age, use of temporary pacemaker (PM), device replacements, *Staphylococcus* sp. as the etiologic agent, prosthetic heart valves, time to device removal, kidney disease, need for blood transfusion, and endocarditis.[1,10-13] The risk of death due to CIED-related infection depends on the device type and persists with time. The 20% mortality rate continues for 3 years for single- or dual-chamber PMs, and for 2 years for the implantable cardioverter-defibrillator (ICD).[14]

In Brazil, information on this subject is scarce; moreover, patient characteristics and etiologies for CIED implantation are different from those observed in developed countries. Therefore, recognizing these patients' profile and their clinical course is an important initial step for implementing the guidelines established by the literature.[15] In view of this information, the objectives of this study were to verify the proportion of patients with CIED-related infection and to analyze their clinical and laboratory profiles, variables related to the infection, and its progression.

Methods

This is a retrospective and longitudinal observational cohort study. Our population consisted of 123 patients with device-related infection, of both sexes and all ages, selected among 6406 CIED implantation procedures performed between 2001 and 2017. Patients with DCEI infection but who underwent implantation of the device in other hospitals were also excluded. We excluded patients with infections related to temporary PMs. Both the research project and the free and informed consent form were approved by the institution's Ethics and Research Committee according to Resolution No. 466/2012. We analyzed clinical and laboratory variables, as well as pharmacological and non-pharmacological treatment data. The diagnosis of CIED-related infection considered clinical examinations associated with a complete blood count, C-reactive protein, blood cultures, and echocardiogram examinations. Infectious endocarditis was diagnosed using modified Duke criteria.[16]

In the institution where the study was conducted, prophylaxis and treatment of CIED-related infections included aseptic techniques with chlorhexidine detergent showers the night before and in the morning of the procedure, hair removal, surgical degerming, and skin antisepsis with chlorhexidine detergent for 2 min, removing excess product and applying an alcoholic chlorhexidine solution. According to the same protocol, antibiotic prophylaxis was performed 1 h before the procedure with a single dose of 2g of cefazolin.

Sepsis was defined as a potentially fatal organic dysfunction caused by a dysregulated immune response to infection.[17] Intra-hospital mortality considered deaths due to infection during hospitalization. After discharge, surviving patients were followed-up for a minimum period of 6 months. We considered post-discharge deaths as natural deaths of cardiac or non-cardiac causes. Total mortality considered intra-hospital deaths (due to CIED-related infection) and post-discharge deaths during follow-up.

Statistical Analysis

Data were analyzed using SPSS version 14.0. Results were expressed as absolute numbers and proportions for categorical variables, and as means and standard deviations for continuous variables. When appropriate, chi-squared and Fisher's tests were used for verifying associations between categorical variables. For comparing continuous variables, an unpaired Student's t-test was used after verifying a normal distribution through the Kolmogorov-Smirnov test. The confidence interval used in the analyses was 95%. Survival analysis used Kaplan-Meier curves, which were compared using a log-rank test. The level of significance used in the analyses was 5%.

Results

General Characteristics of the Studied Cases

The mean age of the 123 patients with CIED-related infection was 60.1 ± 19.4 years (ranging from 3 months to 97 years); 71 (57.7%) patients were male. The mean number of procedures considering implantations, replacements, and electrode manipulations was 1.7. Mean left ventricular ejection fraction was 48.4%. Considering the period of patient inclusion (16 years), the annual infection rate was 1.2 per 1000 procedures.

The main baseline heart diseases are displayed in Figure 1. Regarding CIED, stimulation modes were: PM VVI mode in 38.2% of the patients, DDD mode in 30.9%, and AAI mode in 2.4% of the patients; ICD in 19.5% of the patients; and cardiac resynchronization therapy (CRT) in 9% of patients.
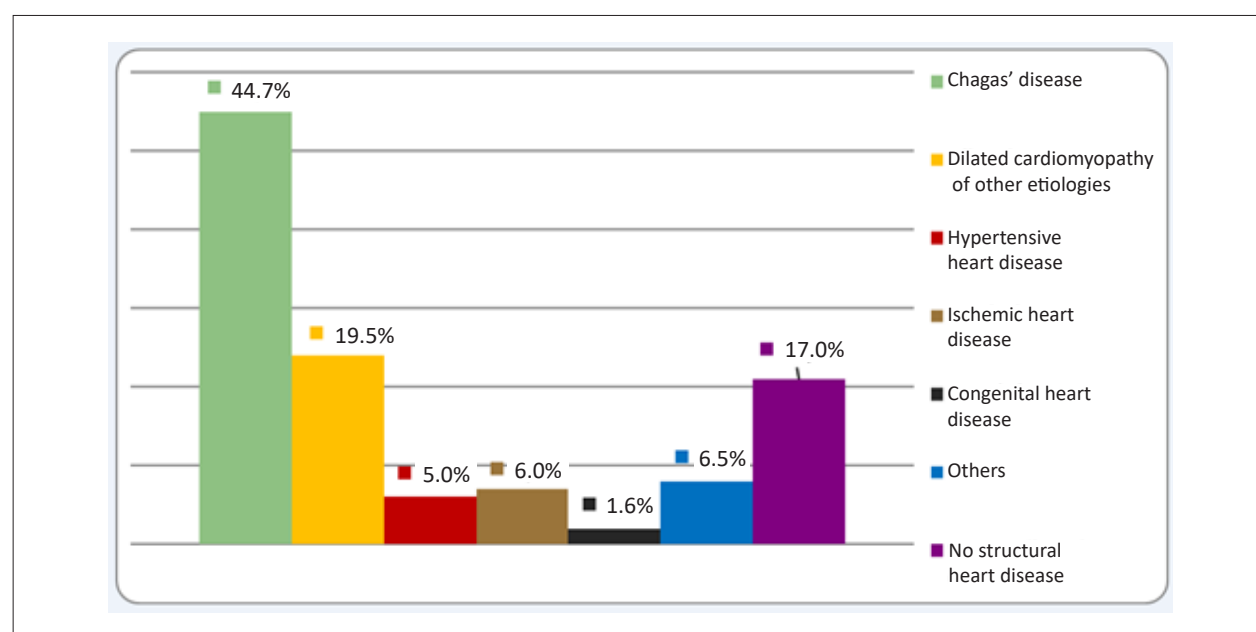
Figure 1 – *Main baseline heart diseases.*

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Variables Related to Infection

All patients presented signs and/or symptoms suggestive of CIED-related infection. We observed pocket discharge in 39 (31.7%) patients, fever and malaise in 23 (18.6%) patients, and pocket with signs of hyperemia and fluctuation in 16 (13.0%) patients. Forty-five (36.5%) patients presented extrusion of the generator.

We performed blood cultures with samples from all patients. The most prevalent etiologic agent, isolated in the cultures of 63 (51.2%) patients, was *Staphylococcus aureus,* followed by *Streptococcus* epidermidis in 2 (1.6%) patients. Other agents such as Serratia sp., *Pseudomonas aeruginosa, Enterococcus faecalis*, and *Klebsiella* sp. were isolated in 20 (16.3%) patients. Thirty-six (29.7%) patients presented more than one etiologic agent. Blood cultures were negative in 38 (30.9%) patients.

Seventy-four patients had blood cultures performed with samples collected from the generator pocket and electrode tips. In cultures performed with generator pocket samples, *S. aureus* was found in 15 (20.2%) patients, and *S. epidermidis* was found in 5 (6.7%) patients. Other etiologic agents such as *Pseudomonas* sp., *Escherichia coli*, and *Acinetobacter baumannii* were isolated in 8 (10.8%) samples.

Catheter tip cultures demonstrated *S. aureus* as etiologic agent in 21 (28.3%) patients. Other agents such as *Serratia marcescens*, *Pseudomonas* sp., and *Aeromonas hydrophila* were isolated in 7 (9.4%) samples.

One hundred and fourteen patients underwent transthoracic echocardiography. Transesophageal echocardiography was performed in 91 (73.9%) patients, of which 44 (35.7%) yielded images suggestive of vegetation.

Other laboratory data (leucocytes, C-reactive protein) and the time between the last implantation and the diagnosis of infection, as well as length of stay, are shown in Table 1.

CIED-related infection occurred after the first implantation procedure in 58 (47.1%) patients. In 55 (44.7%) patients, it happened at generator replacement, and in 10 (8.1%) patients, it occurred after device manipulations such as generator pocket revision, device upgrade, and electrode repositioning.

We observed early infections (when the time between the procedure and diagnosis of infection was shorter than a year) in 78 (63.4%) patients. Sex, age, body mass index, number of procedures, device type, and ejection fraction did not influence the occurrence of infection.

Pharmacological and Non-pharmacological Approaches to Infection

The most widely used antibiotic was vancomycin, in 91 (73.9%) patients, followed by oxacillin in 20 (16.2%) patients. The system was totally removed in 105 (85.4%) patients and was partially removed in 11 (8.9%) cases. Seven (5.7%) patients were treated only with antibiotics. Among those who underwent partial removal, 8 (6.5%) had infection relapse.

New systems were reimplanted in 108 patients, of which 64 (52%) underwent endocardial reimplantation and 44 (35.7%), epicardial reimplantation. Fifteen (12.1%) patients did not undergo CIED reimplantation due to the following reasons: 4 were subjected to cardiac transplants, 3 patients died before reimplantation, and 1 patient's family did not provide authorization for reimplantation. In 3 cases, the medical team opted not to perform reimplantation.

Intra-hospital Patient Course

Mean length of stay was 35.3 ± 22.3 days, ranging from 1 to 131 days. Forty (32.5%) patients progressed without complications during hospitalization. Thirty-seven (30.0%) patients had worsening renal function, 27 (21.9%) had pulmonary thromboembolism, encephalopathy, and meningitis, 11 (8.9%) had pleural effusion, and 8 (6.5%) needed mechanical ventilation. Seventy-one (57.7%) patients had infectious endocarditis, of which 19 (15.4%) progressed to sepsis. Sepsis was diagnosed in 23 (18.7%) patients, and 15 (12.1%) died due to this condition. As for endocarditis and device types, 55.6% of the patients who had endocarditis had a PM, while 62.5% had an ICD, and 54.5% had a CRT device (p = 0.65). Other data on variables associated (or not) to infectious endocarditis are shown in Table 2.

Intra-hospital mortality was 19.5% (24 patients); all deaths were due to CIED-related infection. A comparison between patients who progressed or not to intra-hospital death is presented in 3.

The risk of intra-hospital death, regarding a clinical course with infectious endocarditis, was 4.47 (95% confidence interval 1.42–14.1). As for sepsis, this risk was 4.1 (95% confidence interval 1.3–12.9).

According to device type, 18 (20.5%) patients with PM, 4 (16.6%) with ICD, and 2 (18.2%) with CRT devices died in the hospital (p = 0.42).

Table 1 – Variables related to the infection

Variables	Mean	Standard deviation	Minimum	Maximum	Median
Δ time (days)	563.36	936.43	1	5895	138.5
Leukocytes (cells/mm³)	9502.7	5900.9	1008.0	51310.0	8350.0
C-reactive protein (mg/L)	68.7	81.3	3	376.6	34.3
Length of stay (days)	35.3	22.3	1	131	29.0

Δ time: time between the last implantation and the diagnosis of infection.

Table 2 – Comparison between variable means in patients with or without infectious endocarditis

Variables	No endocarditis	Endocarditis	p-value*
Male sex	31 (25.2%)	39 (31.7%)	0.51
Age (years)	60.2 ± 18.9	60.0 ± 19.9	0.95
BMI (kg/m^2)	24.5 ± 5.1	24.2 ± 4.9	0.77
Ejection fraction (%)	45.0 ± 16.4	50.4 ± 17.7	0.99
Extrusion of the generator	24 (19.5%)	21 (17.0%)	0.045
No. of procedures	1.6 ± 0.8	1.8 ± 0.9	0.405
Sepsis	4 (3.2%)	19 (15.4%)	0.010
Leukocytes (cells/mm^3)	8638 ± 9886	8568 ± 7351	0.96
C-reactive protein (mg/L)	51.6 ± 56.4	80.9 ± 93.6	0.043

*BMI: body mass index. * chi-squared or Fisher's tests, or unpaired Student's t-test.*

Table 3 – Analysis between patients who progressed or not to intra-hospital death

Variables	Intra-hospital death (n = 99)	Intra-hospital death (n = 24)	p-value*
Male sex	57 (46.4 %)	14 (11.3%)	0.94
Age (years)	59.9 ± 18.6	61.2 ± 22.8	0.79
BMI (kg/m^2)	24.7 ± 4.9	22.9 ± 5.9	0.21
Ejection fraction (%)	49.0 ± 17.3	45.9 ± 17.9	0.45
No. of previous procedures	1.73 ± 0.9	1.95 ± 0.9	0.317
Proportion of patients who progressed to IE	52.0	83.3	0.005
Proportion of patients who progressed to sepsis	8.1	62.5	< 0.0001
Leukocytes (cells/mm^3)	8580 ± 8646	8661 ± 7777	0.96
C-reactive protein (mg/L)	62.73 ± 72.0	94.76 ± 111.4	0.22

*BMI: body mass index; IE: infectious endocarditis. * chi-squared or Fisher's tests, or unpaired Student's t-test.*

Progression After Hospital Discharge

Eight patients presented more than one infection. Ninety-nine (80.4%) patients were discharged and followed-up for a mean period of 43.8 months (median 28.3, ranging from 0.6 to 144 months). The mortality rate after hospital discharge was 29.3% (29 patients), and deaths occurred within 3.94 and 164.5 months.

Survival Curves

We constructed Kaplan-Meier survival curves considering the occurrence of total deaths (due to cardiac and non-cardiac causes) and applied a log-rank (Mantel-Cox) test for comparing them.

- Total survival

Fifty-three (43.0%) patients died during the 43.8-month follow-up; 24 patients died in the hospital and 29, after discharge. The annual mortality rate was 11.8% and 0.52 per 1000 procedures/year. Figure 2 represents the total survival curve for this study.

- Sepsis

Out of the 23 patients diagnosed with sepsis, 15 (65.2%) died during the 43.8-month follow-up (p < 0.0001 in the log-rank test, Figure 3). Analyses with 6- and 36-month follow-up periods yielded the same p-value.

- Other variables

No differences were observed regarding sex (p = 0.89) and etiologic agent (p = 11). As for device types, the mortality rate was 48.8% in patients with PM, 29.2% in patients with ICD, and 27.2% among those with CRT devices (p = 0.92). Among patients who presented endocarditis during their hospitalization, 47.8% died during the 43.8-month follow-up (p = 0.93), with no significant differences even when considering 6- and 36-month follow-up periods (p = 0.11 and 0.08, respectively). Considering ejection fractions < 50% or ≥ 50%, the death rate was 44.2% and 41.5% during the whole follow-up (p = 0.06). As for treatment modalities, 42.8% of patients treated only with antibiotics died, while

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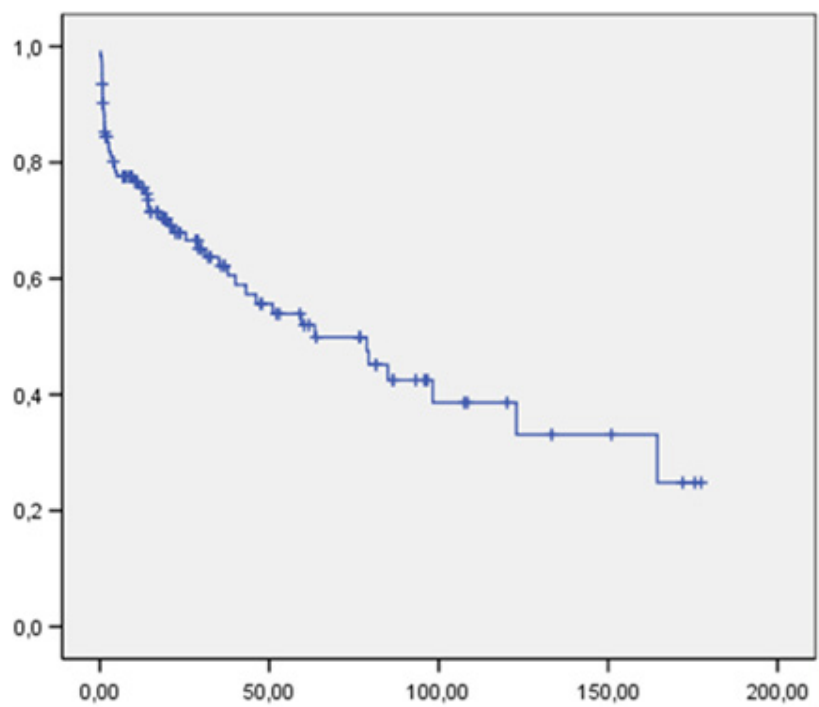
Figure 2 – *Survival curve for the studied cases. X-axis: time (months); Y-axis: cumulative survival probability.*
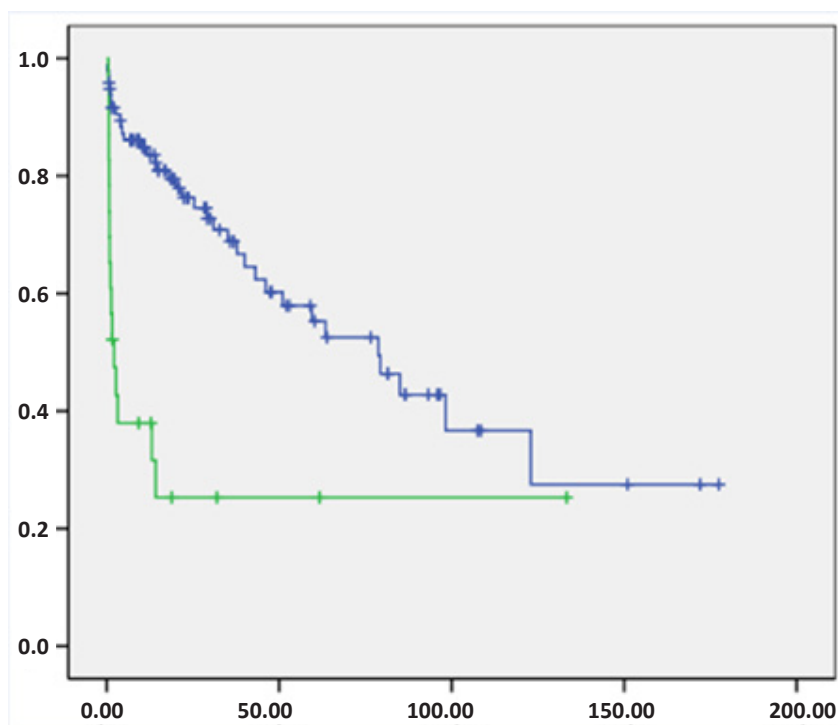
Figure 3 – *Survival curve regarding sepsis. X-axis: time (months); Y-axis: cumulative survival probability. Blue curve: patients who did not have sepsis during hospitalization; green curve: patients who progressed to sepsis during hospitalization.*

18.2% of those subjected to partial removal of the system and 47.7% of those subjected to complete removal died (p = 0.07). Considering implant types, 32.8% of patients who underwent endocardial reimplantation and 52.2% of those who underwent epicardial reimplantation died (p = 0.04).

Comparison between Patients with and without Chagas' Disease

When comparing these 2 groups, no differences were observed regarding variables (age, sex, device type, number of procedures, time between the last implantation and the diagnosis of infection, leukocytes, C-reactive protein, left ventricular ejection fraction, length of stay, infectious agent, extrusion of the generator, proportion of infectious endocarditis and sepsis, and treatment modality). No differences were observed in mortality either (intra-hospital and after discharge).

Discussion

CIED implantation increased significantly in recent years owing to broader indications for these devices, to an increasing life expectancy, and to a higher number of people with heart disease. CIED-related infection represents a severe problem, with high morbidity and mortality indices and a great socioeconomic impact due to the high cost of its treatment.[7,18,19]

In this study, the mean patient age was similar to that observed in other studies,[9,13] as was the predominance of male sex among patients with CIED-related infection.[9,20,21] The main etiology of baseline heart diseases in this study was Chagas's disease, which differed from that observed in other countries where ischemic heart disease is more prevalent.[4,9]

Infection rates may vary according to the follow-up period, device type, and procedure.[5,21] This study revealed that a higher proportion of infections was related to generator replacement, device upgrade, and pocket revision. The mean time between the last manipulation and diagnosis of infection, according to the literature, is 20 months,[13] which is similar to this study but may vary depending on the device. This interval was 4.2 months in relation to the infection of the ICD, according to the literature.[22]

As for infection etiology, staphylococci cause most of CIED-related infections, being responsible for 60% to 80% of the reported cases;[1,23] this rate is higher than that observed in this study. However, a high number of blood cultures provided negative results, which is unlike what is commonly reported in the literature.[1,5,24] This difference may be attributed to previous use of antibiotics by the patients (before hospitalization).[25]

For diagnosing this infection, apart from the clinical method, laboratory and echocardiogram examinations are indicated. The transesophageal echocardiogram is the most indicated examination for diagnosing endovascular infection owing to its 88% sensitivity and 99% specificity. Transthoracic echocardiogram, in turn, presents a sensitivity of only 32%.[3] Therefore, despite the high sensitivity of this imaging test and its precise indication in this picture, clinical correlation and blood culture results are fundamental for the diagnosis and complications of this type of infection. One of these

complications is endocarditis, a severe infection that may occur in 0.06% to 7.0% of CIED-related infections,[13] with an annual incidence of 1.83 cases/million people and 390 cases/million PM recipients,[26] and a reported mortality of up to 26%.[27] In the studied population, 57.7% of the patients developed endocarditis. In agreement with the literature, this study demonstrated worsening prognosis in those who had endocarditis. Another complication was sepsis, which also contributed to a high number of deaths; according to the literature, the death rate due to sepsis can vary from 32.2% to 51.1% and its main agent is *S. aureus*.[28,29] The tendency for an inverse association between endocarditis and extrusion of the generator in this study may derive from the number of patients with endocarditis and extrusion, resulting in a confounding bias since extrusion may or may not be present in cases of endocarditis.

Studies recommend the use of vancomycin as a priority in the beginning of empiric antibiotic therapy when treating CIED-related infections until blood culture results are obtained.[1] In agreement with the literature, in this study vancomycin was used in 73.9% of the cases. In addition to antibiotic therapy, other additional treatment modalities are available, such as the early and complete removal of the system, which has a favorable impact on patient progression and is associated with better survival.[11] In this study, we observed the benefits of complete system removal aiming to cure the infection without relapse. However, complete removal of the system sometimes involves more complex surgery such as cardiotomy, which may worsen the patient's clinical picture. Data in the literature demonstrate that a quick device and electrode removal, associated with proper antibiotic therapy and reimplantation of a new epicardial or contralateral device, resulted in a high cure rate with a low risk of operative mortality and recurrent infection.[30] The percutaneous technique of electrode extraction presents less risk. However, mortality can reach 1.2% in experienced centers due to bleeding, vascular perforations, and cardiac tamponade.[31]

CIED-related infection can result in prolonged hospitalization, which is extended in 13% in comparison to the hospitalization for device implantation.[32] Treatment with antibiotics, extraction and reimplantation, and associated complications contribute to this increase in hospitalization time, which also brings an economic impact. Mean length of stay in this study was 35.5 days. Literature reports indicate a mean stay of 17 days.[22] This difference can be explained by a higher proportion of patients with infectious endocarditis, which resulted in longer antibiotic treatment as recommended by the literature.[3,15]

In addition to morbidity, CIED-related infection also presents mortality, both intra-hospital and after discharge. Intra-hospital mortality varies widely, according to the literature, depending on the number of patients, older age, and the presence of comorbidities and complications during treatment; it can range from 6% to 14%, while total mortality is approximately 20% in one year,[1,6,9] reaching 26.9% during a 5-year follow-up.[1,8,33] In the studied population, the intra-hospital mortality rate was higher than the rates reported in the mentioned studies, which could be justified by a higher number of patients who developed endocarditis and sepsis.

Regarding the post-discharge period, studies with follow-up periods of up to 2 years showed that the total death rate can be substantial, varying from 6% to 35%.[34,35] In this study, the post-discharge mortality rate was 23.5% during the 43.8-month follow-up, with an annual rate of 14.5%, which was within those values described in the literature.

As previously described, some variables are associated with unfavorable outcomes and mortality predictors.[1,10-13,21] In our study, no significant association (according to the Kaplan-Meier curves) of survival with device type, infectious endocarditis during hospitalization, and treatment modality was observed. However, there was a significant difference in sepsis complication during hospitalization, with lower survival after discharge, as well as among those who underwent epicardial implantation.

Considering treatment modalities, Kim et al.[9] reported that patients treated conservatively, ie, only with antibiotic therapy, presented high death rates within a mean time of 25 days.[9] In addition, some studies indicate that early device removal was associated to higher patient survival.[2,36] When total device removal does not happen, mortality can increase up to 7-fold within 30 days.[3] A recent study considering 6859 patients with no CIED-related infection compared the progress of patients subjected to extraction and those with abandoned electrodes, demonstrating that electrode removal was associated to a lower infection rate in a 5-year period, but no impact on patient survival was observed.[37] In a related manner, but with a population that included patients with CIED-related infection, a case-control study demonstrated similar mortality rates for patients with and without infection.[34] This reflects the heterogeneity of study cases when it comes to clinical profile, time of diagnosis and intervention, and comorbidities; these variables interfere with survival, among other factors. Moreover, a study published in June 2019 with the participation of 62 countries demonstrated that only 39.9% of professionals executing CIED implantation performed pocket irrigation with antibiotics and 44% administered prophylactic antibiotics, with complete removal of the system in 62% of the times in case of infection,[38] which illustrates the disparity in approaches to patients with CIED-related infection.

As for the epicardial implant, a study comparing PM electrode reimplantation after infection demonstrated a 3.6-fold risk of late andocarditis or device reintervention in 65 patients undergoing epicardial access when compared to 37 patients undergoing temporary PM and subsequent endocardial reimplantation.[39] This was explained by complications associated with epicardial reimplantation.

The etiology of heart disease in patients with CIED influences its progression. The prognosis of patients with chronic Chagas' heart disease is unfavorable when compared to other etiologies.[40] No specific studies on CIED-related infection and chagasic etiology are present in the literature, except for a study on microbial diagnosis with fluid culture.[41] When comparing 15 patients with infection and 68 without CIED-related infection, with a total of 19 patients with Chagas'

disease, no difference was observed between groups regarding this etiology. In this study, with 55 patients with Chagas' disease, no differences were observed between variables and regarding progression when comparing patients with and without this disease.

Study Limitations

The retrospective nature of the study was a disadvantage considering a lower availability of adequate medical records, in addition to a sub-notification of patients with CIED-related infection. This may have affected the infection rate, bringing some bias to the analysis. Moreover, due to the long period of patient inclusion, echocardiography techniques and equipment have changed over time, with no uniformity in this examination and preventing the verification of the affected valve in case of infected endocarditis. Since not all patients underwent transesophageal echocardiography, the rate of endocarditis may have been underestimated.

Conclusions

The rate of infection was 1.9% (1.2 per 1000 procedures/year), with a predominance of men and patients with dilated cardiomyopathy. During hospitalization, the incidence of infectious endocarditis was 57.7% and that of sepsis was 18.7%. Total system removal was performed in most patients (85.4%). Intra-hospital mortality rate was 19.5% and was associated with the occurrence of endocarditis and sepsis. After discharge, the annual mortality rate was 11.8%, influenced only by the occurrence of sepsis during hospitalization and by epicardial implantation.

Author Contributions

Conception and design of the research, Data acquisition, Analysis and interpretation of the data and Writing of the manuscript: Maciel AS, Silva RMFL; Statistical analysis and Critical revision of the manuscript for intellectual content: Silva RMFL.

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Infections of Cardiac Implantable Electronic Devices – A Growing, Worrying Reality

Eduardo Arrais Rocha,[1,2] *João Lins de Araújo Neto,*[1] *Ricardo Pereira Silva*[3]

Faculdade de Medicina da Universidade Federal do Ceará,[1] *Fortaleza, CE - Brazil*

Centro de Arritmia do Ceará,[2] *Fortaleza, CE - Brazil*

Universidade Federal do Ceará - Hospital Universitário Walter Cantídio,[3] *Fortaleza, CE - Brazil*

Short Editorial related to the article: Clinical Profile and Outcome of Patients with Cardiac Implantable Electronic Device-Related Infection

Infection rates of Cardiac Implantable Electronic Devices (CIEDs) have been increasing, determining the need for a wide debate on the subject. Several reasons can justify the issue, such as: a greater number of devices implanted over the latest years, overaging of the population, new techniques and equipment, with more complex and prolonged procedures.[1]

Maciel and Silva [2] address this topic in a clear, objective manner, bringing an important contribution from the national literature, in a significant case selection, confirming those worrying findings and discussing their impacts, considering the high rates of morbidity and mortality and high costs involved, particularly in the cases of endocarditis and sepsis.

The work presents new data regarding the evolution of patients with Chagas' heart disease and CIED, showing that there are no differences in relation to clinical, laboratory or prognostic variables, when their devices are shown to have infections.[2]

As a retrospective study, it has some inherent limitations, well referred to in its content, such as the inclusion of patients from different periods, under varied therapeutic approaches, including even the most cutting-edge electrode extraction techniques. Such fact should deserve an yearly comparison of the event rates in order to assess the impact of the latest knowledge acquired and the new techniques used in the treatment of such a severe complication.

The use of new diagnostic techniques, such as imaging exams (Positron Emission Tomography with Computed Tomography - PET/CT, Cardiac Computed Tomography and Myocardial Scintigraphy with marked leukocytes) to aid in the diagnosis of infection of the electrodes and visualization of their complications, such as unexpected embolisms or metastatic infections, has grown considerably in the literature, which could not be expressed in the present study.[3,4]

Intracardiac echocardiography has been shown to be useful in some scenarios, enabling mass biopsy, which may assist in

the differential diagnosis between thrombus and vegetation.[1] However, transesophageal echocardiography remains the main imaging test for diagnostic and conduct assistance, and should be repeated after one week, when initially negative.

Considering the scenario of increased procedures and complications, several aspects must be thoroughly analyzed and followed, such as: the need for refined surgical techniques, with expanded DCEI store availability, chiefly for exchanges; the use of submuscular implants, avoiding or minimizing extrusions of generators; the use of rigorous aseptic and hemostatic techniques; the use of appropriate suture stitching techniques and the performance of procedures in a surgical environment, with perfect aseptic conditions, often unavailable in the usual hemodynamic rooms, where most of the implants occur. Single-dose antibiotic prophylaxis at the beginning of surgery remains an effective measure in the guidelines.[1,5,6]

Very common situations such as implants in chronic patients, with dialysis catheters, central catheters, temporary pacemakers, particularly those the time of which was prolonged and sometimes implanted in urgent situations, patients with prolonged hospital stay, in intensive care units, facing delay for implantation, sometimes due to issues related to the authorization and release of the prosthesis, they urgently need to be discussed and resolved by the various entities involved.

The severity of patients who are undergoing implants also needs to be rethought, particularly in elective and primary prevention procedures, since due to the severity of the disease, many will not have enough time to benefit from a preventive CIED implant, as in the case of implantable cardiodefibrillators.

The need for multidisciplinary teams to treat this severe pathology ("endocarditis team") is extremely important, with the involvement of a specialist in cardiac stimulation, infectious disease, microbiologist, radiologist, intensivist, internist, considering that the implementation of an accurate etiological diagnosis and appropriate therapeutic approach is paramount.[7]

The microbiological identification of the germ often requires a longer sowing technique, for atypical and slow-growing germs, with a greater number of samples (> 3 samples) and repetition of the collections with greater intervals, thus allowing an antibiotic therapy directed to the pathogens identified. The inadequate duration of antibiotic therapy and especially the failure to completely remove the system has led to a higher rate of recurrences and morbidity and mortality.[1,7-9]

The team of specialists will allow a joint discussion of the professionals and the family, aiming at a quick decision on the

Keywords

Endocarditis; Sepsis; Pacemakers; Cardiac Defibrillators; Ecotransesophageal; Positron Emission Tomography.

Short Editorial

removal of the system, with sequential planning on the new implant, however, the possibility of not doing so should ever be considered, as in very specific situations. Perhaps, out of all the aspects mentioned, the advancement of extraction techniques and the experience of the teams are the most important elements to be considered within the national reality. National societies need to mobilize in this regard. After the decision for a new implant, the use of subcutaneous devices, such as defibrillators and pacemakers without electrodes, should be considered when available, which have shown lower rates of infections, mainly of endocarditis and sepsis.[1,9-11]

The various guidelines and current studies already published[1,5,6,8,11-13] should serve to standardize and organize

the conduct, which would lead to a lower rate of complications and mortality. SOBRAC - Brazilian Society of Cardiac Arrhythmias is finalizing its guidelines in 2021, with a broad chapter on the topic, which will help a lot in the resolution of these issues, and the Latin American Society of Cardiac Rhythm (LAHRS) has also actively participated in the recent guideline.[1]

Within these aspects mentioned, Maciel and Silva allowed the scientific community to have a wide discussion on the subject, with the wealth of data on the work and generated the need for standardization of local and national society, aiming at monitoring and reducing infection rates and their serious associated consequences.

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Diagnostic Performance of a Machine Learning-Based CT-Derived FFR in Detecting Flow-Limiting Stenosis

Thamara Carvalho Morais,[1,2] Antonildes Nascimento Assunção-Jr,[1,2] Roberto Nery Dantas Júnior,[1,2] Carla Franco Grego da Silva,[1] Caroline Bastida de Paula,[1] Roberto Almeida Torres,[1,2] Tiago Augusto Magalhães,[1,2,3] César Higa Nomura,[1,2] Luiz Francisco Rodrigues de Ávila,[1,2] José Rodrigues Parga Filho[1,2]

Hospital Sírio-libanês,[1] São Paulo, SP - Brazil
Universidade de São Paulo Faculdade de Medicina - CDI - InCor/HCFMUSP - Departamento de Imagem Cardiovascular,[2] São Paulo, SP - Brazil
Complexo Hospital de Clínicas da Universidade Federal do Paraná (CHC-UFPR) - Cardiovascular CT/MR,[3] Curitiba, PR - Brazil

Abstract

Background: The non-invasive quantification of the fractional flow reserve (FFRCT) using a more recent version of an artificial intelligence-based software and latest generation CT scanner (384 slices) may show high performance to detect coronary ischemia.

Objectives: To evaluate the diagnostic performance of FFRCT for the detection of significant coronary artery disease (CAD) in contrast to invasive FFR (iFFR) using previous generation CT scanners (128 and 256- detector rows).

Methods: Retrospective study with patients referred to coronary artery CT angiography (CTA) and catheterization (iFFR) procedures. Siemens Somatom Definition Flash (256-detector rows) and AS+ (128-detector rows) CT scanners were used to acquire the images. The FFRCT and the minimal lumen area (MLA) were evaluated using a dedicated software (cFFR version 3.0.0, Siemens Healthineers, Forchheim, Germany). Obstructive CAD was defined as CTA lumen reduction ≥ 50%, and flow-limiting stenosis as iFFR ≤0.8. All reported P values are two-tailed, and when <0.05, they were considered statistically significant.

Results: Ninety-three consecutive patients (152 vessels) were included. There was good agreement between FFRCT and iFFR, with minimal FFRCT overestimation (bias: -0.02; limits of agreement:0.14-0.09). Different CT scanners did not modify the association between FFRCT and FFRi (p for interaction=0.73). The performance of FFRCT was significantly superior compared to the visual classification of coronary stenosis (AUC 0.93vs.0.61, p<0.001) and to MLA (AUC 0.93vs.0.75, p<0.001), reducing the number of false-positive cases. The optimal cut-off point for FFRCT using a Youden index was 0.85 (87% Sensitivity, 86% Specificity, 73% PPV, 94% NPV), with a reduction of false-positives.

Conclusion: Machine learning-based FFRCT using previous generation CT scanners (128 and 256-detector rows) shows good diagnostic performance for the detection of CAD, and can be used to reduce the number of invasive procedures.

Keywords: Myocardial Fractional Flow Reserve, Coronary Artery Disease, Computed Tomography, Myocardial Ischemic, Machine Learning.

Introduction

According to the most recent clinical guidelines,[1-3] management of chronic and symptomatic coronary artery disease (CAD) may be guided by additional tests for either anatomical (extent, severity, morphology) or functional (ventricular function, presence/extent of ischemia) assessment, with evidence suggesting the superiority of the functional over the anatomical approach in some clinical scenarios.[4-6]

For this purpose, especially in patients with intermediate pretest probability of obstructive CAD, the coronary computed tomography angiography (CTA) stands out among the various existing non-invasive tests as a robust method to rule out obstructive CAD, given its high negative predictive value.[7] Particularly in moderate stenosis (50-69%), the non-invasive measurement of myocardial fractional flow reserve (FFR_{CT}) may help to correctly distinguish which of these are associated with ischemia[8]. Recent studies have shown that the CTA is an accurate test to identify ischemia through non-invasive quantification of fractional flow reserve (FFR_{CT}) when compared to the gold standard, the invasive FFR by cardiac catheterization (iFFR).[8-10]

The use of FFR_{CT} in clinical practice has been mostly restricted by its low availability, especially due to the need for specific software that would run only on supercomputers at large international centers, substantially increasing the cost and delaying the whole diagnostic process.[8] More recently, a non-commercial software prototype (available for standard

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configuration personal computers) that uses artificial intelligence tools – convolutional neural network (deep learning) – to evaluate FFR$_{CT}$ was tested by Rother et al.[11] When compared to iFFR, the FFR$_{CT}$ calculated by this software has shown high accuracy to detect ischemia, with a significant reduction in the calculation time when compared to existing models that use supercomputers.[8] However, it should be noted that their study used only images acquired by a latest generation CT scanner (Siemens Somatom Force – 384 slices). Since this software is capable of calculating the FFR$_{CT}$ from images acquired using CT scanners that employ different technologies, our aim was to use it to investigate the diagnostic accuracy of the FFR$_{CT}$ using previous generation CT scanners, compared to iFFR, with imaging quality that can potentially affect the results of the algorithm used in the software. This study also compared the diagnostic accuracy of FFR$_{CT}$ to the isolated anatomical assessment by CTA.

Methods

Study Population

Retrospectively, this study included symptomatic patients that were referred to CTA for investigating significant CAD and, after the test findings, upon clinical decision, were referred to cardiac catheterization (within less than 30 days) and underwent iFFR analysis at Sírio-Libanês Hospital, São Paulo, Brazil, between January 2014 and February 2018. There was a total of 17 exclusions: 14 owing to factors that limited the FFR$_{CT}$ calculation, as described by the tool manufacturer (8 due to left main coronary artery (LMCA), ostia, or bifurcation lesions, 6 owing to the presence of stent); and 3 due to bad quality image as a result of excessive calcification and significant motion artifacts. During image post-processing, no other patient was excluded as a result of the software technical inability to measure FFR$_{CT}$. It is noteworthy that the manufacturer's recommendations regarding LMCA, ostia, or bifurcation lesions have also been followed by other authors,[11] and they seem to be related to the limited recognition of the anatomical borders in these scenarios. This study was approved by the Sírio-Libanês Hospital Research Ethics Committee.

Acquisition of the CTA images

The images were obtained using a 256-slice Siemens Somatom Definition Flash CT scanner (temporal resolution - TR - of 75 ms; spatial resolution - SR - of 0.30 mm) and a 128-slice Somatom Definition AS CT scanner (TR of 150 ms; SR of 0.30mm) (Siemens Healthineers, Forchheim, Germany). The patients were prepared according to current guideline recommendations, including four-hour fasting, using an IV peripheral venous access catheter (18 Gauge), preferably on the right antecubital vein, and continuous electrocardiographic monitoring.[12] Whenever necessary, a beta-blocker was administered (50-100mg oral metoprolol tartrate 1 hour before the test and/or 5-20mg intravenously a few minutes before image acquisition) to obtain heart rate (HR) control (aim 55-60 bpm). All patients also received sublingual nitrate (Isordil 2.5mg) a few minutes before acquisition, except in cases of symptomatic hypotension or use of phosphodiesterase type 5 inhibitors (according to each drug action onset).

Image acquisition was planned after bolus testing to calculate the contrast peak time in the aorta, with a 10-15 mL volume, followed by 30-50 mL of saline solution at 4.5-5.5 mL/s. The images were acquired using Flash mode (in the Definition Flash CT scanner) or retrospectively (in both CT scanners) with electrocardiographic gating in late diastole (55-75% of RR), tube voltage of 100-120 kVp (adjusted to the individual BMI), rotation time 0.28 (Flash) / 0.33 (AS+) seconds, 160-320 mAs and slice thickness of 0.6/0.3 mm. The Optiray 350 (Ioversol 350 mg/mL-Mallinckrodt-USA) iodinated contrast media infusion used the same parameters of the bolus testing (60-90ml).

Analysis of the CTA and FFR$_{CT}$ images

CTA image analysis was carried out using the Syngo.via imaging software (Siemens Healthineers, Forchheim, Germany). After choosing the images with best technical quality, the coronary tree evaluation was performed by three-dimensional, curved, multiplanar reformation (Vessel Probe), with quantification of stenosis degree and prevalent plaque composition, when present (non-calcified, calcified, and mixed). Luminal reduction quantification was carried out according to the Society of Cardiovascular Computed Tomography recommendations:[13] normal, minimal (<25%), mild (25-49%), moderate (50-69%), severe (70-99%) and occlusion (100%). CTA-assessed stenosis was also classified as obstructive (≥50%) and non-obstructive (<50%).

Post-processing FFR$_{CT}$ was performed in the same series in which visual anatomical analysis was carried out (as described above), using the Frontier platform and the non-commercial prototype of the cFFR software, version 3.0 (Siemens Healthineers, Forchheim, Germany), by a physician experienced in cardiovascular imaging (>4 years).

To calculate coronary artery FFR$_{CT}$, the first step was to perform the automatic detection of the centerline and lumen contours, which were reviewed and corrected by the specialist, when necessary. Next, the upper and lower borders of all plaques in the vessels that had their iFFR values calculated during invasive catheterization were delimited.

To precisely identify the site where the iFFR was calculated, the interventional cardiologist located the point of interest in the fluoroscopic images and documented it using anatomical references (coronary branches) and also a coronary segmentation model suggested by the Society of Cardiovascular Computed Tomography (SCCT). The CTA expert used this documentation to select the same anatomical location of the plaques that had the FFR$_{CT}$ calculated.

The cFFR software calculates FFR values only for vessels ≥1.5mm in diameter and automatically calculates the value of the minimal lumen area (MLA) of each delimited plaque. The steps for FFR$_{CT}$ calculation are shown in Figure 1. This software was developed with new artificial intelligence tools, using machine-learning techniques (deep learning). All of them were installed in a standard computer used for radiology reports. The total post-processing time of all steps was around 10 minutes.

Cardiac catheterization and iFFR analysis

Cardiac catheterization was performed through radial or femoral access, using 6 or 7 French (F) diagnostic catheters. To calculate the iFFR, the degree of stenosis was visually evaluated

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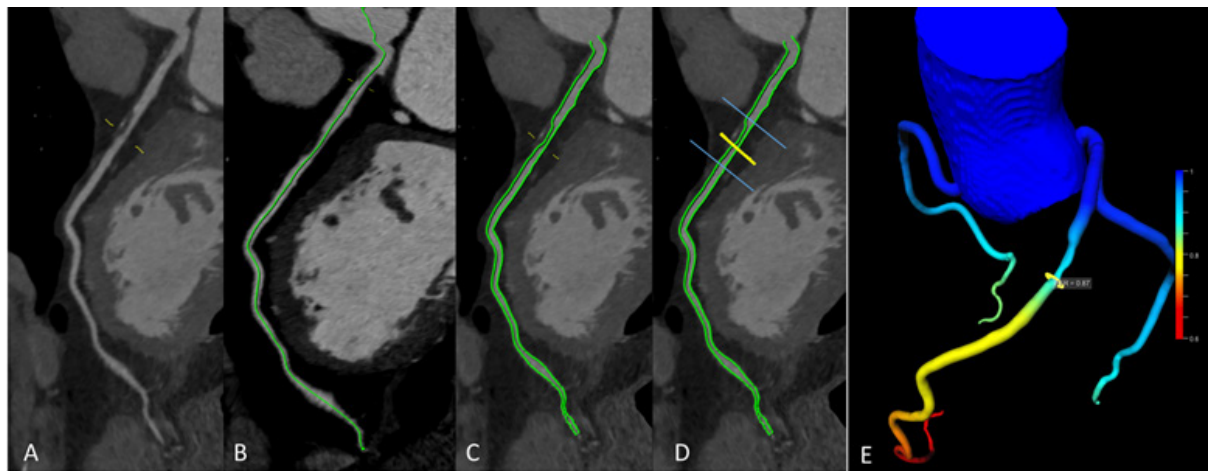
Figure 1 – *Steps to calculate FFRCT using the cFFR software. A) Visual detection of the coronary lesion. Definition of centerline B) and lumen contours C) using the cFFR software D) definition by the operator of the lesion borders and the point of higher lumen reduction. E) FFR result at the point with higher lumen reduction shown in the coronary tree (after determining the centerline and lumen contours in the 3 main coronary arteries: LAD, LCx, and RCA).*

by the interventional cardiologist using at least two orthogonal projections. Intracoronary nitroglycerin (0.2 mg) was injected in all patients before the angiograms. A pressure monitoring guidewire was placed distal to the index lesion, and the mean pressures were recorded when they were stable. Intracoronary adenosine was manually injected through the guide catheter, through an $80\,\mu g$ bolus injection (left coronary artery) or $40\,\mu g$ bolus (right coronary artery) into 10 mL of saline solution. After the administration, the lowest stable FFR value during the hyperemic steady state was recorded. This value corresponds to the ratio between the mean coronary pressure distal to the stenosis and the mean aortic pressure at the time of the pharmacologically-induced hyperemia.

The exact position of the iFFR measurement sensor was documented by the interventional cardiologist on the report, and this documentation was used by the CTA expert to measure FFR$_{CT}$ at the same anatomical location.

Statistical Analysis

Descriptive analyses were expressed as frequency (percentage) for categorical variables, and as mean $\pm$ standard deviation for continuous variables. The distribution of the continuous variables was visually assessed using QQ plots and checked using the Shapiro-Wilk test. Comparisons between the continuous variables found in the CTA and the catheterization (degree of coronary stenosis, FFR) were made using Student's t-test for paired samples. Likewise, the correlation between these variables was made using Pearson's correlation.

The agreement between FFR$_{CT}$ and iFFR was determined by Bland-Altman analysis. Assuming iFFR ≤ 0.8 as the gold standard for the presence of ischemia, the diagnostic performance of FFR$_{CT}$ and other CTA anatomical parameters were evaluated by calculating sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV).

In addition, the area under the ROC curve (AUC) to detect coronary lesions associated with ischemia was calculated, and comparisons between the AUCs were performed according to the method described by DeLong et al.[14] The best FFR$_{CT}$ cut-off point for the detection of ischemia (iFFR ≤ 0.8) was calculated using the Youden index, which corresponds to the one with the highest value in the equation (sensitivity [Sens] + specificity [Spec] - 1).[15] It is noteworthy that the degree of stenosis was explored as a continuous and categorical variable (obstructive CAD, >50%, or not). The choice to include the categorical form in the model was based on the fact that it is a clinical threshold for further decision-making.

Considering the potential correlation between multiple vessels in the same individual, the generalized estimating equations (GEE) method with exchangeable correlation structure was used at a per-vessel level. Statistical analyses were carried out using the R software (R Foundation for Statistical Computing, Vienna, Austria). All reported *P* values are two-tailed, and when <0.05, they were considered statistically significant.

Results

Characteristics of the patients and plaques

Ninety-three patients were included in the study, with a total of 152 vessels. Fifty patients (54%) underwent CTA in the Flash CT scanner (256-detector rows), and 43 (46%) in the AS+ CT scanner (128-detector rows). The average HR during image acquisition was 58 ± 8 bpm.

Seventy-four patients (80%) showed obstructive CAD (stenosis >50%) in the CTA, 48 with moderate stenosis (50-69%) and 26 with severe stenosis (>70%). In the per-vessel analysis, plaques were more often the mixed type (70%), and most commonly located in the left anterior descending

coronary artery (LAD) (73%) and had a mean MLA of 3.2 ± 1.6 mm². Clinical and CT characteristics of the patients are shown in Tables 1 and 2, respectively.

Comparison between FFR$_{CT}$ and iFFR

There was a strong correlation between the FFR$_{CT}$ and iFFR values (r = 0.73, p<0.001) (Figure 2). On average, FFR$_{CT}$ values were slightly higher than iFFR values (0.88 ± 0.08 vs. 0.86 ± 0.08, p = 0.02), a systematic error confirmed by the Bland-Altman analysis (bias of -0.02 with a confidence interval of -0.14 to 0.09) (Figure 2). The type of CT scanner used did not change the association between iFFR and FFR$_{CT}$ (p-value for interaction of 0.73).

Ischemia Detection

For the identification of flow-limiting obstructive coronary lesions (iFFR ≤0.8 as the gold standard), FFR$_{CT}$ showed a significantly superior performance compared to the isolated visual classification of coronary obstruction (AUC 0.93 vs. 0.61, p<0.001) and to MLA by CTA (AUC 0.93 vs. 0.75, p<0.001) (Figure 3). The best cut-off point (with fewer false-positive results) for FFR$_{CT}$, defined using the Youden index, to distinguish lesions with from those without ischemia was 0.85, which achieved the following accuracy values: 87% sensitivity, 86% specificity, 73% PPV, and 94% NPV at this cut-off point (Figure 4). These performance metrics using this cut-off point (0.85) were slightly higher when analyzing only the plaques with moderate lumen reduction (50-69%, n=95), with 89% sensitivity, 91% specificity, 74% PPV, 97% NPV. Out of the 152 evaluated lesions, three (2%) were false-positives and 18 (12%) were false-negatives using the traditional cut-off point (FFR$_{CT}$ ≤ 0.80). Using the highest cut-off point (FFR$_{CT}$ <0.85), 12 (7%) were false-positives and 9 (6%) false-negatives.

When evaluating the lumen reduction degree, the plaques with visually moderate reduction (50-69%) showed 86 (56%) false-positive cases in relation to the gold standard (iFFR ≤0.8), while the plaques with visually severe lumen reduction (≥70%) showed 23 (15%) false-positive cases, which for the latter represent a 50% higher magnitude when compared to the results of FFR$_{CT}$ <0.85 (15% *versus* 7%).

Discussion

FFR$_{CT}$ analysis using a machine learning-based software showed good agreement with iFFR measurements, emphasizing that CTA image post-processing was carried out using standard computers in about 10 minutes. Regarding its diagnostic performance, even using previous-generation CT scanners, FFR$_{CT}$ performed better than the isolated anatomical evaluation, both in visual stenosis quantification and in the calculation of MLA, significantly reducing the number of false-positives.

In agreement with Rother et al.,[11] which retrospectively studied a cohort of 71 patients using the same software version used in this study (cFFR version 3.0),[11] the FFR$_{CT}$ showed considerable agreement with the iFFR measurement, with minimal overestimation. These results are in disagreement with previous versions of this same software (cFFR version 1.4),[16-19]

where an underestimation was described, which probably reflects algorithm changes with the software upgrade.

Although comparable to the three major multicenter studies published to date (DISCOVER-FLOW, Defacto, and NXT),[8-10] it should be noted that the limit of agreement of our study was wider in the Bland-Altman analysis (~0.20), which means lower repeatability of the method, compared to what was observed by

Table 1 – Demographic Data

Variables	n = 93
Age, years*	64 ± 11
Male, n (%)	70 (75)
Hypertension, n (%)	54 (58)
Dyslipidemia, n (%)	45 (48)
Diabetes, n (%)	24 (26)
Smoking, n (%)	7 (8)
BMI, kg/m²*	28 ± 4
HR, bpm*	58 ± 8

BMI: body mass index; HR: heart rate. *mean ± standard deviation.

Table 2 – Coronary plaque characterization

Per patient	n = 93
Stenosis ≥ 50%, n (%)	74 (80)
Stenosis 50-69%, n (%)	48 (52)
Stenosis ≥ 70%, n (%)	26 (28)
FFR$_{CT}$ ≤ 0.8, n (%)	32 (34)
iFFR ≤ 0.8, n (%)	39 (42)
Per vessel	**n = 152**
Location	
LAD, n (%)	111 (73)
LCx, n (%)	26 (17)
RCA, n (%)	16 (10)
Stenosis ≥ 50%, n (%)	124 (82)
Stenosis 50-69%, n (%)	95 (63)
Stenosis ≥ 70%, n (%)	29 (19)
MLA, mm²*	3.2 ± 1.6
Morphology	
Calcified, n (%)	16 (10)
Mixed, n (%)	106 (70)
Non-calcified, n (%)	30 (20)
FFR$_{CT}$*	**0.88 ± 0.08**
FFR$_{CT}$ ≤ 0.8, n (%)	32 (21)
iFFR*	**0.86 ± 0.08**
iFFR ≤ 0.8, n (%)	47 (31)

CAD: coronary artery disease; iFFR: invasive fractional flow reserve; FFR$_{CT}$: fractional flow reserve derived from computed tomography; MLA: minimal lumen area. *mean ± standard deviation.

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Figure 2 – *Correlation (A) and agreement using Bland-Altman analysis (B) between FFR$_{CT}$ and iFFR (per-vessel analysis): EQUIPMENT: <u>AS</u> refers to the 128-detector row CT scanner and <u>FLASH</u> to the 256-detector row CT scanner.*
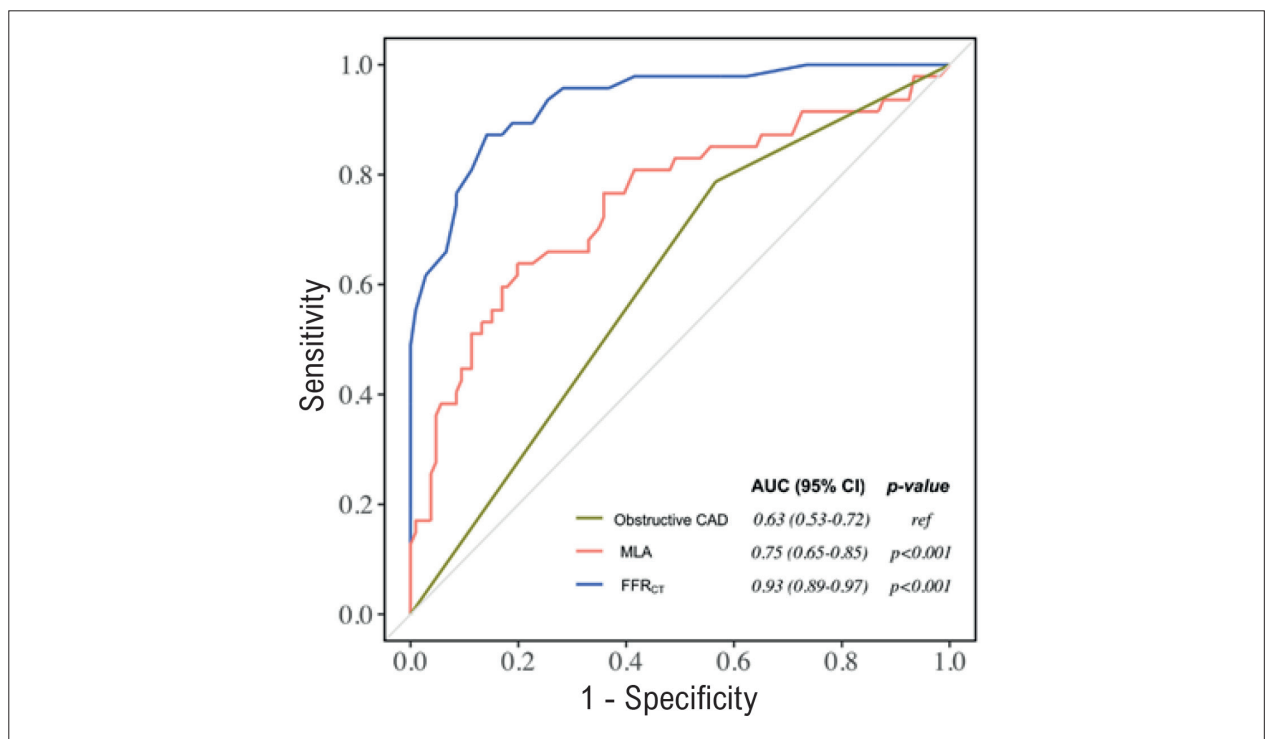
Figure 3 – *FFR$_{CT}$ performance for the diagnosis of flow-limiting obstructive lesions (iFFR<0.8).*

Rother et al.[11] As our patients had an HR <60 bpm on average, which results in good image quality, we believe that the superior performance of that study can be explained, in part, by the use of a CT scanner with 20% higher spatial resolution (0.3 vs. 0.24mm), in addition to the use of a more recent and robust reconstruction algorithm (ADMIRE). These factors may have led to a better detection of coronary contours (centerline and lumen) by that study, with consequent better results. Another justification that cannot be ruled out would be the broader experience by the observer with the new version of cFFR at that center.

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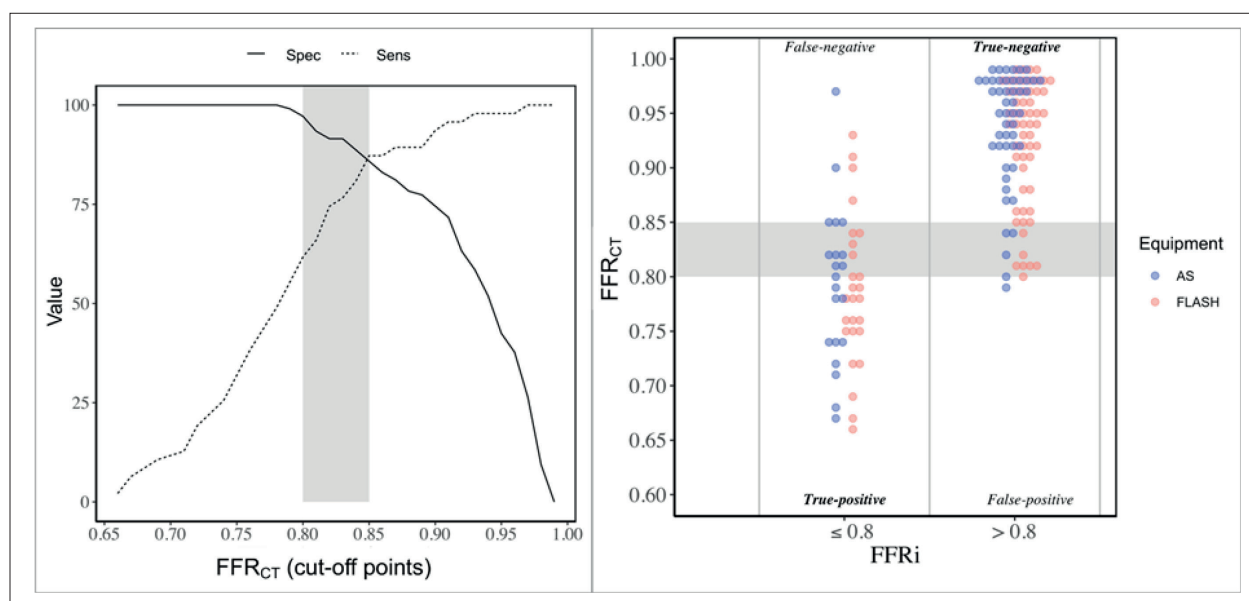
Figure 4 – *Diagnostic performance of FFR$_{CT}$ <0.85. EQUIPMENT: AS refers to the 128-detector row CT scanner and FLASH to the 256-detecttor row CT scanner.*

Regarding the power to distinguish flow-limiting from non-flow-limiting coronary stenosis, the FFR$_{CT}$ was superior in comparison to the CTA isolated anatomical evaluation, both qualitatively (visual classification of obstructive CAD), and quantitatively (MLA). Using a cut-off point of 0.85 for the FFR$_{CT}$, the NPV and PPV were comparable to those of other cohorts that used this software.[16-19] In addition, we point out the following aspects: 1) FFR$_{CT}$ performance was better in cases with moderate lesions (50-69%); 2) FFR$_{CT}$ led to a reduction of over 50% in the number of false-positive cases observed when only the anatomical evaluation of severe CAD (≥70%) was used. These findings are highly relevant in clinical practice, since moderate lesions in CTA are relatively frequent and often these patients are referred to additional tests.[20] In fact, the opportunity of global reduction in unnecessary referrals to catheterization may be even greater using this new FFR$_{CT}$ tool, since only 42% of our patients had iFFR <0.8.

Finally, we point out this new software fast image post-processing based on machine-learning technology (deep learning). When using pioneering softwares,[8-10] which use computational fluid dynamic algorithms, the calculation of the FFR$_{CT}$ takes from 1 to 4 hours to be processed, and it is carried out by supercomputers located only in specific centers in the United States (whose headquarters is in California), the UK, and Japan. In addition to the high cost, in general, about 24 hours are required to obtain the results, and the DICOM images need to be sent out of the institution environment. Therefore, this new software could have a real impact on clinical practice for the care of patients with CAD.

Limitations

This is a retrospective, unicentric study, with a relatively small study population, which predominantly had obstructive CAD. When following the manufacturer's recommendations regarding the tool appropriate use, patients with significant stenosis in the left main coronary artery, main coronary ostia, or in bifurcations; chronic arterial occlusions; previous history of revascularization surgery or stent implantation were excluded. Likewise, patients with typical symptoms were not always submitted to invasive functional testing (iFFR) by clinical decision. Therefore, this study should be interpreted while giving due attention to the clinical context of its population (less severe/complex CAD and/or clinical scenarios of greater diagnostic uncertainty).

Conclusion

This new version of FFR$_{CT}$, even when using previous-generation CT scanners, showed good diagnostic performance for the detection of flow-limiting obstructive coronary lesions, with a significant reduction in the number of false-positive cases, which can significantly decrease the number of patients who are referred to additional tests. The clinical importance of these findings needs to be validated by studies specifically designed to evaluate clinical outcomes. This software features innovative technology that uses machine learning, which enables greater accessibility, rapid performance and potential cost reduction.

Author contributions

Conception and design of the research: Magalhães TA, Nomura CH, Ávila LFR, Parga Filho JR; Acquisition of data: Morais TC, Silva CFG, Paula CB, Torres RA, Magalhães TA; Analysis and interpretation of the data: Assunção-Jr AN, Dantas Júnior RN, Parga Filho JR; Statistical analysis: Assunção-Jr AN, Dantas Júnior RN; Writing of the manuscript: Morais TC, Assunção-Jr AN, Dantas Júnior RN, Magalhães TA, Parga Filho JR; Critical revision of the manuscript for intellectual content:

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One-Stop Shop for Non-Invasive Cardiovascular Imagers?

Rodrigo Julio Cerci[1] and *Afonso Akio Shiosaki[2,3]*

Quanta Diagnóstico por Imagem,[1] Curitiba, PR - Brazil
Centro Diagnóstico do Hospital Paraná,[2] Maringá, PR - Brazil
Ômega Diagnóstico,[3] Londrina, PR - Brazil
Short Editorial related to the article: Diagnostic Performance of a Machine Learning-Based CT-Derived FFR in Detecting Flow-Limiting Stenosis

Over the past fifteen years, coronary computed tomography angiography (CCTA) has witnessed rapid technological and scientific advances in the detection of anatomical coronary artery disease (CAD), leading to an improvement in patient care.[1] Visual assessment of stenosis severity using CCTA has a high sensitivity and negative predictive value when compared to invasive angiography, making it an ideal test to exclude obstructive CAD.[2] With its high diagnostic performance associated with an important prognostic impact in the management of CAD, CCTA has finally established itself as a Class I recommendation in international guidelines (European Society of Cardiology – ESC).[3]

However, CCTA is limited by modest diagnostic specificity and only provides anatomical assessment, which does not inform hemodynamic significance of specific lesions.[4] CCTA combined with stress tomography evaluation of myocardial perfusion (CTP) is an accurate modality to determine regional myocardial flow repercussions of coronary stenosis, though it usually requires additional acquisition and is still underused.[5] Derived flow fractional reserve – computed tomography (FFR-CT) is another "physiologic" CT approach in which computational fluid dynamics is applied to standard CCTA data and has emerged as a promising tool for the functional assessment of coronary stenosis. The diagnostic value of remotely performed FFR-CT has been prospectively validated in several large multicenter studies, but requires the use of offsite supercomputers, which can be time-consuming and cost-intensive, limiting its widespread clinical utility.[6-8]

The paper by Morais et al.[9] presented data from 93 patients submitted to CCTA in scanners from different generations,

applying a FFR-CT technique that can be performed on site and in real time, using artificial intelligence tools in a prototype software that runs on a standard workstation. This tool abbreviates the need of supercomputers to perform coronary flow reserve calculations that usually take up to 48 hours, coupled with an additional cost for the coronary functional analysis that is currently performed by unique offsite software, preventing universal access to all patients who could benefit from this technology. Unlike the offsite FFR-CT, onsite FFR-CT estimates the coronary flow reserve by a deep learning algorithm based on anatomical maps of coronary arteries, as well as degrees of stenosis.[10]

Although limited by referral bias from a relatively small, unicenter, and retrospective analysis, the authors must be congratulated for reproducing similar results when compared to larger offsite FFR-CT trials. This means that one may expect the same results, as well as the same limitations for the onsite FFR-CT. It should be noted that the data are consistent with findings of several studies in which, compared to CCTA and SPECT, FFR-CT has superior diagnostic accuracy in discriminating ischemia (AUC = 0,93).[6,7,11-13]

For routine application, however, clinicians must have in mind that the FFR-CT cut point of < 0.80 derived a false negative rate of 12% while a cutoff point of < 0.85 derived only 6% of false negatives and may be a more conservative and safer approach to using FFR-CT as a gatekeeper for invasive angiography.

Unfortunately, FFR-CT is not for all patients, as evaluation of stent or graft patency was not yet validated. Also, heavy calcified, ostial, and bifurcated lesions remain a challenge. Another important hurdle is image quality, which needs to be free of motion and step artifacts to be processed, leaving a variable but significant rejection rate of 3 to 20%.[13,14]

Nevertheless, the possibility of an onsite FFR-CT has been the dream of cardiovascular CT imagers, integrating anatomical and physiological data into a single set of acquisition data (one-stop shop), increasing the test's resolution in a democratic manner, with much less time of analysis and costs when compared to offsite FFR-CT. The article from Morais et al.[9] brings us closer to the "dream coming true".

Keywords

Mailing Address: Rodrigo Julio Cerci •
Quanta Diagnóstico por Imagem -Rua Almirante Tamandaré, 1000.
Postal Code 80045-170, Curitiba, PR – Brazil
E-mail: rodrigo@quantamn.com.br, rjcerci@gmail.com

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Percutaneous Coronary Intervention in Unprotected Left Main Coronary Artery Lesions

Douglas dos Santos Grion,[1] Debora Carvalho Grion,[2] Igor Veiga Silverio,[1] Leonardo Shingu de Oliveira,[1] Isabela Faria Larini,[1] Anna Victória Martins,[1] Juliana Moreira,[1] Marianne Machado,[1] Lissa Shizue Tateiwa Niekawa,[1] Adriana dos Santos Grion,[3] Cintia Magalhães Carvalho Grion[1]

Universidade Estadual de Londrina,[1] Londrina, PR - Brazil
Universidade Federal Fluminense,[2] Niterói, RJ - Brazil
Hospital Evangélico de Londrina,[3] Londrina, PR - Brazil

Abstract

Background: The advent of drug-eluting stents allowed the percutaneous coronary intervention to present safe results in lesions in the left main coronary artery.

Objectives: To analyze the results of the percutaneous treatment of unprotected left main coronary artery lesion with the use of intravascular ultrasound.

Methods: Study of consecutive case series carried out from January 2010 to December 2018. Clinical data were collected from patients as well as prognostic scores and data on coronary lesion. Low-grade residual lesion (less than 50%) on angiography and minimum luminal area greater than 6 mm² on intravascular ultrasound were considered successful. The adopted significance level was 5%.

Results: 107 cases were analyzed. The multivessel lesion was predominant, with most (39.25%) of the lesions being found in three vessels in addition to the left main coronary artery. The SYNTAX score had a mean of 46.80 (SD: 22.95), and 70 (65.42%) patients had a SYNTAX score above 32 points. Angiographic success of percutaneous intervention was considered in 106 (99.06%) patients. The overall rate of major cardiac and cerebrovascular events in the hospital outcome was 6.54%, being similar in patients with SYNTAX score ≤ 32 (8.10%) and ≥ 33 (5.71%; p = 0.68).

Conclusions: Percutaneous intervention in cases of unprotected left main coronary artery lesion was safely performed and presented excellent results. Considerable angiographic success of treatment guided by intravascular ultrasound was achieved. The rate of major cardiac and cerebrovascular events was similar between patients at low and high risks.

Keywords: Percutaneous Coronary Intervention/methods; Coronary Artery Diseases; Myocardial Reperfusion; Drug–Eluting Stents/trends; Ultrasonography, Interventional/methods.

Introduction

The treatment of unprotected left main coronary artery lesions by collateral circulation or coronary bypass remains a major challenge for interventional cardiology nowadays. The left main coronary artery irrigates most of the left ventricle in individuals with right coronary dominance and practically this entire ventricle in the left coronary dominance. Therefore, any adverse event in this area results in a high risk of morbidity and mortality.[1] Thus, clinical treatment may not be the best option, and the myocardial revascularization procedure is

still the most appropriate treatment for these patients.[2,3] Conversely, technological advances and the advent of drug-eluting stents allowed, in selected cases, for percutaneous coronary intervention to present safe results for left main coronary artery lesions.[4-6]

This form of presentation and treatment represents 1% of percutaneous coronary interventions in acute coronary syndromes, being half cases of acute myocardial infarction and 70% of distal impairment of the left main coronary artery.[7,8] All possibilities for optimizing the search for better results in percutaneous coronary intervention should be available. The use of intravascular ultrasound is recommended, as it assists in the optimal stent implantation and can have an impact on reducing mortality.[9,10]

A recent study demonstrated non-inferiority when comparing surgical treatment carried out with coronary angioplasty with drug-eluting stent in left main coronary artery lesions. Percutaneous coronary intervention has been reported as a viable and safe alternative to the myocardial

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revascularization procedure and can be used in daily clinical practice in selected patients.[11] Long-term results confirm that, in patients with left main coronary artery lesions of low to moderate complexity, angioplasty is as safe and effective as long-term surgery and, consequently, constitutes a valid alternative for this group of patients.[12]

Percutaneous coronary intervention has been increasingly used for revascularization of patients with unprotected left main coronary artery lesions, and the use of intravascular ultrasound has been increasingly and frequently described, though it is still considered a recommendation and performed in some of the patients who undergo treatment.[13] The present study aimed at analyzing the results of the percutaneous treatment of unprotected left main coronary artery lesion with the use of intravascular ultrasound.

Methods

Case series study carried out from January 2010 to December 2018. This research was approved by the Research Ethics Committee of the Associação Evangélica Beneficente de Londrina, according to the Opinion No. 2.149.472 of June 30, 2017, CAAE No. 68385917.0.0000.5696.

The study was carried out in a hemodynamics laboratory from a private philanthropic hospital. It is a general hospital of high complexity, with 269 beds, a reference in urgent and emergency care. The hemodynamics laboratory provides continuous care to patients, with a nursing team and staff under an on-duty regime and dimensioned according to current national regulations. Drug-eluting stents embedded in sirolimus, everolimus, or biolimus and GE® interventional cardiology equipment were used, and Philips Volcano® and Boston® intravascular ultrasound exams were available. All study procedures were guided by intravascular ultrasound and performed by the first author of this article, considering that he is an experienced hemodynamicist and trained for the treatment of these coronary lesions.

Convenience sampling was performed on adult patients who underwent percutaneous coronary angioplasty due to unprotected left main coronary artery lesion on a consecutive basis during the study period.

The coronary lesions considered for indication of percutaneous coronary angioplasty were diagnoses of stable angina, unstable angina, silent ischemia, or acute myocardial infarction without ST-segment elevation. All patients should have a recent diagnosis of unprotected stenosis greater than 50% of the diameter of the left main coronary artery, visually estimated, and be considered candidates for the myocardial revascularization procedure. Success of percutaneous intervention was considered a low-grade residual lesion, of less than 50% on angiography, and a minimum luminal area greater than 6 mm² on intravascular ultrasound.

The general data collected were: age, sex, dates of hospitalization and outcome in the hospital, dates of admission and outcome in the intensive care unit (ICU), diagnosis for hospital admission, presence of chronic diseases, prognostic score Simplified Acute Physiology Score 3 (SAPS 3)[14] on admission to the ICU, and SYNTAX score derived from the study "SYNergy between percutaneous coronary intervention

with TAXus and cardiac surgery".[15] Data collected from the angiographic procedures were: number of detected arterial lesions, number of treated vessels, and number of implanted stents. All complications that occurred during the intrahospital follow-up period were noted.

The major cardiac and cerebrovascular events considered were: myocardial infarction, cerebrovascular accident, and death. Cerebrovascular accident was defined as an acute neurological deficit lasting more than 24 hours. Type I myocardial infarction, unrelated to the procedure, was defined as an increase in troponin exceeding the 99th percentile associated with at least one of the following aspects: symptoms of acute myocardial ischemia, new ischemic changes on the electrocardiogram, development of pathological Q waves, or evidence of new loss of viable myocardium or new regional wall motion abnormality on image examination consistent with ischemic etiology.

Procedure-related myocardial infarction was defined as an increase in troponin levels exceeding more than five times the 99th percentile up to 48 hours after percutaneous intervention in patients with normal baseline values. In patients with high troponin values before the procedure, there should be an increase exceeding 20% of the baseline value, and the absolute postoperative value should be at least more than five times the 99th percentile. In addition, one of the following elements must be present: new ischemic changes on the electrocardiogram, development of pathological Q waves, evidence of new loss of viable myocardium or new regional wall motion abnormality on imaging examination consistent with ischemic etiology or angiographic findings consistent with a complication that limits coronary flow (coronary artery dissection, occlusion of the epicardial coronary artery or lateral branch, limitation of collateral flow, or distal embolization).[16]

Patients were divided into two groups according to the SYNTAX score for the comparison of clinical characteristics and main study outcomes. The group with SYNTAX score ≤ 32 was considered to be at low or intermediate risk; and the group with score ≥ 33, at high risk for the occurrence of major cardiac and cerebrovascular events.

The sources used for data collection were the patient's medical record and the electronic database of the hospital. Data were collected throughout the hospital length of stay. As the primary outcome, major cardiac and cerebrovascular events until hospital discharge were considered.

Statistical analysis

Data were analyzed using the MedCalc Statistical Software, version 15.2.2 (MedCalc Software, Ostend, Belgium). The adopted level of significance was 5% and the confidence interval was 95%.

In descriptive statistics, continuous quantitative variables were described after assessing adherence to normal distribution by the Kolmogorov-Smirnov test. For the variable close to the normal distribution, the mean and standard deviation (SD) were calculated; otherwise, the median and interquartile ranges (IQR) (25th percentile and 75th percentile) were considered. Categorical variables were described in absolute and relative frequencies (%).

In analytical statistics, categorical variables were compared using Fisher's exact test. To compare two groups of continuous variables with independent samples, Student's t-test was used for variables with normal distribution. For cases with non-normal distribution, the Mann-Whitney test was considered. Hospital mortality was described as frequency.

Results

Percutaneous coronary angioplasty was performed due to left main coronary artery lesion in 107 patients during the study period, and no patient was excluded (Table 1). Most patients aged over 60 years (75.00%) at the beginning of the study, with prevalence of men (72.89%). Echocardiogram was performed in 57 patients, and the mean ejection fraction was 53.74% (SD: 10.90).

The single lesion only affecting the left main coronary artery was found in one patient. The multivessel lesion was predominant, with most (39.25%) of the lesions being found in three vessels in addition to the left main coronary artery. The most frequently impaired arteries, in addition to the left main coronary artery, were 91 (85.04%) cases of anterior descending artery; 83 (77.57%) of the circumflex artery; 50 (46.72%) of the right coronary artery; 28 (26, 26%) of marginal artery; 24 (22.42%) of diagonal artery; 16 (14.95%) of posterior descending artery; and 9 (8.41%) of posterior interventricular

artery. The SYNTAX score had a mean of 46.80 (SD: 22.95), and 70 (65.42%) patients had a SYNTAX score above 33 points (Table 2).

Angiographic success of percutaneous intervention by intravascular ultrasound was considered in 106 (99.06%) patients. In each procedure, a mean of 4.4 (SD: 2.4) lesions were treated, and a mean of 3.9 (SD: 2.3) stents were implanted. Intravascular ultrasound was used in all patients. The mean coronary artery lumen diameter measured by intravascular ultrasound was 4.52 mm^2 (SD: 1.05) before the angioplasty procedure, and this mean increased to 15.39 mm^2 (SD: 3.15) after percutaneous intervention. In 51 (47.66%) cases, it was decided to perform staged procedures. In these cases, between two and four procedures were performed to complete the treatment of all coronary lesions.

Complications during the procedure occurred in 13 patients (14.95%), of whom 9 presented hematoma at the puncture site, without the need for blood transfusion or surgical intervention. Two patients had hospital-acquired pneumonia, one patient had acute pulmonary edema, and one patient had coronary artery perforation. In the latter case, pericardiocentesis was performed, and the patient was referred for surgical drainage via the pericardial window. There were five (4.67%) cases of postoperative myocardial infarction, all cases of infarction being related to the percutaneous procedure, and two deaths; there was no stroke after the

Table 1 – Clinical characteristics of patients

Variable	N	%
Age, years (mean-SD)	69.05	10.61
Men	78.00	72.89
Ejection fraction (mean-SD)	53.74	10.90
Diabetes mellitus	61.00	57.01
Arterial hypertension	90.00	84.11
Hypercholesterolemia	83.00	77.57
Previous angioplasty	41.00	38.32
Previous AMI	5.00	4.67
Hypothyroidism	8.00	7.47
Cancer	6.00	5.60
Chronic kidney disease requiring dialysis	2.00	1.87
Other chronic diseases	3.00	2.80
SAPS 3 (mean-SD)	34.78	7.30
LMCA lesion (%) (mean-SD)	65.07	11.76
Distal LMCA lesion	53.00	49.53
Number of affected vessels		
LMCA	1.00	0.93
LMCA + 1 vessel	28.00	26.17
LMCA + 2 vessels	36.00	33.64
LMCA + 3 vessels or over	42.00	39.25
SYNTAX score (mean-SD)	46.80	22.95
Number of stents (mean-SD)	3.90	2.33

SD: standard deviation; AMI: acute myocardial infarction; SAPS: Simplified Acute Physiology Score; LMCA: left main coronary artery.

Table 2 – Comparison of groups of patients according to the SYNTAX score

Variable	SYNTAX ≤ 32 N = 37	SYNTAX ≥ 33 N = 70	p-value
Age, years (mean-SD)	70.24 (9.79)	68.42 (11.04)	0.40
Men N (%)	24.00 (64.86)	54.00 (77.14)	0.25
Ejection fraction (mean-SD)	51.23 (9.21)	55.33 (11.71)	0.18
Diabetes mellitus N (%)	20.00 (54.05)	41.00 (58.57)	0.68
Arterial hypertension N (%)	33.00 (89.19)	57.00 (81.43)	0.40
Hypercholesterolemia N (%)	29.00 (78.38)	54.00 (77.14)	0.54
Previous angioplasty N (%)	33.00 (89.19)	22.00 (31.43)	0.05
Previous AMI N (%)	2.00 (5.41)	3.00 (4.29)	0.56
SAPS 3 (mean-SD)	35.05 (7.34)	34.64 (7.33)	0.78
LMCA lesion (%) (mean-SD)	65.73 (8.20)	64.69 (13.54)	0.74
Distal LMCA lesion	18.00 (48.64)	35.00 (50.00)	0.50
ICU length of stay, days (median-IQR)	2.00 (1.00 – 4.50)	2.00 (1.50 – 5.00)	0.33
Hospital length of stay, days (median-IQR)	4.00 (2.50 – 6.50)	3.50 (2.50 – 7.00)	0.87
Major cardiac and cerebrovascular event N (%)	3.00 (8.10)	4.00 (5.71)	0.68
Hospital mortality N (%)	0 (0.00)	2.00 (2.82)	0.54

SD: standard deviation; AMI: acute myocardial infarction; SAPS: Simplified Acute Physiology Score; LMCA: left main coronary artery; ICU: intensive care unit.

percutaneous procedure during the intrahospital follow-up period. The frequency of major cardiac and cerebrovascular events in the hospital outcome was 6.54%. Patients had a median length of stay of two days (IQR: 1.0 – 5.5 days) in the ICU and four days (IQR: 2.5 – 7.0 days) in the hospital (Table 3).

When comparing patients according to the SYNTAX score, there was no difference in clinical characteristics or relevant outcomes between the group of patients with high score and those with low or intermediate score. The two deaths reported in the sample occurred in patients in the high SYNTAX score group (Table 2). In one case, death was attributed to massive pulmonary embolism immediately after the percutaneous angioplasty procedure, and the second case was considered to be due to acute coronary occlusion during the procedure.

Discussion

In the present study, experience with the performance of percutaneous intervention for the treatment of unprotected left main coronary artery lesion guided by intravascular ultrasound is reported. In this report of a large number of cases, the angioplasty procedure as a choice for the treatment of these complex coronary lesions proved to be safe and with high angiographic success, including for the group of patients considered to be at high risk.

The optimization of percutaneous intervention with the use of intravascular ultrasound represents a technological advance that has changed the practice of interventional cardiology. In addition, the use of risk stratification by the residual SYNTAX score can be useful to identify patients who benefit from the option for percutaneous intervention.[17] Hemodynamicists aim at achieving optimal expansion of the stent in order to minimize the risk of stent thrombosis and restenosis. The use of intravascular ultrasound is an important component for the success of the procedure.[18] In the experience reported in the present study, intravascular ultrasound was used in all patients for better studying the lesions and assessing angiographic success after the procedure.

Until recently, the main studies evaluating the use of percutaneous intervention in unprotected lesions were SYNTAX[19] and PRECOMBAT.[2] The composite outcome of major cardiac and cerebrovascular events was similar in the SYNTAX study comparing percutaneous intervention (36.9%) and myocardial revascularization procedure (31.0%, p = 0.12) as well as mortality from all causes. The need for myocardial revascularization was more frequent in patients allocated for percutaneous intervention, and stroke was more frequent in patients allocated for the revascularization procedure. The PRECOMBAT[2] study confirmed these results and described a higher frequency of ischemia related to the revascularized vessel in the percutaneous intervention group. Both studies report a greater benefit of percutaneous intervention for patients with SYNTAX score ≤ 32.

More recently, two other large studies have brought new evidence on the subject.[20,21] Both were non-inferiority studies comparing percutaneous intervention and myocardial revascularization procedure to treat unprotected left main coronary artery lesion. The EXCEL study, which included 1,905 patients with left main coronary artery lesion and at low or intermediate risk by the SYNTAX score, showed non-inferiority of percutaneous intervention compared with the myocardial revascularization procedure in all outcomes over a three-year follow-up period.[20] This study demonstrated

Table 3 – Length of hospital stay and patients' outcomes

Variable	N	%
ICU length of stay, days (median-IQR)	2	1.00 – 5.50
Hospital length of stay, days (median-IQR)	4	2.50 – 7.00
Major cardiac and cerebrovascular event	7	6.54
Hospital mortality	2	1.87

ICU: intensive care unit; IQR: interquartile range.

that stent thrombosis was less frequent than coronary graft occlusion. In the five-year follow-up period of the EXCEL study, the frequency of major events remained similar between groups.[22] Conversely, the NOBLE study, which analyzed 1,201 patients, suggests superiority of the procedure at five years of follow up due to the more frequent need for myocardial revascularization in the percutaneous intervention group.[21] In both studies, mortality at three or five years of follow up did not differ between the two procedures. The apparent contradictory results of these two studies are probably due to differences in primary outcomes and definition of myocardial infarction unrelated to the procedure between studies. The EXCEL study selected as composite outcome the mortality rate from all causes, cerebrovascular accident, and acute myocardial infarction, whereas the NOBLE study expanded this outcome by adding the need for a new revascularization. In the present study, the composite outcome is similar to the EXCEL study, and the low rate of its occurrence is consistent with the results of the large studies reported.

A recent meta-analysis[23] including these large studies suggests that patients with unprotected left main coronary artery lesion undergoing percutaneous intervention have rates of occurrence of stroke, acute myocardial infarction, and death similar to patients undergoing the myocardial revascularization procedure in five years of follow up. Drug-eluting stents have shown superior results compared with nondrug-eluting stents, and the latter can no longer be considered the gold standard of safety in percutaneous interventions.[24] The use of new-generation drug-eluting stents is associated with a lower frequency of postoperative complications, including stent thrombosis.[25]

The first case on treatment of unprotected left main coronary artery lesion by percutaneous intervention described in Brazil was the treatment of a patient with stable angina and without contraindication for surgery, in which percutaneous intervention was performed with first-generation drug-eluting stent and presented good results in the short-term.[26] Other Latin American authors describe good results in case reports or studies with small samples of patients with SYNTAX score graded as low or intermediate risk.[27-29] Costantini et al.[30] describe an experience with 142 patients, including 63 cases with high-risk SYNTAX score and with the use of intravascular ultrasound in most cases. The authors verified 81.0% of success assessed by ultrasound and a hospital mortality rate of 1.4%, results similar to those found in the sample of the present study.

In the present study, a high value was found for the mean SYNTAX score (46.80) compared with reports in the literature. The SYNTAX[31] study described a mean of 29 and 30 between groups; the EXCEL study evaluated low- and intermediate-risk patients and had a mean score of 20;[20] and the NOBLE study described a mean score of 22 between groups.[21] Thus, it is possible to infer that the present cases have a high anatomical complexity of coronary lesions.

The performance of percutaneous intervention is described even in patients with a high SYNTAX score, with results similar to those found in patients with low or intermediate risk. Intuitively, patients with a SYNTAX score above 32 should benefit from the option for myocardial revascularization procedure, but this score does not include clinical variables that can have a major impact on the measured outcomes. The EuroSCORE is likely to perform better as a predictor of these events. Another possible explanation for the similar results between the studied groups may be the performance of complete revascularization of the coronary lesions in the studied patients, reducing the chances of major postoperative events. Similarly, other authors in a single-center study did not find an increase in mortality or restenosis after three years of follow up of the percutaneous intervention, comparing patients with low-intermediate and high SYNTAX scores.[32] The increased risk of culprit-lesion revascularization in percutaneous interventions found in the SYNTAX and PRECOMBAT studies has not been reproduced in the more recent EXCEL and NOBLE studies.

In clinical practice, patients with unprotected left main coronary artery lesion generally have more comorbidities and worse outcomes when compared with patients evaluated in large clinical trials. Prediction models are useful tools to assist in the therapeutic planning of these complex coronary lesions and to optimize the outcome of patients through individualized medicine. The combination of the SYNTAX score and the EuroSCORE possibly improves the outcome prediction as for the indication to percutaneous intervention for unprotected left main coronary artery lesions.[33]

Studies of this type present information that broadens the indications to percutaneous interventions for selected patients. The periprocedural profile of short hospital stay, low rates of infection, reduced need for blood transfusion, and cost-effectiveness make percutaneous intervention very attractive. Decisions regarding the choice of treatment procedure must be made by a team of specialists considering each patient's individual characteristics, comorbidities, life expectancy, disease extension, angiographic anatomy, and preferences.

As limitations of this study, the retrospective design of the case series, the fact that it is a single-center study, and the procedures being performed by the same hemodynamicist

could be considered. The generalization of results should be carefully done for centers with similar characteristics as well as the clinical profile of patients. The greatest contribution of the study is the use of intravascular ultrasound in all procedures and the large number of reported cases, which is similar to the number of cases of some of the large clinical trials found in the literature.

Conclusions

Percutaneous intervention in cases of unprotected left main coronary artery lesions was safely performed and presented excellent results. Considerable angiographic success of treatment guided by intravascular ultrasound was achieved. The rate of major cardiac and cerebrovascular events was low and similar between patients at low and high risks.

Author Contributions

Conception and design of the research: Grion DS, Grion CMC; Acquisition of data: Grion DS, Grion DC, Silverio IV, Oliveira LS, Larini IF, Martins AV, Moreira J, Machado M,

Niekawa LST, Grion AS; Analysis and interpretation of the data and Critical revision of the manuscript for intellectual contente: Grion DS, Grion DC, Silverio IV, Oliveira LS, Larini IF, Martins AV, Moreira J, Machado M, Niekawa LST, Grion AS, Grion CMC; Statistical analysis: Grion CMC; Writing of the manuscript: Grion DS, Grion DC, Grion CMC.

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Left Main Coronary Artery Percutaneous Intervention. Why are Real-World Data so Important?

Vinicius Daher Vaz[1]

Hospital do Coração Anis Rassi,[1] Goiânia, GO - Brazil

Short editorial related to the article: Percutaneous Coronary Intervention in Unprotected Left Main Coronary Artery Lesions

The estimated prevalence of left main artery disease found during diagnostic angiography is 6% in published series. The enthusiasm for a less invasive therapy than coronary artery bypass grafting (CABG) for patients with unprotected left main coronary artery (ULMCA) disease dates back to the 90s.[1] Although the contribution of CABG in the survival of patients with ULMCA disease is undeniable, in the last few years, several authors have demonstrated the safety and efficacy of percutaneous coronary intervention (PCI).

Despite the controversies regarding the 5-year publication of the Evaluation of XIENCE versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization (EXCEL)[2] trial, when it comes to hard outcomes, as death and stroke, in the last years several randomized and non-randomized trials have demonstrated non-inferiority or even superiority of PCI against CABG.[2-6] Recently, these data were compiled in two meta-analysis where long term follow-up has shown no significant difference in mortality and stroke rate between PCI and CABG.[7,8] In addition, two of these randomized trials with extended long-term follow-up, up to 10 years, have demonstrated sustained good results after PCI, with death rates similar to CABG, respectively, 14.5% x 13.8% and 27% x 28%.[4,5]

In this issue of *Arquivos Brasileiros de Cardiologia*, Grion et al.[9] present their experience with PCI for ULMCA disease in a consecutive series of 107 patients.[9] These data are very important for the entire medical community involved in the treatment of coronary artery disease, in light of the scarcity of data regarding CABG or PCI for ULMCA disease in our region. From the point of view of evidence-based medicine, randomized control trials (RCT) are the "gold standard" for evaluating the safety and efficacy of therapeutic agents, even more in the complex scenario of comparing two invasive treatment methods as distinct as CABG and PCI. However, registries and local experience, such as that of Grion et al.[9] are important for providing the full spectrum of

Keywords

Intervention Coronary Percutaneous; Coronary Artery Disease; Angiography/diagnostic imaging; Precalenve; Myocardial Revascularization; Stroke; Mortality.

Mailing Address: Vinicius Daher Vaz •
Serviço de Hemodinâmica - Hospital do Coração Anis Rassi - Rua José Alves, 453.
Postal Code 74110-020, Goiânia, GO Brazil
E-mail: viniciusdahervaz@gmail.com

patients treated in the real world setting and the possibility of assessing whether the treatments and results of the RCTs are actually applied on a daily basis. The necessary strict inclusion and exclusion criteria implies that trial populations are often not representative of the patients encountered in clinical practice. For example, in the EXCEL and NOBLE trials, more than one-third of the eligible patients were actually excluded and almost half of them were so due to clinical conditions, which leads the participating cardiac surgeon or interventional cardiologist to believe that clinical equipoise were not present.

The present study included a real-world population, usually excluded from randomized clinical trials with increased complexity. Diabetes was present in more than half of the patients (57%) and the mean age was as high as 69 years old. The mean ejection fraction of 53% is lower than those from RCTs and a higher number of stents were implanted per patient (3.9). Finally, the mean SYNTAX score was 46 ± 23, substantially higher than those from the EXCEL,[2] NOBLE[3] and PRECOMBAT[4] trials. Notwithstanding these hugely clinical and lesion risk profiles, they have achieved very good short-term results with high procedural success (99%) and low rate of in-hospital mortality (1.86%). Similar rates were observed in our country by Constantini et al.[10] in 2011 (in-hospital mortality of 1.4%), as well as in the major all-comers[11] international registries like DELTA 1, DELTA 2[12] and MAIN-COMPARE,[13,14] where the hospital mortality was respectively 2.0% and 1.1% and 0.8%. Despite the relevance of in-hospital results, obviously long-term follow-up outcomes are still needed to confirm these good in-hospital findings. Having said that, we must bear in mind that in order to accomplish good long-term results in any kind of intervention for patients with stable multivessel coronary artery disease or ULMCA, it is essential to have in-hospital mortality below 2%.

On the other hand, it has been widely demonstrated that even the contemporary PCI, compared to CABG, has a greater risk of repeated revascularization in the long-term follow-up. In this context, it is worth mentioning the excellence of the current group, using intracoronary ultrasound (IVUS) to guide PCI in 100% of the ULMCA disease patients. Even in the RCTs, IVUS-guided PCI does not exceed 70% of use. Moreover, there is plenty of experience and a wealth of evidence supporting routine use of IVUS in ULMCA PCI. IVUS during ULMCA PCI is safe and associates with substantial reductions in MACE in the long-term follow up, including repeated revascularization and even death.[15]

In conclusion, Grion et al.[9] demonstrated very good in-hospital results of IVUS-guided complex ULMCA PCI in our environment. Knowing and publicizing our in-hospital results is

Short Editorial

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Evaluation of Coronary Circulation after Arterial Switch Operation

Mariana Nicoletti Ferreira Baldo,[1] Henrique Simão Trad,[2] *Tarcisio José da Silva Junior,[1] Paulo Henrique Manso[1]*
Universidade de São Paulo,[1] Ribeirão Preto, SP - Brazil
Lotus Radiologia,[2] Ribeirão Preto, SP - Brazil

Abstract

Background: Coronary artery evaluation remains after arterial switch operation a clinical challenge.

Objective: This study aims to correlate anatomical changes diagnosed by cardiac computed tomography (CCT) with physiological alterations on clinical evaluation to diagnose coronary obstruction in late ASO patients.

Methods: This study included 61 consecutive patients with mean age of 9.4 years who underwent ASO. The patients were submitted to echocardiography, electrocardiography, cardiopulmonary exercise test, and cardiac computed tomography to evaluate functional capacity and coronary artery anatomy.

Results: Cardiac computed tomography revealed that only 3.3% of the patients had coronary stenosis. These patients were asymptomatic, and no signs of myocardial ischemia were detected by the tests.

Conclusion: The incidence of coronary abnormalities in late ASO patients was 3.3% in our cohort. There is no clear guideline as to why, when, and how these patients should be screened or what to propose when a coronary obstruction is diagnosed in asymptomatic patients.

Keywords: Coronary Artery; Coronary Circulation; Jatene's Surgery; Arterial Switch Operation; Tomography, X-Ray; Diagnostic, Imaging.

Introduction

Although arterial switch operation (ASO) is associated with a low early mortality and morbidity in most centers,[1] late complications, such as obstructive coronary artery lesions, right ventricular outflow tract obstruction, and neoaortic root dilation and regurgitation may be present in up to 25% of the cases.[2] In addition, late abnormalities in coronary artery circulation have been reported to occur in up to 18% of the cases in late follow-up.[3] However, the true incidence of late coronary artery problems after ASO is unknown because most patients with coronary artery stenosis or occlusion may be asymptomatic, the reported incidences tend to depend on the depth of investigations.[4] Besides, there are no clear guidelines about when these patients should be screened or the best screening method in this situation.[5]

In addition to clinical evaluation, ASO patients require a multimodality assessment for possible late complications. Transthoracic echocardiography (TTE), electrocardiography (ECG), and cardiopulmonary exercise test (CPET) are usually used for the long-term follow-up of these patients. Nevertheless, these screening methods are not sensitive enough to detect coronary artery abnormalities.[6]

Cardiac computed tomography (CCT) is a good method to evaluate coronary artery anatomy of ASO patients in the late post-operative phase, with a high spatial resolution within a short acquisition time. CCT is an ideal method for patients that need detailed evaluation of reimplanted coronary arteries.[7]

Objective

To evaluate coronary artery circulation in a cohort of ASO patients in the late operative period by TTE, ECG, CPET, and CCT.

Methods

This prospective study was approved by the local institutional review board (43493315.6.0000.5440). Patients that were submitted to ASO at our institution between 1998 and 2009 were recruited. Inclusion criteria were age over five years, and written consent of the parents to participation. Patients with known allergy to iodinated contrast were excluded from the study. Medical data regarding initial diagnosis, coronary artery anatomy, and age at surgery were collected from the medical records. The patients were then submitted to ECHO, ECG, CCT, and CPET within a four-month period.

ECG and TTE were performed according to routine protocols. CPET was performed on an inclined treadmill at constant speed, with an increase in the inclination during the test.

CCT was performed in a 64-slice device (Somaton Sensation, Siemens, Germany). When necessary, an oral beta-blocker was administered two hours before the exam so that a

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heart rate below 80 bpm would be achieved. The participating children had been previously trained to hold their breath for 10 seconds. When the patient was not able to cooperate, intravenous midazolam was given (0.1 to 0.2 mg/kg). Image acquisition parameters were adapted to enable the use of the lowest radiation dose possible. Two independent radiologists analyzed the images.

Statistical analysis

A descriptive analysis of the data was carried out. Continuous data are expressed as median and range; categorical data are expressed as percentage. All statistical analyses were performed using GraphPad Prism 5.0 (GraphPad Software, La Jolla, CA, USA) with the level of statistical significance set at P< 0.05.

Results

Patient demographics

Of the 69 initially recruited patients, four did not agree to participate, two missed follow-up, and two died (one patient died during pulmonary artery stenting in the cath lab, and one patient died of unknown cause). The remaining 61 patients were submitted to ECG and TTE; 60 patients were subjected to CCT; and 51 patients did CPET. All patients were asymptomatic and were not using any cardiac medications.

Seventy percent of the patients were male. Most patients had transposition of the great arteries (TGA) with intact interventricular septum (56.7%), 31.7% had TGA with

ventricular septal defect (VSD), and 11% had the Taussig-Bing anomaly. In 90% of the patients, the coronary artery arose from its usual origin in the pre-operative period (the left coronary arose from sinus 1 and right coronary arising from sinus 2).

ASO was performed at a mean of 14 days (range: 2 to 38 days), median age of participants was 9.4 years (5 to 18 years), median weight was 29.9 Kg (20 to 84 Kg), and median height was 134 cm (112 to 183 cm).

Clinical investigation

All patients had ECG and TTE results. Most patients (96%) were in sinus rhythm, while 4% had right atrial rhythm. No patient had ST changes or ventricular ectopy in the resting ECG. The TTE showed that all patients had normal ejection fraction (>55%) and normal ventricular regional wall motion.

CPET: Fifty-one patients were able to perform the CPT (10 patients had limb or neurological conditions and were not able to perform the test), and none of them presented ST segment abnormalities or arrhythmia during the test. They presented a VO_2 max of 31.7 mL/Kg/min (22.3 – 43.2) and reached a mean of 9 (6.4-12.3) METS.

CCT: Sixty patients were able to undergo CCT. The mean dose length product (DLP) was 138 (56 -490) mGy-cm; the mean dose was 2 (0.9–8.7) mSv. Only two (3.3%) patients had coronary artery abnormalities; one of the patients had moderate left coronary artery stenosis, and the other presented severe right coronary artery obstruction (Figure 1). We graded coronary artery obstruction according to published guidelines.[8] Both patients were asymptomatic, and all the other tests (resting ECG, TTE, and CPET) revealed normal findings

Figure 1 – Cardiac computed tomography image; right coronary artery with severe obstruction (arrow)

(Table 1). We could not find any correlation between primary cardiac diagnosis or coronary artery pattern and the presence of coronary stenosis.

Discussion

Evaluation of patients undergoing ASO remains a clinical challenge: there is no consensus regarding the appropriate interval and modality for surveillance imaging. A defined management strategy is lacking when subclinical anatomical or physiological abnormalities are identified; and symptoms attributable to potential complications are rare.[5] None of our patients with coronary artery abnormalities had abnormal findings in routine tests (ECG, echocardiography, and CPET), which has also been described by other authors.[4]

Evaluation of the coronary circulation after ASO remains an important issue. Kinkings, stenosis, and obstruction may arise any time after ASO, and a bimodal pattern has been described.[6] However, the true incidence of late coronary artery problems after ASO is unknown. While some studies on coronary artery stenosis have reported no abnormalities at all, other studies have reported the occurrence in up to 18% of the cases.[9] In a cohort of 130 consecutive children aged about five years, Ou and colleagues showed a prevalence of 9.2% of coronary artery lesions.[7] In the study by Tsuda et al.,[4] of 40 patients submitted to coronary angiography, 11 (27.5%) had coronary artery abnormalities. Most patients seemed to have some degree of intimal thickening, but the clinical relevance of this information still has not been understood.[10] Although the risk of myocardial ischemia in the postoperative period has been extensively described, the long-term risk for coronary artery lesions and ischemia remains unclear.[11] Patients with severe coronary artery lesions may not show any symptoms or evidence of myocardial ischemia.[3] Because asymptomatic patients might be at risk, coronary arteries are

often investigated. Most of the described obstructions are ostial or stem obstruction, caused by compression in the initial portion coronary artery. Therefore, investigating coronary artery patency in the long-term follow-up is essential.

Nevertheless, a paper on a large series showed that as few as 0.26% of patients who had undergone ASO were submitted to coronary artery interventions in the long-term follow-up.[12] Moreover, a meta-analysis that enrolled 8,798 patients in 66,450 patient follow-up years showed that only five sudden cardiac deaths occurred in asymptomatic patients. In a cohort of 647 patients followed up for 10 years, only one patient (0.1%) had to be re-operated due to coronary artery abnormality one year after ASO.[11]

Most studies regarding coronary arteries in the late post-operative period after ASO have been conducted in small samples of patients that required coronary artery evaluation for some reason. Despite the small number of patients included in the present study, the coronary arteries were evaluated in almost our entire cohort of patients.[13] Indeed, 94% of our patients underwent multimodal assessment. We could not identify a predisposition factor for coronary obstruction in these patients. Some patients were not able to perform the CPET, and other patients had to be sedated before CCT. There is no consensus about who should be assessed for coronary artery disease following ASO. While several groups advocate that every ASO patient should be investigated in the post-operative period, other groups claim that only patients with abnormalities in clinical examination or routine tests should be evaluated. Series have varied from 27% to 100% of ASO patients undergoing assessment for coronary artery disease.[6,14] Some authors recommend that an early angiographic evaluation be conducted in all patients[3] even though a meta-analysis has shown a sudden cardiac death chance of only 0.05%.[11] Other series have shown the need for coronary reintervention in only 0.26% of the patients.[12]

Table 1 – Characteristics of the patients with coronary artery abnormalities as demonstrated by cardiac CT

	Patient 1	Patient 2
Coronary artery lesion	Moderate left coronary artery occlusion	Severe right coronary artery obstruction
Age (years)	14.7	6.6
Gender	Female	Male
Initial diagnosis	TGA without VSD	TGA with VSD
Pre-operative coronary artery pattern	Usual	Usual
Balloon atrial septostomy	Yes	No
Weight (kg)	56.1	26.8
Height (cm)	168.5	120.5
ECHO	LVEF 72% No regional wall motion abnormalities	LVEF 73% No regional wall motion abnormalities
ECG	Sinus rhythm HR: 75 bpm	Sinus rhythm HR: 64 bpm
CPET	RER 1.1 No ST-segment changes	RER 0.96 No ST-segment changes

ECG: Eletrocardiography; ECHO: Echocardiography; HR: Heart Rate; TGA: transposition of the great arteries; VSD: Ventricular Septal Defect; LVEF: Left Ventricle Ejection Fraction; RER: Respiratory Exchange Rate; CPET: Cardiopulmonary Exercise Test.

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In our cohort, patients older than five years were enrolled; the median age was 9.4 years. There is no consensus concerning the appropriate time to look for coronary artery abnormalities in ASO patients in the late operative period. Patients are either routinely investigated or are only investigated when they present any clinical sign or abnormal findings in routine exams like TTE and ECG. Authors have investigated coronary artery circulation routinely in ASO patients three to eight years after the surgery.[3,9] Some authors found that coronary artery abnormalities did not progress over time,[10] while others noted progression that the coronary artery abnormalities may be progressive.[6] However, there is no consensus as to whether these patients should be screened once in a lifetime or every five years after ASO.[6,14] Also, whenever some authors suggest a coronary angiogram around 12 years of age,[4] others suggest that a computed tomography (CT) scan be performed in all patients at puberty.[15] Other authors recommend that coronary arteries be routinely investigated after 17 years of age.[16] Some centers recommend CCT or invasive coronary angiography at least once in adulthood in all ASO patients.[17]

Patients with coronary artery stenosis or occlusion may be asymptomatic, and echocardiography findings may be elusive. Regional wall motion abnormalities or progressive ventricular dilation and dysfunction may arouse suspicion of coronary artery stenosis or occlusion,[18] but these findings are rare.

Although the routine tests (ECG, TTE, CPET) usually performed in the follow-up of these patients provide low sensitivity (about 43%), but high specificity (about 93%) for coronary artery abnormalities.[6] Some authors recommend that adult ASO patients perform a noninvasive ischemia testing every three to five years.[19] In our cohort, none of the 61 patients had any abnormal finding in the ECG or TTE, and the two patients with coronary abnormalities also had normal CPET. Although the CPET may detect signs of ischemia in patients after ASO, these abnormalities do not correlate well with perfusion studies.[20,21]

For a long time, selective coronary angiography was considered the most accurate method to assess coronary artery obstruction after ASO[6,9] mostly because of its wide availability. Nevertheless, the coronary catheter may pass through an ostial stenosis and fail to visualize an ostial obstruction. In addition, the coronary arteries are not visualized in the context of adjacent structures that may compress or kink said arteries. Furthermore, selective coronary angiography is an invasive procedure with potential vascular risk and requires exposure to radiation and general anesthesia in young children. Even after the coronary arteries are evaluated by CT, some groups still perform angiography as a routine method, considering it as the method of choice since it allows intervention if an obstruction is diagnosed.[3]

In the last decade, however, CCT has emerged as a safer and faster method to evaluate coronary artery circulation as compared to coronary angiography. Sixty-four-slice CCT can be successfully performed in children aged over five years and is both sensitive and specific to detect coronary artery stenosis or occlusion after ASO. Exposure to radiation, use of iodinated contrast, and need for a vascular access are the drawbacks of this method.[18] CT was performed in our patients safely, without complications.

Although cardiac magnetic resonance can assess coronary arteries without the use of ionizing radiation, it requires that the patient remain still for 60 minutes, and thus also anesthesia or sedation in children aged less than nine years.[18] The presence of metallic devices, like stents, may interfere in the images. Since half of our patients would need sedation, and six other patients older than nine years had pulmonary artery stents, all of them were evaluated by CCT.

Our two patients with coronary artery abnormalities were not submitted to any intervention. Even after an occlusion or obstruction is diagnosed, there is no consensus as to what should be done because most of the patients are asymptomatic without alterations in ECG, TTE, or CPET. In several series, the rate of re-intervention after diagnosis of coronary artery alterations varied from 3.8 to 12% of the investigated patients[6,7,9,14,15] or 1 to 2% of all patients undergoing ASO. Moreover, there is usually a delay between the coronary artery lesion diagnosis and its surgical correction. In one series of patients with coronary artery obstructions, the time elapsed between the diagnosis of coronary artery abnormality and its repair was three years on average, but the gap between diagnosis and surgical treatment could be as long as eight years.[14,15] Patients were submitted to surgical coronary ostium enlargement, mammary artery graft, or balloon dilation and stenting.[7,14,15]

A systematic review that analyzed 8,798 patients showed that only five patients (0.05%) had sudden cardiac death due to coronary artery abnormalities, although 7.3% of patients presented some level of coronary obstruction. Another issue to consider is that 4.9% of the patients that had to undergo re-intervention due to coronary artery obstruction died. In another large series of 7,951 patients, only 0.26% needed coronary artery intervention and the mortality rate was 20%.[12]

The present study involved a single-institutional patient cohort, so selection bias may have occurred. The number of cases may also be inadequate to show a correlation between initial diagnosis or original coronary artery pattern and subsequent coronary abnormalities.

Conclusions

In our study, the incidence of coronary artery abnormalities after ASO was 3.3%, and all of them were asymptomatic. Although the medical group must be aware of these conditions after ASO, there are no clear guidelines as to when and how these coronaries should be addressed or about what to do if coronary artery alterations arise in asymptomatic patients.

Our study has shown that patients with anatomical obstruction in coronary arteries may be asymptomatic even at CPET, and with normal ECG and TTE. A multimodality approach with functional and anatomical information is still necessary. Based on our findings, we have decided to keep an annual follow-up with TTE, ECG, and CPET. If the patient presents clinical symptoms (arrhythmia, thoracic pain, or excessive fatigue) or an alteration in a routine exam, we recommend a CCT.

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Coronary Arteries after Jatene Operation for Transposition of Great Arteries: The Role of CT Coronary Angiography on Follow-up

Antonio Joaquim Marinho-da-Silva[1] (ID)

Centro Hospitalar e Universitário de Coimbra,[1] Coimbra- Portugal
Short Editorial related to the article: Evaluation of Coronary Circulation after Arterial Switch Operation

The correction of transposition of the great arteries (TGA) by the Jatene technique was one of the greatest achievements of cardiac surgery in congenital heart disease.[1] By replacing the transposed arteries in their proper anatomical arrangement, this technique — atrial switch operation (ASO) – achieves a normal spatial arterial relationship. However, this new arrangement requires excision of the coronary artery buttons and their implantation in the new aorta. The difficulty of this step relates to the type of coronary origin and distance to the new insertion site.

Once this anatomical normalization step has been achieved, cardiac functional normalization is sought. The most common post-surgical complications are related to the complexity of associated anomalies (ventricular septal defect (VSD), coarctation of the aorta, valve stenosis, and others), suture sites of the neovessels, pulmonary ramification and dilation of the neoaorta,[2] Not neglectable and object of concern, late complications of either congenital or acquired coronary circulation are well known.[3] The actual incidence of such complications ranges from 0,8% to 27,5% according to reporting series and time of follow-up.[3,4]

The mechanism of coronary complications is well known and described, going from anatomic distortion, acute angle, kinking, coronary interarterial course to different types of stenosis, particularly critical ostial stenosis that may be life-threatening.[3,5] The best method to either geometrical or functional coronary circulation evaluation is still a matter of discovering and discussion. In this issue of ABC, the article by Baldo et al.[6] addresses this important question. Although functionally asymptomatic, 3,3% of these patients revealed potentially significant coronary abnormalities. This was a basal study, regardless of symptoms. Although some international guidelines support this view,[7] others do not.[8]

Most coronary problems and events described so far tend to occur in childhood in the first few years after surgery where complaints are difficult to access. Furthermore, owing to lack of testing sensitivity, conventional screening approach by electrocardiogram ECG or Doppler echocardiography are not always helpful. So, it seems logical to investigate patients after ASO looking for coronary artery abnormalities despite apparent "normality". In the past, we did this screening using conventional angiography with unnecessary exposure to radiation and catheterization complications.

Since the beginning of the year 2000, coronary angiography by computed tomography (CCT-angiography) has assumed an increasingly important role in the assessment of coronary anomalies, namely after TGA correction by the Jatene technique.[9] Identifying those anomalies in patients that can ultimately compromise their lives is the challenge that this text poses, reinforcing the importance of one method of diagnostic imaging. Owing to ostial lesions, conventional coronary angiography may not eventually identify them. I agree that at least one basal evaluation of coronary circulation in all post-operative patients would be reasonable. Then, diagnostic superiority of CT angiography compared to conventional coronary angiography should be highlighted.[10] Cardiac and coronary magnetic resonance angiography (CMR) (avoiding radiation) may also be an option for evaluating coronary patency.[11] Eventually, a new CT technique like dual-energy CT combining perfusion with anatomic visualization will be more useful in some particular cases, too.[12] Annual multi-modality follow-up with Doppler echocardiography, echocardiography, and CPT or ergometric stress test will be necessary as the authors emphasize. But other non-invasive techniques such as Doppler-derived strain and strain rate may eventually be helpful in functional evaluation rather than conventional ultrasound.[13] Of course, if clinical symptoms (arrhythmia, thoracic pain or excessive fatigue) or abnormalities are found in the standard tests, cardiac evaluation by coronary computed tomography (or CMR) should be done immediately at any time.

But at what age should basal coronary assessment in ASO be performed still remains in discussion. Despite the absence of symptoms, in my opinion, it should be before adulthood. And it should be prudent to do such assessment also in adults on whom this information has not yet been obtained.[14]

Short Editorial

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Macroscopic Evaluation of Atherosclerosis in the Arteries: An Autopsy Assessment Tool

Mariana Silva Oliveira,[1] Bianca Gonçalves Silva Torquato,[1] Maria Helena Soares,[1] Maria Luiza Gonçalves dos Reis Monteiro,[1] Guilherme Ribeiro Juliano,[1] Laura Sanches Aguiar,[1] Vicente de Paula Antunes Teixeira,[1] Mara Lúcia da Fonseca Ferraz[1]

Universidade Federal do Triângulo Mineiro,[1] Uberaba, MG – Brazil

Abstract

Background: Atherosclerosis, in some cases, is an asymptomatic condition, and it is important to know the degree of arterial impairment caused by plaques and its association with risk factors. Autopsy examination provides understanding of basic disease processes and assessment to data about macroscopic characteristic of atherosclerotic involvement.

Objective: To macroscopically assess and standardize atherosclerotic involvement of aorta, carotid and iliac arteries and compare with age, gender and causes of death.

Methods: We collected 53 aortic arteries, 53 right carotid arteries, 53 left carotid arteries, 53 right iliac arteries and 53 left iliac arteries. For this assessment, the extension of fatty streaks, atheromatous plaques, fibrosis and calcification were considered, being the reference to score the degree of atherosclerotic involvement. Many degrees of atherosclerosis and accurate values were observed for mild, moderate and severe classification. For statistical analysis, data were analyzed using the software GraphPad Prism® 7.0. Differences were considered statistically significant if p-value was less than 5% (p <0.05).

Results: Carotid arteries had greater atherosclerotic involvement compared to the other arteries (K = 15.73, p = 0.0004). Atherosclerosis was progressive and significant with increasing age (carotid arteries: t = 6.321; p <0.0001; aorta: U = 83.5; p <0.0001; iliac: U = 306; p <0.0001) and as cause of cardiovascular death (carotids: t = 5.047; p <0.0001; aorta: U = 98.5; p = 0.0068; iliac: U = 467.5; p = 0.0012).

Conclusion: Macroscopic assessment of atherosclerosis is an innovative and low-cost way of direct visualization of atherosclerotic plaques, enabling an association with risk factors such as increasing age and cardiovascular diseases, providing important data for clinical practice.

Keywords: Cardiovascular Diseases; Atherosclerosis; Risk Factors; Asymptomatic Disease; Arteries; Autopsy; Heredity; Early Diagnosis.

Introduction

Atherosclerosis is a multifactorial disease associated with hereditary factors, sex and lifestyle habits such as smoking, inadequate diet and sedentary lifestyle.[1] Inflammation and deposition of lipids in the artery wall are involved in triggering and progression of atherosclerotic plaques[1] leading to cardiovascular diseases with high incidence worldwide.[2]

The early diagnosis of atherosclerosis as a predictor of coronary artery disease and acute myocardial infarction reduces morbidity and mortality associated with the disease. Studies explore prevalence and association of factors that contribute to risk stratification.[3] Evaluation and early diagnosis in patients of these groups are important.

It is known that the autopsy exam is extremely important, as it allows the understanding of the basic processes of diseases.[4] Studies have shown that in addition to eliminating risk factors associated with atherosclerosis, there are currently effective drugs for the treatment of this disease.[5] However, for the treatment to be effective, it is worthy to know the degree of arterial impairment caused by atherosclerotic plaques.[6] This fact makes our assessment and data on the macroscopic characteristics even more valuable, as autopsy studies allow a broad and direct view of atherosclerosis.[7,8]

As atherosclerosis is a multifactorial cardiovascular disease, responsible for the development of serious illnesses, its macroscopic assessment in autopsy material is important to provide a reliable and standardized description of atherosclerotic plaque progression. The association of macroscopic aspects with risk factors provides epidemiological data for clinical practice. The objective of this study was to identify macroscopically the intensity of atherosclerotic involvement of aorta, carotid and iliac arteries and to compare

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the degree of involvement with risk factors such as age, gender and cause of death.

Methods

We evaluated 2931 autopsy protocols performed between 1963 and 2018. Based on these protocols, biological materials (carotid, aorta and iliac arteries) were selected from those patients who presented complete autopsy report, with information about age (included those over 18 years old), gender and the cause of death (cardiovascular or not). Cases with biological materials in inadequate conditions or with incomplete autopsy reports were excluded from the study. A sample of 53 autopsied patients was obtained from the anatomical specimen file of the Discipline of General Pathology, totalizing 53 aortic arteries, 53 right carotid arteries, 53 left carotid arteries, 53 right iliac arteries and 53 left iliac arteries.   The study was developed in the Discipline of General Pathology of Federal University of Triângulo Mineiro and approved by the Research Ethics Committee of Federal University of Triângulo Mineiro with the Certificate of Presentation of Ethical Appreciation (CAAE) number: 56931816.4.0000.5154 in accordance with the resolution 466/2012.

Macroscopic evaluation of atherosclerosis

Three examiners evaluated macroscopic degree of atherosclerosis in aorta, right carotid, left carotid, right iliac and left iliac arteries, using criteria already described in the literature.[9] The progression of fatty streaks, atheromatous plaques, fibrosis and calcification on artery walls were a reference to score the degree of involvement (Figure 1). A 12.0 cm non-millimeter line was made on a sheet (Figure 2A) and this line was used as a scale for atherosclerosis involvement.

After opening the artery, examiners observed the degree of lesions, then a point was recorded on the scale regarding the degree of involvement, the closer to 0.0 cm the lesser the involvement, and the closer to 12.0 cm the greater the involvement (Figure 2B).

After the end of all evaluations, the distance from the 0.0 cm point to the point marked on the scale by examiners was measured, in order to avoid interferences in classifications (Figure 2C). The intensity of atherosclerosis was classified as mild if the evaluation was from 0.1 cm to 4.0 cm; moderate, from 4.1cm to 7.0cm and accentuated, from 7.1cm to 12.0cm.[9] Many degrees of atherosclerosis and accurate values were observed in mild, moderate and accentuated classification (Figure 3).

Statistical analysis

For statistical analysis, a database was created in the program *Microsoft Excel*®. Data were analyzed using the *software GraphPad Prism*® 7.0. To verify the type of distribution of variables, the statistical test of *Kolmogorov-Smirnov* (with *Dallal-Wilkinson-Lillie* for p-value). For continuous variables with normal distribution, the mean and standard deviation were presented, and for those with non-normal distribution, the median and interquartile range. We used the unpaired

student's t-test (t) for normal distribution and the *Mann-Whitney* (U) for non-normal distribution comparison between two groups. For the comparison of three groups, Kruskal-Wallis (H) test was used, followed by Dunn post-test. Spearman's correlation coefficient (rS) for non-normal distribution was used for correlation. A p-value less than 0.05 (typically ≤ 0.05) was considered statistically significant.

Results

Regarding general distribution of the sample, data are described in Table 1.

Carotid arteries showed greater atherosclerotic involvement than other arteries assessed (H = 15.73, p = 0.0004), with a significant difference found between carotid and iliac arteries (p = 0.0002). Variation in macroscopic degrees of atherosclerosis is described in Table 2.

Macroscopic assessment and different degrees of macroscopic involvement of atherosclerosis in carotid, aortic and iliac arteries are shown in Figure 4.

The occurrence of atherosclerosis was progressive and significant with age in carotid arteries (rS = 0.5133; p <0.0001), in aortic (rS = 0.716; p <0.0001) and in iliac arteries (rS = 0.7378; p <0.0001) (Figure 5).

Data regarding atherosclerosis macroscopic assessment and the variables analyzed are described in Table 2.

Discussion

Using autopsy material we demonstrated atherosclerosis in different arterial beds, which are of great importance for the body's blood supply. Macroscopic analysis is a way to understand disease development process, being a valid and accurate instrument for research, providing data to clinical practice as already demonstrated in other studies.[9-11]

The present study demonstrated a greater involvement of carotid arteries, compared to aorta and iliac arteries, but with significant difference only between carotid and iliac arteries. Although atherosclerosis is a process that can affect the entire vascular tree, being found in any large or medium-sized arteries, the disease tends to be located in particular areas, such as aortoiliac, iliac-femoral segments or carotid arteries. Factors such as changes in blood flow, in extra vascular pressure and anatomical and biochemical features seem to explain the prevalence of lesions for these vessels.[12] Furthermore, carotid arteries are evaluated in several other studies for atherosclerosis degree and determination of cardiovascular diseases development.[13-15]

In general, atherosclerosis degree varied between mild and moderate. In lesions evaluated as mild, fatty streaks were present, which indicates the beginning of injury process. Although these lesions do not alter blood circulation as they do not obstruct vascular lumen, their location facilitates continuous lipid deposition and progression to atherosclerosis.[16]

Elderly patients had significantly greater degree of atherosclerosis than non-elderly. Age was a significant predictor for atherosclerosis development.[17,18] An increase in
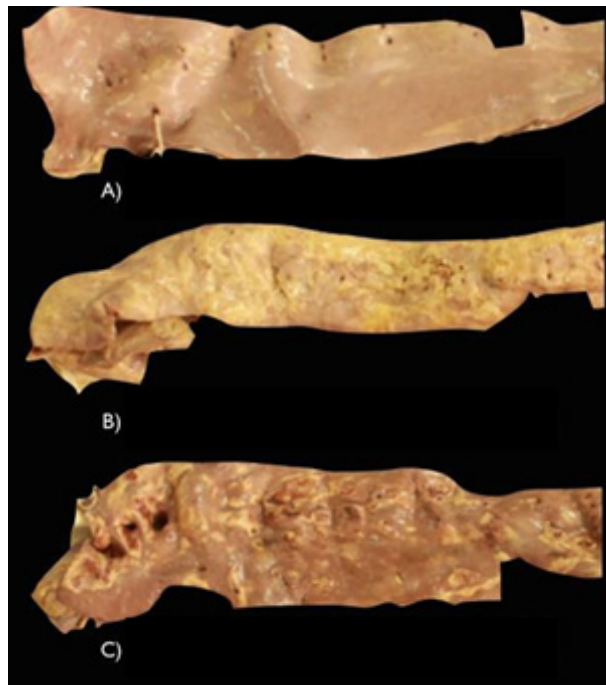
Figure 1 – *A) Aortic artery with fatty streaks. B Aorta with atheromatous plaques. C) Aorta with atheromatous plaques, fibrosis and calcifications.*
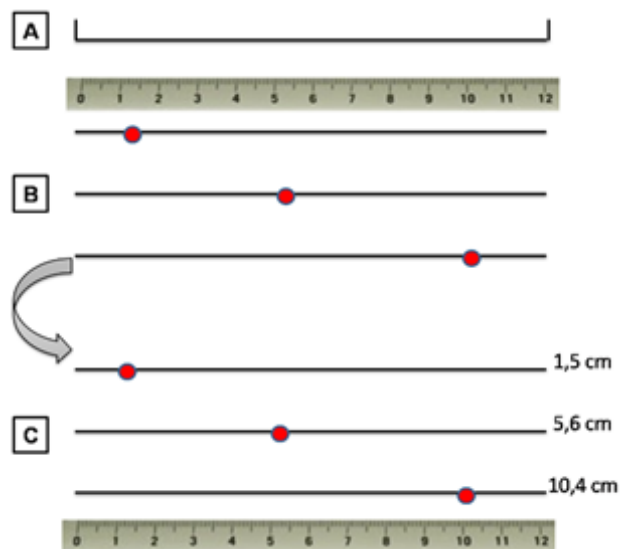
Figure 2 – *A) A 12.0 cm non-millimeter line model used as a scale for measurement of atherosclerosis degree. B) Registration of the point on the non-millimeter scale, referring to the degree of involvement after evaluation of lesions. C) Measure of the distance from the 0.0 cm point to the marked point after finishing evaluations in all arteries.*

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Figure 3 – A) Atherosclerosis in aortic artery assessed as mild. B) Atherosclerosis in aortic artery assessed as moderate. C) Atherosclerosis in aortic artery assessed as accentuated.

Table 1 – General characteristics of the sample

Variables	n (%)	Mean age (years ± SD)
Total	53 (100%)	49.9 ± 18.6
Age		
Elderly	17 (32.1%)	72.88 ± 8.1
Non elderly	3,983±2.59	39.05 ± 10.24
Gender		
Male	26 (49.1%)	49.77 ± 16.40
Female	27 (50.9%)	50.04 ± 20.77
Elderly male	7 (41.18%)	72 ± 6.35
Elderly female	10 (58.82%)	74 ± 9.42
Non elderly male	19 (52.78%)	41.58 ± 9.84
Non elderly female	17 (47.22%)	36.24 ± 10.22
Cause of death		
Cardiovascular	10 (18.9%)	64.3 ± 17.09
Non cardiovascular	43 (81.1%)	46.56 ± 17.43

n: sample; SD: standard deviation.

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Table 2 – Macroscopic evaluation of right and left carotid, aorta and right and left iliac arteries of autopsied patients

Variables	Carotid (cm)	Aorta (cm)	Iliac (cm)
n=53 (100%)	mean ±standard deviation or median (minimum-maximum)		
Age			
Elderly	7,256±2,254	8.6 (1.3-9.8)	5.9 (1.2-9.07)
Non elderly	3,983±2.59	1.8 (0.5-3.6)	1.15 (0.1-2.5)
	t=6,321; p<0.0001	U=83.5; p<0.0001	U=306; p<0.0001
Gender			
Male	4,675±2,593	2.6 (0.5-10)	1.85 (0.1-10.8)
Female	5,378±3,178	3.7 (0.5-11.6)	2.85 (0.1-11.6)
	t=1,245; p=0.2160	U=285; p=2442	U=1165; p=0.1316
Cause of death			
Cardiovascular	7.7±2,617	7.25 (1.9-11.6)	5.1 (0.9-11)
Non cardiovascular	4,413±2,625	2.2 (0.5-11)	1.8 (0.1-11.6)
	t=5,047; p<0.0001	U=98.5; p=0.0068	U=467.5; p=0.0012

n: sample; cm: centimeters.
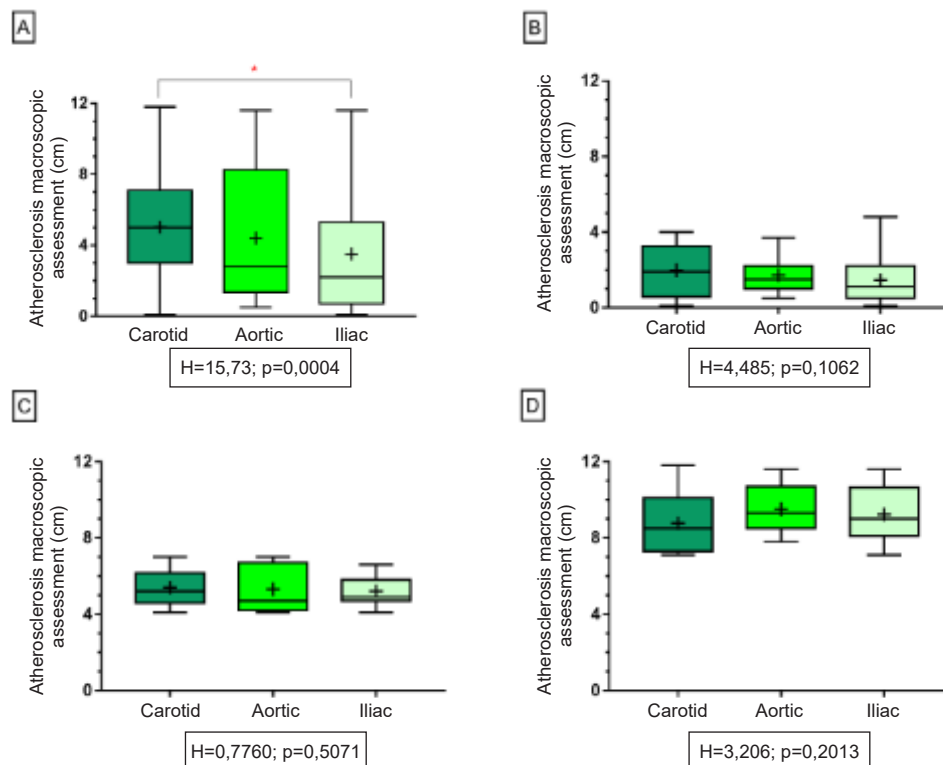
Figure 4 – A) Comparison of atherosclerosis macroscopic assessment in carotid, aortic and iliac arteries. B) Comparison between macroscopic evaluation of atherosclerosis in carotid, aortic and iliac arteries classified as mild (0 to 4 cm). C) Comparison between macroscopic assessment of atherosclerosis in carotid, aortic and iliac arteries classified as moderate (4.1 to 7 cm). D) Comparison between macroscopic assessment of atherosclerosis in the carotid, aortic and iliac arteries classified as accentuated (7.1 to 12 cm).
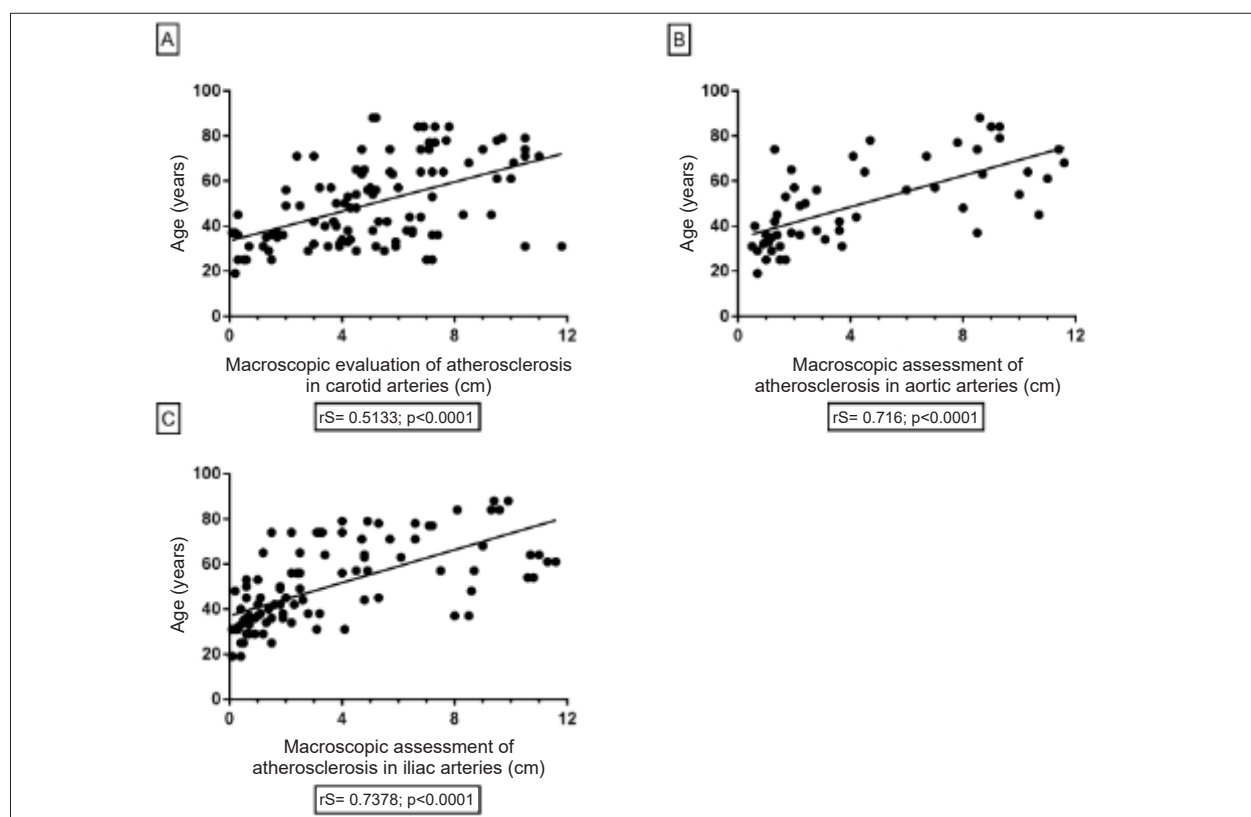
Figure 5 – A) Correlation between macroscopic evaluation of atherosclerosis in carotid arteries with age. B) Correlation between the macroscopic assessment of atherosclerosis in aortic arteries with age. C) Correlation between macroscopic assessment of atherosclerosis in iliac arteries with age.

marked and asymptomatic atherosclerotic plaques was found in arteries from elderly patients,[19] as well as calcifications,[20] which corroborates our findings.

Regarding gender, a higher degree of atherosclerosis was found in women, but without significant difference, which agrees with a similar study that used ultrasound to analyze atherosclerosis, in which authors found no differences between genders.[21] A recent study proved that genders have diferente physiological responses to risk factors (smoking, obesity, diabetes and systemic arterial hypertension) and females are the most affected and sensitized with such aggressions. Although many studies showed higher rates of cardiovascular events in men, there are divergent researches showing female physiological response is more sensitive to risk factors, which contributes to the development or worsening of cardiovascular disease.[22]

In the present study, patients who died due to cardiovascular causes had a significantly higher degree of atherosclerosis. The anatomopathological study of patients who died due to cardiovascular causes provides the best sample of population to study atherosclerosis.[4] Cardiovascular diseases are directly associated with the occurrence of systemic atherosclerosis, asymptomatic in most cases,[23] which makes prevention difficult, although extremely important.

As a *post-mortem* study, it has some limitations such as the absence of some data about patients' lifestyle as

medications, food, smoking, among other risk factors that are related to atherosclerosis development. In addition, some deaths occurred without atherosclerosis being previously investigated during patient's hospitalization, which would be a good predictor for macroscopic evaluation accuracy. However, there are several positive points that strengthen the work, such as the direct and precise macroscopic evaluation through visualization of the entire plaque and the confirmation of association of intrinsic risk factors such as age and gender with cause of death that may have occurred due to extrinsic factors. In addition, several important arterial beds were collected (right and left carotid, right and left aorta and iliac) with similar results compared to risk factors and confirmed to be adequate sites for systemic atherosclerosis assessment.

Conclusions

Atherosclerosis is a progressive lesion throughout life, which affects different arterial beds, with carotid arteries being the most affected, constituting an adequate sites for studying and assessing atherosclerotic plaque progression. The study highlights the importance of assessing atherosclerosis and shows an innovative form of assessment, as it is possible to measure the macroscopic degree of impairment through direct visualization of atherosclerotic plaques and compare with risk factors that, in association, can contribute to plaque progression and development of other cardiovascular

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diseases. Advanced age, female gender and death due to cardiovascular causes contribute as risk factors for greater lipid accumulation in these arteries. Macroscopic evaluation is a low-cost, effective and standardized method for measuring atherosclerosis degree and allows a better understanding of cardiovascular events development at the time of autopsy, in addition to providing data for clinical practice.

Author Contributions

Conception and design of the research: Oliveira MS, Torquato BGS, Juliano GR, Aguiar LS, Ferraz MLF; Acquisition of data: Oliveira MS, Torquato BGS, Soares MH; Analysis and interpretation of the data: Oliveira MS, Torquato BGS, Soares MH, Ferraz MLF; Statistical analysis: Oliveira MS, Torquato BGS; Obtaining financing: Teixeira VPA, Ferraz MLF; Writing of the manuscript: Oliveira MS, Torquato BGS, Aguiar

L; Critical revision of the manuscript for intellectual contente: Monteiro ML, Juliano GR, Aguiar LS, Teixeira VPA, Ferraz MLF.

Potential Conflict of Interest

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

Study Association

This article is part of the thesis of master submitted by Mariana Oliveira, from Universidade Federal do Triângulo Mineiro.

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Influence of Consumption of Orange Juice (Citrus Sinensis) on Cardiac Remodeling of Rats Submitted to Myocardial Infarction

Bruna C. Oliveira,[1] Priscila P. Santos,[1] Amanda M. Figueiredo,[1] Bruna P. M. Rafacho,[1] Larissa Ishikawa,[2] Silméia G. Zanati,[1] Ana A. H. Fernandes,[2] Paula S. Azevedo,[1] Bertha F. Polegato,[1] Leonardo A. M. Zornoff,[1] Marcos F. Minicucci,[1] Sergio A. R. Paiva[1,3]

Universidade Estadual Paulista Júlio de Mesquita Filho Campus de Botucatu - Faculdade de Medicina de Botucatu,[1] Botucatu, SP - Brazil
Instituto de Biociências Campus de Botucatu (UNESP),[2] Botucatu, SP - Brazil
Food Research Center FoRC,[3] São Paulo, SP - Brazil

Abstract

Background: Orange juice (OJ) is rich in polyphenols with anti-inflammatory and antioxidant properties. After myocardial infarction (MI), complex changes occur in cardiac structure and function, which is known as cardiac remodeling (CR). Oxidative stress and inflammation can modulate this process. We hypothesized that the consumption of OJ attenuates the CR after MI.

Objectives: To evaluate the influence of OJ on CR after MI by analysis of functional, morphological, oxidative stress, inflammation, and energy metabolism variables.

Methods: A total of 242 male rats weighing 200-250 g were submitted to a surgical procedure (coronary artery ligation or simulated surgery). Seven days after surgery, survivors were assigned to one of the four groups 1) SM, sham animals with water and maltodextrin (n= 20); 2) SOJ, sham animals with OJ (n= 20); 3) IM, infarcted animals with water and maltodextrin (n= 40); and 4) IOJ, infarcted animals with OJ (n = 40). Statistical analysis was performed by the two-way ANOVA supplemented by Holm-Sidak. Results are presented as mean ± standard deviation, the level of significance adopted was 5%.

Results: After 3 months, MI led to left ventricular (LV) hypertrophy, with systolic and diastolic dysfunction, and increased oxidative stress and inflammatory mediators. OJ intake reduced LV cavity and improved systolic and diastolic function. The OJ animals presented lower activity of glutathione peroxidase and higher expression of heme-oxygenase-1 (HO-1).

Conclusion: OJ attenuated CR in infarcted rats and HO-1 may be play an important role in this process.

Keywords: Myocardial Infarction; Fruits Juices (orange); Polyphenols; Ventricular Remodeling; Anti-Inflammatory Agents; Antioxidants. *Full*

Introduction

The name *polyphenols*, or *phenolic compounds*, refers to a large group of molecules found in leaf vegetables, fruits, cereals, tea, coffee, cocoa, wine, soy, and fruit juice.[1] These compounds have been studied because of their potential biological effect in prevention and treatment of different diseases.[2,3]

In a review of the literature, Hyson showed that fruit juices, defined as pure juice or 100% fruit juice, retained most of nutrients and phytochemicals of the whole fruit and therefore may have an important potential to benefit and protect human health.[4] Orange juice (OJ) is a source of phenolic compounds in the form of different flavonoids. The main flavonoid of interest is hesperidin and its hydrolyzed form, hesperetin.[5] The research interest in the properties of OJ has increased because of its anti-inflammatory and antioxidant action in chronic diseases.[6]

For example, in myocardial injury, antioxidant supplements may have beneficial effects in cardiac remodeling (CR). In studies using myocardial infarction (MI) model, bioactive compounds present in rosemary, tomato, green tea, and antioxidants such as ascorbic acid, quercetin, alpha-tocopherol, and vitamin A showed protection against CR.[1, 3, 7-10]

Ischemic heart disease, including MI, is a leading cause of heart failure and death worldwide. After MI, complex changes in the left ventricle can cause changes in cardiac size, mass, geometry, and function.[11,12] These changes are defined as CR and can lead to heart failure and increased mortality.[13] Many factors may be involved in CR, such as oxidative stress, inflammation, fibrosis, and apoptosis.[14,15]

In MI, ischemia initiates the generation of reactive oxygen species (ROS). ROS directly damage cell membranes, activate the inflammatory response, and lead to cell death. They can also act as transduction signals, stimulating nuclear factor κB (NF-κB), which, in turn, stimulates proinflammatory cytokines

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synthesis.[14-16] In addition, the Kelch-like ECH-associated protein 1/nuclear factor erythroid 2-related factor 2 (KEAP-1/Nrf2) system could be activated during cellular oxidative stress and play a critical role in redox homeostasis. This is a universal mechanism that acts in Nrf2 target genes called antioxidant response elements. Glutathione peroxidase (GSH-Px) and heme-oxygenase-1 (HO-1) are examples of proteins regulated by this system.[17]

Therapeutic strategies to attenuate CR after MI have been extensively studied.[18,19] Aldosterone blockers, angiotensin-converting enzyme inhibitors, and beta-blockers are some of these strategies.[20] In this context, bioactive compounds of natural products, with cardioprotective properties such as flavonoids, can be an important adjuvant in the treatment of MI. On the other hand, studies show that a focus on food and dietary patterns instead of individual nutrients or phytochemicals is better for cardiometabolic health.[21] Thus, the aim of this study was to evaluate the influence of OJ intake on CR after MI.

Materials and Methods

Experimental protocol

All experiments and procedures were performed in accordance with the National Institutes of Health's (NIH) Guide for the Care and Use of Laboratory Animals and were approved by the Ethics Committee for Animal Experimentation of the Botucatu Medical School, UNESP, São Paulo, Brazil (1126/2015). A total of 242 male Wistar rats weighing 200 to 250 g were used in this study. MI was induced by coronary artery ligation, as previously described.[22,23]

After surgery, the animals were placed in boxes with six animals each. Seven days after surgical procedure, the first echocardiographic study was performed to evaluate the efficacy of the surgical procedure.[24] Then, the animals were randomly placed in boxes with two animals each, to receive either OJ or a maltodextrin (M) solution. The groups were 1) SM, sham animals that received M solution (n = 20); 2) SOJ, sham animals that received OJ (n = 20); 3) IM, infarcted animals that received M solution intake (n = 40); and 4) IOJ, infarcted animals that received OJ (n = 40). The sample size used was based on other studies from our laboratory.[3,8,25] The number of rats in the infarcted groups was higher, since the expected mortality in these animals during the experimental period is around 50%. In addition, only rats with a left ventricular (LV) infarcted area greater than 30% were included.[24]

Food was supplied *ad libitum*. The animals were treated for 3 months, and mortality was observed in this period (Figure 1 of the supplementary data). The rats were housed in a temperature-controlled room (22 ± 2°C) with a 12-h light/12-h dark cycle.

Coronary artery ligation

MI was conducted by coronary artery ligation, as previously described.[22,23] In brief, the rats were anesthetized with ketamine (70 mg/Kg) and xylazine (1 mg/Kg), and after a left thoracotomy, the heart was exteriorized. The left atrium was retracted to facilitate the ligation of the left coronary artery with 5-0 mononylon between the pulmonary outflow tract and the left atrium. The heart was then replaced in the thorax, the lungs were inflated by positive pressure, and the thoracotomy was closed. A sham group, in which animals were submitted to surgery but without coronary occlusion, was also created. After anesthetic effect, the rats were medicated orally with metamizole sodium (30 mg / kg Dipirona®, Biovet, Vargem Grande Paulista, Sao Paulo, Brazil).

Orange juice

Supplemented groups (SOJ and IOJ) received OJ *ad libitum*. Control groups (SM and IM) received a solution of water and M at a concentration of 100 g/L. The M solution was given to control animals to provide the same amount of carbohydrates as the OJ. Treatment began seven days after surgery. The OJ and M solutions were changed every 24 hours, and intake was monitored daily. Nutritional composition of the OJ is shown in supplementary data.

Echocardiographic study

After three months, all rats were weighed and evaluated by transthoracic echocardiography.[26,27] For the echocardiographic study, the rats were anaesthetized with intramuscular injection of ketamine (50 mg/kg) and xylazine (1 mg/kg) solution. All measurements were made by the same observer, according to the leading-edge method recommended by the American Society of Echocardiography/European Association of Echocardiography.[28] Echocardiography was performed with the General Electric Vivid S6 System (GE Medical Systems, Tirat Carmel, Israel) equipped with a 5- to 12-MHz phased array transducer.

After echocardiography, the animals were euthanized with a large dose of pentobarbital, and their hearts were removed. The left ventricle was isolated and LV samples were immediately frozen and stored at –80°C. One transverse section of the LV was separated and fixed in 10% buffered formalin and was then embedded in paraffin for histological study.

Morphometric analysis

Five-micrometer-thick sections were stained with hematoxylin and eosin for calculations of infarction size as previously described. All animals were included in the morphometric analysis. After infarction size calculation, infarcted animals with less than 30% of LV infarcted area were excluded from analysis. All images were collected with a video camera attached to Leica microscope; the images were analyzed with the Image-Pro Plus 3.0 software program (Media Cybernetics, Silver Spring, MD).

Cardiac lipid hydroperoxide, antioxidant enzyme activity, and cardiac energy metabolism

LV samples (100 mg) were used to determine total protein and lipid hydroperoxide (LH) concentrations, and activity of the following antioxidant enzymes – GPx (E.C.1.11.1.9), superoxide dismutase (SOD, E.C.1.15.1.1), and catalase (E.C.1.11.1.6). Cardiac energy metabolism

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was assessed by 3-hydroxyacyl coenzyme-A dehydrogenase (OHADH; E.C.1.1.1.35.), phosphofructokinase (PFK; E.C.2.7.1.11), lactate dehydrogenase (LDH; E.C.1.1.1.27), pyruvate dehydrogenase (E.C.1.2.4.1), citrate synthase (CS; E.C.4.1.3.7.), and adenosine triphosphate (ATP) synthase (EC 3.6.3.14) activities.[3,9] The enzyme activity assays were performed at 25°C with a microplate reader (μQuant-MQX 200-EONC with Gen5 2.0 software connected to a computer system control; Bio-Tec Instruments, VT, USA). All the reagents were obtained from Sigma (Sigma-Aldrich, St. Louis, MO, USA).

Inflammatory mediators

Interferon-γ (IFN-γ) and interleukin-10 (IL-10) concentrations in LV samples were determined by ELISA according to the manufacturer's instructions (R&D Systems, Minneapolis, MN).

Western blot

Western blot was performed to analyze protein expression of GPx-1 (ab 22604 - Abcam Inc, Cambridge), HO-1 (ab13248 - Abcam Inc, Cambridge), total and phosphorylated NF-kB (NF-kB- sc 8008 and sc 3302- Santa Cruz Biotechnology, Inc, Europe), and sirtuin-1 (Sirt-1- sc 15404-Santa Cruz Biotechnology, Inc, Europe), in total cellular extract. To determine nuclear erythroid factor 2 (Nrf-2-sc 722-Santa Cruz Biotechnology Inc, Europe), LV samples were extracted with nuclear extraction buffer.[9] Samples were separated on a 10% sodium dodecyl sulfate–polyacrylamide gel, and the proteins were transferred to a nitrocellulose membrane. The membrane was blocked with 5% nonfat dry milk and then incubated with primary and secondary antibodies. Glyceraldehyde-3-phosphate dehydrogenase GAPDH (sc 32233, Santa Cruz Biotechnology, Inc., Europe) was used for normalization of all proteins.

Statistical analysis

The normality of the data was verified by Kolmogorov–Smirnov statistical test. Data are presented as the mean ± standard deviation (SD). Variables with normal distributions were analyzed by 2-factor analysis of variance, which gives three p values: 1) factor 1, presence of MI (I); 2) factor 2, OJ intake (OJ); and 3) interaction between factors I and OJ. The 2-factor analysis of variance requires an assumption of normality. If a measurement variable does not fit a normal distribution, data transformation was performed. The Student's unpaired t-test was used to analyze the initial echocardiogram; the χ^2 test was used to evaluate mortality, and Student's unpaired t-test used to evaluate the infarct size in infarcted animals. Differences were considered statistically significant if $p < 0.05$. Statistical analyses were performed using SigmaPlot for Windows 12.0 (Systat Software Inc., San Jose, CA).

Results

The initial echocardiogram showed that animals of both infarcted groups did not present differences in the systolic and diastolic area or in the infarct size (Table 1 of Supplementary material).

During the 3-month experimental period, mortality was 5.0% in the SM (1 rat died), 0% in the SOJ, 22.5% in the IM (9 rats died), and 22.5% in the IOJ group (9 rats died). When all groups were analyzed, a difference in mortality was observed between the groups (p=0.04). However, mortality was not different between the infarcted groups (p=0.836). After the period of OJ intake, euthanasia of surviving animals was performed. Then, histological analysis of the left ventricle of infarcted animals was performed to verify the infarction size (Figure 1 of the Supplementary material). These animals did not present a difference in infarct size (IM= 40.1±7.41%; IOJ=38.1±5.76%; p= 0.528). The final body weight (BW) was not different among the groups (Table 1).

Effect of MI in rat hearts

MI led to adverse CR. Regarding morphological data, MI led to higher values of LV diastolic diameter/BW, LV systolic diameter/BW, left atrial diameter/aorta, LV mass index (LVMI), LV weight/BW, and right ventricular weight/BW (Table 1), LV posterior wall thickness/BW, interventricular septum wall thickness/BW, and left atrial diameter/BW (Table 1 of Supplementary material). These changes characterize the enlargement of the left cavities and LV hypertrophy. MI impaired cardiac systolic function, as shown by the lower values of fractional area change (FAC), S´ mean (Table 1), endocardial fractional shortening, and ejection fraction (Table 2 of Supplementary material). Cardiac diastolic function was also impaired, as shown by decreased mean E´ (Table 1), E wave deceleration time, E´ lateral, and E´ septal (Table 2 of Supplementary material) and increased A wave, A´ mean; E/E´ ratio (Table 1), Tei index, E/A ratio, isovolumetric relaxation time adjusted by heart rate, A´ lateral, and A´ septal.

MI also increased oxidative stress, as presented with higher LH and SOD activity (Table 2), lower expression of HO-1 (Figure 1A), and of Nrf2 (Figure 1B). The inflammatory mediators IL-10 and INF-γ were higher in MI (Table 2), and there was no difference in NF-κB and Sirt-1 between infarcted and noninfarcted animals (Table 2 and Figure 2 of Supplementary material). A greater oxidation of carbohydrates than fatty acids and impaired energy metabolism were observed, as shown by higher activity of LDH and PFK and lower activity of OHADH, CS, and ATP synthase. No difference was observed for activity of pyruvate dehydrogenase (Table 3).

Effect of OJ intake on rat hearts

OJ intake reduced the LV cavity, with lower values of LV end-diastolic diameter (LVDD) and LV end-systolic diameter (LVSD); improved systolic function, with higher values of S´ mean; and improved diastolic function, with lower left atrial diameter adjusted for aorta diameter (Table 1)[29] after MI. No differences were observed for other echocardiographic variables (Table 1). The other function variables were not valued because of the higher heart rate[30] in the IOJ group (presented in Supplementary material Table 2).

In addition, the animals that consumed OJ presented lower activity of GSH-Px (Table 2). No differences were observed for LH, SOD activity, catalase activity, or GSH-Px expression (Table 2 and Figure 2 of the Supplementary material).

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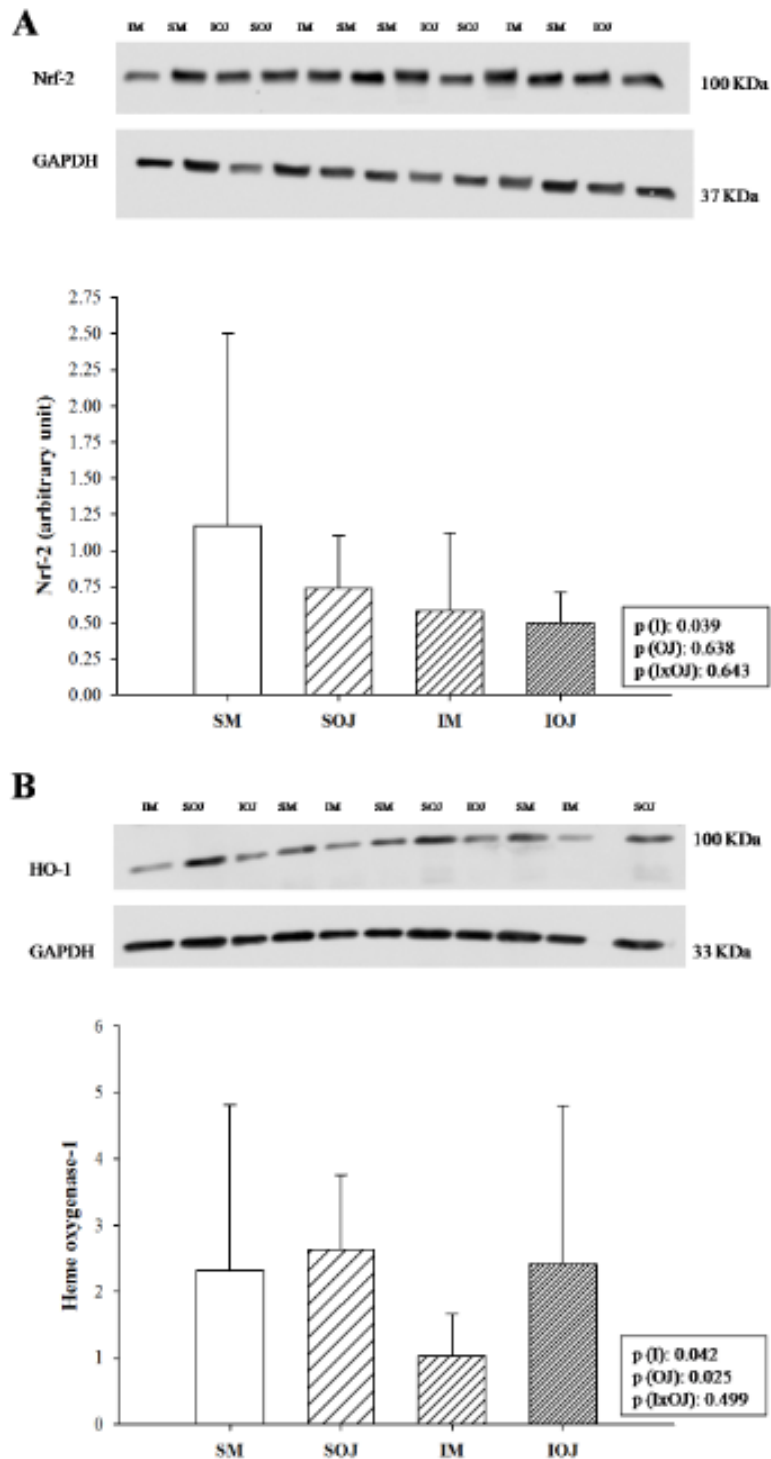
Figure 1 – *Nuclear factor erythroid 2-related factor 2 (Nrf2) and heme-oxygenase-1 (HO-1) expression in sham and infarcted rats by Western blot. Bar chart showing the expression of Nrf2 and HO-1 proteins in each group (A) Nrf2 expression and representative Western blot; sample size: 8 in each group. (B) HO-1 expression and representative Western blot; sample size: SM = 5; SOJ = 6; IM = 5; IOJ = 5. GAPDH glyceraldehyde-3-phosphate dehydrogenase. Data are expressed as mean ± SD. p(I): p value between non-infarcted animals vs. infarcted animals; p(OJ): p value between animals that received maltodextrin vs. animals that received orange juice; p(IxOJ): p-value for the interaction between the factors of infarction and orange juice intake.*

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Table 1 – Infarction size, final echocardiogram, and morphometric analysis.

Variable	SM (n = 19)	SOJ (n = 20)	IM (n = 9)	IOJ (n = 9)	p (I)	p (OJ)	p (I×OJ)
BW (g)	454±47.9	480±56.3	443±66.6	462±25.9	0.338	0.135	0.852
HR (bpm)	290±30.9	296±34.9	268±26.7	324±30.0[aB]	0.756	**0.001**	**0.009**
LA/Ao	1.32±0.09	1.21±0.09[b]	1.78±0.21[A]	1.42±0.18[Ba]	**<0.001**	**<0.001**	**0.003**
LVEDD/BW (mm/kg)	15.9±1.31	15.0±1.79	22.1±2.70	20.2±2.10	**<0.001**	**0.019**	0.398
LVESD/BW (mm/kg)	6.67±0.87	6.02±0.89	15.1±2.70	12.8±2.70	**<0.001**	**0.007**	0.556
LVMI (g/kg)	1.63±0.22	1.56±0.27	2.62±0.60	2.36±0.36	**<0.001**	0.124	0.640
FAC (%)	67.3±8.28	67.4±8.27	34.5±8.28	36.6±8.28	**<0.001**	0.661	0.707
E wave (ms)	79.7±11.3	81.4±7.16	89.1±10.8	80.7±19.2	0.204	0.325	0.139
A wave (ms)	49.9±8.28	52.6±7.16	42.5±16.5	62.7±24.9[a]	0.730	**0.004**	**0.025**
S´ mean (cm/s)	5.78±0.04	5.82±0.31	4.60±0.30	5.01±0.3	**<0.001**	**0.028**	0.078
E´ mean (cm/s)	5.62±0.44	5.82±0.45	4.23±0.60	4.77±0.60	**<0.001**	0.054	0.357
A´ mean (cm/s)	3.67±0.44	4.02±0.45	4.54±0.90	5.55±1.20	0.058	0.058	0.28
E/E´ ratio	13.7±3.49	14.1±1.79	21.3±3.30[A]	16.9±2.40[Ba]	**<0.001**	**0.002**	**0.003**
LVW/BW (mg/g)	1.85±0.13	1.93±0.27	2.13±0.42	2.10±0.15	**0.005**	0.550	0.822
RVW/BW (mg/g)	0.46±0.09	0.43±0.05	0.65±0.24	0.59±0.27	**<0.001**	0.294	0.776

Data are expressed as mean ± standard deviation. n: numbers of animals included in each experimental group. SM: sham animals that received maltodextrin; SOJ: sham animals that received orange juice; IM: infarcted animals that received maltodextrin; IOJ: infarcted animals that received orange juice. BW: body weight; HR: heart rate; LA: left atrial diameter; Ao: aorta diameter; LVEDD: left ventricular end-diastolic diameter; LVESD: left ventricular end-systolic diameter; LVMI: left ventricular mass index (left ventricular mass/BW); FAC: fractional area change; E wave: early diastolic mitral inflow velocity; A wave: late diastolic mitral inflow velocity; S´ mean: mean of systolic annular mitral velocity septal and lateral; A´ and E´ mean: mean of diastolic annular mitral velocity septal and lateral (E´: early and A: late); LVW: left ventricular weight; RVW: right ventricular weight. pI: p value for the effect of infarction. pOJ: p value of the effect of orange juice intake. pIxOJ: p value of interaction. Bold numbers represent statistically significant effects; [a]: IM≠IOJ; [b]: SM≠SOJ; [A]: SM≠IM e [B]: SOJ≠IOJ.

Regarding the inflammatory mediators, the SOJ group showed higher IL-10 and INF-γ than the SM group (Table 2). Also, the IOJ group had lower INF-γ values than the IM group (Table 2). No differences were observed for NF-κB or Sirt-1 between animals that consumed or did not consume OJ (Table 2 and Figure 2 of the Supplementary material).

An improvement in the use of substrate occurred in the animals that consumed OJ. We observed higher values in PFK activity in the IOJ group compared with the IM group and higher activity of ATP synthase in animals that consumed OJ. No difference was observed in the activity of other energy metabolism enzymes between the groups (Table 3).

Interestingly, the animals with OJ intake had a higher expression of HO-1 (Figure 1A), although they did not present a difference in Nrf2 expression (Figure 1B).

Discussion

In the present study, MI induced by coronary artery ligation in rats resulted in LV hypertrophy and diastolic dysfunction, which was compatible with changes observed in chronic infarction.[11] Our data also showed increased oxidative stress and inflammatory markers as well as alterations in energy metabolism, with impairment of fatty acid β-oxidation. These alterations characterize the CR process.[31-33] We also observe a decrease in Nrf2 and HO-1 expression. In the chronic phase of MI, the Nrf2

pathway may be diminished by abnormal expression of the Nrf2 target gene, affecting the maintenance of redox homeostasis via enzymes mediated by antioxidant response elements.[34] In a previous study conducted in our laboratory with the MI model, lower expression of Nrf2 and HO-1 was observed.[3] These findings suggest either a lower expression or greater catabolism of the Nrf2 protein, thus leading to the lower synthesis of HO-1.

In the present study, OJ intake resulted in attenuation of CR in infarcted animals. This attenuation can be observed in the decrease of LV cavity (LVDD and LVSD) and in the improvement of systolic function, characterized by the increase in the S´ mean,[35] and diastolic function (lower left atrial diameter). In the study by Yu et al.,[36] infarcted rats, by left coronary ligation, treated with hesperidin for four weeks had lower LVDD and LVSD and improved systolic function than infarcted animals. These data are similar to ours and may show the effect of hesperidin of OJ on the CR process. In other study, another phenolic compound, hesperetin, also had an effect on the heart. In pressure-overload model, Deng et al.[37] found lower values of LVDD and LVSD at eight weeks of hesperetin administration.

MI leads to an imbalance between the production of ROS and antioxidant defenses, leading to oxidative stress. After ischemia, some ROSs damage cell membranes, initiating the process of lipid peroxidation.[38] For example, Bagatini et al.[39] described an increase in lipid peroxidation

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Table 2 – Oxidative stress and inflammatory markers

Variable	SM (n = 8)	SOJ (n = 8)	IM (n = 4)	IOJ (n = 4)	p (I)	p (OJ)	p (I×OJ)
LH (nmol/g)	209±28.3	215±28.3	256±28.0	277±26.0	<0.001	0.293	0.573
Catalase (µmol/g)	64.4±6.79	61.8±7.07	55.4±7.00	58.1±7.60	0.056	0.993	0.404
SOD (nmol/mg)	12.9±2.83	13.5±2.83	18.7±1.80	17.1±1.40	<0.001	0.639	0.355
GSH-px activity (nmol/mg)	62.5±6.51	50.2±7.07	58.0±7.00	45.3±6.00	0.134	<0.001	0.951
GSH-px expression (arbitrary unit)	7.56±7.39	7.62±10.8	6.63±5.82	6.37±3.78	0.600	0.649	0.546
IL-10 (pg/mg)	23.9±7.92	39.6±13.0[b]	42.0±9.60[A]	34.1±7.60	0.135	0.352	0.008
IFN-γ (pg/mg)	7.1±2.26	13.2±3.96[b]	17.7±6.80[A]	11.2±2.00[a]	0.037	0.928	0.003
NF-κB (arbitrary unit)	7.03±11.0	4.61±4.98	3.40±3.12	6.80±4.00	0.942	0.330	0.266
p NF-κB (arbitrary unit)	5.40±10.2	3.18±2.40	3.28±3.12	5.22±3.34	0.587	0.084	0.980
Sirt 1 (arbitrary unit)	1.81±0.82	2.34±1.41	2.42±1.44	1.65±0.56	0.925	0.813	0.203

Data are expressed as mean ± standard deviation. n: numbers of animals included in each experimental group. SM: sham animals that received maltodextrin; SOJ: sham animals that received orange juice; IM: infarcted animals that received maltodextrin; IOJ: infarcted animals that received orange juice. LH: lipid hydroperoxide; SOD: superoxide dismutase; GSH-px: glutathione peroxidase; IL-10: interleukin-10; INF-γ: interferon- γ; NF-κB: nuclear factor–κB total and phosphorylated (p NF-κB); Sirt 1: sirtuin 1. pI: p value for the effect of infarction. pOJ: p value of orange juice intake effect. pIxOJ: p value of interaction. Bold numbers represent statistically significant effects. [a]: IM≠IOJ; [b]: SM≠SOJ; [A]: SM≠IM e [B]: SOJ≠IOJ.
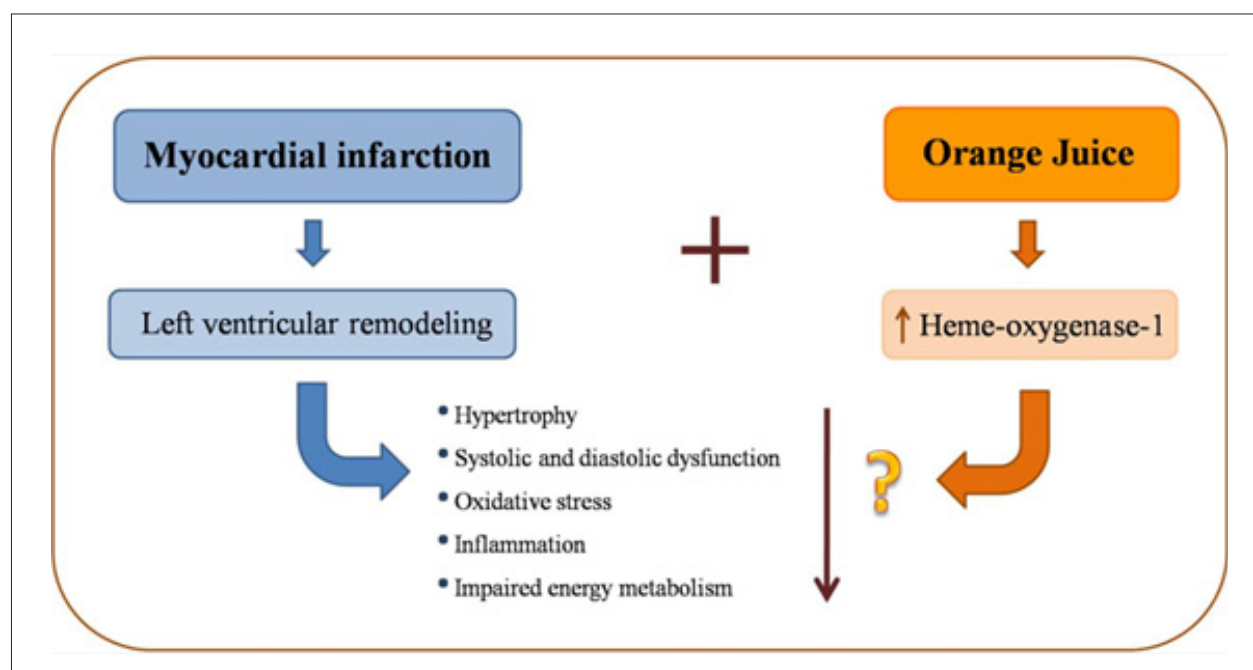
Figure 2 – *Scheme illustrating the main findings of this study.*

in patients with MI. Our data also show a higher concentrations of lipid hydroperoxides in infarcted animals compared to non-infarcted animals. The SOD enzyme is the organism's first defense against ROS.[40] Our data show that infarcted animals compared to non-infarcted animals showed greater activity of the SOD enzyme, as previously described.[3,25] Regarding OJ intake, we observed that the animals that consumed OJ presented lower GSH-Px activity. A similar result was shown by Selvaraj and Pugalendi[41] in

myocardial ischemia model induced by isoproterenol: rats that received hesperidin presented lower activity of the antioxidant enzymes, among them GSH-Px.[41]

In relation to energy metabolism, the heart, like other organs, can adapt and use the best energy substrate in each situation. PFK acts in glycolysis regulation, and catalyzes the phosphorylation of glucose in fructose-6-phosphate and subsequently in fructose 1,6-bisphosphate.[42] PFK is activated when ATP concentrations become low and is

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Table 3 – Enzymes involved in cardiac energy metabolism

Variable	SM (n = 8)	SOJ (n = 8)	IM (n = 4)	IOJ (n = 4)	p (I)	p (OJ)	p (I×OJ)
PFK (nmol/g)	128±17.0	112±24.6	139±26.0	178±26.0[aB]	<0.001	0.257	0.011
LDH (nmol/mg)	88.5±18.7	82.6±18.1	111±18.6	134±16.	<0.001	0.320	0.092
PDH (nmol/g)	344±53.7	385±31.1	345±100	341±42.0	0.386	0.461	0.376
OHADH (nmol/mg)	33.2±6.22	33.9±6.22	23.8±8.40	24.5±2.80	0.003	0.798	0.992
CS (nmol/mg)	50.0±6.22	49.4±6.51	34.5±7.40	40.5±4.80	<0.001	0.350	0.254
ATP synthase (nmol/mg)	21.0±3.11	27.8±5.37	11.4±1.20	15.9±4.40	<0.001	0.005	0.532

Data are expressed as mean ± standard deviation. n: numbers of animals included in each experimental group. SM: sham animals that received maltodextrin; SOJ: sham animals that received orange juice; IM: infarcted animals that received maltodextrin; IOJ: infarcted animals that received orange juice. PFK: phosphofructokinase; LDH: lactate dehydrogenase; PDH: pyruvate dehydrogenase; OHADH: 3-hydroxyacyl coenzyme-A dehydrogenase; CS: citrate synthase; ATP: adenosine triphosphate. pI: p value for the effect of infarction. pOJ: p value of orange juice intake effect. pIxOJ: p value of interaction. Bold numbers represent statistically significant effects. ᵃ: IM≠IOJ; ᵇ: SM≠SOJ; ᴬ: SM≠IM e ᴮ: SOJ≠IOJ.

inhibited when cells have sufficient supply of ATP and other substrates such as fatty acids.[42] Our data showed higher values of PFK in infarcted animals with OJ intake. These data show that increased PFK activity may lead to regulation of the glycolytic pathway, by providing more substrate for energy production. Another important finding that indicates a greater use of substrate is the higher ATP synthase activity in the animals that received OJ.

In addition to oxidative stress and metabolic changes, we found that the infarcted animals that received OJ presented lower values of IFN-γ. Since a chronic phase of inflammation is related to an increased production of IFN-γ,[43] our findings suggest more advanced phase towards the resolution of the inflammatory process. An interesting result is that sham animals who consumed OJ demonstrated an immunomodulatory effect, as shown by higher values of IL-10 and INF-γ. Similar to our findings in animals in the sham group, which had no cardiac injury, studies in healthy, middle-aged humans showed that OJ altered leukocyte gene expression to an anti-inflammatory and anti-atherogenic profile[44] and provided an early protection of mononuclear blood cell against oxidative DNA damage.[45] In addition, OJ intake with the high-carbohydrate meal prevented meal-induced oxidative and inflammatory stress.[46]

Another intriguing finding in our study was the higher values of HO-1 in animals that consumed OJ.[47] Lin et al.[47] in 2005 also showed that hesperetin induced protein expression of HO-1.[47] The HO-1 enzyme plays important role in cell homeostasis because of its catabolic action on the heme group of hemoproteins, generating by-products such as iron, biliverdin, and carbon monoxide. Through these by-products, HO-1 exerts anti-inflammatory, antioxidant, and antiapoptotic action.[48,49] In addition to this classical function, HO-1 participates in cell signaling as amplifier of inductors (heme, oxidants, cytokines,

hemodynamic forces, growth factors, hypoxia, and hormones) of transcription factors.[48]

Wang et al.[50] showed that HO-1 is important for heart homeostasis by protecting it from ischemia and reperfusion-induced lesions and oxidative damage.[50] In another study, hemin administration in infarcted mice induced HO-1 activation, which caused a change in infarct macrophages toward a M2 anti-inflammatory phenotype, reduction of infarct scar expansion, and improvement of cardiac function.[51] Thus, increased HO-1 may also play an important role in CR attenuation by OJ (Figure 2). In addition, this increase was independent of the Nrf2 pathway, since OJ did not lead to alterations in the expression of this protein. Similar to our findings, Wang et al.[52] found that isoliquiritin and isoliquiritigenin, flavonoids derived from liquorice, induced HO-1 expression independent of Nrf2 expression.[52] The HO-1 expression can be induced by different pathway and may vary according to the model and treatment used.[47]

Limitations

The OJ used in the study was a commercial, ready-to-eat, pasteurized juice, free of preservatives and sugar. The choice of ready juice was to ensure its standardization. However, the use of other types of juices, made with other types of oranges, could possibly show different responses.

Conclusion

OJ attenuated CR after MI, with decreased LV diameter as well as improvement in systolic and diastolic function; HO-1 may play an important role in this process.

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Author Contributions

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*Supplemental Materials

For additional information, please click here.

Antioxidant and Anti-Inflammatory Effects of Orange Juice

Paula Felippe Martinez,[1] Marianna Rabelo de Carvalho,[1] Maria Lua Marques Mendonça,[1] Marina Politi Okoshi,[2] Silvio Assis de Oliveira-Junior[1]

Universidade Federal de Mato Grosso do Sul (UFMS),[1] Campo Grande, MS - Brazil

Departamento de Clínica Médica, Faculdade de Medicina de Botucatu, Universidade Estadual Paulista Júlio de Mesquita Filho (UNESP),[2] Botucatu, SP - Brazil

Short editorial related to the article: Influence of Consumption of Orange Juice (Citrus Sinensis) on Cardiac Remodeling of Rats Submitted to Myocardial Infarction

Post myocardial infarction cardiac remodelling progression is a complex event involving several biological reactions; these include oxidative stress and inflammatory response.[1-4] The release of reactive oxygen species (ROS) after myocardial ischemia stimulates pro-inflammatory mediators involved in fibroblast proliferation and tissue repair in the infarcted area. However, sustained ROS production in combination with hemodynamic overload and antioxidant system incapacity leads to oxidative stress in non-infarcted areas, which also undergo cardiac remodelling.[1-3] These changes, associated with energy metabolism disorders, metalloproteinases activation, cardiomyocyte death and hypertrophy, interstitial fibrosis, and cardiac dysfunction characterize the cardiac remodelling process.[1]

Studies on various bioactive compounds, often extracted from food, have been undertaken to assess their attenuating powers on disorders common to cardiac remodelling, such as oxidative stress and inflammation.[4-6] However, the extraction and isolation of these substances can require a complex network of costly specialized technical procedures making it financially difficult for a large part of the population to access this resource. Additionally, taken in isolation one cannot evaluate the potential effects of interactions between food matrix components and the organism which may alter the metabolic effects.[7] Alternatively, consuming the food in its entirety acts as a buffer in the digestive system allowing greater bioavailability of its active compounds. Therefore, nutritional approaches involving ingestion of natural foods, such as fruits and their products (peels, juices, pulps, puree, and jams, etc), which contain substances with antioxidant and anti-inflammatory properties, have increasingly gained interest.[6,8] It is worth mentioning citrus fruits, which are rich in bioactive compounds that may change the metabolism and protect tissues from ROS accumulation injuries.[7] Citrus fruit juices, in general, are abundant sources of vitamin C and other nutrients, such as potassium, folate, magnesium, vitamin A,[9] and polyphenolic compounds.[10] In this sense, orange juice is a complex food matrix with cardioprotective potential due to its antioxidant and anti-inflammatory capacity.[9-11]

In this edition of ABC, Oliveira et al.[12] show the benefits of orange juice consumption, taking into account its antioxidant and cardioprotective role, in rats with cardiac remodelling after myocardial infarction. As expected, myocardial infarction triggered the cardiac remodelling process, characterized by cardiac hypertrophy and impaired left ventricle systolic and diastolic performance, accompanied by increased oxidative stress and inflammatory markers, and changed energy metabolism. Consumption of orange juice improved left ventricle systolic and diastolic dysfunction, and decreased myocardial glutathione peroxidase activity and interferon gamma (INF-γ) concentration. Regarding energetic metabolism, infarcted rats that consumed orange juice had higher myocardial ATP synthase and phosphofructokinase activity, key enzymes of energy metabolism. Another important finding in the study was increased heme-oxigenase-1 expression, suggesting an antioxidant and anti-inflammatory response to treatment with orange juice in infarcted animals.

There is therefore evidence that including natural products in the diet contributes as an adjunct in attenuating cardiac remodelling after myocardial infarction. Future studies are needed to better elucidate the cardioprotective effects of interventions with this and other natural products.

Keywords

Fruit and Vegetable Juices; Citrus Sinensis; Oxidative Stress; Metabolism; Anti-Inflammatory Agents; Ventricular Remodeling; Antioxidants.

Mailing Address: Paula Felippe Martinez •
Universidade Federal de Mato Grosso do Sul - Instituto Integrado de Saúde Av. Costa e Silva, s/n. Postal Code 79070-900, Cidade Universitária, Bairro Universitário, Campo Grande, MS – Brazil
E-mail: paula.martinez@ufms.br, paulafmartinez@gmail.com

Acknowledgments

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Comparative Study between Subcutaneous and Endovascular Defibrillator Recipients Regarding Tolerance to the Implant Procedure and Perception of Quality of Life

Pablo Esteban Auquilla-Clavijo,[1] Naiara Calvo-Galiano,[1] Marina Povar-Echeverría,[2] Teresa Oloriz-Sanjuan,[1] Francisco Diaz-Cortejana,[1] Antonio Asso-Abadia[1]

Hospital Universitario Miguel Servet – Cardiologia,[1] Zaragoza - Spain
Hospital Universitario Miguel Servet-Medicina Interna,[2] Zaragoza - Spain

Abstract

Background: The totally subcutaneous implantable cardioverter-defibrillator (S-ICD) is a safe alternative to the conventional transvenous ICD (TV-ICD) system to prevent sudden death.

Objective: To compare the impact of the type of ICD system and surgical technique on patients' quality of life, as well as the severity of discomfort and pain, between S-ICD and TV-ICD recipients.

Methods: Consecutively implanted patients with an S-ICD system were matched with patients with a TV-ICD system. In addition, patients undergoing S-ICD implantation after removal of a TV-ICD due to complications were included. Quality of life (measured with the 12-item short-form health survey) and severity of pain and discomfort were evaluated. Statistical significance was defined as p < 0.05.

Results: A total of 64 patients implanted with S-ICD or TV-ICD under local anesthesia and conscious sedation were analyzed. Patients with S-ICD and TV-ICD systems did not differ significantly in quality of life scores. S-ICD patients had a higher level of perioperative pain; no differences were found regarding severity of intraoperative pain. The magnitude of aesthetic discomfort and sleep disturbances did not differ between groups. An S-ICD was implanted in 7 additional patients after removal of a TV-ICD. All but one of these patients recommended the S-ICD system.

Conclusions: The type of ICD system and the surgical technique have negligible impact on patients' quality of life. These results suggest that conscious sedation, provided by an experienced electrophysiology team, could be considered as an alternative to general anesthesia to manage patients undergoing S-ICD implantation.

Keywords: Defibrilators; Implantable; Defibrillators Subcutaneous Implantable; Comparative Study; Conscious Sedation; Quality of Life.

Introduction

Sudden cardiac death (SCD) of arrhythmic origin is the main cause of cardiovascular mortality. The efficacy of the implantable cardioverter-defibrillator (ICD) for reducing SCD mortality in selected populations has been extensively demonstrated in many clinical trials.[1] Conventional defibrillator systems consist of a pulse generator located in the pectoral area, connected to the endocardium by means of transvenous leads. This type of device is therefore prone to complications inherent in the mechanism of implantation and the intravascular position of the leads.

Because of problems accessing the heart through the venous system and the potential for complications, the subcutaneous implantable cardioverter-defibrillator (S-ICD, Boston Scientific, Natick, MA, USA) has been developed. This system consists of a generator (S-ICD®, EMBLEM MRI S-ICD A219, Boston Scientific) connected to a lead (3401, Boston Scientific) located subcutaneously in a parasternal position, generally on the left.[2] Current clinical guidelines include it with a Class IIa indication as an alternative to the conventional transvenous ICD (TV-ICD) in patients who do not require antibradycardia, antitachycardia, or resynchronisation therapy. It also has a Class IIb indication in patients with no venous access, following removal of a transvenous system due to of infection, and in young patients facing a lifetime requirement for device-based therapy.[2] A limited implantation-related complication rate has been reported. Moreover, although there are no randomized comparative studies of S-ICDs versus TV-ICDs to date, the available data show the S-ICD to be a very effective device for detecting and treating malignant ventricular arrhythmias.[3-6]

Original Article

The use of S-ICD in Spain is increasingly accepted by scientific societies. The study by Arias et al.[4] in a Spanish center in 2017 has made it possible to obtain excellent acute and long-term results in a cohort of 50 patients with S-ICD.[7] The latest Spanish ICD implant registry in 2017 indicates a progressive increase in S-ICD implants from 2.5% in 2015 to 5.3% in 2017.[8] The higher cost of the S-ICD compared to TV-ICD could be one of the reasons that the adoption of this device has been slow, despite its revolutionary design.[9] The development of multicentre studies that support these results[7] would allow us to expand the use of this device.

In terms of the impact of ICD implantation on quality of life, the literature contains contradictory evidence.[10-17] Whereas initial ICD experiences were associated with worse quality of life, more recent studies have demonstrated quality of life at least as good as in patients in the general population, without an ICD.[16,18] The only study to have evaluated and compared quality of life in TV-ICD patients versus S-ICD recipients was published recently. There was an improvement in quality of life in both patient groups, as measured by the SF-12 health survey, and no significant differences were seen between the groups.[19]

Objective

The objective of our study was to compare perceived quality of life, as well as severity of pain and discomfort, resulting from the surgical technique and type of device, between a population of patients receiving S-ICD and a conventional TV-ICD recipient control group.

Methods

All patients implanted with an S-ICD at our hospital from 2014 to 2016 were consecutively enrolled. Patients were matched by age, sex, and body mass index with a sample of patients who were undergoing their first implantation of a single-chamber TV-ICD, with no indication for antibradycardia therapy or antitachycardia pacing, during the same period. Patients previously implanted with a single-chamber TV-ICD, who were receiving an S-ICD after having the transvenous system removed due to a complication, formed their own control group.

The study was approved by the Ethics Committee at our hospital.

ICD implantation procedure

In all cases, prior to considering the implant of either device, health education was carried out regarding the physical and psychological consequences that the device could have on each patient.

All implantations were carried out in the electrophysiology laboratory by the same medical and nursing team.

Prior to implantation, all patients were given prophylactic intravenous antibiotics. Implantation took place without withdrawal of oral anticoagulant medication, except in cases of low thromboembolic risk (CHADS-VASc < 2).

Hemodynamic parameters (blood pressure, heart rate, and arterial oxygen saturation) were non-invasively monitored during the procedure.

Subcutaneous ICD implantation procedure

All patients passed the ICD pre-implantation ECG screening test in at least one lead in the right or left parasternal region. The procedure took place under local anesthesia and sedation, according to a conscious sedation protocol (Table 1). This was adapted from a previously described sedation protocol[20] used routinely at our hospital for conducting complex interventional procedures.

The S-ICD implantation technique was as described previously.[21] In all cases, the generator was inserted in the fifth or sixth left intercostal space, and the defibrillation lead was positioned in the right or left parasternal region, depending on screening test results or findings during the implantation procedure. The two-incision technique was used in all cases.[22]

At the end of the procedure, a defibrillation test was done, and two shock zones were programmed with a minimum heart rate of 200 bpm.

Transvenous ICD implantation procedure

Implantation was carried out under local anesthesia and light sedation on demand. Via the left subclavian vein, an active fixation single-coil defibrillation lead was attached to the right ventricular apex. The generator was inserted subcutaneously in the left infraclavicular region. No patients underwent a defibrillation test. The devices were programmed in VVI mode with a minimum heart rate of 40 bpm. Device therapy programming was done on an individual basis, according to the indication for ICD implantation and the type of heart disease.

Follow-up

Follow-up consisted of site visits after 15 days, 3 months, and then every 6 months post-implantation. Intraoperative, perioperative, and long-term complications were recorded, as was the occurrence of appropriate or inappropriate therapy.

Questionnaires about quality of life and satisfaction/discomfort with the type of system implanted

At least 3 months after the system was implanted, a telephone survey took place. This included two questionnaires: 1) the 12-item short-form health survey (SF-12) and 2) a questionnaire specifically designed to compare the severity of pain/discomfort related to the system type and surgical technique (ICD QoL) (Supplementary Materials 1 and 2).

The survey was administered over the telephone by the same investigator, who was blinded to the type of system implanted.

SF-12

The SF-12 survey consists of a subset of 12 items from the SF-36, selected by means of multiple regression. Physical and mental component summaries of patients' quality of life were designed based on these items.

SF-12 response options take the form of Likert scales evaluating intensity or frequency. The number of response options ranges from 3 to 6, depending on the item, and each question is given a value that is subsequently transformed on

Table 1 - Protocol for conscious sedation during S-ICD implantation

PREMEDICATION: Administered on arrival in the electrophysiology laboratory, once the patient is being monitored:
• Ondansetron 8 mg
• Paracetamol 1 g
• Midazolam 1 mg
• Pethidine 25 mg
• Continuous infusion pump: 0.30 mg fentanyl (2 ampoules) + 120 cc physiological saline
If < 65 kg: 30 ml/h
If > 65 kg: 40 ml/h
DURING THE PROCEDURE:
One-off doses of midazolam or fentanyl as a bolus on demand
DEFIBRILLATION TEST MEDICATION (with fentanyl infusion pump stopped):
• 3-5 mg bolus of etomidate
• 3-5 mg bolus of midazolam
PREPARED RESCUE MEDICATION:
• Atropine
• Naloxone
• Flumazenil

a scale of 0 to 100. Scores have a mean of 50 with a standard deviation of 10. Consequently, values above or below 50 indicate a better or worse state of health, respectively, than the reference population. Published studies of SF-12 measurement characteristics indicate reliability, validity, and sensitivity (Cronbach's alpha > 0.7; intraclass correlation coefficient for test-retest reproducibility rho ≥ 0.75).[23-25]

ICD QoL

The ICD QoL questionnaire consisted of 8 items evaluating severity of pain (intra-, peri- and post-procedural and long-term pain), degree of aesthetic discomfort, limitations to activities of daily living and leisure activities, physical sleep limitations due to potential discomfort caused by mechanical compression by the device, and patient satisfaction. All parameters in the questionnaire were measured on a numerical severity rating scale from 0 to 10. Pain was defined as follows: intraprocedural pain as pain suffered during the intervention; perioperative pain as pain that occurred during the hospital stay; postprocedural pain as pain within 3 months of being discharged; and long-term pain as pain from 3 months post-implantation up to the time of the survey. Pain severity was measured using the numerical rating scale, where 0 means "no pain" and 10 means "worst pain imaginable".[26]

The seven S-ICD patients who had also had a TV-ICD in the past answered the questionnaire for both types of ICD. These patients were also asked which of the two types of ICD they would recommend.

Statistical analysis

Continuous variables are expressed using statistics of central tendency and spread (mean and standard deviation for normally distributed variables; median and interquartile range for non-parametric variables). Normality tests were performed with the Lilliefors (Kolmogorov-Smirnov) test. Categorical variables are expressed as percentages.

To compare the overall characteristics of both groups, we used the chi-square test for dichotomous qualitative variables, Student t test for independent samples for parametric quantitative variables (assuming equal variances in all cases because Levene's test was > 0.05), and the Mann-Whitney U-test for non-parametric variables. Statistical significance was defined as $p < 0.05$.

The Mann-Whitney U-test was used to compare the SF-12 survey results, whereas the ICD QoL results were compared by means of the chi-square test.

Calculations were performed with the SPSS statistics package (Version 19, SPSS Inc., Chicago, IL, USA).

Results

Baseline characteristics

In all, 71 ICD patients were enrolled. Their characteristics are shown in Table 2. A total of 64 patients underwent their first implantation of an S-ICD or a TV-ICD. In the other 7 patients, an S-ICD was implanted following removal of a TV-ICD. The reasons for the transvenous system being removed were endocarditis, pocket infection, pressure ulcer, and lead dislodgement (Table 3). No significant differences were found in patient baseline characteristics according to the type of system implanted. Mean age was 53 years (minimum 13; maximum 76), and 80% of patients were male. The most common underlying heart condition was ischemic disease (37%), followed by hypertrophic cardiomyopathy (20%). In most cases (56%), the system was implanted as primary prevention of SCD.

Table 2 – Baseline patient characteristics

	Overall N=71	TV-ICD	S-ICD	P value
Age (years)	53 ± 11[a]	52 ± 10.3[a]	50.8 ± 10.6[a]	p=0.869[b]
Male (%)	62 (79.5)	31 (80)	31 (80)	p=1[c]
Body mass index	24.8 ± 4.6[a]	25.8 ± 3.7[a]	25.6 ± 4.3[a]	p=0.876[b]
Prevention type (%)				p=0.648[c]
Primary	44 (56.4)	23 (59)	21 (53.8)	
Secondary	34 (43.6)	16 (41)	18 (46.2)	
Heart disease type (%)				p=0.319[c]
Ischemic	29 (37.2)	14 (35.9)	15 (38.5)	p=0.319[c]
Valvular	2 (2.6)	1 (2.6)	1 (2.6)	p=0.319[c]
Idiopathic dilated	6 (7.7)	4 (10.3)	2 (5.1)	p=0.319[c]
Hypertrophic	16 (20.5)	5 (12.8)	11 (28.2)	p=0.319[c]
Non-compaction	6 (7.7)	3 (7.7)	3 (7.7)	p=0.319[c]
Brugada	2 (2.6)	1 (2.6)	1 (2.6)	p=0.319[c]
Long QT	6 (7.7)	2 (5.1)	4 (10.3)	p=0.319[c]
Congenital	5 (6.4)	5 (12.8)	0	p=0.319[c]
Unknown	6 (7.7)	4 (10.3)	2 (5.1)	p=0.319[c]
Ejection fraction (%)	46 ± 30[a]	45.8 ± 14.8[a]	44.8 ± 16[a]	p=0.867[b]
Rhythm at implant. (%)				p=0.867[c]
Sinus	70 (90)	35 (89.7)	35 (89.7)	
Atrial fibrillation	8 (10)	4 (10.3)	4 (10.3)	
Antiplatelet Tx (%)	31 (39.7)	15 (38.5)	16 (41)	p=0.817[c]
Anticoagulant Tx (%)	14 (19.7)	7 (17.9)	7 (17.9)	p=1[c]

Tx: therapy; aMean and standard deviation; bStudent t test for independent samples; cChi-square test.

Follow-up

Patient follow-up results are summarized in Table 4. In terms of perioperative complications, one patient in the S-ICD group had a pocket hematoma that required surgical drainage. One TV-ICD patient experienced lead dislodgement as a complication during follow-up.

Two patients with S-ICD and 9 with TV-ICD received appropriate therapy (2 cases were treated by antitachycardia pacing, and electric shock was required in 7 cases). One TV-ICD patient received inappropriate therapy because of ventricular lead dislodgement. Another patient, with an S-ICD, suffered an inappropriate shock due to supraventricular tachycardia with a heart rate above the therapy cut-off rate (240 bpm).

Questionnaires

Table 5 shows the results obtained with the ICD QoL questionnaire in patients implanted for the first time. No significant differences were found with respect to intraoperative pain assessments according to the type of system implanted. However, patients implanted with an S-ICD had more severe perioperative pain. No significant differences were found between the two types of systems in terms of sleep disturbances, although there was a trend towards more disturbed sleep among S-ICD recipients. In most patients,

these disturbances were of low to moderate severity. Likewise, there were no significant differences in daily activities or aesthetic discomfort. All patients, regardless of the system implanted, were satisfied with the intervention, and they said they would recommend the device to other eligible patients.

The results obtained with the SF-12 survey are shown in Table 6. Similar values were recorded in both groups, with medians of 44.3 ± 12.8 for the S-ICD and 48.8 ± 9.8 for the TV-ICD on the physical health scale. The mental health scale gave medians of 45.9 ± 13.7 for the S-ICD and 50.8 ± 10.3 for the TV-ICD.

Tables 7 and 8 show the results of the ICD QoL questionnaire and the SF-12 survey, respectively, in patients implanted with an S-ICD after removal of a transvenous system. In terms of intraoperative pain assessments, no patients in the S-ICD group reported pain, compared with 57% who reported pain with transvenous systems. This pain was moderately severe, at most. No statistically significant differences were found in perioperative, postoperative or long-term pain. Likewise, there were no differences between ICD types as regards sleep disturbances or degree of aesthetic discomfort. All the patients were satisfied with the intervention and would recommend having the device implanted if necessary. When asked which type of ICD they would recommend, all but one of them preferred the subcutaneous system.

Table 3 – Reasons for TV-ICD removal

Reasons for replacement	N (%)
Endocarditis	2 (28.6)
Recurrent pocket infection	2 (28.6)
Lead fracture	2 (28.6)
Pocket decubitus	1 (14.3)

Table 4 – Patient follow-up

Complications	Overall	TV-ICD	S-ICD	P value
Perioperative complications (%)	1 (1.3)	0	1 (2.6)	p=0.314[a]
Pneumothorax	0	0	0	
Pericardial effusion	0	0	0	
Pocket hematoma	1 (1.3)	0	1 (2.6)	p=0.152[a]
Complications during follow-up (%)	1 (1.3)	1 (2.6)	0	p=0.152[a]
Pocket infection	0	0	0	
Infectious endocarditis	0	0	0	
Venous thrombosis	0	0	0	
Lead dislodgement	1 (1.3)	1 (2.6)	0	p=0.314[a]
Pocket decubitus	0	0	0	
Therapy				
Appropriate therapy (%)	11 (14.1)	9 (23.1)	2 (5.1)	p=0.023
ATP	2 (2.6)	2 (5.1)	0	
Shock	9 (11.5)	7 (17.9)	2 (5.1)	
Inappropriate therapy (%)	2 (2.6)	1 (2.6)	1 (2.6)	p=1[a]

ATP: Antitachycardia pacing. [a]Chi-square test.

Discussion

This study demonstrates that there are no statistically significant differences in impact on quality of life in patients with an S-ICD versus those with a TV-ICD. Moreover, specific evaluation of variables that prove more controversial when assessing and choosing the type of system to implant, such as parameters related to the surgical procedure or technical specifications of the device, likewise showed no significant differences between the two patient groups.

Previous study results regarding the impact of ICD on patients' quality of life are contradictory. Whereas some studies found that quality of life worsened or did not change significantly after ICD implantation,[27] others noted gradual improvement.[28] However, only one study to date has assessed quality of life in S-ICD patients. EFFORTLESS QoL[19] is an international multicentre registry substudy that compared quality of life in S-ICD patients against a historical TV-ICD patient population. No statistically significant differences were found in quality of life, as evaluated by the SF-12 survey.

Our study results resemble those of Pedersen et al.[19] Our results with the SF-12 quality-of-life survey, administered to patients implanted with an ICD for the first time, showed no differences in either the mental or the physical health scales.

Ours is the first study evaluating quality-of-life impact in S-ICD patients, emphasizing the analysis of potential features (involving both surgical technique and type of system implanted) that might influence the results. Many studies have now demonstrated the efficacy and safety of this type of ICD compared with conventional devices. This has allowed the indications to be expanded, and has contributed to approval by medical staff. Even today, however, some uncertainty is commonly encountered among patients and, especially, health professionals, when it comes to indicating and choosing this type of system in selected patients, mainly on account of the size difference, the different location, and the implantation technique. In an attempt to address these issues, we designed a specific questionnaire and compared our S-ICD patient population against a TV-ICD group for whom antibradycardia therapy, antitachycardia pacing, and resynchronisation therapy were not indicated (i.e. potential S-ICD candidates). Patients were matched by age, sex, and body mass index. We regard these as potential confounding variables when evaluating quality-of-life impact according to the type of system implanted.

It is apparent that some degree of pain occurred in general with both systems, with perioperative pain more severe among S-ICD patients. There were no differences in severity of intraoperative pain or long-term pain. Somewhat inconsistent postoperative management of these patients may

Table 5 – ICD QoL questionnaire results in patients implanted with their first ICD

	Subcutaneous N=32	Transvenous N=32	p value
Intraoperative pain			p=0.073[a]
No pain	23 (74.2)	21 (65.6)	
Mild	5 (16.1)	3 (9.4)	
Moderate	0	5 (15.6)	
Severe	3 (9.7)	1 (3.1)	
Very severe	0	2 (6.3)	
Perioperative pain			p=0.005[a]
No pain	9 (29)	15 (46.9)	
Mild	5 (16.1)	12 (37.5)	
Moderate	7 (22.6)	5 (15.6)	
Severe	9 (29)	0	
Very severe	1 (3.2)	0	
Postoperative pain			p=0.170[a]
No pain	13 (41.9)	22 (68.8)	
Mild	10 (32.3)	6 (18.8)	
Moderate	5 (16.1)	4 (12.5)	
Severe	1 (3.2)	0	
Very severe	2 (6.5)	0	
Current pain			p=0.087[a]
No pain	27 (87.1)	26 (81.3)	
Mild	1 (3.2)	6 (18.8)	
Moderate	2 (6.5)	0	
Severe	0	0	
Very severe	1 (3.2)	0	
Aesthetic discomfort			p=0.683[a]
None	20 (64.5)	21 (65.6)	
Mild	7 (22.6)	6 (18.8)	
Moderate	3 (9.7)	2 (6.3)	
A lot	0	2 (6.3)	
Very much	1 (3.2)	1 (3.1)	
Activities of daily living limited			p=0.080[a]
None	22 (71)	22 (68.8)	
A little	1 (3.2)	7 (21.9)	
Moderate	5 (16.1)	2 (6.3)	
A lot	3 (9.7)	1 (3.1)	
Very much	0	0	
Sleep disturbance			p=0.232[a]
None	13 (41.9)	21 (65.6)	
Mild	10 (32.3)	8 (25)	
Moderate	5 (16.1)	3 (9.4)	
Severe	2 (6.5)	0	
Very severe	1 (3.2)	0	
Would recommend to others			
Yes	31 (100)	32 (100)	
No	0	0	
Satisfied with intervention			
Yes	31 (100)	32 (100)	
No	0	0	

[a]*Chi-square test.*

Table 6 – SF-12 survey results in patients implanted with their first ICD

	Subcutaneous N=32				Transvenous N=32				p value
	Median	IQR	Minimum	Maximum	Median	IQR	Minimum	Maximum	
Physical health scale	44.3	12.8	27.4	56.7	48.8	9.8	31.6	62.6	p=0.302[a]
Mental health scale	45.9	13.7	26.3	56.8	50.8	10.3	18.7	55.5	p=0.345[a]
Physical functioning scale	47.9	17.2	22.1	56.5	56.5	15.1	22.1	56.5	p=0.099[a]
Physical limitation scale	29.5	9.2	20.3	29.5	29.5	9.2	20.3	29.5	p=0.656[a]
Pain scale	57.4	0	16.7	57.4	57.4	0	37.1	57.4	p=0.150[a]
General health scale	44.7	10.8	18.9	62	55.5	10.8	18.9	62	p=0.354[a]
Vitality scale	57.8	30.2	17.6	67.9	67.9	20.2	27.6	67.9	p=0.157[a]
Emotional limitation scale	56.6	9.2	16.2	56.6	56.6	10.1	26.3	56.6	p=0.317[a]
Social function scale	22.5	0	11.3	22.5	22.5	0	11.3	22.5	p=0.263[a]
Mental health scale 2	64.5	18.3	21.9	70.6	64.5	18.3	21.9	70.6	p=0.163[a]

IQR: Interquartile range. [a]Mann-Whitney U test.

have influenced this result, as these patients are admitted to the ward and cared for by different medical and nursing teams. Nevertheless, these findings are undoubtedly relevant, and S-ICD recipients should therefore be given stronger perioperative analgesia. No statistically significant differences were found when aesthetic discomfort, sleep disturbances, and daily activities were compared between the two groups.

Another novel aspect of this study is the assessment of perceived quality of life in patients who have had both types of therapy. These patients reported more severe intraoperative pain, aesthetic discomfort, and sleep disturbances with the transvenous system, although these differences are not statistically significant, possibly because of the group's small sample size (7 patients). This was undeniably a biased population, because the subcutaneous system was implanted after a complication had occurred with the transvenous system. The parameters assessed, however, such as severity of pain during the surgical intervention, sleep disturbances, and aesthetic discomfort, are unrelated to the complications that arose with the conventional device; these issues are, thus, potentially independent of the negative repercussions of the system.

These data demonstrate that the different size and location of the S-ICD do not negatively influence patient quality of life.

On the other hand, our study provides the first data on patient safety and comfort/pain during surgical interventions to implant an S-ICD using a conscious sedation protocol, managed entirely by an electrophysiology team (medical and nursing staff). Although TV-ICDs are now mainly implanted under local anesthesia, S-ICDs are implanted under general anesthesia at most hospitals. In the largest multicentre study to date, 63% of sites implanted S-ICDs under general anaesthesia.[5] This resource has limited availability at most sites. It involves organizational effort, more staff during the intervention, and higher healthcare costs. The literature contains several clinical case series describing experiences with S-ICD implantation under sedation, with strict supervision by expert anesthetists. The study by Essandoh et al.[29] retrospectively analyzed the efficacy and safety of S-ICD implantation under anesthetist-supervised sedation, in a total of 10 selected patients. No hemodynamic or respiratory complications were reported.

The safety and efficacy of conscious sedation have already been demonstrated in patients undergoing ablation for atrial fibrillation,[20] and this method is routinely used in our laboratory. For S-ICD implantation, we used a sedation protocol adapted for this type of procedure, in order to ensure adequate analgesia for the patients throughout the entire intervention. No complications were recorded during the procedure. It should be noted that 100% of patients implanted with both types of system described a complete absence of pain during S-ICD implantation, whereas fewer than half of those patients reported not having felt any pain during the TV-ICD procedure.

Limitations

One limitation of the study is potential interviewer bias. In order to prevent this, surveys were administered over the telephone by the same blinded investigator. To avoid recall bias in the interview subject, only patients implanted with an ICD in the last 2 years were included.

The control population consisted of TV-ICD patients matched by age, sex, and body mass index. These are variables that we think might influence patients' response regarding degree of discomfort/satisfaction with the S-ICD versus the TV-ICD. Nevertheless, other variables not controlled for by the study design, such as ICD indication, type of heart disease, or functional class, as well as pre-implantation quality of life, could have influenced these patients' quality of life, and thus affected assessment of the specific impact of the ICD. However, the absence of statistically significant differences in baseline patient characteristics lessens this potential limitation considerably.

A possible limitation of this study is the lower prevalence of discharges suffered by the S-ICD group (5.1% versus 17.9%), which could have some influence on the perception of quality of life when analyzing this subgroup of patients. However, the prevalence of discharges in both groups was low (11%). We thus believe that this has not significantly influenced the overall results of our study.

Table 7 – ICD QoL questionnaire results in patients implanted with an S-ICD following removal of a TV-ICD

	Subcutaneous N=7	Transvenous N=7	p value
Intraoperative pain			p=1[a]
No pain	7 (100)	3 (42.9)	
Mild	0	2 (28.6)	
Moderate	0	2 (28.6)	
Severe	0	0	
Very severe	0	0	
Perioperative pain			p=0.224[a]
No pain	4 (57.1)	4 (57.1)	
Mild	2 (28.6)	1 (14.3)	
Moderate	1 (14.3)	2 (28.6)	
Severe	0	0	
Very severe	0	0	
Postoperative pain			p=0.659[a]
No pain	6 (87.1)	6 (87.1)	
Mild	1 (14.3)	1 (14.3)	
Moderate	0	0	
Severe	0	0	
Very severe	0	0	
Current pain			p=0.659[a]
No pain	6 (87.1)	6 (87.1)	
Mild	1 (14.3)	1 (14.3)	
Moderate	0	0	
Severe	0	0	
Very severe	0	0	
Aesthetic discomfort			p=0.717[a]
None	5 (71.4)	4 (57.1)	
Mild	1 (14.3)	2 (28.6)	
Moderate	1 (14.3)	1 (14.3)	
A lot	0	0	
Very much	0	0	
Activities of daily living limited			p=0.427[a]
None	5 (71.4)	5 (71.4)	
A little	2 (28.6)	2 (28.6)	
Moderate	0	0	
A lot	0	0	
Very much	0	0	
Sleep disturbance			p=0.350[a]
None	5 (71.4)	4 (57.1)	
Mild	0	0	
Moderate	1 (14.3)	3 (42.9)	
Severe	1 (14.3)	0	
Very severe	0	0	

[a]Chi-square test.

Table 8 – SF-12 survey results in patients implanted with an S-ICD following removal of a TV-ICD

	Median	IQR	Minimum	Maximum
Physical health scale	51.3	5.3	30.5	52.9
Mental health scale	46	4.8	40.2	51.3
Physical functioning scale	56.5	0	22.1	56.5
Physical limitation scale	29.5	0	20.3	29.5
Pain scale	57.4	10.1	47.3	57.4
General health scale	55.5	10.8	29.6	62
Vitality scale	57.8	0	27.6	67.9
Emotional limitation scale	56.6	10.1	16.2	56.6
Social function scale	22.5	0	11.3	22.5
Mental health scale 2	58.4	6.1	58.4	64.5

IQR: Interquartile range.

Lastly, the sample was small in size, being obtained from just one hospital, thereby limiting the statistical power needed to detect differences. However, our quality-of-life data resemble those published recently from a larger population.[5]

Conclusions

The type of ICD implanted does not significantly influence patients' perception of mental or physical quality of life. Our study demonstrates that differences in the surgical procedure (both location and surgical technique) or type of system implanted (such as weight and size) do not have a negative impact on patient quality of life. On the other hand, these findings suggest that the S-ICD can be safely implanted under conscious sedation by an electrophysiology team. Larger, randomized studies are needed to compare against and confirm these results.

Key Points

What is already known about this subject?

• The subcutaneous ICD has been shown to be similar in efficacy to the conventional ICD at preventing sudden cardiac death.

• The subcutaneous ICD is an alternative to the transvenous ICD in patients not requiring antibradycardia, antitachycardia, or cardiac resynchronisation pacing; patients with difficult venous access; young patients; or following removal of a conventional ICD because of infection.

• The subcutaneous ICD employs a different surgical technique from the conventional ICD, and the generator is larger and heavier than in current transvenous systems.

What does this study add?

• There are no significant differences in mental or physical quality of life among a Spanish population of patients with subcutaneous or transvenous ICDs.

• Differences in surgical technique or type of system implanted do not negatively affect patient quality of life.

• Patients implanted with a subcutaneous ICD after having a transvenous ICD removed because of complications assess the new device positively.

• The subcutaneous ICD can safely be implanted under conscious sedation by an electrophysiology team.

Author contributions

Conception and design of the research, Data acquisition, Analysis and interpretation of the data, Statistical analysis and Writing of the manuscript: Auquilla-Clavijo PE, Calvo-Galiano N, Povar-Echeverría M.; Critical revision of the manuscript for intellectual content: Auquilla-Clavijo PE, Calvo-Galiano N, Povar-Echeverría M, Oloriz-Sanjuan T, Diaz-Cortejana F, Asso-Abadía A.

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*Supplemental Materials

For additional information, please click here.

Importance of the Anesthetic Technique and Analgesia in the Implantation of Subcutaneous and Endovascular Defibrillator: An Aspect Often Ignored

Jorge Elias Neto[1]

Vitória Apart Hospital - Serviço de Eletrofisiologia,[1] Serra, ES - Brazil
Short editorial related to the article: Comparative Study between Subcutaneous and Endovascular Defibrillator Recipients Regarding Tolerance to the Implant Procedure and Perception of Quality of Life

Originally introduced by Mirowski 50 years ago, the implantable cardioverter-defibrillator (ICD) has become a cornerstone to preventing SCD related to ventricular tachyarrhythmias.[1]

However, besides their lifesaving capacities, the transvenous leads carry their own risk.

The technological improvement and the observation of these complications and limitations led to the appearance of the subcutaneous ICD (S-ICD).[1]

This technique is rapidly evolving to become a safe and effective alternative for the TV-ICD, leaving the heart and vasculature untouched, with reduced lead-related complications.[1-5]

New interventions and devices necessarily demand a constant analysis of the appropriate anesthetic technique to be used. Only recently, the first studies that deal with the implantation of S-ICD have appeared and analyzed the issue of perioperative safety and postoperative analgesia, as well as its impact on the patient. However, as the authors have pointed out, there is a lack of formatted studies to compare these two types of ICD.

In this edition Auquilla-Clavijo et al.,[6] address these two fundamental questions: comparing QOL and the perception of pain and discomfort resulting from the surgical technique (and, more importantly, the anesthetic protocol used), taking into account the type of device implanted in the patient (TV-ICD x S -ICD).[6]

As reported, the authors used the anesthesiological technic, called non-anesthesiologist-administered sedation and analgesia (NASA).[6]

Although safe and perfectly feasible, it is not possible to consider that the current results are reproduced in services that have a dedicated team of anesthetists. That is, the results are valid for similar situations but do not rule out

the possibility of obtaining a more favorable result in QOL research during sedation conducted by the anesthesia team.

In fact, there is some hesitation regarding the use of local anesthesia with conscious sedation for cardiac resynchronization defibrillator therapy (CRT-d) or S-ICD implantation procedures.[7] This question is plausible if we consider the significant differences between the perioperative management of the S-ICD and the TV-ICD[1] (Ref 2). The S-ICD requires more extensive tissue dissection and tunneling of a lead, and despite recent results with the PRAETORIAN SCORE, defibrillation testing (DT) remains routine.[4,6]

The best anesthesia for S-ICD implantation and DT is unknown, as a paucity of randomized data exists. However, a review of the literature demonstrates efficacy and safety for S-ICD implantation using several modalities: general anesthesia (GA); Monitored Anesthesia Care (MAC), a service provided by an anesthesiologist or certified registered nurse anesthetist; and regional anesthesia and local anesthesia supplemented with sedation/analgesia techniques.[8] A successful procedure can most likely be accomplished with a variety of anesthesia modalities that must take into account clinical aspects and comorbidities of patients, as well as the experience and preference of the medical team.[8]

GA can be used, but it is not required for S-ICD implants, and professionals should, whenever possible, choose MAC. If the team, as in this article, opts for the NASA approach during the ICD implant, both a learning curve phase (initial 5-10 implants) and the completion of an appropriate training program are suggested. This training should include policies and procedures to guide the administration of sedation, patient monitoring, and airway management.[8]

The recent incorporation of truncal plane nerve block techniques, called PECS I&II, guided by ultrasound, provides anesthesia to the transversus thoracic muscle plane, and the serratus anterior plane blocks, covering both the anterior thoracic region (including the pectoralis major and minor muscle) as well as anesthetizes the intercostobrachial nerve, intercostal nerves three through six, and the long thoracic nerve.[1,8-10] The advantages of truncal plane blocks are that they are quick and easy for anesthesia. However, even with adequate regional block, patients undergoing S-ICD may still require GA or MAC but perhaps to a lesser extent.

Another relevant issue concerns the protocol (drugs and respective doses) used for conscious sedation. Benzodiazepine (in this case midazolam) is associated with delirium, particularly in elderly patients; and propofol in infusion pumps produces better arousal, less postoperative

Keywords

Tachycardia, Ventricular; Cardioversor–Defibrillator Implantable/trends; CDI Subcutaneous/trends; Quality of Life; Conscious Sedation; Anesthesy; Analgesia.

Mailing Address: Jorge Elias Neto •
Av. Nossa Sra. dos Navegantes, 451/814. Postal Code 29050-335. Enseada do Suá, Vitória, ES – Brazil
Email: jeliasneto@gmail.com

nausea and vomiting, and a shorter post-anesthetic recovery time.[7-9]

We know that ICD recipients' mortality is significantly predicted by their quality of life (QOL). A recent meta-analysis has shown that psycho-educational interventions improve the physical component but not the mental component of QOL in patients with ICD. This point is also relevant concerning the results to be obtained with the perception of the intervention (regardless of the type of implanted device).[11]

What this study also makes clear is that the patient's mental (psychological, personality type) situation directly interferes in the results obtained in the commonly used questionnaires.

This observation leads us to another aspect that we would like to consider: about 20% of the patients submitted to the ICD implant show symptoms of depression. The psychological aspect is fundamental, however, given that depressive symptoms not only affect patients' quality of life, but also increase their risk of premature death despite state-of-the-art treatment with the ICD.[12]

Studies show that D-type personality research is possibly essential, since it is an independent predictor of post-implant depression and may compromise the results of studies that do not attempt to investigate this variable. Another aspect is that the predominance of males in this study may compromise the degree of positive attitudes toward technology dependency, thus making generalizability difficult.

In the current study, the SF-12 questionnaire (12-Item Short-Form Health Survey) was used. We know that the SF-12, as well as the SF-36, are the most widely used QOL in studies on the ICD population internationally.[13] However, SF-12 may not detect ICD specific QOL outcomes, especially mental health wellbeing, which proved to be a limiting aspect of this study.[11]

For example, the EFFORTLESS S-ICD Registry, in addition to the use of the SF-12 was careful to avoid possible bias attributable to the type of personality of the patient. For this, they used the DS 14. The authors took this care, as already indicated above, due to the knowledge that personality type D is a vulnerability factor in poorer QoL, life-threatening arrhythmias, and premature mortality in patients with an ICD.[14]

Another possibility would be for the author to use the SF-12v2 version, which also includes two summary measures, including a physical health component score (PCS) and a mental health component score (MCS).[11,15]

Finally, due to the important bias resulted from the re-operated patients after previous complications with a TV-ICD device, we consider that the comparative analysis of QoL between groups cannot be valued.

We expect that the continuous increase of S-ICD and prospective trials may be possible to reproduce these single-center observations and determine the best way to provide a safe, efficient, and comfortable anesthetic implant technique, always maintaining focus on the impacts on patients' QoL.

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2020 Top 10 Original Articles in the *Arquivos Brasileiros de Cardiologia* and the *Revista Portuguesa de Cardiologia*

Ricardo Fontes-Carvalho,[1,2]* Gláucia Maria Moraes de Oliveira,[3,4]* Nuno Cardim,[7] Carlos Eduardo Rochitte[5,6]

Departamento de Cardiologia – Centro Hospitalar de Vila Nova de Gaia/Espinho,[1] Vila Nova de Gaia - Portugal

Departamento de Cirurgia e Fisiologia – Faculdade de Medicina – Universidade do Porto,[2] Porto - Portugal

Faculdade de Medicina – Universidade Federal do Rio de Janeiro,[3] Rio de Janeiro, RJ - Brazil

Instituto do Coração Edson Saad – Universidade Federal do Rio de Janeiro,[4] Rio de Janeiro, RJ - Brazil

Instituto do Coração (InCor) – Faculdade de Medicina da Universidade de São Paulo,[5] São Paulo, SP - Brazil

Hospital do Coração (HCOR),[6] São Paulo, SP - Brazil

Hospital da Luz-Lisboa - Faculdade de Ciências Médicas da Universidade Nova de Lisboa,[7] Lisboa - Portugal

* Both authors equally contributed to this article

Introduction

In recent years, the *Revista Portuguesa de Cardiologia* (RPC) and the *Arquivos Brasileiros de Cardiologia* (ABC Cardiol) have gotten together annually to elaborate a list of the most relevant papers published in both journals,[1,2] highlighting some of the best scientific articles in Portuguese.

Based on the success of that initiative, the editors of both journals have decided to cooperate once again to elaborate the 'Top 10' list of 2020 of each journal. The year 2020 was marked by the huge impact of the COVID-19 pandemic in both countries, with an enormous pressure on the healthcare institutions and professionals. Despite those challenges, the scientific quality of the publications in both journals remained extremely high, with excellent original articles.

The selection of the best publications is always complex and sometimes can be imperfect and even unfair, and the process occurred independently of the citations obtained by the articles. This selection included only original articles; no review was considered.

We briefly present the major results of the articles selected along with their scientific relevance. Tables 1 and 2 list the most important papers published in 2020.

Prevention and cardiovascular risk

Cardiovascular disease (CVD) is the leading cause of death in Portugal, Brazil, and developed countries. Therefore, the implementation of public health measures directed to the general population is fundamental to reduce the impact of CVD on society. In the years 2000-2010, Portugal

Keywords

Cardiovascular Diseases; Technical Cooperation/trends; Researcher Exchange/trends; Information Dissemination; Journal of Impact Factor; Periodicals as Topic; Portugal; Brazil.

implemented a set of public health policies to reduce mortality from CVD. Some examples of such measures were the smoking ban in 2008, the salt reduction regulation in 2010, and the implementation of the fast-track system to the coronary unit in 2007. In a study published in the RPC in 2020, *Abreu* et al.[3] assessed the impact of those three health policies on the reduction of the case-fatality rate from acute coronary syndrome (ACS), analyzing the epidemiological CVD data from 2000 to 2016. That study has suggested that the smoking ban and the coronary fast-track system implementation had an immediate decrease in the ACS case-fatality rate, which was not observed with the salt reduction regulation. The reduction in salt intake is known to mainly reduce the risk of stroke, which might explain the results of that study. In addition, those data are consistent with those observed in the Portuguese National Registry of Acute Coronary Syndromes, showing a consistent increase in revascularization rates after the coronary fast-track system implementation.[4] Another study published in the RPC in 2020 showed that a comprehensive smoking ban in the Community of Valencia (Spain) associated with a marked reduction in the adjusted hospitalization rates for myocardial infarction.[5] This type of study and analysis are fundamental to the implementation of new public health measures to reduce the impact of CVD on society.

Still regarding cardiovascular (CV) risk, the RPC has published an interesting study by Dores et al.[6] assessing the coronary atherosclerotic burden of 105 asymptomatic veteran male athletes with low to intermediate CV risk. Those athletes were mainly engaged in high-dynamic sports and underwent cardiac computed tomography (CT) for coronary artery calcium scoring and computed tomography angiography (CT angiography). Although that population seemed "healthy", that study showed a high coronary atherosclerotic burden in 25.7% of the athletes and coronary obstructive lesions in 5.7%. The extent and severity of coronary plaques did not relate to exercise volume or type. Those data are important to understand the best screening strategies in veteran athletes[7] and raise the possibility of using coronary CT for the routine assessment of those individuals, as discussed in the editorial by Pelliccia about that article.[8]

Regarding the age-standardized mortality rates from CVD attributable to risk factors in 2018 in Brazil, for women and men, dietary risks rank second, behind only arterial hypertension.[9] Basilio et al.[10] have studied the influence of the combination of intermittent fasting (with calorie restriction) and physical exercise on physical functioning,

glucose metabolism, and cardiac remodeling in male Wistar rats for 12 weeks. Those authors have hypothesized that physical exercise would increase physical performance and attenuate myocardial remodeling because of intermittent calorie restriction. They have observed that physical exercise increased physical functioning and promoted cardiac fibrosis. They have concluded that intermittent fasting associated with improved glucose tolerance and attenuated cardiac remodeling induced by physical exercise but did not interfere in physical functioning.

The increase in body mass index (BMI), representing the changes observed in obesity, is the third risk factor for women and the fourth for men, in the previously mentioned ranking.[9] Oliveira-Júnior et al.[11] have hypothesized that obesity would associate with changes in myocardial functional performance sustained in different stimulation conditions and reduced by AT1-receptor blockade. Those authors have studied Wistar rats fed either a control or high-fat diet and divided according to the presence of obesity. The obese and control groups received losartan (30 mg/kg/day) in drinking water for four weeks. Those authors have concluded that diet-induced obesity promoted cardiac remodeling, sustained by ventricular hypertrophy and myocardial dysfunction, confirming the initial hypothesis that the stimulation of AT1 receptors would associate with myocardial dysfunction in obese rats. Losartan improved the myocardial function of rats with diet-induced obesity.

It is worth noting that obesity has increased not only in the adult population, but in children and adolescents worldwide as well. The measure of waist circumference, which is an easily obtainable parameter, has high sensitivity to predict children's visceral fat levels. Santos et al.[12] have performed a multicenter, prospective, cross-sectional study with 22 000 children (11 199 boys) aged 6-10 years, registered at public and private elementary schools in 13 cities of São Paulo State. They measured height, weight, and waist circumference. The prevalence of obesity ranged from 17% (6 years of age) to 21.6% (9 years of age) among boys and from 14.1% (7 years of age) to 17.3% (9 years of age) among girls. That study confirms the findings on childhood obesity from the ERICA Study,[13] highlighting the importance of early intervention in dietary risks and obesity to prevent CV deaths in adulthood.

Coronary artery disease and acute coronary syndrome

Although mortality from coronary artery disease has decreased in recent years, several studies have reported the persistence of great differences in diagnosis and treatment of coronary artery disease between genders,[14] suggesting that women often undergo worse treatment. In a study published in the RPC, including 49 113 patients (34 936 men and 14 177 women), Roque et al.[15] have assessed the differences between genders in the treatment of ACS by using data from the Portuguese National Registry on Acute Coronary Syndromes. Those authors have observed that, as compared to men, women are more frequently admitted for non-ST elevation ACS and more often have atypical symptoms. That might explain the women's longer time from symptom onset to reperfusion. The risk of in-hospital mortality was significantly higher in the female sex (OR 1.94; 95%CI: 1.78-2.12) as was their risk of major bleeding, heart failure (HF), atrial fibrillation, mechanical complications, and cardiogenic shock. It is worth noting that women were less likely to receive the recommended secondary prevention therapies, both during hospitalization and at hospital discharge. Briefly, as discussed in the Thomas Lüscher's editorial about that article,[16] those data show the importance of shedding light on the theme of inequality between genders in the treatment of CVD and highlight the need to implement specific measures that can reduce the difference in treatment between genders.

In another study published in the RPC in 2020 based on data from the Portuguese National Registry of Acute Coronary Syndromes, the authors have assessed one of the major themes in current scientific discussion, the optimal time to administer the loading dose of an antiplatelet agent (P2Y12 inhibitor) to patients with ST-elevation ACS: before or during catheterization.[17,18] For that analysis, 4 123 patients with ACS were included, 66% of whom received the P2Y12 inhibitor before catheterization.[19] Multivariate analysis showed that patients who received the P2Y12 inhibitor before catheterization had a significant increase in the composite bleeding endpoint (major bleeding, need for transfusion or hemoglobin drop > 2g/dL), hemoglobin drop > 2g/dL, and reinfarction, in addition to no benefit regarding reduction in major CV adverse events (MACE) or in-hospital death. These data are similar to those observed in other registries,[20] contributing, thus, to this important discussion.

Acute myocardial infarction is also the leading cause of death in Brazil, where regional and gender-related disparities in the temporal trends of mortality rates in most recent years have been observed. Ferreira et al.[21] have conducted a 21-year time-series study (1996-2016) using data from the Brazilian Mortality Information System (SIM) with corrections for ill-defined causes of death, garbage codes, and underreporting. The authors have observed that mortality decreased more significantly in the female sex (–2.2%; 95% CI: –2.5; –1.9) than in the male sex (–1.7%; 95% CI: –1.9; –1.4) and more in the capitals (–3.8%; 95% CI: –4.3; –3.3) than in the inner areas (–1.5%; 95% CI: –1.8; –1.3). In addition, they have found regional differences with increase for men living in the inner areas of the Northern (3.3; 95% CI: 1.3; 5.4) and Northeastern (1.3%; 95% CI: 1.0; 1.6) regions. They have concluded that the corrections of the number of deaths are essential to more reliable estimates on the myocardial infarction mortality trends in Brazil.

Of the ischemic heart diseases, ST-elevation myocardial infarction (STEMI) has the highest proportional mortality. Population-based studies on hospitalizations from that cause in Brazil are scarce. Alves L & Polanczyk CA[22] have performed a population-based prospective cohort study with consecutive registries of hospitalizations for STEMI in a Brazilian southern city from 2011 to 2014. They reported an annual incidence of 108 cases/100 000 inhabitants with reperfusion rate of 80.9%, in-hospital mortality of 8.9%, and CV event rate of 6.1%. Those authors have concluded that, compared to developed countries, Brazil had a higher number of hospitalizations,

but the therapeutic approach and in-hospital mortality were similar to those of developed countries.

Valvular diseases

Aortic valve stenosis is currently the most frequent valvular disease in the western world and its prevalence will continue to increase exponentially due to population aging.[23] Aortic stenosis changes the left ventricular structure and function, and several mechanisms are involved in its pathophysiology. In a study published in 2020 in the RPC, Santos-Faria et al.[24] have assessed the role of microRNA post-transcriptional modulation in the appearance of hypertrophy and myocardial fibrosis. Analyzing the myocardial biopsies of 11 patients undergoing aortic valve replacement, those authors have observed that microRNA-101-3p and microRNA-4268 have potential new roles in the hypertrophic response of patients with aortic stenosis and may be used as predictors of post-surgery reverse remodeling. In addition, the role of those microRNAs in the regulation of the renin-angiotensin-aldosterone system may help find new therapeutic targets for hypertrophy regression.[25]

Transcatheter aortic valve implantation (TAVI) has changed the paradigm of severe aortic stenosis treatment. In 2020, the RPC published an article assessing the short- and long-term results of TAVI in Portugal, using data from the Portuguese National Registry of TAVI, in an analysis of 2346 procedures.[26] In general, TAVI associated with high efficacy and safety, with a 30-day mortality rate of 4.8%. The predictors of 30-day mortality were peripheral arterial disease, previous angioplasty, left ventricular dysfunction, and NYHA functional class III-IV. The predictors of one-year mortality were NYHA functional class III-IV, non-transfemoral route and life-threatening bleeding. In addition, the type of route (transfemoral or another) was analyzed, showing the association of transapical approach with higher mortality and higher risk of complications, related to the patient's profile (severity and more comorbidities).

Despite its benefits, the penetration rate of TAVI in Portugal is still low, with rates much lower than the means of the European Union. In addition, TAVI has high costs, being important to ensure the sustainability of the Portuguese healthcare system. Another article on the same theme published in the RPC in 2020 analyzed the current and future economic impact of TAVI in Portugal.[27] In the initial phase, the authors analyzed all direct and indirect costs related to TAVI, showing that its costs in Portugal were 22 134.5€ for the self-expanding valves (SEV) and 23 321.5€ for the balloon-expanding valves (BEV). Most of the cost related to the price of the prosthesis (SEV 74.5% *versus* BEV 81.5%). To assess the global economic impact of the procedure, three scenarios were constructed. In scenario 1, with TAVI penetration rates according to current guidelines (189 procedures/million inhabitants), the economic impact of TAVI in Portugal would be 43 770 586€. In scenario 2, with TAVI indication extending to intermediate-risk patients (estimated penetration of 241 procedures/million inhabitants), the economic impact would be 55 904 116€. In scenario 3, with TAVI indication extending to low-risk patients aged

> 75 years (penetration of 391 procedures/million inhabitants), the economic impact would be 90 754 310€. Briefly, that study shows that the implementation of TAVI to treat aortic stenosis is associated with a significant economic impact on the Portuguese healthcare system; thus, ways to improve access to the procedure should be discussed but maintaining the sustainability of the healthcare system.

Heart failure and cardiomyopathy

In 2020, the RPC published a study by Gouveia et al.[28] on the economic impact of HF, because, knowing that HF is the major responsible for hospital costs in the United States, its impact should be known in every country. Those authors calculated the annual costs of HF in Portugal, including direct (resource consumption) and indirect (productivity losses) costs, based on data from real clinical practice. In that study, the direct costs with HF in 2014 were €299 million (39% for hospitalizations, 24% for medicines, 17% for diagnostic and therapeutic tests, 16% for consultations, and the rest for other needs, such as emergencies and long-term care). The indirect costs were €106 million (16% for absenteeism and 84% for reduced employment). Those values represent 2.6% of total public health expenditure. In addition, the projection of total costs of HF up to 2036, estimating they significantly increase from €405 million to €503 million, shows the importance of current and future economic impact of HF in Portugal.

Regarding the prognostic predictors of HF with reduced ejection fraction, Ozenc et al.[29] have published in the RPC an article assessing the prognostic value of the right ventricular stroke work index (RVSWI). That study prospectively enrolled 132 patients undergoing right heart catheterization for RVSWI calculation. Those authors concluded that RVSWI predicts the risk of cardiac decompensation and correlates with NYHA functional class in advanced stages of HF. Those data reinforce the relevance of right ventricular assessment in those patients[30] and suggest the importance of combining the information on right cardiac hemodynamics with that of right ventricular function.

It is worth noting the article by Menezes et al.[31] published in 2020 in the RPC about a theme that has not received much attention in the literature, the endomyocardial biopsy. Some studies have suggested that left ventricular endomyocardial biopsy is safer and has a higher diagnostic yield than that of the right ventricle. Those authors have assessed the efficacy, safety, and usefulness of performing transradial left ventricular endomyocardial biopsy in a group of 27 patients. Those authors have reported a success rate of 100% and no significant complications, showing the safety and good diagnostic yield of the technique when used in properly selected patients.

There is a background of systemic oxidative damage in HF, but how HF can affect different structures other than the CV system, mainly DNA damage, is yet to be known. Thus, aiming at assessing DNA damage in different tissues, such as the left ventricle, lungs, and skeletal muscles (diaphragm, gastrocnemius, and soleus), Stefani et al.[32] have submitted male Wistar rats to left coronary artery ligation

with consequent myocardial infarction. Those authors have reported higher DNA damage (% tail DNA, tail moment, and Olive tail moment) in the HF group as compared to the placebo group, and soleum was the most damaged tissue as compared to left ventricle and gastrocnemius in the HF group. They have concluded that HF affects all tissues, centrally and peripherally, in addition to being positively correlated with left ventricular dysfunction.

Chronic cardiomyopathy from Chagas disease is frequent in Brazil, causing severe public health problems. It is believed to result from persistent, diffuse, low-grade infectious myocarditis with focal myocytolysis and intense reactive and reparative fibrosis.[33] It is estimated that 20-40% of patients with Chagas heart disease have atypical angina resulting from myocardial perfusion abnormalities caused by exercise that reverse at rest, probably associated with microvascular ischemia. Campos et al.[34] have compared patients with Chagas disease-related microvascular ischemia to patients with microvascular ischemia of other etiologies. They have concluded that the clinical, hemodynamic, and myocardial perfusion characteristics were similar in both groups but left ventricular segmental and global dysfunction was more severe in patients with Chagas disease-related microvascular ischemia.

Congenital heart diseases

Of the deaths from congenital malformations, those from malformations of the circulatory system (MCS) have a higher impact on the possibility of mortality reduction because they are preventable (if correctly diagnosed and treated) and frequent. Their relative importance has increased, and they became the third cause of death in 2015, representing 40% of the total. Salim et al.[35] have assessed the distribution of mortality from MCS, according to sex, age groups, and Brazilian geographical regions, from 2000 to 2015, in individuals under the age of 20 years. In both sexes, the annual mortality from MCS was 5.3/100 000 inhabitants and proportional mortality was 4.2%. Those authors have concluded that the frequency of misdiagnosis of deaths from MCS is high at all ages, both sexes, and mainly in the Northern and Northeastern regions. That is a severe public health problem in Brazil, because of the lack of diagnosis and proper surgical treatment.

In an analysis of 105 599 CV surgeries performed at the Heart Institute of the Hospital das Clínicas of the University of São Paulo (InCor), between January 1984 and June 2019, a 5.63% global mortality has been reported. Regarding congenital heart diseases, a significant improvement in mortality has been observed after the implementation of the Continuous Quality Improvement Program (CQIP), and, in 2019, mortality from that cause was 7%. In addition, improvement was observed in coronary artery bypass grafting and valvular surgeries with the CQIP. It is worth noting that the mortality rates have come closer to international standards, corroborating the heterogeneity of the deaths from MCS in different Brazilian regions.[36]

Pulmonary embolism

Pulmonary embolism has a heterogeneous clinical presentation, and CT angiography is the gold-standard method for its diagnosis, with right ventricular dilation being the most frequently used parameter for prognostic stratification. That finding should be associated with the measurement of troponin and N-terminal B-type natriuretic peptide.[37] Soriano et al.[38] have proposed that pulmonary vascular volume (PVV), automatically estimated using a software, could be an accurate and easily obtainable mortality predictor. Those authors have conducted a retrospective cohort study with reanalysis of the CT angiography of 61 patients with pulmonary embolism and calculation of the PVV automatically using the Yacta software. They have concluded that adjusted PVV estimated by using that software seems a promising tool for prognostic stratification in acute pulmonary embolism, especially when compared to other classic prognostic parameters of CT angiography.

Covid-19 and cardiovascular disease

The year 2020 has changed forever the medical practice because of the huge impact of the COVID-19 pandemic, whose repercussions on CVD have been enormous and will be felt for years. A single-center study published in the RPC has reported a 49.7% reduction in ACS admissions.[39]

In addition, the pandemic has reinforced the concept that the cardiac impairment of patients with COVID-19 is not uncommon and comprises a wide range of presentations, such as arrhythmias, cardiomyopathies, and myocardial injury (MI), all associated with worse clinical outcomes. Two original single-center studies have shown a high incidence of MI in COVID-19, associated with higher in-hospital mortality. Nascimento et al.[40] have shown the presence of MI in 36% of the patients with COVID-19 in the intensive care unit. Systemic arterial hypertension and BMI were independent predictors of risk for MI, and high-sensitivity troponin I >48.3 ng/mL was associated with higher in-hospital mortality. Almeida Júnior et al.[41] have shown that, within the first 24 hours from admission, troponin T was an independent marker of mortality or need for invasive mechanical ventilation in patients admitted with COVID-19. In addition, titrated C reactive protein was independently associated with worse prognosis. Both studies have emphasized the importance of MI, evidenced by the elevation in troponins I and T, as a predictor of mortality and adverse effects in patients admitted with COVID-19.

However, the sequelae from this crisis are even more frightening. In a remarkable article published in the RPC, General Ramalho Eanes, former president of Portugal, reflects on the impacts on society of this sanitary, economic, social, political, ecological, national, and planetary crisis. He emphasizes the need for rethinking society as a whole to integrate the individual and the group, encompassing all living things.[42]

Scientific and editorial perspectives

Once again, this joint effort of the journals ABC Cardiol and RPC presents a teaser for the reader avid for updated and original scientific information. The specific data on the population from Brazil and Portugal are highly relevant, especially regarding the epidemiological aspects of coronary artery disease and the costs associated with new procedures, such as TAVI.

Other areas have been highlighted in the 2020 issues, such as congenital and valvular diseases, cardiomyopathies, HF, pulmonary embolism, and COVID-19.

We hope this selected 2020 menu triggers the readers' irresistible desire to digitally browse all 2020 ABC Cardiol and RPC issues, searching for their preferred subjects out of the 330 and 138 publications in 2020, respectively.

Finally, we reassure the relevance of this scientific and editorial cooperation regarding the most important publications in cardiology in Portuguese.

Best regards to you all, looking forward to select the 2021 Top 10!

Author Contributions

Conception and design of the research; Acquisition of data; Analysis and interpretation of the data; Writing of the manuscript and Critical revision of the manuscript for intellectual content: Fontes-Carvalho R, Oliveira GMM, Cardim N, Rochitte CE

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Study Association

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

Table 1 – List of the ten best articles published in the *Revista Portuguesa de Cardiologia* in 2020

Authors	Title of the article
D Abreu et al.[3]	Impact of public health initiatives on acute coronary syndrome fatality rates in Portugal
H Dores et al.[6]	Coronary atherosclerotic burden in veteran male recreational athletes with low to intermediate cardiovascular risk
D Roque et al.[15]	Understanding a woman's heart: Lessons from 14 177 women with acute coronary syndrome
JP Moura Guedes et al.[19]	P2Y12 inhibitor loading dose before catheterization in ST-segment elevation myocardial infarction: Is this the best strategy?
J Santos-Faria et al.[24]	MicroRNAs and ventricular remodeling in aortic stenosis
C Guerreiro et al.[26]	Short and long-term clinical impact of transcatheter aortic valve implantation in Portugal according to different access routes: Data from the Portuguese National Registry of TAVI
R Fontes-Carvalho et al.[27]	Present and future economic impact of transcatheter aortic valve replacement on the Portuguese national healthcare system
M Gouveia et al.[28]	Current costs of heart failure in Portugal and expected increases due to population aging
E Ozenc et al.[29]	Impact of right ventricular stroke work index on predicting hospital readmission and functional status of patients with advanced heart failure
M Nobre Menezes et al.[31]	Transradial left ventricular endomyocardial biopsy feasibility, safety and clinical usefulness: Initial experience of a tertiary university center

Table 2 – List of the ten best articles published in the *Arquivos Brasileiros de Cardiologia* em 2020

Authors	Title of the article
Soriano L[38]	1. Volume Vascular Pulmonar Estimado por Software Automatizado é um Preditor de Mortalidade após Embolia Pulmonar Aguda Pulmonary Vascular Volume Estimated by Automated Software is a Mortality Predictor after Acute Pulmonary Embolism http://abccardiol.org/wp-content/uploads/articles_xml/1678-4170-abc-115-05-0809/1678-4170-abc-115-05-0809.x64000.pdf http://abccardiol.org/wp-content/uploads/articles_xml/1678-4170-abc-115-05-0809/1678-4170-abc-115-05-0809-en.x64000.pdf
Oliveira-Junior SA[11]	2. Bloqueio de Receptores AT$_1$ Melhora o Desempenho Funcional Miocárdico na Obesidade AT$_1$ Receptor Blockade Improves Myocardial Functional Performance in Obesity http://abccardiol.org/wp-content/uploads/articles_xml/0066-782X-abc-115-01-0017/0066-782X-abc-115-01-0017.x64000.pdf http://abccardiol.org/wp-content/uploads/articles_xml/0066-782X-abc-115-01-0017/0066-782X-abc-115-01-0017-en.x64000.pdf
Salim TR[35]	3. Desigualdades nas Taxas de Mortalidade por Malformações do Sistema Circulatório em Crianças Menores de 20 Anos de Idade entre Macrorregiões Brasileiras Inequalities in Mortality Rates from Malformations of Circulatory System Between Brazilian Macroregions in Individuals Younger Than 20 Years http://abccardiol.org/wp-content/uploads/articles_xml/0066-782X-abc-115-06-1164/0066-782X-abc-115-06-1164.x64000.pdf http://abccardiol.org/wp-content/uploads/articles_xml/0066-782X-abc-115-06-1164/0066-782X-abc-115-06-1164-en.x64000.pdf
Mejia OAV[36]	4. Análise de >100.000 Cirurgias Cardiovasculares Realizadas no Instituto do Coração e a Nova Era com Foco nos Resultados Analysis of >100,000 Cardiovascular Surgeries Performed at the Heart Institute and a New Era of Outcomes http://abccardiol.org/wp-content/uploads/articles_xml/0066-782X-abc-S0066-782X2020000400603/0066-782X-abc-S0066-782X2020000400603-pt.x64000.pdf http://abccardiol.org/wp-content/uploads/articles_xml/0066-782X-abc-S0066-782X2020000400603/0066-782X-abc-S0066-782X2020000400603.x64000.pdf
Alves L[22]	5. Hospitalização por Infarto Agudo do Miocárdio: Um Registro de Base Populacional Hospitalization for Acute Myocardial Infarction: A Population-Based Registry http://abccardiol.org/wp-content/uploads/articles_xml/1678-4170-abc-115-05-0916/1678-4170-abc-115-05-0916.x64000.pdf http://abccardiol.org/wp-content/uploads/articles_xml/1678-4170-abc-115-05-0916/1678-4170-abc-115-05-0916-en.x64000.pdf
Campos FA[34]	6. Estudo Comparativo da Doença Coronariana Microvascular Causada por Doença de Chagas com Outras Etiologias Chagas Cardiomyopathy as the Etiology of Suspected Coronary Microvascular Disease. A Comparison Study with Suspected Coronary Microvascular Disease of Other Etiologies http://abccardiol.org/wp-content/uploads/articles_xml/0066-782X-abc-115-06-1094/0066-782X-abc-115-06-1094.x64000.pdf http://abccardiol.org/wp-content/uploads/articles_xml/0066-782X-abc-115-06-1094/0066-782X-abc-115-06-1094-en.x64000.pdf
Stefan GP[32]	7. Quantificação de Dano em DNA em Diferentes Tecidos em Ratos com Insuficiência Cardíaca Quantification of DNA Damage in Different Tissues in Rats with Heart Failure http://abccardiol.org/wp-content/uploads/articles_xml/0066-782X-abc-S0066-782X2020000200234/0066-782X-abc-S0066-782X2020000200234-pt.x64000.pdf http://abccardiol.org/wp-content/uploads/articles_xml/0066-782X-abc-S0066-782X2020000200234/0066-782X-abc-S0066-782X2020000200234.x64000.pdf
Basilio PG[10]	8. Dieta Intermitente Atenua a Remodelação Cardíaca Causada pelo Exercício Físico Intermittent Fasting Attenuates Exercise Training-Induced Cardiac Remodeling http://abccardiol.org/wp-content/uploads/articles_xml/0066-782X-abc-115-02-0184/0066-782X-abc-115-02-0184.x64000.pdf http://abccardiol.org/wp-content/uploads/articles_xml/0066-782X-abc-115-02-0184/0066-782X-abc-115-02-0184-en.x64000.pdf
Santos JL[12]	9. Os Percentis e Pontos de Corte da Circunferência Abdominal para Obesidade em uma Ampla Amostra de Estudantes de 6 a 10 Anos de Idade do Estado de São Paulo, Brasil Waist Circumference Percentiles and Cut-Off Values for Obesity in a Large Sample of Students from 6 To 10 Years Old Of The São Paulo State, Brazil http://abccardiol.org/wp-content/uploads/articles_xml/0066-782X-abc-114-03-0530/0066-782X-abc-114-03-0530.x64000.pdf http://abccardiol.org/wp-content/uploads/articles_xml/0066-782X-abc-114-03-0530/0066-782X-abc-114-03-0530-en.x64000.pdf
Ferreira LCM[21]	10. Mortalidade por Infarto Agudo do Miocárdio no Brasil de 1996 a 2016: 21 Anos de Contrastes nas Regiões Brasileiras Mortality Due to Acute Myocardial Infarction in Brazil from 1996 to 2016: 21 Years of Disparities in Brazilian Regions http://abccardiol.org/wp-content/uploads/articles_xml/1678-4170-abc-115-05-0849/1678-4170-abc-115-05-0849.x64000.pdf http://abccardiol.org/wp-content/uploads/articles_xml/1678-4170-abc-115-05-0849/1678-4170-abc-115-05-0849-en.x64000.pdf

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*Supplemental Materials

For additional information, please click here.

17-Year-Old Man with Pulmonary Atresia and Intact Ventricular Septum Submitted to Fontan Operation, and with Persistent Coronary-Cavitary Fistula

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

Introduction

Pulmonary atresia with intact ventricular septum is a congenital anomaly with total interruption of blood flow between the right ventricle and the pulmonary trunk, and in general it is not accompanied by associated defects, except for interatrial septal defect, present in 20%, with predominance of patent foramen ovale.[1] Valve atresia results from the lack of embryological development of this fibrous structure, which can be located at the valve level (fibrous membrane) but also at the infundibular level (blind fundus). As a consequence, myocardial hypertrophy and hypoplasia of the right ventricle, hypoplasia of the ring and tricuspid valve, mild tricuspid insufficiency and pulmonary flow dependent on the ductus arteriosus appear. In view of greater hypertension in right ventricle, direct connections with the coronary circulation are formed through sinusoids, with flow towards the aorta. In this situation, it is said that the coronary circulation is dependent on the right ventricle, and when these connections are present in great magnitude, they predispose to myocardial infarction, arrhythmias and right ventricular volume overload, due to retrograde flow from the aorta.[2]

In cases where valve atresia develops later in the fetus, the right ventricular cavity may be well formed with its three portions, the entrance route, the trabecular and the exit route and, as a consequence, there is marked tricuspid insufficiency, even with Ebstein-type alteration of the redundant and myxomatous valve, ventricular wall thinning, ventricular dysfunction and right heart failure, the latter superimposed on hypoxia. In general, it is not accompanied by other associated defects and the pulmonary arteries are of adequate size. In these cases, there is no connection between the right ventricle and the coronary arteries by sinusoids.

How it exteriorizes and evolves

In the first type, with hypoplasia of the right ventricle, the clinical condition is expressed early in life with variable

Keywords

Heart Defects Congenital; Fontan Surgery; Pulmonary Atresia/surgery; Cardiomegaly; Right Ventricle/Abnormalities; Arrhythmias, Cardiacs; Coronary-cavitary fistula.

hypoxia and intensity dependent on the functionality of the ductus arteriosus. Clinical semiology is shown with a smooth continuous murmur in the pulmonary area, second heart sound of diminished intensity, left ventricular overload on the electrocardiogram, but without left anterior and superior divisional block, in addition to a heart with dimensions close to normal. In type II, with greater tricuspid regurgitation and dilated ventricular cavity, hypoxia is associated with right heart failure with hepatomegaly. There is a clinical demonstration of cardiomegaly by clear systolic impulses in the precordium, intense systolic murmur of tricuspid regurgitation, diastolic biventricular overload on the electrocardiogram, and cardiomegaly at the expense of the right cavities.

Evolution is always unfavorable and takes a few days, in both types, depending on progressive or even sudden ductus arteriosus decrease, degree of tricuspid insufficiency and right heart failure.

How it is treated

Clinical treatment: As in both types of pulmonary atresia, the one with a hypoplastic right ventricle and the one with an enlarged right ventricle, there is dependence on the arterial ductus for pulmonary circulation functionality, and the use of prostaglandin E1 becomes essential. In overlying right heart failure, restrictive volume measures are also used, even with the use of diuretics, but always with caution, due to hypoxemia.

Surgical treatment: Blalock-Taussig pulmonary systemic anastomosis in the first type in which hypoxia needs to be minimized promptly. In cases in which the right ventricle is well formed, especially with greater dilation and in addition to the continuity of the structures of the right ventricular outflow tract and the pulmonary trunk, the flow between these structures is made possible by actuation through catheters piercing the atretic valve with radio frequency. Coronary circulation, dependent on the right ventricle, is generally preserved, except when there is greater flow from left to right, functioning as arteriovenous fistulas, of great magnitude.

How it evolves after the operation

Control of hypoxia is better achieved than that of tricuspid regurgitation, especially when it is marked. In a later evolution, Fontan operation is performed on a timely manner, initially preceded by the Glenn technique. In the possibility of restitution of the pulmonary flow, after direct connection of the right structures, a more favorable evolution is observed, except for the appearance of pulmonary valve insufficiency, which may require evolutionary repair.

The purpose of this evaluation is to demonstrate the favorable evolution after Fontan operation in patients in whom the coronary-cavitary fistula remains between the right ventricle and the left coronary artery, as long as it has a slight repercussion.

Description of the Clinical Case

Clinical data: Right after birth, the patient developed a severe hypoxic condition that required Blalock-Taussig anastomosis to be performed at 2 days of age. After 12 months, bidirectional Glenn operation was performed and, at the age of 5, the patient completed the Fontan principle, with a fenestrated external tube. Since then, patient has remained symptom-free, using warfarin, with oxygen saturation of 88%. Systolic and diastolic murmur accompanies it from the beginning, due to persistent coronary-cavitary fistula between the right ventricle and the anterior descending artery, with bidirectional flow.

Physical examination: Eupneic, acyanotic, normal pulses, no jugular turgency. Weight: 58 kg; height: 163 cm; BP: 90/60 mm Hg; HR: 74 bpm, oxygen saturation = 88%. Aorta not palpated in the suprasternal notch.

In the precordium, apical impulse in the 4th left intercostal space and discrete systolic impulses at the left external border. Accentuated heart sounds; systolic murmur, ++/4 intensity, rough, and mild diastolic murmur ++/4, along the left sternal border. The liver was not palpable and the lungs were clean.

Complementary Exams

Electrocardiogram showed sinus rhythm and signs of right ventricular overload with Rs complex in V1 and negative T wave from V1 to V5. Left ventricular potentials were prominent with qRs complex in left precordial leads. No signs of atrial overload. AQRS: + 80°, AT: -30°, AP: + 30° (Figure 1).

Chest radiography shows normal cardiac area (cardiothoracic index: 0.46) with protruding ventricular arch, rectified medium arch and normal pulmonary vascular network (Figure 1).

Echocardiogram showed good functioning of the cavopulmonary operation. Inferior and superior vena cava, with laminar flows at a speed of 0.38 m/s; external tube for right pulmonary artery with a speed of 0.46 m/s. The fenestration flow was directed to the right atrium at a speed of 1.04 m/s. The right ventricle was hypoplastic with ventricular septum deviated to the right with a slightly hypertrophic and dilated left ventricle, with normal function of 60% using the Simpson method. Fistula between the right ventricle and the small anterior descending artery, with bidirectional flow (Figure 1).

Cardiac catheterization performed before the Fontan operation highlighted the good functionality of the bidirectional Glenn, with left ventricle compressed by the higher pressure of the right ventricle, and coronary-cavitary fistula of the hypertrophic and hypoplastic right ventricle to the left coronary artery and aorta (Figure 2).

Clinical Diagnosis: Pulmonary atresia with intact ventricular septum with hypoplastic right ventricle and persistent coronary-cavitary fistula between the right ventricle and the left coronary artery in a 17-year-old man, evolving 11 years after the Fontan operation.

Clinical Characteristics

a. Clinical Reasoning: Evolution of Fontan operation is generally without heart murmurs and with some physical limitation due to decreased cardiac output. In the cardiac auscultation of this patient, systolic and diastolic murmur drew a lot of clinical attention and the first assumption with previous diagnosis of pulmonary atresia with intact ventricular septum was coronary-cavitary fistula in the right ventricle, which persisted since birth. Higher pressure in the right ventricle directs the passage of blood towards the coronary artery during ventricular systole (systolic murmur) and, in contrast, in diastole, when blood from the aorta goes to the right ventricle itself (diastolic murmur). Complementary exams highlighted the presence of right ventricular overload on the electrocardiogram, resulting from the diastolic overload imposed by the coronary-cavitary fistula, but not enough to cause right ventricular dilation. It can be concluded from this that this fistula did not cause anatomo-functional overload that would influence the circulatory dynamics.

b. Differential Diagnosis: Rarely after the Fontan operation systolic and diastolic murmur is heard, except in unusual situations such as a double associated aortic valve injury, for example. But, in this situation, the clinical repercussion becomes unfavorable in view of the retrograde increase in pulmonary arterial pressure. The same auscultation can also occur in the presence of an injury to one of the atrioventricular valves, with predominance of stenosis, which in turn also causes evolutionary problems, in the same way. Thus, considering the finding of a systolic and diastolic murmur in this patient after the Fontan operation, coronary-cavitary fistula would be the only cause compatible with the good evolution.

Management: In view of the favorable evolution of the patient due to the small clinical repercussion of the coronary-cavitary fistula, the expected management was smoothly continued along with the recommended anticoagulant medication.

Discussion

Although Fontan operation is palliative, with evolutionary complications, it continues to offer good prospects as long as it strictly complies with the indication criteria. In the known presence of coronary-cavitary fistula and in association of pulmonary atresia with intact ventricular septum, its closure was not considered, due to its slight repercussion, thus not highlighting unfavorable consequences, and also because it is located in the same arterial blood system, without interference with the venous system. In the event that the fistula shows greater repercussions, fistula closure must be indicated upon the Fontan operation. On this occasion, choosing to close the tricuspid valve is also appropriate to make the fistula less dynamic. This management is adopted upon the Fontan procedure or even before.[3] Such procedure becomes necessary before Fontan, in view of the well-known mortality of patients with arterial circulation of right ventricle-dependent
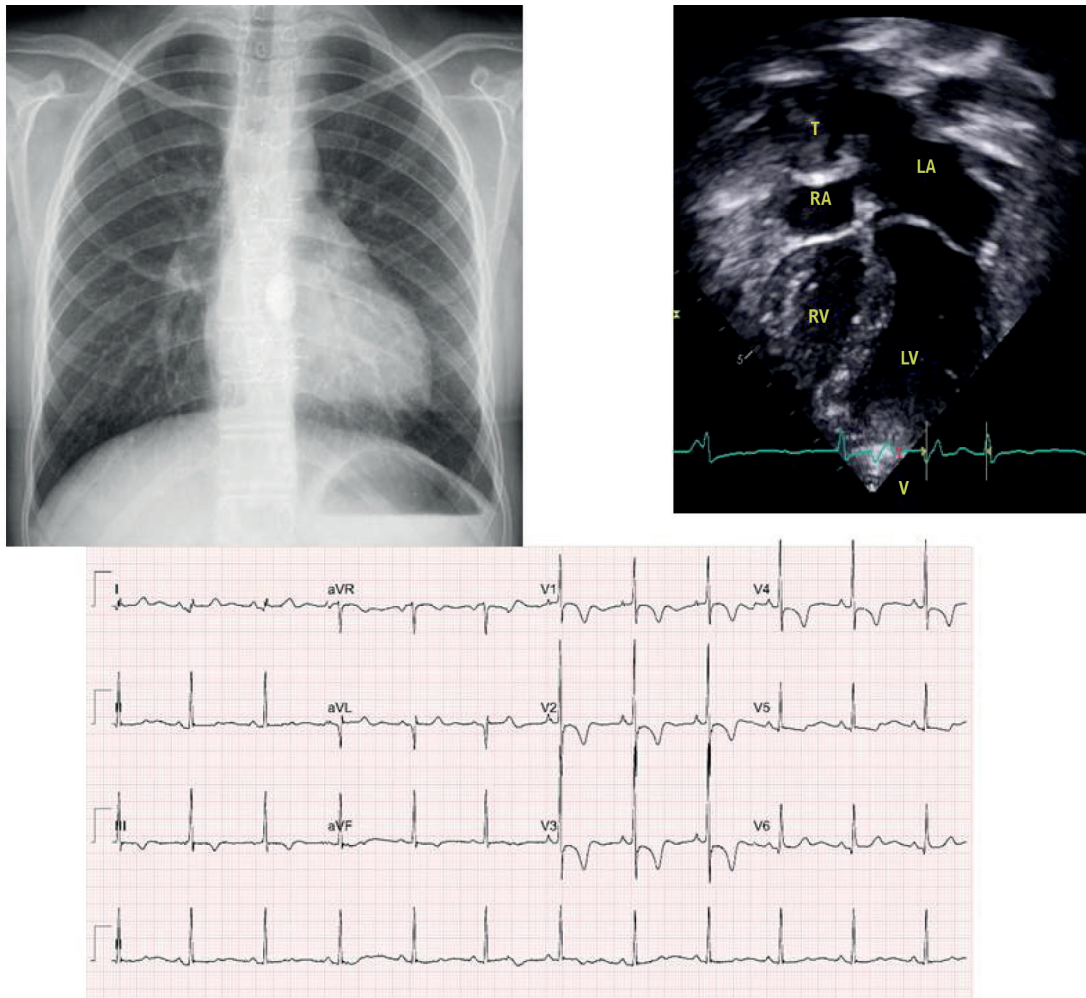
Figure 1 – *Chest X-ray shows normal cardiac area, rectified medium arch and normal pulmonary vascular network. Electrocardiogram highlights right ventricular overload with Rs complex in V1 and negative T waves from V1 to V5. Apical 4-chamber echocardiogram highlights right ventricular hypoplasia with ventricular septum deviated to the left side, with normal cardiac cavities in addition to the right intraatrial fenestration tube (t). RA: right atrium; LA: left atrium; RV: right ventricle; LV: left ventricle.*
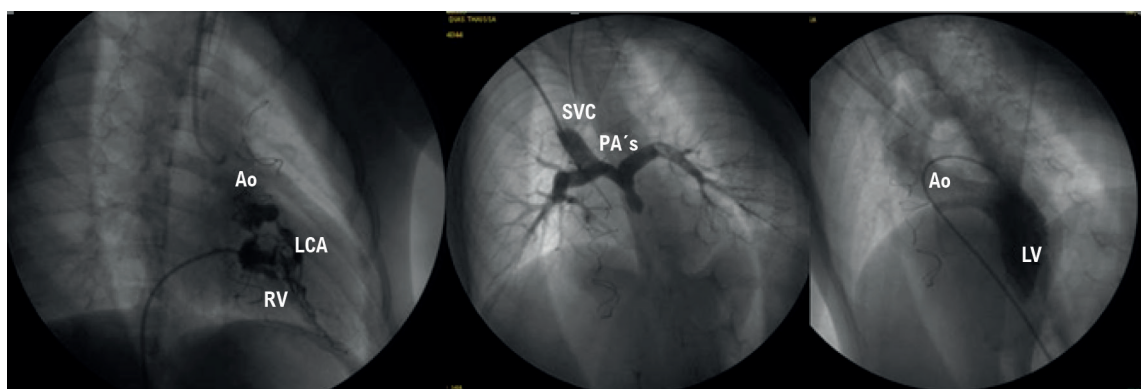
Figure 2 – *Cardiac angiocardiography before the Fontan operation shows the good functionality of the bidirectional Glenn in B, with the left ventricle rejected by the higher pressure of the right ventricle in C, and the coronary-cavitary fistula of the hypertrophic and hypoplastic right ventricle to the left coronary artery and aorta, in A. AO: aorta; RV: right ventricle; LV: left ventricle; LCA: left coronary artery; PA´s: pulmonary arteries; SVC: superior vena cava.*

coronary arteries.[4,5] According to Calder,[5] mortality reached 40% (47 out of 116 patients), mainly related to interruptions and stenosis of the coronary arteries. It should be noted that the presence of coronary-cavitary fistulas, per se, is not responsible for mortality, except with associated arterial obstructive lesions and large fistulas.

There are few articles in the literature correlating the Fontan operation with persistent coronary-cavitary fistulas. Cheung[6] found myocardial ischemia in 2 of the 4 cases with persistent coronary-cavitary fistulas after Fontan. On the other hand, Guleserian[7] found a good evolution of the 19 patients with cavitary-coronary fistulas submitted to Fontan and in 7 cases after Glenn. The survival of these patients was 81.3% at 5, 10 and 15 years after Fontan, with an average survival of 12.1 years. This author also points out that mortality was restricted to patients with a more exuberant ischemic condition (6 out of 32–18.8%), but also in an early period, just 3 months after Blalock-Taussig. In this group, aortocoronary atresia was present in 3 of these patients.

However, more unfavorable evolution was reported by Elias,[8] in view of the 9% mortality (11/120 patients) in an evolutionary period of 9.1 years after Fontan. In these patients, sudden death occurred in 6 of the 11 patients and, of these, 4 had coronary artery circulation dependent on the right ventricle. The cause of death of these patients was related to myocardial ischemia.

In summary, it can be concluded that patients with repercussion coronary-cavitary fistulas should be repaired early and those submitted to the Fontan principle, even with lesser repercussions, should be monitored and investigated by stress tests under strict evaluation.[9]

Author Contributions

Conception and design of the research, Acquisition of data, Analysis and interpretation of the data, Writing of the manuscript and Critical revision of the manuscript for intellectual content: Atik E.

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Study Association

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

Ethics approval and consent to participate

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

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Spiked Helmet Sign: An Atypical Case of Transient ST-Segment Elevation on ECG

Acácio F. Cardoso,[1] *Marco Alexander V. Akamine,[1]* *Rafael M. Pessoa,[1]* *Elizabeth T. Takitani,[1]* *José V. Kairiyama,[1]* *Manfredo K. Naritoni[1]*
Serviço de Cardiologia do Hospital Nipo-Brasileiro,[1] São Paulo, SP - Brazil

Case report

Male, 35 years old, smoker, user of illicit drugs (marijuana, cocaine and inhalant solvents), on antipsychotics and antidepressants (haloperidol and escitalopram), several episodes of vomiting and diarrhea for the past two days, mental confusion at home, and admitted to the emergency room with reduced level of consciousness and irregular breathing. Soon afterwards, he presented cardiopulmonary arrest (CRP) with ventricular fibrillation (VF) on the cardiac monitor. After six minutes of cardiopulmonary resuscitation maneuvers, adrenaline infusion and two cardiac defibrillations, pulse and heart rate were recovered. An electrocardiogram (ECG) was performed, which demonstrated atypical and diffuse ST-segment elevation (Figure 1 A). Initial laboratory tests showed severe metabolic acidosis with high serum lactate (serum lactate = 26 mg/dl), in addition to hypernatremia (serum sodium = 153 mg/dl), hypokalemia (serum potassium = 3.2 mg/dl), severe leukocytosis and a slight increase in serum troponin. The patient was intubated and placed on mechanical ventilation. Volume resuscitation was performed, metabolic acidosis was corrected, and broad-spectrum antibiotics were initiated. One hour after initial consultation, a new ECG was performed, which demonstrated a reduction of approximately 50% in ST elevation (Figure 1B). Given the atypical character of the ST segment abnormalities on ECG, we chose not to perform an emergency coronary angiography. Six hours after the event, the initial ECG abnormalities receded completely (Figure 1C). An echocardiogram was performed, which showed severe left ventricular dysfunction at the expense of diffuse hypokinesia (ejection fraction = 0.36). A new echocardiogram was performed two days later, which revealed complete recovery of ventricular function (ejection fraction = 0.69). Coronary angiotomography was performed during hospitalization, which demonstrated the absence of obstructive lesions and ruled out coronary anomalies. The patient progressed well and was discharged after eight days of hospitalization.

Keywords

ST-Elevation; Electrocardiography/methods; Echocardiography/methods; Death, Sudden Cardiac; Critical Illness.

Discussion

In this intriguing case report, a young patient, an user of illicit drugs, on regular use of haloperidol and escitalopram, was admitted to the emergency department in a serious clinical condition, on the verge of a cardiac arrest. After a VF episode was promptly reversed, the initial ECG demonstrated tachycardic rhythm, with enlarged QRS complexes, apparently preceded by low amplitude P waves. Initial activation of QRS was rapid and accompanied by ST elevation with convex morphology in multiple electrocardiographic leads, followed by inversion and alternation of the amplitude of T waves, a phenomenon known as macroalternation of T waves (Figure 1A).

Spiked helmet sign (SHS) was described by Littmann et al.[1] in 2011 as a transient ST-segment elevation in severe clinical conditions of non-cardiac origin, associated with normal or slightly increased serum levels of troponin, in addition to an unfavorable clinical outcome with a high mortality rate.[1] In their series, 6 of 8 patients died after an initial ECG within 1 to 10 days.[1] Initially described as ST segment elevation restricted to lower leads, new cases have been reported involving multiple electrocardiographic leads.[2] Morphology on ECG is similar to the pickelhaube, a helmet studded with a pointed rod, worn by military Prussian and German army personnel in the 19th and 20th centuries.

The main SHS characteristics on the ECG are an upward elevation of the isoelectric line that precedes the QRS, followed by a narrow R wave and a convex ST-segment elevation[2] (figure 2). The pathophysiological mechanisms related to this ECG morphological pattern are not yet fully understood. A previous giant T-U wave that advances over the next QRS and/or prolongation of ventricular repolarization superimposed at high heart rates are potential causes attributed by some authors.[3] Initial cases were identified in thoracic and abdominal pathologies and are associated with muscle artifacts and acute pressure increase in these cavities. Subsequently, other reports involving intracerebral hemorrhage, severe metabolic abnormalities and septic shock pointed to an intense adrenergic discharge as a common final route for triggering these ECG abnormalities. Clinical manifestations associated with hyperadrenergic states such as after stellate ganglion[4] ablation and Taktsubo[5] cardiomyopathy reinforce this hypothesis.

T-wave macroalternation is a rare ECG manifestation; it reflects severe dispersion of ventricular repolarization and generally precedes the onset of VF.[6] This morphological pattern is more commonly seen in patients with congenital or acquired high-risk QT syndrome and announces the beginning of Torsade de Pointes. In our case, the T-wave macroalternation was observed after an aborted VF and

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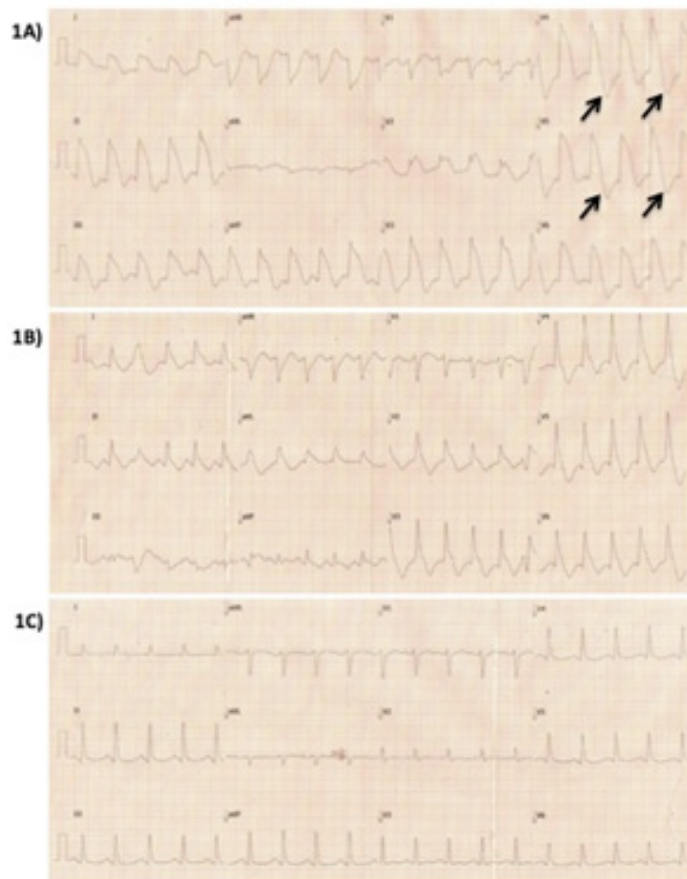
Figure 1 – *Sequence of ECG on patient admission. 1A) Initial ECG with atypical ST-segment elevation in multiple leads followed by T-wave macroalternation easily observed in V4 and V5 (arrows). 1B) One hour after the initial ECG, a new scan showed a reduction of approximately 50% in ST-segment elevation. The characteristic findings of SHS are more evident in leads V2 and V3. 1C) Six hours after the initial ECG, complete resolution of ST-segment elevation is seen with only mild ventricular repolarization abnormalities.*
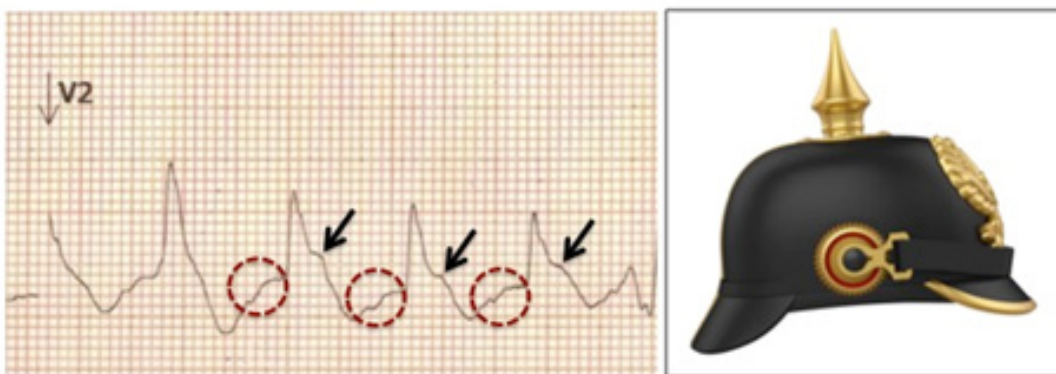
Figure 2 – *Main SHS findings on ECG. An upward isoelectric line (red circles) is followed by convex ST-segment elevation (arrows). The abnormal findings are similar to the spiked helmet worn by the armies of Prussia and Germany in the 19th and 20th centuries. Key: SHS – Spiked helmet sign.*

indicates that in extreme manifestations of SHS, ventricular repolarization may last for a very prolonged time and lead to the onset of potentially fatal ventricular arrhythmias. Particularly in psychiatric patients, these abnormalities may be exacerbated by antipsychotics and antidepressants, which are known to prolong the cardiac cell action potential by blocking potassium ion currents.[7] Previous publication of SHS involving QT prolongation, T-wave alternation and Torsade de Pointes has found that SHS may be a possible mechanism of sudden death in these patients.[8] Given the rarity of the phenomenon, the relationship between SHS and the risk of sudden death is yet to be established in future publications.

Other clinical situations associated with ST-segment elevation, such as bundle branch block, pericarditis, massive pulmonary embolism, and especially acute coronary syndromes, should be considered as the main differential diagnoses of SHS.[9] In our case, coronary vasospasm associated with cocaine abuse and cardiac defibrillation are two other situations that involve abnormalities in ventricular repolarization and should be considered in this analysis. In the first case, cocaine precipitates episodes of coronary vasospasm and can act as a potent inhibitor of ion channel currents responsible for the cardiac cell action potential. Both conditions may promote the prolongation of ventricular repolarization and the onset of severe ventricular arrhythmias.[10] However, coronary vasospasm is usually preceded by chest pain, ST-segment abnormalities are usually restricted to some leads, last only a few minutes, and are followed by symmetrical and wide T-waves on ECG.[11] ST-segment elevation associated with electrical defibrillation is a short-term phenomenon, it reaches its maximum amplitude right after the shock and has an average duration of approximately 60 seconds, returning to the normal pattern around 5 minutes after the shock.[12] Although it is not possible to totally rule out the participation of these two conditions in the abnormalities evidenced in the ECG, these findings make these hypotheses less likely.

Metabolic and electrolytic abnormalities are common in critically ill patients and may have electrocardiographic manifestations similar to those observed in SHS. Metabolic acidosis associated with severe hyperkalaemia often increases QRS duration and causes ST-segment elevation mainly in the right precordial leads, and is easily confused with acute anterior wall myocardial infarction.[13] Marked hypocalcemia is another metabolic condition that may cause ST-segment elevation and, with hypokalemia, may

significantly prolong the QT interval.[14] ECG abnormalities related to serum sodium levels are rarer. ST-segment depression and shortening of the PR interval have been described in extreme cases of hypernatremia.[15] In our case, severe metabolic acidosis, hypernatremia and mild hypokalemia were the only metabolic abnormalities identified in laboratory tests.

These findings are not sufficient to explain all the abnormalities observed in the sequence of ECG, which makes SHS a unique electrocardiographic manifestation with quite adverse prognosis in most cases.

Conclusions

SHS is a rare manifestation on the ECG of critically ill patients with non-cardiac pathologies. Prolongation of ventricular repolarization associated with T-wave macroalternation seems to be a plausible mechanism of malignant ventricular arrhythmias in this scenario and requires prompt recognition and intervention.

Author Contributions

Conception and design of the research and Writing of the manuscript: Cardoso AF; Acquisition of data and Analysis and interpretation of the data: Cardoso AF, Akamine MAV, Pessoa RM, Kairiyama JV; Critical revision of the manuscript for intellectual content: Cardoso AF, Akamine MAV, Takitani ET, Naritoni MK.

Potential Conflict of Interest

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Study Association

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

Ethics approval and consent to participate

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

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Pulmonary Arterial Intramural Hematoma Due to Acute Aortic Dissection

Lucas de Pádua Gomes de Farias,[1] Ana Cristina Favaretto,[1] Luciana de Pádua Silva Baptista,[1] Gustavo Borges da Silva Teles[1]

UnitedHealth Group Brazil,[1] São Paulo, SP - Brazil

A 54-year-old male patient, who was a smoker, was admitted to the emergency room with acute chest pain and dyspnea. Investigation was initiated by means of computed tomography angiography of the chest, which showed extensive dissection of the thoracic aorta, beginning in the ascending segment (Stanford type A), associated with intramural hematoma of the pulmonary artery trunk and its main branches. It was more evident on the right, which determines local pulmonary luminal reduction, in addition to a small para-aortic and subaortic mediastinal hematoma. There were no signs of pulmonary thromboembolism, and the evaluation of the parenchyma showed no signs of pulmonary hemorrhage (Figures 1 and 2).

Acute aortic dissection is a life-threatening condition, and mediastinal hematoma dissecting the pulmonary artery sheath is considered a rare complication,[1-3] which can simulate pulmonary thromboembolism and vasculitis.[4] This generally occurs because, at the level just above the aortic valve, the ascending aorta and the pulmonary artery trunk share a common adventitia, which caudally becomes the visceral pericardium.[1,4,5] In most cases, there is a rupture of the middle bed adjacent to the right pulmonary artery, and blood flows from the ascending aorta into the interstitial space that limits the pulmonary arteries (intramural hematoma) (Figure 3), and this can extend into the interlobular septa, or even the alveoli, through the peribronchovascular interstitium.[1,2,4] Some isolated cases of pulmonary artery hematoma may be related to patent ductus arteriosus, pulmonary hypertension, or connective tissue disorders.[6-9]
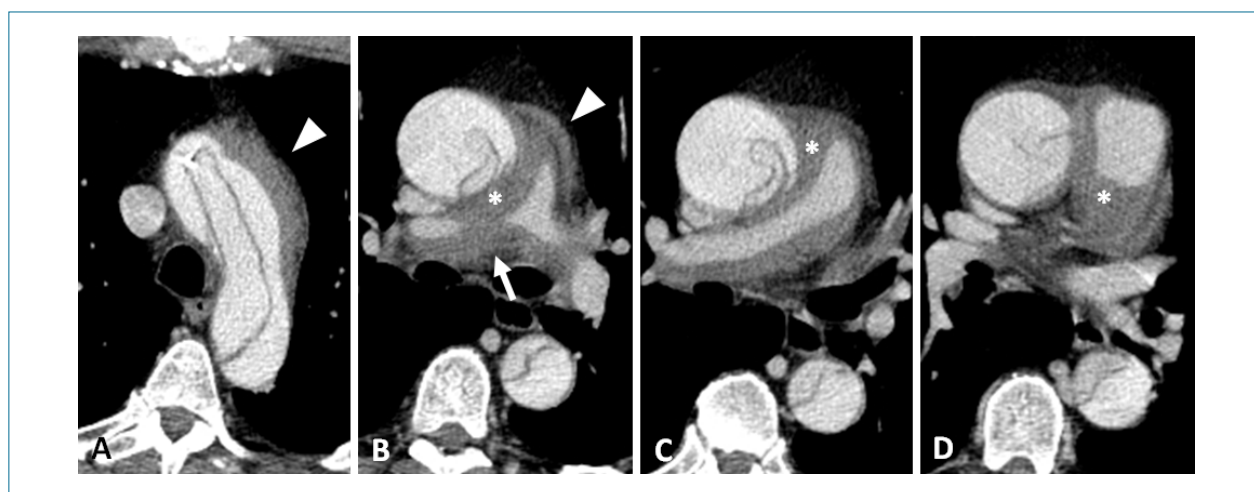
Figure 1 – *16-row multi-detector computed tomography angiography of the chest (A to D – axial multiplanar reconstruction), shows acute aortic dissection (Stanford type A) associated with secondary hematoma (asterisk), involving the pulmonary artery trunk and its main branches. It is more evident on the right, determining luminal reduction of its proximal portion (white arrow). Note, as well, the mediastinal hematoma in the para-aortic and subaortic regions (white arrowhead).*

Keywords

Chest Pain; Hematoma; Pulmonary Artery; Computed Tomography Angiography/methods; Pulmonary Artery; Aneurysm, Dissecting

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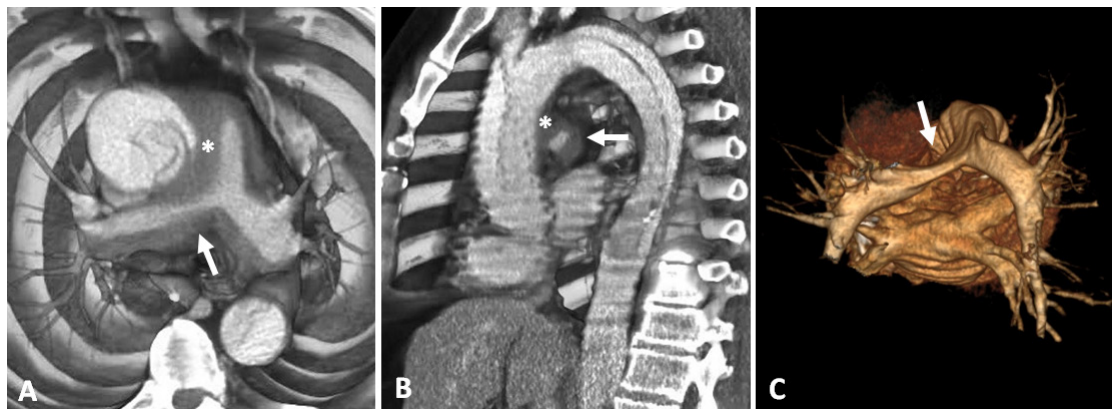
Figure 2 – *Three-dimensional reconstructions of a 16-row multi-detector computed tomography angiography, show acute aortic dissection (Stanford type A) associated with secondary hematoma (asterisk), involving the pulmonary artery trunk and its main branches. It is more evident on the right, determining luminal reduction of its proximal portion (white arrow).*
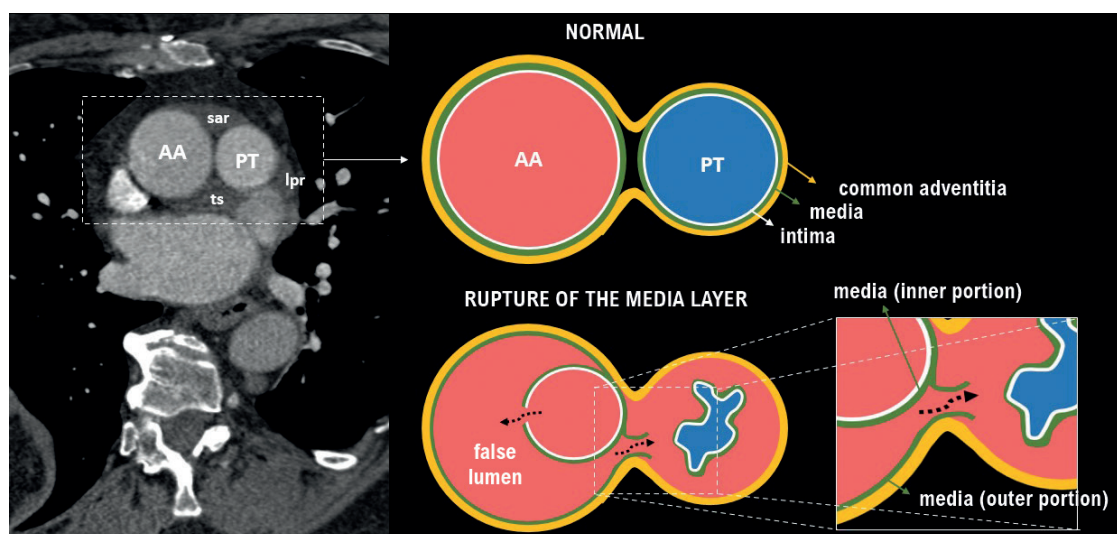
Figure 3 – *Schematic illustration showing the rupture of the outermost portion of the media layer in the false lumen of the aortic dissection, adjacent to the pulmonary artery, resulting in leakage of blood into the common adventitia between the aorta and the pulmonary artery, which can narrow the pulmonary arterial lumen. AA: ascending aorta; lpr: left pulmonary recess of the transverse sinus; PT: pulmonary trunk; sar: superior aortic recess; ts: transverse sinus. Adapted from Roberts.[5]*

Author Contributions

Conception and design of the research, Acquisition of data, Analysis and interpretation of the data and Writing of the manuscript: Farias LPG, Favaretto AC; Critical revision of the manuscript for intellectual content: Baptista LPS; Teles GBS.

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Ethics approval and consent to participate

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

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Letter to the Editor

Teachers who were Academic Examples

Charles Mady[1]
Universidade de São Paulo Faculdade de Medicina - Unidade Clínica de Miocardiopatias e Doenças da Aorta,[1] São Paulo, SP - Brazil

We currently live in an extremely competitive and individualistic society, which makes mistakes and defects more apparent. The health pandemic, in addition to the endemics of corruption in politics and the social fabric, has led us to a perfect storm. Its damage is difficult to solve, as several factors are chronic, ingrained, almost atavistic, and are present in all segments of society. The solution is called education. As Paulo Freire says, educated and respected, but criticized by the uneducated, education changes individuals, making them evolve. These change society. It is, therefore, a long-term project.[1-3]

As I have commented in several articles in the press, we have human resources of high moral and intellectual level. However, with the current political system, malignant, consisting of corporatism and solid physiologisms, which dispute, command, and disengage, evolution is blocked. This criminal system removes most of the well-meaning people from the scene. Some manage to win by overcoming obstacles. Moreover, they make history. In addition, they leave positive marks, making us more educated and prepared to carry out their teachings. Quality is recognized by the heirs, carrying out the good school. InCor is an example to be followed; it has been recently qualified as one of the best public hospitals in the world. It is a source of pride for our country.

In Medicine, which is my field, I found the best and the worst, referring to the human being. When the unrestrained search for prestige and money occupies the minds of people who are morally weak, bad examples emerge. This disease is increasing in my profession, following in the footsteps of other sectors of society. The word character is gradually being eroded. However, with optimism, let us remember those who followed Paulo Freire's booklet, training and educating in the right way, leading our Medicine to international recognition. I had memorable examples, which marked my education, giving lessons of humility and wisdom. They did not chase spotlights, as the profession was an end, not a means. I take the liberty of naming some, with whom I had a direct relationship.

At the beginning of my course, in 1965, at the School of Medicine of USP, I was a student of Odorico Machado de Sousa, always present, who could transform the difficult anatomy course into something pleasurable. He and his team remained with us daily, ready to answer any questions. He was demanding, and taught us to see the subject constructively, valuing it, and relating it to other subjects. He turned rejection into learning. So, he raised us. In my fourth year, I met Luiz Décourt and Euryclides de Jesus Zerbini, academics in the exact definition of the word. They went to international school, had had countless disciples, who became leaders in their places of origin, and in our university. They made a point of personally teaching, remaining Socratically close to the students. The primary purpose was college. They built InCor with their teams, educated by them, and further raised the concept of USP. They left a revered heritage to this day. They were real professors, with a capital P. Their students are proud to have been their disciples.

Décourt was succeeded by Fulvio Pileggi, who dedicated all his prestige and political strength to further aggrandize InCor. With a demanding character, he personally requested donations from society, because public funds were insufficient to carry out his project. He stimulated care, teaching and research, knowing that these were the determinants of academic quality. He personally pursued results, with constant presence in InCor. He left the door always open. His stiffness hid a heart unable to hold sorrows. Macruz and Tranchesi, also disciples of Décourt, were his collaborators, academics of the highest level, who also taught us a lot. Today, his heirs are up to the masters.[4]

On trips around this country, I had the opportunity to meet university centers that impressed me by the enormous cultural potential. The late Prof. Pareto, from the Fluminense Federal University, was an example of humility and wisdom, and marked me a lot. He went to school, teaching to see, listen, and humanely understand the patient, with tests and screens. He educated brilliant heirs who succeeded him. The master is recognized for his products.

How many more, little known, and often undervalued, scattered around? We have to learn to recognize values and merits. These few examples serve to show that we can have a better future with political will, starting from educated and determined leaders. The masters in all subjects are there, in the difficult task of educating. Relieving obstacles. Let them show their values. We have to learn to recognize them and cultivate them. As I say, anyone who does not worship the Masters will never be a Master.

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Emerging Topics Update of the Brazilian Heart Failure Guideline – 2021

Development: Department of Heart Failure (Departamento de Insuficiência Cardíaca – DEIC) of the Brazilian Society of Cardiology (Sociedade Braziliera de Cardiologia – SBC)

Norms and Guidelines Council (2020-2021): Antonio Carlos Sobral Sousa, Aurora Felice Castro Issa, Bruno Ramos Nascimento, Harry Corrêa Filho, Marcelo Luiz Campos Vieira

Norms and Guidelines Coordinator (2020-2021): Brivaldo Markman Filho

Update Authors: Fabiana G. Marcondes-Braga,[1] Lídia Ana Zytynski Moura,[2] Victor Sarli Issa,[3] Jefferson Luis Vieira,[4] Luis Eduardo Rohde,[5,6,7] Marcus Vinícius Simões,[8] Miguel Morita Fernandes-Silva,[9,10] Salvador Rassi,[11] Silvia Marinho Martins Alves,[12,13] Denilson Campos de Albuquerque,[14] Dirceu Rodrigues de Almeida,[15] Edimar Alcides Bocchi,[1] Felix José Alvarez Ramires,[1,17] Fernando Bacal,[1] João Manoel Rossi Neto,[18] Luiz Claudio Danzmann,[19,20] Marcelo Westerlund Montera,[21] Mucio Tavares de Oliveira Junior,[1] Nadine Clausell,[5] Odilson Marcos Silvestre,[22] Reinaldo Bulgarelli Bestetti,[23] Sabrina Bernadez-Pereira,[16] Aguinaldo F. Freitas Jr,[11] Andréia Biolo,[5] Antonio Carlos Pereira Barretto,[1] Antônio José Lagoeiro Jorge,[24] Bruno Biselli,[1] Carlos Eduardo Lucena Montenegro,[12,13] Edval Gomes dos Santos Júnior,[25,26] Estêvão Lanna Figueiredo,[27,28] Fábio Fernandes,[1] Fabio Serra Silveira,[29,30] Fernando Antibas Atik,[31] Flávio de Souza Brito,[32] Germano Emílio Conceição Souza,[33,34] Gustavo Calado de Aguiar Ribeiro,[35] Humberto Villacorta,[24] João David de Souza Neto,[4] Livia Adams Goldraich,[5] Luís Beck-da-Silva,[5,7] Manoel Fernandes Canesin,[36] Marcelo Imbroinise Bittencourt,[14,37] Marcely Gimenes Bonatto,[38] Maria da Consolação Vieira Moreira,[39] Mônica Samuel Avila,[1] Otavio Rizzi Coelho Filho,[40] Pedro Vellosa Schwartzmann,[41,42] Ricardo Mourilhe-Rocha,[14] Sandrigo Mangini,[1] Silvia Moreira Ayub Ferreira,[1] José Albuquerque de Figueiredo Neto,[43] Evandro Tinoco Mesquita[24,44]

Instituto do Coração (InCor) do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (HCFMUSP),[1] São Paulo, SP – Brazil
Pontifícia Universidade Católica de Curitiba,[2] Curitiba, PR – Brazil
Universidade da Antuérpia,[3] – Belgium
Hospital do Coração de Messejana Dr. Carlos Alberto Studart Gomes,[4] Fortaleza, CE – Brazil
Hospital de Clínicas de Porto Alegre,[5] Porto Alege, RS – Brazil
Hospital Moinhos de Vento,[6] Porto Alegre, RS – Brazil
Universidade Federal do Rio Grande do Sul (UFRGS),[7] Porto Alegre, RS – Brazil
Faculdade de Medicina de Ribeirão Preto da Universidade de São Paulo,[8] São Paulo, SP – Brazil
Universidade Federal do Paraná (UFPR),[9] Curitiba, PR – Brazil
Quanta Diagnóstico por Imagem,[10] Curitiba, PR – Brazil
Hospital das Clínicas da Universidade Federal de Goiás (UFGO),[11] Goiânia, GO – Brazil
Pronto Socorro Cardiológico de Pernambuco (PROCAPE),[12] Recife, PE – Brazil
Universidade de Pernambuco (UPE),[13] Recife, PE – Brazil
Universidade do Estado do Rio de Janeiro (UERJ),[14] Rio de Janeiro, RJ – Brazil
Universidade Federal de São Paulo (UNIFESP),[15] São Paulo, SP – Brazil
Hospital de Coração (HCor),[16] São Paulo, SP – Brazil
Hospital Israelita Albert Einstein,[17] São Paulo, SP – Brazil
Instituto Dante Pazzanese de Cardiologia,[18] São Paulo, SP – Brazil
Universidade Luterana do Brazil,[19] Canoas, RS – Brazil
Hospital São Lucas da PUC-RS,[20] Porto Alegre, RS – Brazil
Hospital Pró-Cardíaco,[21] Rio de Janeiro, RJ – Brazil
Universidade Federal do Acre,[22] Rio Branco, AC – Brazil
Departamento de Medicina da Universidade de Ribeirão Preto (UNAERP),[23] Ribeirão Preto, SP – Brazil
Faculdade de Medicina da Universidade Federal Fluminense (UFF),[24] Niterói, RJ – Brazil
Universidade Estadual de Feira de Santana,[25] Feira de Santana, BA – Brazil
Santa Casa de Misericórdia de Feira de Santana,[26] Feira de Santana, BA – Brazil
Instituto Orizonti,[27] Belo Horizonte, MG – Brazil

Hospital Vera Cruz,[28] Belo Horizonte, MG – Brazil
Fundação Beneficência Hospital de Cirurgia (FBHC-Ebserh),[29] Aracaju, SE – Brazil
Centro de Pesquisa Clínica do Coração,[30] Aracaju, SE – Brazil
Universidade de Brasília (UnB),[31] Brasília, DF – Brazil
Universidade Estadual Paulista Júlio de Mesquita Filho (UNESP),[32] São Paulo, SP – Brazil
Hospital Alemão Oswaldo Cruz,[33] São Paulo, SP – Brazil
Hospital Regional de São José dos Campos,[34] São Paulo, SP – Brazil
Pontifícia Universidade Católica de Campinas (PUCC),[35] Campinas, SP – Brazil
Hospital Universitário da Universidade Estadual de Londrina,[36] Londrina, PR – Brazil
Hospital Universitário Pedro Ernesto,[37] Rio de Janeiro, RJ – Brazil
Hospital Santa Casa de Misericórdia de Curitiba,[38] Curitiba, PR – Brazil
Universidade Federal de Minas Gerais (UFMG),[39] Belo Horizonte, MG – Brazil
Faculdade de Ciências Médicas da Universidade Estadual de Campinas (UNICAMP),[40] Campinas, SP – Brazil
Hospital Unimed Ribeirão Preto,[41] Ribeirão Preto, SP – Brazil
Centro Avançado de Pesquisa, Ensino e Diagnóstico (CAPED),[42] Ribeirão Preto, SP – Brazil
Universidade Federal do Maranhão (UFMA),[43] São Luís, MA – Brazil
Centro de Ensino e Treinamento Edson de Godoy Bueno / UHG,[44] Rio de Janeiro, RJ – Brazil

Note: These updates are for information purposes and should not replace the clinical judgment of a physician, who must ultimately determine the appropriate treatment for each patient.

Correspondence: Sociedade Brazileira de Cardiologia – Av. Marechal Câmara, 360/330 – Centro – Rio de Janeiro – Posta Code: 20020-907. E-mail: diretrizes@cardiol.br

Update

Content

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Introduction

The latest Heart Failure Guidelines by the Department of Heart Failure of the Brazilian Society of Cardiology (DEIC/SBC) were finalized on March 2018. Since then, a significant number of therapeutic interventions and diagnostic approaches has arisen or consolidated their position in international clinical practice and in clinical research. In addition, the COVID-19 pandemic has taught us much about the pathophysiological model of myocardial damage and raised many questions about the continuity and safety of medication use in patients with chronic HF suffering from an acute manifestation of this new and complex clinical entity.

In the last few months, we have been working quickly and collaboratively, and for the first time in 20 years, DEIC used digital platforms to discuss, deliberate, and draft this important document, opting for a focused update instead of a full-text guideline.

We were inspired by the 2020 Canadian Heart Failure Guidelines,[1] but had the benefit of observing the impact on clinical practice and the consolidation of this new knowledge, in addition to new results from clinical trials published over the last 12 months. In order to report on these developments, we hosted a pioneering scientific conference on September 19, 2020, the I Heart Failure Summit Brazil 2020 (digital), with approximately 900 participants, many of them DEIC associates.

The leadership of the Science Board was key in organizing the various working groups and developing a secure and practical method for discussions and votes. With social distancing and the use of digital technology, the conference enabled wide-ranging debates from various perspectives, based on the best available scientific evidence.

In this document, DEIC/SBC provides reviews and detailed updates to its Chronic Heart Failure Guidelines. The work started in July 2020, with the choice of the Editorial Board, which established priorities, divided the 52 participants into working groups, and developed a schedule of activities. These working groups, each consisting of five to seven participants, began intense online discussions that led to the elaboration of preliminary tables, widely circulated before their subsequent review by the 11-member Review Board. The final discussions took place during a virtual plenary session on December 4, 2020, with all collaborators, who had the opportunity to vote on the main recommendations. Decisions regarding classes of recommendation required a three-quarters supermajority vote.

Class of Recommendation and Level of Evidence follow the same definitions used in the last guideline, as established by SBC/CONDir. See below.

The therapeutic recommendations proposed in this document are based on the latest available scientific evidence, considering not only the aspects of clinical efficacy from large clinical trials. We have sought to summarize the primary recommendations in flowcharts and algorithms that are easy to understand and to apply in clinical practice, proposing approaches for the diagnosis and treatment of heart failure.

Our commitment to the scientific community, linked to research and assistance to heart failure patients, public and private managers, and policy-makers, will certainly have the benefit of

Classes of Recommendation
Class I
Conditions for which there is conclusive evidence or, if not, there is general agreement that the procedure is safe and useful/effective.
Class II
Conditions for which there is conflicting evidence and/or divergence of opinion about the safety and usefulness/efficacy of the procedure.
Class IIA
Weight or evidence/opinion in favor of the intervention. Most approve.
Class IIB
Less well-established safety and usefulness/efficacy, without predominance.
Class III
Conditions for which there is evidence and/or general agreement that the procedure is not useful/effective, and in some cases may be harmful.
Levels of Evidence
Level A
Data derived from multiple consistent randomized controlled clinical trials, and/or a robust meta-analysis of randomized clinical trials.
Level B
Data derived from a less robust meta-analysis, one single randomized trial or non-randomized trials (observational).
Level C
Data derived from consensual expert opinion.

a document that sought to present scientific interventions in an accessible format, facilitating its implementation in the various spheres where heart failure patients receive care.

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Dr. Evandro Tinoco Mesquita
</div>

1. Innovations in Heart Failure with Preserved (HFpEF), Mildly Reduced (HFmrEF) and Improved (HFimpEF) Ejection Fraction

1.1. Diagnosis of Heart Failure with Preserved Ejection Fraction (HFpEF)

In patients with unexplained fatigue or dyspnea, assessing the pretest probability of heart failure (HF) should be based on clinical, electrocardiography, echocardiography, and laboratory data. Next, two scoring systems have been developed to check that diagnosis; both the H_2FPEF (Table 1.1) and the HFA-PEFF (Table 1.2) scores may be used. In these models, high- and low-probability patients can be classified as having or not heart failure with preserved ejection fraction (HFpEF), respectively. In patients with intermediary probability for HFpEF, assessing diastolic function during stress, which can be based on a diastolic stress echocardiogram or invasive hemodynamic monitoring, can help the diagnosis. In patients with low probability of HFpEF, investigating other causes of dyspnea and fatigue is recommended[2] (Figure 1.1 and Table 1.3).

Update
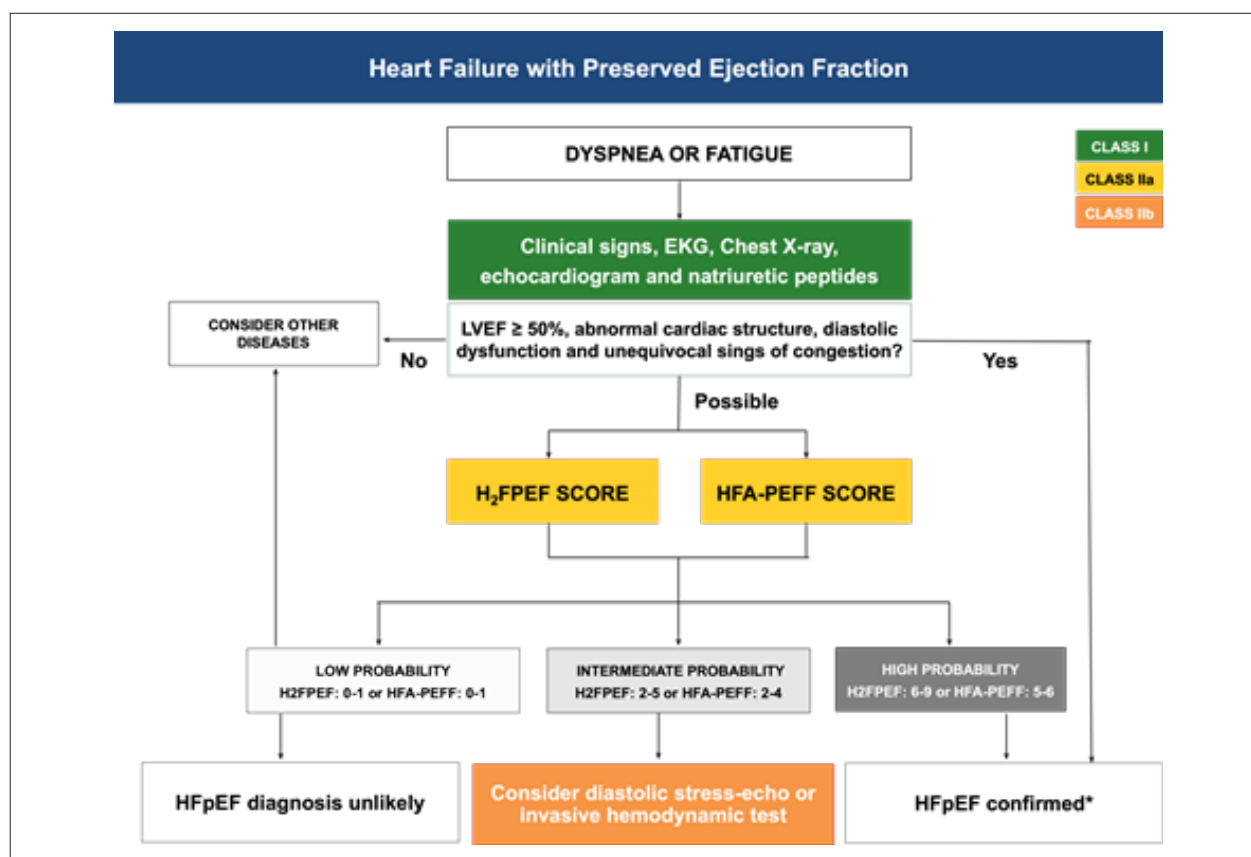
Figure 1.1 – *Diagnostic flowchart for heart failure with preserved ejection fraction (HFpEF)*
Adapted from Borlaug BA.2 Nat Rev Cardiol. 2020; 17:559-573. ECG: electrocardiogram; HF: heart failure; LVEF: left ventricular ejection fraction.

Tabela 1.1 – H$_2$FPEF score for HFpEF diagnosis

	Clinical Variable	Characteristics	Points
H$_2$	*Heavy*	BMI > 30 Kg/m^2	2
	Hypertension	2 or more anti-hypertensive drugs	1
F	Atrial **F**ibrillation	Paroxysmal or Persistent	3
P	**P**ulmonary Hypertension	PASP > 35 mmHg	1
E	**E**lderly	Age > 60 years	1
F	**F**illing Pressures	E/e´ > 9	1

Adapted from Reddy YNV et al.[5] Circulation. 2018; 138:861-870. BMI: body mass index; PASP: pulmonary artery systolic pressure.

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Table 1.2 – HFA PEFF score HFpEF diagnosis

DOMAIN	MAJOR CRITERIA (2 points)	MINOR CRITERIA (1 point)
FUNCTIONAL	e' septal < 7 or e' lateral < 10 or E/e' > 15 or RT velocity > 2.8 m/s (PSAP > 35 mmHg)	E/e': 9-14 or GLS < 16%
MORPHOLOGIC	LA Vol index > 34 mL/m² or LVMI > 149/122 g/m² (H/M) and RWT > 0.42	LA Vol index: 29 - 34 mL/m² or LVMI > 115/95 g/m² (H/M) or RWT > 0.42 or left ventricular wall thickness ≥ 12 mm
BIOMARKER (sinus rhythm)	NT-proBNP > 220 pg/mL or BNP > 80 pg/mL	NT-proBNP: 125 - 220 pg/mL or BNP 35 - 80 pg/mL
BIOMARKER (atrial fibrilation)	NT-proBNP > 660 pg/mL or BNP > 240 pg/mL	NT-proBNP: 365 - 660 pg/mL or BNP: 105 - 240 pg/mL

Adapted from Pieske B et al.[7] Heart Failure Association (HFA) of the European Society of Cardiology (ESC). Eur J Heart Fail. 2020; 22:391-412. BNP: B-type natriuretic peptide; GLS: global longitudinal systolic strain; LAVI: left atrial volume index; LV: left ventricular; m: men / w: women; NT-proBNP: N-terminal B-type natriuretic peptide; PW: posterior wall; RWT: relative wall thickness; TR velocity: tricuspid regurgitation velocity. BNP: B-type natriuretic peptide; GLS: global longitudinal systolic strain; LAVI: left atrial volume index; LV: left ventricular; m: men / w: women; NT-proBNP: N-terminal B-type natriuretic peptide; PW: posterior wall; RWT: relative wall thickness; TR velocity: tricuspid regurgitation velocity.

Table 1.3 – HFpEF diagnosis recommendations

Recommendations	Class	LE	Comments	Table 2018	Ref.
Natriuretic peptides for HFpEF screening.	I	B	**NEW:** The wide variation in serum levels of natriuretic peptides in this population and the conditions that modify its accuracy, such as atrial fibrillation and obesity, should be considered.	New	3, 4
Comprehensive echocardiogram for diagnosis confirmation.	I	B	**NEW:** Echocardiogram with presentation of Doppler indices to estimate pulmonary and diastolic pressures, as well as cardiac mass and volume indices indexed to body surface.	New	4, 5
H₂FPF or HFA PEFF diagnostic scores to improve diagnostic accuracy for suspected cases of HFpEF.	IIa	B	**NEW:** Scores validated using retrospective cohorts.	New	6-8
Assessment of diastolic function during stress by echocardiogram or invasive hemodynamic monitoring in cases of intermediate probability in the H2FPF or HFA PEFF scores.	IIb	B	**NEW:** Scores validated using retrospective cohorts.	New	9,10

The initial strategy for HFpEF diagnosis is to determine the pretest probability of HF through the use of clinical findings associated with supplementary tests, such as electrocardiograms, chest X-rays, echocardiograms, and natriuretic peptides, if available. When interpreting natriuretic peptide test results, it is important to consider there is a wide range of serum levels in this population and that, in the presence of atrial fibrillation (AF), higher thresholds need to be considered.[3,4] If HF is a plausible diagnosis, it is reasonable to apply H₂FPEF[5,6] and HFA PEFF[7] scores (the first with clinical and echocardiography data, the latter with comprehensive echocardiography and natriuretic peptide data), which have been validated in international populations[6,8] to determine high, intermediate and low probability. In patients with low probability of HFpEF, the objective pursuit of other etiologies for dyspnea is suggested. In individuals with intermediate probability, recent studies have shown that data on diastolic function during stress may identify patients with abnormal responses, representing a noninvasive (echocardiographic diastolic assessment) [9] or invasive (pulmonary artery catheter) diagnostic strategy.[10] The scoring systems above require comprehensive echocardiograms; in other words, the examination should provide information on diameters, left atrial volume, flow Doppler, tissue Doppler (septal and/or lateral e'), and, if possible, myocardial strain and strain rate data.[5]

AF: atrial fibrillation; HF: heart failure; HFpEF: heart failure with preserved ejection fraction

1.2. Treatment for Heart Failure with Preserved Ejection Fraction (HFpEF)

To date, there is no specific intervention to reduce cardiovascular events in patients with HFpEF. Clinical trials assessing the use of angiotensin-converting enzyme II inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), angiotensin II receptor-neprilysin inhibitors (ARNIs), and spironolactone were neutral in terms of risk reduction compared to placebo for patients with HFpEF.[11-14] Post-hoc analysis according to LV ejection fraction (LVEF) has consistently shown lack of benefit among subgroups with higher LVEF (above 50%). A meta-analysis of randomized controlled trials of beta-blockers provides similar findings.[13] Therefore, the 2018 guideline recommendations for pharmacological treatment of HFpEF stand, including the use of diuretics for congestion and the treatment of comorbidities such as myocardial ischemia, atrial fibrillation, and hypertension, to reduce symptoms and potentially reduce the progression of HFpEF.[15] Hence, it is essential to investigate potentially reversible conditions associated with 'secondary' HFpEF, such as infiltrative and restrictive cardiomyopathies, in addition to considering alternative causes of exercise intolerance.

Update

1.3. Treatment for Heart Failure with mildly reduced Ejection Fraction (HFmrEF) (Table 1.4)

Table 1.4 – HFmrEF treatment recommendations

Recommendations	Class	LE	Comments	Table 2018	Ref.
Bisoprolol, carvedilol or metoprolol succinate for HFmrEF patients in sinus rhythm to reduce morbidity and mortality.	IIa	A		New	13
ACEI or ARB to reduce morbidity and mortality	IIa	B	**NEW:** Currently available data indicate that the response of patients with HFmrEF to the treatment for HF is similar to that of patients with HFrEF.	New	11
Spironolactone to reduce morbidity and mortality	IIa	B		New	12
Sacubitril-valsartan, instead of ACEI (or ARB), for symptomatic patients using guideline-directed medical therapy (GDMT) including triple therapy to reduce hospitalization.	IIa	B		New	14

Despite the absence of studies assessing therapeutic interventions directed specifically to patients with heart failure with mildly reduced ejection fraction (HFmrEF), secondary analyses of clinical trials with patients with HFrEF and HFpEF indicate HFmrEF patients (LVEF 41-49%) may benefit from interventions currently indicated for HFrEF patients (LVEF ≤ 40%). A meta-analysis of 11 randomized controlled trials found beta-blockers are associated with lower mortality in patients with HFmrEF and in sinus rhythm.[13] A subanalysis of the TOPCAT trial identified the beneficial effect of spironolactone for cardiovascular mortality in patients with LVEF ranging between 44 and 50 percent;[12] a subanalysis of the CHARM trial found benefits from candesartan on combined endpoints of cardiovascular mortality and hospitalization for patients with LVEF from 40 to 49%.[11] The combined analysis of the *PARAGON-HF (Angiotensin–Neprilysin Inhibition in Heart Failure with Preserved Ejection Fraction)* and *PARADIGM-HF (Prospective Comparison of ARNi with ACE-I to Determine Impact on Global Mortality and Morbidity in Heart Failure)* trials suggest that sacubitril-valsartan is associated with lower hospitalizations for mildly reduced LVEF levels, and that the effect is more intense for female patients with higher LVEF levels.[14]

ACEI: angiotensin-converting enzyme inhibitors; ARB: angiotensin recepter blockers; HFpEF: heart failure with preserved ejection fraction;[15] HFmrEF: heart failure with mildly reduced ejection fraction; HFrEF: heart failure with reduced ejection fraction; LVEF: left ventricular ejection fraction.

1.4 Treatment for Heart Failure with Improved Ejection Fraction (HFimpEF) (Table 1.5)

Table 1.5 – HFimpEF treatment recommendations

Recommendations	Class	LE	Comments	Table 2018	Ref.
Continuing disease-modifying drug therapy used in treating HFrEF in improved dilated cardiomyopathy.	I	B	**NEW:** Indication supported by a randomized multicenter trial with limited sample and surrogate endpoints.	New	16

Advancements in the treatment of HF with reduced ejection fraction (HFrEF) has led to improved left ventricular ejection fraction (LVEF) and a reduction in left ventricle size of about 40 percent in patients, depending on etiology.[17] In that setting, the 2013 ACC/AHA guideline for the management of HF created the term "HF with improved or recovered LVEF," establishing a new classification for patients with prior HFrEF who improved their LVEF at rates above 40%.[18] More recently, Halliday BP et al.[16] tested the safety of withdrawing HF medication in a small group of patients with recovered dilated cardiomyopathy in an unblinded but randomized and multicenter pilot trial. The inclusion criteria were: prior diagnosis of dilated cardiomyopathy with LVEF 40 percent or lower; absence of heart failure symptoms; treatment with loop diuretics and disease-modifying drug therapy; current LVEF of 50% or greater; left ventricular end diastolic volume indexed to normal body surface and NT-proBNP below 250 pg/mL. Patients were randomly assigned to the medication withdrawal group for 6 months and the primary endpoint was a combination of a reduction in LVEF, LV dilation, and return of HF symptoms. After 6 months of follow-up, 44% of patients assigned to the treatment withdrawal group met some of the criteria of the primary endpoint, compared to no members of the treatment continuation group, recording a 45.7% estimated event rate (95% CI 28.5–67.2; p = 0.0001). Despite a small sample size and a suboptimal design, this is the best evidence available in the HFimpEF population, suggesting that continuation of drugs in this context is the best strategy, at least until the publication of a more robust study.

This guideline uses the denominations and definitions according to the new universal classification of heart failure.[18] HFrEF: heart failure with reduced ejection fraction; LVEF: left ventricular ejection fraction; NT-proBNP: N-terminal portion of B-type natriuretic peptide.

2. Innovations in Cardiac Amyloidosis

We have recently seen great advances in cardiac amyloidosis, with a profound transformation of its clinical and epidemiological significance and the development of specific treatments. Evidence suggests that cardiac amyloidosis is not a rare disease, but rather a largely underdiagnosed condition, now considered a relatively common and treatable cause of HFpEF, particularly transthyretin amyloidosis (ATTR) in its wild type (ATTR-wt), of which diagnosis has increased expressively.[19-22]

It is a multisystemic disease caused by the tissue deposition of insoluble fibrillary proteins that lose their conformation, leading to organ dysfunction, including the heart. Over 30 types of amyloidogenic proteins have been described,[23] with two of them responsible for 95% of all cases of cardiac involvement: light-chain amyloidosis (AL), related to monoclonal production of immunoglobulins due to plasma cell dyscrasias; and transthyretin amyloidosis (ATTR), caused by misfolded transthyretin, a plasma protein that transports thyroxine and retinol and is secreted mainly by the liver. ATTR can be secondary to an abnormal (mutant or variant) protein (ATTRm) or to the wild-type form (ATTRwt), caused by post-transcriptional modification or by chaperone-related mechanisms, both associated with aging.

AL incidence ranges from 6 to 10 million people/year and, until recently, was considered the primary cause of cardiac amyloidosis.[24] However, with the development of noninvasive diagnosis techniques and effective treatment, the diagnosis of ATTR, especially of ATTRwt, has increased significantly.[19] Studies demonstrate ATTR in up to 13% of patients with HFpEF and left ventricular wall thickening greater than 12 mm,[20] with up to 25% of necropsies of very elderly people showing TTR in the heart.[22] ATTRm is an autosomal dominant condition, with more than 130 mutations described and several phenotypes of neurological and cardiac impairment.

2.1. When to Suspect Amyloidosis

Considering that ATTR, particularly ATTRwt, is more prevalent than previously expected, it is important to suspect it in the presence of clinical clues for further diagnostic investigation (Table 2.1). ATTR commonly manifests as infiltrative restrictive cardiomyopathy, with ventricular wall thickening, diastolic dysfunction, and conduction disorders. In certain clinical contexts, a differential diagnosis with hypertrophic cardiomyopathy, HFpEF[25], advanced atrioventricular blocks and atrial arrhythmias with no apparent cause are necessary. The simultaneous finding of ATTRwt and calcific aortic stenosis may cause severe ventricular hypertrophy and can present as low-flow, low-gradient aortic stenosis. In addition, some multisystemic manifestations may raise suspicion of ATTR: bilateral carpal tunnel syndrome, biceps tendon rupture, orthostatic hypotension, spinal canal stenosis, digestive problems, and intolerance to antihypertensive medications.[26] Family history is very important in the hereditary forms of amyloidosis, carrying a worse prognosis than the wild-type form.

2.2. Cardiac Amyloidosis Diagnosis (Table 2.1)

When suspected, the first step in investigating cardiac amyloidosis is the search for the presence of immunoglobulin light chains for the diagnosis of AL, which requires specific treatment with chemotherapeutic agents and has a worse prognosis with delayed treatment initiation. Confirmation of AL depends on the detection of amyloid protein in the tissues involved (biopsy), but the ATTR form can be confirmed noninvasively, using cardiac scintigraphy with bone-avid radiotracers. In Brazil, Tc-99m pyrophosphate is used in the examination.

Update

Table 2.1 – Clinical clues for amyloidosis diagnosis

History and physical examination
HFpEF, particularly in elderly men (over 65)
Intolerance to ACEI/ARB/ARNI and/or beta-blockers
Bilateral carpal tunnel syndrome
Spinal canal stenosis
Rupture of the biceps tendon
Unexplained peripheral neuropathy, particularly when associated with autonomic dysfunction
Periorbital ecchymosis
Macroglossia
Clues from Imaging Examinations and Laboratory Tests
Grade 2-3 myocardial uptake in Tc-99m pyrophosphate scintigraphy
Infiltrative phenotype on echocardiogram, with biventricular hypertrophy, pericardial effusion, valve thickening, and interatrial septum thickening
Longitudinal strain rate reduction that spares the apical region (apical sparing)
Restrictive abnormality of ventricular filling with right ventricular wall thickening
Cardiac magnetic resonance imaging showing late gadolinium enhancement with diffuse subendocardial or transmural pattern, increased extracellular volume
Proteinuria
Combined Clues
Heart failure with unexplained LV wall thickening and a nondilated ventricular cavity (intraventricular septum larger than 12 mm)
Concentric left ventricular hypertrophy with reduced or non-increased QRS amplitude proportional to degree of LV wall thickening
Reduced longitudinal left ventricular systolic function despite normal LVEF
Aortic stenosis with right ventricular wall thickening, particularly in paradoxical low-flow, low-gradient cases

ACEI: angiotensin-converting enzyme II inhibitors; ARB: angiotensin II receptor blockers; ARNI: angiotensin II receptor-neprilysin inhibitors; HFpEF: heart failure with preserved ejection fraction; LV: left ventricular; LVEF: left ventricular ejection fraction.

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2.3. Diagnostic Methods

2.3.1. Electrocardiogram

A low-amplitude QRS complex is a frequent finding in AL, but less prevalent in ATTR (around 30% of cases), that more commonly presents discrepancy between the magnitude of the hypertrophy on the echocardiogram and the amplitude of QRS complexes is more frequent. Atrial fibrillation and a "pseudo-infarction" pattern may also be found.

2.3.2. Echocardiogram

Echocardiogram is the most important exam to raise the suspicion of CA. Suggestive findings include left ventricular wall thickening greater than 12 mm, especially in the absence of hypertension, bi-atrial enlargement disproportionate to ventricle size, atrioventricular valve and interatrial septum thickening, and increased myocardial echogenicity with a granular aspect. Myocardial longitudinal systolic strain rates may show the preservation of left ventricular apical contractility as compared to the remaining segments (apical sparing or "cherry on top" pattern) as compared to the reduced contractility in the remaining segments.[27]

2.3.3. Cardiac Scintigraphy with Bone-Avid Radiotracers

Cardiac scintigraphy with bone-avid radiotracers, such as Tc-99m pyrophosphate as used in Brazil, can be used for the differential diagnosis between amyloidosis AL and ATTR, with the latter showing anomalous myocardial uptake, higher than or equivalent to bone uptake. However, cardiac uptake may occur, albeit with milder intensity, in up to 30% of AL cases. The combination of intense cardiac uptake (grades 2 or 3) and the absence of light chains in biochemical exams presents 100% specificity for ATTR, and can obviate a cardiac biopsy for the diagnosis of the disease.[19]

2.3.4. Cardiac Magnetic Resonance Imaging

Cardiac magnetic resonance imaging has high sensitivity and specificity for the diagnosis and discrimination between cardiac amyloidosis and other cardiomyopathies. Amyloid deposits in the myocardium cause an increase in the distribution volume of paramagnetic contrast agent in myocardial regions where cardiomyocytes are replaced or displaced by inflammation or fibrosis, originating a diffuse subendocardial and circumferential late enhancement pattern of the left ventricle; a diffuse transmural pattern can also be found.[27]

2.4. Treatment of Cardiac Transthyretin Amyloidosis (ATTR-CA) (Table 2.2)

Table 2.2 – Recommendations for specific treatment for cardiac transthyretin amyloidosis (ATTR-CA)

Recommendation	Class	LE	Comment	Table 2018	Ref.
Tafamidis 80 mg/day for treatment of patients with cardiac transthyretin amyloidosis patients in order to reduce mortality and cardiovascular hospitalizations.	I	B	**NEW:** A multicenter randomized clinical trial supports the recommendation.	New	28

Several steps of amiloid fibers formation constitute therapeutic targets in transthyretin amyloidosis (ATTR). The first disease-modifying therapy to show any evidence of benefit in patients with amyloid cardiomyopathy is tafamidis, a TTR tetramer stabilizer. Tafamidis was tested in a multicenter, placebo-controlled, randomized trial involving 441 patients with cardiac amyloidosis patients, of which 264 were assigned to receive tafamidis at doses of 20 mg or 80 mg daily (*ATTR-ACT [Tafamidis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy] study*).[28] The primary results showed that the use of tafamidis was associated with a 30% reduction in all-cause mortality (RR = 0.70 [95% CI: 0.51-0.96]) and 32% reduction of cardiovascular-related hospitalizations (RR = 0.68 [95% CI: 0.56 -0.81]), in addition to reduced worsening of functional capacity and quality of life. Based on these results, tafamidis was approved by ANVISA in Brazil for treatment of CA-ATTR, at a dose of 80 mg / day.[28]

ATTR: transthyretin amyloidosis; RR: relative risk

Given its clinical and epidemiological importance, in addition to new emerging therapies for the condition, a Position Paper on Diagnosis and Treatment of Cardiac Amyloidosis will be published shortly, and should review the different aspects of the disease more broadly.

Update

3. Innovations in Telemonitoring for Heart Failure (Table 3.1)

Table 3.1 – Recommendations for telemonitoring, wearables, artificial intelligence, and machine learning in heart failure

Recommendations	Class	LE	Comment	Table 2018	Ref.
Use of telemonitoring to manage patients with chronic HF.	IIa	A	NEW: Meta-analyses show reduction in mortality rates and in hospitalizations for HF.	New	29-32
Wearables as complementary tools in the diagnosis and treatment of patients with chronic or acute HF.	IIa	B	NEW: Several observational studies show the benefits of wearables use for HF patients.	New	33, 34
Artificial intelligence use in the diagnosis, prognostic assessment, or selection of patients who can most benefit from different therapies.	IIb	B	NEW: Observational studies indicate the benefits of using Machine Learning and Artificial Intelligence in the diagnosis and prognosis of HF.	New	35

Meta-analyses involving observational and randomized trials on invasive and noninvasive distance monitoring and support has found a positive impact on the prognosis for HF patients.[29-32] Reductions in all-cause mortality may range from 19 to 31% with telemonitoring for HF patients, while the reduction in frequency of hospitalizations for HF ranges from 27 to 39%, especially for patients in functional class (FC) III/IV, according to the New York Heart Association (NYHA). Artificial intelligence has applications in HF, either for diagnosis, prognostic assessment, telemonitoring or selection of patients who can most benefit from various therapies.[33,34] This is possible, for instance, in distinguishing phenotypes, assigning patients in different signature profiles; more accurate diagnosis of acute HF as compared to physicians; and also helping in referral for new or established therapies, such as additional analysis of baseline ECG to identify patients who would better respond to cardiac resynchronization therapy.[35]

FC: functional class; HF: heart failure.

4. Innovations in Cardiac Interventions

4.1. Percutaneous Intervention in Secondary Mitral Insufficiency (Table 4.1)

Table 4.1 – Recommendations for percutaneous interventions in severe secondary mitral insufficiency

Recommendation	Class	LE	Comments	Table 2018	Ref.
Percutaneous mitral valve clipping					
Ischemic or dilated					
Refractory symptoms (NYHA II-IV), despite guideline-directed medical therapy and after Heart Team evaluation.	IIa	B	**NEW:** Recommendation supported by a randomized trial with mortality endpoint.	Item 11.3 (page 467)	36

We recommend optimization of guideline-directed medical therapy (GDMT), including cardiac resynchronization therapy and revascularization, when appropriate, before considering percutaneous mitral insufficiency (MI) treatment for patients with HFrEF and severe MI. The *COAPT (Transcatheter Mitral-Valve Repair in Patients with Heart Failure)* trial assessed whether the edge-to-edge device might benefit patients with moderately severe or severe secondary MI (EROA greater than or equal to 30 mm^2 and/or regurgitation volume greater than 45 mL) with LVEF 20 to 50%, LV end-systolic diameter smaller than 7 cm and persistent symptoms, despite maximized evidence-based therapy.[36] The 2020 Valve Disease Guidelines overlooks this distinction when selecting patients. In order to maintain linearity between the Guidelines, it remains as established in the 2020 Valve Disease Guidelines.[37]

HF: heart failure; HFrEF: heart failure with reduced ejection fraction; LV: left ventricle; LVEF: left ventricular ejection fraction; MI: mitral insufficiency.

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4.2. Atrial Fibrillation Ablation (Table 4.2)

Table 4.2 – Recommendations for atrial fibrillation ablation in HFrEF

Recommendation	Class	LE	Comments	Table 2018	Ref.
AF ablation to reestablish sinus rhythm in symptomatic patients, intolerant or refractory to antiarrhythmic medications to reduce mortality and hospitalizations for HF.	IIa	B	2018 recommendation remains current.	Item 10.1 (page 465)	See 2018
AF ablation as an alternative to clinical treatment for selected patients with symptomatic persistent AF refractory or intolerant to at least one antiarrhythmic medication.	I	A	**NEW:** Randomized trials have shown a higher rate of success in sustaining a sinus rhythm with AF ablation, without antiarrhythmic medications side effects.	Item 10.1 (page 465)	38-43
AF ablation to promote reverse remodeling in patients with AF-induced tachycardiomyopathy if refractory to pharmacological treatment or if patient chooses ablation, regardless of symptoms.	I	B	**NEW:** A randomized trial showed AF ablation can promote reverse remodeling in patients with tachycardiomyopathy.	Item 10.1 (page 465)	39-44

In patients with HF, AF ablation is superior to medical treatment, as it is associated with improved maintenance of sinus rhythm, functional capacity and quality of life (6-minute walk test, VO_2 max), in addition to greater reduction in biomarkers (BNP). It can be considered for selected patients with symptomatic persistent AF refractory or intolerant to at least one antiarrhythmic medication or even as initial therapy.[38-43] Reverse remodeling was observed in several AF ablation trials, leading to increased LVEF.[38-42,44] When the HF etiology is unknown and AF-induced tachycardiomyopathy is considered as a possible etiology, the expected increase in LVEF after ablation is even more significant.[39,44] Studies demonstrated a reduction of 45% in hospitalizations for HF, 47/56% in all-cause mortality and 38% in mortality or hospitalization for HF.[41,42,44] However, AF ablation success rates range from 60 to 80% in the first year and structural heart disease is a major risk factor for recurrence.[45] Pulmonary vein isolation can be done by radiofrequency or cryoablation, and these techniques may be combined with the ablation of other substrates.

AF: atrial fibrillation; FC: functional class; HF: heart failure.

5. COVID-19 and Heart Failure (Table 5.1)

Table 5.1 – Recommendations for COVID-19 management in heart failure patients

Recommendation	Class	LE	Comments	Table 2018	Ref.
RT-PCR testing for SARS-CoV-2 in individuals with chronic HF and acute respiratory symptoms.	I	C	**NEW:** Editorials and society recommendations (online publication).	New	46,47
ACEI, ARB or ARNI maintenance in HF patients who develop COVID-19, in the absence of hypotension or other signs of hemodynamic impairment.	I	C	**NEW:** Controlled observational studies with large numbers of participants, but a smaller number of HF patients.	New	48-50
Outpatient follow-up of HF through remote appointments (telemedicine and telemonitoring) during the COVID-19 pandemic.	I	C	**NEW:** Experts and Society recommendations	New	51,52

Considering COVID-19 symptoms can simulate decompensated HF, RT-PCR testing for SARS-CoV-2 is recommended for patients seeking medical care in the emergency department or outpatient clinic setting.[46,47] There is no evidence for routine discontinuation of ACE inhibitors, ARBs or ARNI in patients with symptomatic HF diagnosed with COVID-19. Decisions to add or remove these medications should be guided by standard clinical practice, and individualized treatment decisions should be made according to each patient's hemodynamic status and clinical presentation.[48-50] Online and/or remote tools (phone calls, telemonitoring, online appointments, and video calls, among others) may be used to keep continuous care for HF patients during the COVID-19 pandemic. These actions that are useful to reduce patients' virus exposure, has being effective for usual care, and are expected to endure in the post-pandemic world. For patients with clinical instability (post-discharge for HF decompensation or recent-onset HF) and candidates for advanced HF therapies (transplantation or ventricular assistant devices), we recommend at least one in-person appointment, in between virtual visits, especially considering the pandemic tends to decrease the number of transplants performed, and to increase the waiting-list period of time.[51,52]

ACEI: angiotensin-converting enzyme II inhibitors; ARB: angiotensin II receptor blocker; ARNI: angiotensin II receptor-neprilysin inhibitor; HF: heart failure.

6. Innovations in Advanced Heart Failure

6.1. Definition of Advanced Heart Failure

The natural history of HF is characterized by a progressive deterioration of cardiac function and HF symptoms. Despite advances in pharmacological treatment and the prognostic impact of implantable devices such as cardiac resynchronization therapy, HF patients may progress to a clinical condition known as advanced HF, where traditional treatment is not effective and advanced therapies are required, such as heart transplantation, mechanical circulatory support device (MCSD) or palliative care are required.

Although the expression advanced HF has been used since 2007, recent updates were described to include clinical situation that may also require advanced therapies such as HFpEF patients with severe restrictive condition, rather than limiting it to patients with HF with severely reduced ejection fraction.[1-3,4] In this scenario, isolated severe right ventricular dysfunction and severe inoperable valvular disease as well as congenital abnormalities may also be considered causes of severe cardiac dysfunction (Table 6.1). [53-68]

Different societies of cardiology adopt different criteria for the condition, but all of them include the presence of persistent severe symptoms, exercise intolerance, and recurrent episodes of systemic or pulmonary congestion requiring hospitalization, as described in Table 6.2.

Early recognition is decisive for the prognosis of patients with advanced HF, since it allows timely referral to a specialized center able to provide the necessary advanced therapies to manage such cases.

A particularly useful mnemonic that may help identify patients requiring referral to a HF specialist is I-NEED-HELP, which combines clinical history, hospitalizations and intolerance to medications, as well as symptoms and end-organ dysfunction. (Table 6.3)

6.2. The Role of the Specialist in Advanced Heart Failure

As the specific profile of patients fitting the current definition of advanced HF becomes increasingly clear, there is also a need to define the importance of the specialist in advanced HF in specialized centers. These professionals must be familiar (and trained) in the care of potential heart transplant candidates and their subsequent follow-up, as well as in patients with CS. They should coordinate the work of the shock team and therefore must be familiar with the diverse and growing options for circulatory support. Finally, the advanced HF specialist should be able to understand the timing and implications of discussing palliative care and advanced directives for patients who are not eligible for heart transplantation, as well as the use of long-term devices.

Table 6.1 – Criteria for the definition of advanced heart failure

Criteria for advanced HF
1. Persistent and severe HF symptoms (NYHA III or IV).
2. Severe ventricular dysfunction defined by: • LVEF ≤ 30% or • Isolated right HF or • Severe inoperable valvular alterations or • Congenital abnormalities Persistently elevated BNP or NT-proBNP levels and data showing severe diastolic dysfunction or structural LV abnormalities, according to the criteria for HFpEF or HFmrEF.
3. Episodes of systemic or pulmonary congestion requiring high doses of intravenous diuretics (or combinations of diuretics) or episodes of low cardiac output requiring the use of inotropes or vasoactive medications or malignant arrhythmias causing more than one unplanned visit to the emergency department or hospitalization in the last 12 months.
4. Severely reduced physical exercise capacity, with inability to perform or low capacity in the 6-minute walk test (6MWT < 300 m) or VO$_2$ peak (< 12-14 mL.kg^{-1}.min^{-1}), of likely cardiac origin.

Adapted from Metra M et al.[65] Eur J Heart Fail. 2007; 9(6-7): 684-94; Metra M et al.[66] Cardiac Fail Rev. 2019; Crespo-Leiro MG et al.[67] Eur J Heart Fail. 2018; 20(11): 505-35; Trusby LK et al.,[68] JACC Heart Fail. 2020; 8(7): 523-36.
6MWT: 6-minute walk test; BNP: B-type natriuretic peptide; HF: heart failure; HFmrEF: heart failure with mid-range ejection fraction; HFpEF: heart failure with preserved ejection fraction; LV: left ventricle; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association; NTproBNP: N-terminal portion of B-type natriuretic peptide; VO$_2$: oxygen consumption.

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Table 6.2 – Criteria proposed by various cardiology societies to identify advanced HF patients

Criterion	SBC	ACC/AHA	ESC	HFSA
Severe and persistent symptoms despite optimized therapy	✓	✓	✓	✓
Major functional limitation (NYHA III or IV functional class)	✓	✓	✓	✓
Persistent dyspnea in daily living activities		✓		
Recurring hospitalizations	✓	✓	✓	✓
Frequent unplanned visits to the emergency department	✓		✓	✓
Intolerance to maximum optimal medical therapy	✓	✓		✓
End-organ dysfunction	✓	✓		✓
Persistent hyponatremia	✓	✓		✓
Pulmonary or systemic congestion refractory to diuretics	✓	✓		✓
Frequent ICD shocks	✓	✓		✓
Cardiac cachexia	✓	✓		✓
Systolic blood pressure frequently ≤ 90 mm Hg		✓		
Persistently elevated BNP or NT-proBNP values	✓		✓	
Severe dysfunction with reduced LV ejection fraction (LVEF < 30%)	✓		✓	✓
Severe LV dysfunction with pseudonormal or restrictive pattern	✓		✓	
Elevated filling pressures (PCWP > 16 mm Hg +/- CVP > 12 mm Hg)			✓	
Low capacity in 6MWT (< 300 m) or VO_2 peak < 12-14 mL.kg^{-1}.min^{-1}	✓		✓	✓
Dependence on intravenous inotropes	✓			✓
Progressive RV dysfunction and secondary PH	✓			✓

Adapted from Metra M et al.[65] Eur J Heart Fail. 2007; 9(6-7): 684-94; Metra M et al.[66] Cardiac Fail Rev 2019; Crespo-Leiro MG et al.[67] Eur J Heart Fail. 2018; 20(11): 505-35; Trusby LK et al.[68] JACC Heart Fail. 2020; 8(7): 523-36.
6MWT: 6-minute walk test; ACC/AHA: American College of Cardiology/American Heart Association; BNP: B-type natriuretic peptide; CVP: central venous pressure; ESC: European Society of Cardiology; HF: heart failure; ICD: implantable cardiac defibrillator; HFSA: Heart Failure Society of America; LV: left ventricle; NT-proBNP: N-terminal portion of B-type natriuretic peptide; NYHA: New York Heart Association; PCWP: pulmonary capillary wedge pressure; PH: pulmonary hypertension; RV: right ventricle; VO_2: oxygen consumption.

Table 6.3 – Warning signs in advanced HF patients

I	IV inotrope dependence
N	Persistent NYHA III/IV, persistent elevation in natriuretic peptides
E	End-organ dysfunction
E	Ejection (fraction) below 20%
D	Defibrillator shocks (recurring appropriate shock)
H	Recurring hospitalizations and emergency department visits in the last 12 months
E	Persistent edema, refractory to escalating diuretics
L	Low systolic blood pressure, persistently below 90 mm Hg
P	Progressive intolerance to optimized medical therapy

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6.3. Approach to the Advanced Heart Failure Patient
(Figure 6.1)
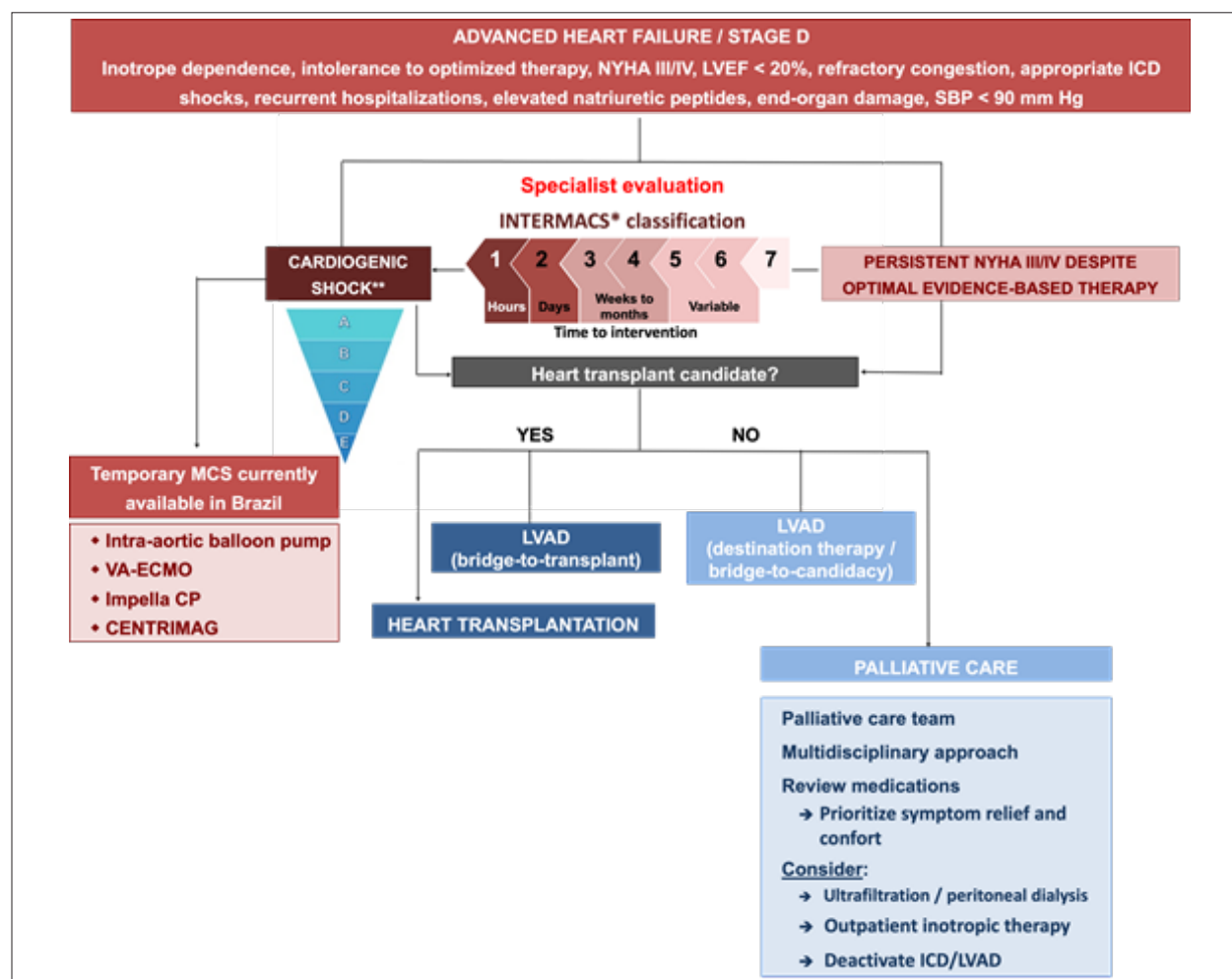
Figure 6.1 – *Treatment algorithm for patients with advanced heart failure*
Clinical classification of patients with advanced heart failure from the Interagency Registry for Mechanically Assisted Circulatory Support (Intermacs), see Brazilian Guidelines on Chronic and Acute Heart Failure.15 Arq Bras Cardiol. 2018; Quadro 4.6 (page 505).
**Cardiogenic shock classification proposed by the Society for Cardiovascular Angiography and Interventions (SCAI). Stage A: at risk of shock; Stage B: beginning shock; Stage C: classic shock; Stage D: deteriorating shock; Stage E: extremis. Adapted from Baran DA et al.[58] Catheter Cardiovasc Interv. 2019; 94(1): 29-37.
FC: functional class; HF: heart failure; ICD: implantable cardiac defibrillator; IVAD: implantable ventricular assist device; MCSD: mechanical circulatory support device; NYHA: New York Heart Association; VA-ECMO: venoarterial extracorporeal membrane oxygenation.

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6.4. Innovations in Managing Congestion in Patients with Advanced Heart Failure (Table 6.4)

Table 6.4 – Ambulatory monitoring of congestion in heart failure

Recommendation	Class	LE	Comment	Table 2018	Ref.
Invasive remote monitoring of congestion using an implantable, wireless pulmonary artery pressure sensor to reduce hospitalizations and mortality in outpatient HFrEF patients.	IIa	B	**NEW:** The current recommendation reflects data from small randomized trials and real-world studies, with impact in reducing hospitalizations and mortality.	New	30,53-57

While there has been relatively little innovation in the management of congestion in advanced HF, recent evidence suggests a potential benefit of remote monitoring, impacting the prognosis for HF patients. Studies of non-invasive home telemonitoring have shown improvements in hospital length of stay and all-cause mortality.[30] Similar results were observed with the implantable CardioMEMS™ HF System, which provides direct pulmonary artery pressure monitoring. The impact of invasive monitoring was tested in the *CHAMPION (Wireless pulmonary artery haemodynamic monitoring in chronic heart failure: a randomised controlled trial)* trial, which involved outpatients with HF (FC III, NYHA) and demonstrated a 28% reduction in hospitalizations for HF. Among patients receiving at least two medications from standard HF therapy, invasive monitoring was associated with a 57% reduction in mortality.[53] The CardioMEMS™ proved to be safe and effective in "real-world",[54] as well as in cost-effectiveness studies.[55] The data were recently replicated in a study conducted by multiple European centers[56] and in an open multicenter prospective study of 1200 FC III patients, which found a significant decrease in hospitalizations for HF with low rates of complications associated with the implantable monitor over the one-year follow-up period.[57] This is a promising strategy, with potential to be translated into clinical practice.

FC: functional class; HF: heart failure; NYHA: New York Heart Association; PAP: pulmonary artery pressure.

6.5. Current Classification of Cardiogenic Shock

In 2019, the Society for Cardiovascular Angiography and Interventions (SCAI) proposed a new classification for cardiogenic shock (CS) in order to make it easier to identify the various stages of clinical deterioration as well as the need for more intensive treatment.[58,59] The 5-stage classification incorporates signs of tissue hypoperfusion and organic dysfunction, offering a simple hemodynamic definition and granularity to the INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support) classification (Figure 6.2, Table 6.5).

Stage A includes patients at risk of cardiogenic shock, while stages B through E describe progressive stages of conventional cardiogenic shock. The difference between stages B and C is the presence of hypoperfusion, present in stages C and above. Stage D indicates initial cardiogenic shock management measures were not enough to restore hemodynamic stability or tissue perfusion within at least 30 minutes of observation, while stage E characterizes extreme cases, where patients present as hemodynamically unstable and frequently in circulatory collapse. Patients in SCAI stages D and E have higher mortality rates and may benefit from early referral to specialized centers, where more advanced modes of circulatory support may be available.[59]
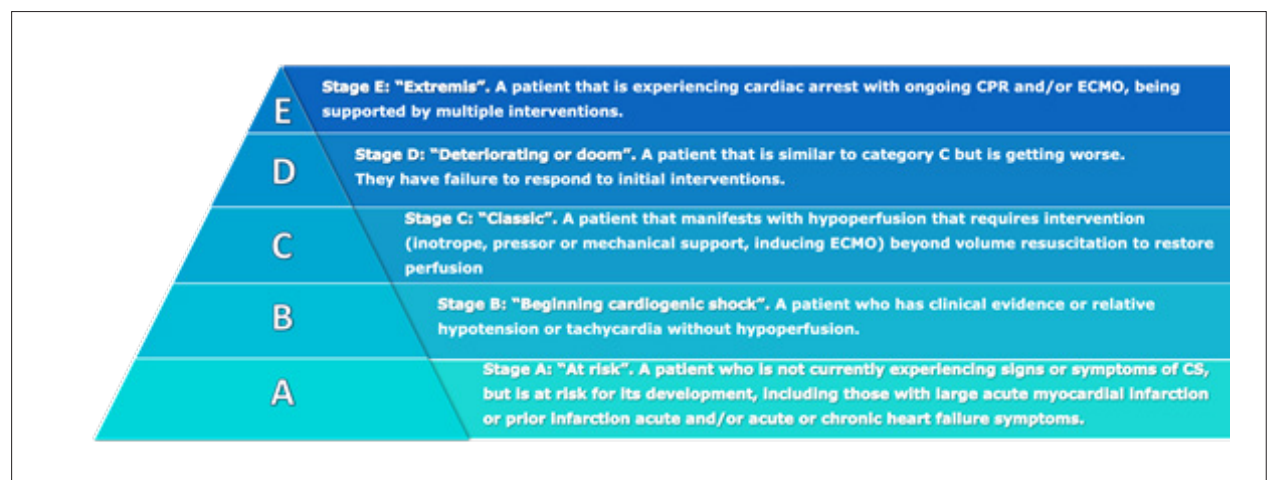
Figure 6.2 – *Society for Cardiovascular Angiography and Interventions (SCAI) classification of cardiogenic shock.*
Adapted from Baran DA et al.[58] SCAI clinical expert consensus statement on the classification of cardiogenic shock. Catheter Cardiovasc Interv. 2019; 94(1): 29-37.
AMI: acute myocardial infarction; CPR: cardiopulmonary resuscitation; CRA: cardiorespiratory arrest; CS: cardiogenic shock; ECMO: extracorporeal membrane oxygenation; HF: heart failure.

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Table 6.5 – Descriptors of shock stages: physical exam, biochemical markers, and hemodynamics

Stage of CS	Bedside findings	Biomarkers	Hemodynamics
A (at risk)	Normal JVP Lung sounds clear Dry-warm profile Strong distal pulses Normal mentation	Normal labs Normal renal function Normal lactate	SBP $\geq$ 100 mm Hg (or normal for patient) If PAC: • CI $\geq$ 2.5L/min/m^2 • CVP< 10 mm Hg • SvO$_2$ $\geq$ 65%
B (beginning)	High JVP Rales in lung fields Dry-warm profile Strong distal pulses Normal mentation	Normal lactate Minimal renal dysfunction Elevated BNP	SBP < 90 OR MAP < 60 OR > 30 mm Hg drop from baseline HR $\geq$ 100 bpm If PAC: CI $\geq$ 2.2 L/min/m^2 SvO$_2$ $\geq$ 65%
C (classic)	*May include any of:* Looks unwell Panicked Ashen, mottled, dusky Volume overload Extensive rales Kilip class 3 or 4 BiPap or mechanical ventilation Cold, clammy Acute alteration in mental status Urine output < 30 mL/h	*May include any of:* Lactate $\geq$ 2 mmol/L Creatinine doubling OR >50% drop in GFR Altered liver enzymes Elevated BNP	*May include any of:* SBP < 90 OR MAP < 60 OR >30 mm Hg drop from baseline. Pressor drugs and/or devices used to maintain BP PAC: • CI < 2.2L/min/m^2 • PCWP > 15 mm Hg • CVP/PCWP $\geq$ 0.8 • PAPi < 1.85 • CPO $\leq$ 0.6W
D (deteriorating)	*May include any of the findings from stage C*	*Any of stage C and deteriorating.*	*Any of stage C and:* Requiring multiple pressors and/or addition of mechanical circulatory support devices to maintain perfusion
E (extremis)	Near pulselessness Circulatory collapse Mechanical ventilation Defibrillator used	CRA (A-modifier*) pH $\leq$ 7.2 Lactate $\geq$ 5 mmol/L	Inaudible SBP / CRA VTWP or refractory VT/VF Hypotension despite maximal support

* The modifier (A) is used to describe patients who have gone into cardiac arrest, regardless of duration.
Adapted from Baran DA et al.[58] SCAI clinical expert consensus statement on the classification of cardiogenic shock. Catheter Cardiovasc Interv. 2019; 94(1):29-37.
AMI: acute myocardial infarction; BiPap: bi-level positive airway pressure; BNP: B-type natriuretic peptide; CI: cardiac index; CPO: cardiac power output; CS: cardiogenic shock; CVP: central venous pressure; GFR: glomerular filtration rate; HF: heart failure; HR: heart rate; JVP: jugular venous pressure; MAP: mean arterial pressure; PAC: pulmonary artery catheter; PAPi: pulmonary artery pulsatility index; PCWP: pulmonary capillary wedge pressure; SBP: systolic blood pressure; SvO2: mixed venous oxygen saturation; VF: ventricular fibrillation; VT: ventricular tachycardia; VTWP: ventricular tachycardia without a pulse.

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6.6. Applicability of Pulmonary Artery Catheters in Advanced Heart Failure (Table 6.6)

Table 6.6 – Recommendations for pulmonary artery catheter use in patients with advanced HF

Recommendations	Class	LE	Comment	Table 2018	Ref.
In patients with advanced HF, heart transplantation candidates or receiving mechanical circulatory support.	I	B	2018 recommendation remains current.	Item 2.2.6. (page 495)	See 2018
To help treatment and hemodynamic support for patients with HF refractory to standard treatment or patients with cardiogenic shock.	IIa	B	**MODIFIED:** New evidence supports the change in class of recommendation.	Item 2.2.6. (page 495)	60-61

The use of a pulmonary artery catheter (PAC) in hemodynamic monitoring for patients hospitalized for refractory HF remains controversial.[62,63] In 2005, the *ESCAPE (Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness)* trial found no benefits from the routine use of PACs in managing decompensated HF patients without CS.[64] However, recent advances in the field of mechanical circulatory support devices (MCSDs) have prompted the development of algorithms to manage CS guided by PAC parameters. Early recognition, identification of the shock subtype and understanding of the expected impact of each type of device on hemodynamic parameters such as cardiac output, pulmonary capillary wedge pressure (PCWP), central venous pressure (CVP), and mean arterial pressure (MAP) allow choosing the most suitable MCSD for each stage of CS (Figure 6.1). In addition, the information obtained via PAC assist the phenotype characterization of CS into predominantly left ventricular shock (CPO < 0.6 W, PAPi > 1, CVP < 15 mm Hg and PCWP > 15 mm Hg), right ventricular shock (CPO < 0.6 W, PAPi <1, CVP > 15 mm Hg and PCWP < 15 mm Hg) or biventricular shock (CPO < 0.6 W, PAPi < 1, CVP > 15 mm Hg and PCWP > 15 mm Hg).[60,65-68] Recently, in one of the first studies by the Cardiogenic Shock Working Group (CSWG), Garan et al.[61] evaluated the association between CS management guided by CAP parameters and hospital mortality in 1,414 patients with CS, most with indication for MCSD use and in stage D of the SCAI classification. CS management guided by PAC parameters obtained before implanting a MCSD was associated with a significant decrease in mortality, especially in the more advanced stages of CS (stages D or E of the SCAI classification).[61] It should be emphasized that the PAC is a diagnostic tool, not a therapeutic one, and its effectiveness depends on clinical decisions taken by the team involved in managing the CS.

CPO: cardiac power output; CS: cardiogenic shock; CVP: central venous pressure; HF: heart failure; MAP: mean arterial pressure; MCSD: mechanical circulatory support device; PAC: pulmonary artery catheter; PAPi: pulmonary artery pulsatility index; PCWP: pulmonary capillary wedge pressure.

6.7. Innovations in Short-Term Circulatory Support Devices in Advanced Heart Failure (Table 6.7)

Table 6.7 – Recommendation for left ventricular venting in patients receiving extracorporeal membrane oxygenation (ECMO)

Recommendations	Class	LE	Comment	Table 2018	Ref.
Consider strategies for left ventricular venting in patients receiving mechanical circulatory support via peripheral venoarterial ECMO, evidence of ventricular distension associated with severe hypocontractility and pulmonary congestion.	IIa	C	**NEW:** The current recommendation reflects data from observational studies and meta-analyses.	New	69-73

The use of peripheral venoarterial extracorporeal membrane oxygenation (ECMO) is characterized by an increase in LV afterload caused by blood flow from the arterial return cannula, which can worsen cardiac hypocontractility, causing ventricular distension and pulmonary congestion. In many cases, the reduction in ECMO flow combined with inotropic therapy may be sufficient to decompress the LV.[74] However, in refractory cases, other methods of venting may be used, including atrial septostomy; surgical implantation of a transapical catheter; percutaneous pulmonary artery venting through the jugular vein; and mechanical circulatory support device (MCSD), such as the intra-aortic balloon pump (IABP), Impella®, or CentriMag®. In observational studies, LV venting has been associated with reduced mortality, increased myocardial recovery, and shorter weaning time from ECMO in patients with CS treated with peripheral venoarterial ECMO.[69-72] Each venting technique presents inherent risks that must be considered individually according to the etiology of the underlying disease, limitations of the access site, presence of coagulopathies, availability of MCSDs and experience of each center.[75] Despite known limitations, IABPs remain the most commonly used devices, with a recent meta-analysis suggesting lower risk of complications such as stroke, peripheral ischemia, and hemolysis from decompression by IABP as compared to other methods, at the cost of increased bleeding.[73] However, no randomized clinical trial has been conducted to date to establish the ideal LV venting method, and prospective studies are needed. There is also no consensus on whether LV venting should be performed preventively or as a rescue measure. Known indications for LV venting include elevated PCWP, distended and hypocontractile LV, LV with echocardiographic evidence of blood stasis, decreased aortic valve opening during the cardiac cycle, hypoxemia, progressive pulmonary edema, and refractory ventricular arrhythmia.

CS: cardiogenic shock; ECMO: extracorporeal membrane oxygenation; LV: left ventricle; MCSD: mechanical circulatory support device; PCWP: pulmonary capillary wedge pressure.

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6.8. Innovations in Palliative Care for Advanced Heart Failure (Table 6.8)

Table 6.8 – Outpatient use of intravenous inotropes in patients with advanced HF who are not eligible for heart transplantation or mechanical circulatory support devices

Recommendations	Class	LE	Comment	Table 2018	Ref.
Continuous outpatient intravenous inotrope therapy as palliative care for symptom control in advanced HF patients who are not eligible for mechanical circulatory support devices or heart transplantation.	IIb	C	**NEW:** The current recommendation reflects data from studies with limitations in design and execution.	New	76-78
Intermittent use of inotropes or inodilator to improve symptoms in advanced HF patients or palliative care in patients without other advanced therapy options.	IIb	B	**NEW:** New evidence from moderate-quality meta-analysis and RCT support the recommendation.	New	79

The evidence assessing the risks and benefits of palliative care with intravenous inotrope therapy on an outpatient basis for patients with advanced HF is limited, consisting primarily of observational studies without a control group. Meta-analyses of small randomized controlled trials and heterogeneous observational studies suggest a potential clinical benefit of continuous or intermittent outpatient inotrope therapy for patients with advanced HF who are not eligible for an MCSD or heart transplantation.[76-78] Benefits include relief of symptoms and lower readmission rates. However, the need for a central catheter for continuous infusion of inotropes is associated with greater special care and risk of infections. The *LION-HEART (Efficacy and safety of intermittent intravenous outpatient administration of levosimendan in patients with advanced heart failure)* pilot trial randomly assigned 69 patients with advanced HF to either placebo or intermittent levosimendan at a dosage of 0.2 µg/kg/min for 6 hours every 2 for 12 weeks and demonstrated the benefit of inotropic therapy in relation to lower plasma NT-proBNP levels, higher quality of life scores, and lower readmission rates, with no difference in rates of adverse events between groups.[79] To date, there are no cost-effectiveness studies evaluating the impact of outpatient inotropic infusion as palliative therapy for patients with advanced HF.

HF: heart failure; NT: N-terminal portion of B-type natriuretic peptide; RCT: randomized controlled trial

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7. Treatment of Heart Failure with Reduced Ejection Fraction (HFrEF)

7.1. Previously Consolidated Pharmacological Strategies for Treatment of Heart Failure with Reduced Ejection Fraction (HFrEF) (Table 7.1)

Table 7.1 – Recommendations for pharmacological treatment of HFrEF previously consolidated in 2018

Recommendations	Class	LE	Comment	Table 2018	Ref.
Bisoprolol, carvedilol or metoprolol succinate for symptomatic LV dysfunction to reduce morbidity and mortality.	I	A	2018 recommendation remains current.	Item 7.2 (page 457)	See 2018
ACEI for symptomatic LV dysfunction to reduce morbidity and mortality.	I	A	2018 recommendation remains current.	Item 7.1 (page 456)	See 2018
ARB for symptomatic LV dysfunction (for those intolerant to ACEI due to coughing/angioedema) to reduce morbidity and mortality.	I	A	2018 recommendation remains current.	Item 7.1 (page 456)	See 2018
Mineralocorticoid receptor antagonists for symptomatic LV dysfunction, associated with standard treatment with ACEI/ARB/ARNI and BB, to reduce morbidity and mortality.	I	A	**MODIFIED:** The use of mineralocorticoid receptor antagonists is justified for patients using ACEI/ARB as well as ARNI.	Item 7.3 (page 457)	80-84
Sacubitril-valsartan, instead of ACEI (or ARB), for patients with symptomatic LV dysfunction, already receiving optimal medical therapy for HF with triple therapy to reduce morbidity and mortality.	I	B	2018 recommendation remains current.	Item 7.4 (page 458)	See 2018
Hydralazine and nitrate combination for symptomatic systolic dysfunction, NYHA II-IV, with contraindication for ACEI/ARB (renal failure and/or hypercalcemia) regardless of race or for self-declared black patients with symptomatic systolic dysfunction, NYHA III-IV, despite optimized therapy.	I	B	2018 recommendation remains current.	Item 7.7 (page 459)	See 2018
Ivabradine for symptomatic LV dysfunction in patients with optimal medical therapy for HF, sinus rhythm, and HR above 70 bpm to reduce hospitalization, cardiovascular death, and HF death.	IIA	B	2018 recommendation remains current.	Item 7.5 (page 458)	See 2018
Digoxin for symptomatic LV dysfunction despite optimal medical therapy for HF, to reduce symptoms and hospitalizations.	IIA	B	2018 recommendation remains current.	Item 7.6 (page 458)	See 2018
Loop diuretic for congestion control.	I	C	2018 recommendation remains current.	Item 7.7 (page 459)	See 2018
Thiazide diuretic, associated with loop diuretic for persistent congestion.	I	C	2018 recommendation remains current.	Item 7.7 (page 459)	See 2018

In recent decades, advances in pharmacological treatment and in the use of implantable devices have changed the prognosis of HFrEF patients.[80-91] However, there is still a high risk of morbidity and mortality, even with the adoption of optimal medical therapy. In this new era, drugs acting on various pathophysiological mechanisms of HF have emerged to supplement the inhibition of the neurohormonal system. It should be noted that the benefits observed with the new drugs add to the optimal medical therapy, highlighting the need to maintain triple therapy, including beta-blockers, renin-angiotensin-aldosterone system (RAAS) blockers, and mineralocorticoid antagonists. Once triple therapy has been initiated and disease-modifying new therapies (with proven benefits in reducing cardiovascular death, all-cause mortality, and hospitalizations for HF) added, we can also include medications impacting morbidity. The choice of additional therapies should take into consideration each patient's profile.

ACEI: angiotensin-converting enzyme II inhibitors; ARB: angiotensin II receptor blockers; ARNI: angiotensin II receptor-neprilysin inhibitors; HF: heart failure; HFrEF: heart failure with reduced ejection fraction; HR: heart rate; LV: left ventricle; RAAS: renin-angiotensin-aldosterone system.

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7.2. Sacubitril-Valsartan (Table 7.2)

Table 7.2 – Recommendations for the use of sacubitril-valsartan in HFrEF patients

Recommendations	Class	LE	Comment	Table 2018	Ref.
Sacubitril-valsartan, instead of ACEI/ARB, for symptomatic LV dysfunction, patients with optimal medical therapy for HF with triple therapy to reduce morbidity and mortality.	I	B	2018 recommendation remains current.	Item 7.4 (page 458)	See 2018
Sacubitril-valsartan, as initial treatment for symptomatic chronic HF, may be considered instead of ACEI or ARB.	IIa	C	**NEW:** Analysis of subgroups of randomized and non-randomized trials have found it safe for patients without prior use of ACEI/ARB.	New	84,92,93
Sacubitril-valsartan, instead of ACEI/ARB, may be considered for hospitalized patients with decompensated HF.	IIa	B	**NEW:** Randomized trial using surrogate endpoint (reduction of biomarkers) supports the new recommendation.	New	84,92,94

The *PARADIGM-HF* trial investigated the effects on morbidity and mortality in HFrEF patients of attenuating the deleterious effects of angiotensin II associated with enhancing the protective effect of endogenous natriuretic peptides through the inhibition of neprilysin (an enzyme responsible for the degradation of BNP) using a new medication class, the angiotensin II receptor-neprilysin inhibitor (ARNI), of which the molecule currently available is sacubitril-valsartan, as compared to enalapril.[83] The trial included 8,442 patients with symptomatic outpatient HFrEF in an optimized clinical therapy regimen with persistent LVEF ≤ 40%, elevated plasma natriuretic peptide levels, and estimated creatinine clearance ≥ 30 mL/min/1.73 m^2. In this population, sacubitril-valsartan was associated with a 21% decrease in hospitalizations for worsening HF, 20% decrease in cardiovascular death, 20% decrease in sudden death, and 16% decrease in overall mortality when compared to enalapril. Based on the results from the *PARADIGM-HF* trial, we recommend replacing ACEI/ARB with sacubitril-valsartan in HFrEF patients whose symptoms persist even after the use of optimized doses of neurohormonal blockers. More recently, the *PIONEER-HF (Angiotensin–Neprilysin Inhibition in Acute Decompensated Heart Failure)* trial compared sacubitril-valsartan (n = 440) to enalapril (n = 441) in patients hospitalized for decompensated HF, where the primary outcome was the time-averaged proportional change in the NT-proBNP concentration from baseline through weeks 4 and 8.[84] The results show a significant decrease in NT-proBNP, higher with sacubitril-valsartan than with enalapril, and the reduction was already noticeable after the first week of treatment, regardless of prior HF history and/or use of ACEIs or ARBs.[94] The side effects were similar for both groups, including hypercalcemia, renal dysfunction, and hypotension. In an open analysis, at the end of 8 weeks (*PIONEER-HF extended*) where all patients received sacubitril-valsartan for an additional 4 weeks, there was a significant decrease in NT-proBNP in the enalapril group after initiating sacubitril-valsartan use.[92] Another prospective observational study, the *TRANSITION (Initiation of sacubitril/valsartan in haemodynamically stabilised heart failure patients in hospital or early after discharge) Trial*,[93] initiated sacubitril-valsartan in 1,002 hemodynamically stabilized HF patients in hospital or early after discharge and found it to be safe and well tolerated, with half of patients reaching the target dose within 10 weeks and few adverse events.[93] These results suggest that the use of sacubitril-valsartan is safe in hemodynamically stabilized patients with acute HF; extrapolating the results of the *PARADIGM-HF* trial, sacubitril-valsartan may be considered for treatment of patients hospitalized for decompensated HF instead of ACEI/ARB. The results from these recent trials also indicate the safety and tolerability of initiating treatment with sacubitril-valsartan instead of ACEIs/ARBs in HFrEF patients, which made up 34% of the sample in the *PIONEER-HF* trial and 29 of patients in the *TRANSITION* trial.[84,92,93] Taken as a whole, these data suggest initiating sacubitril-valsartan for patients with no prior treatment with ACEIs/ARBs and during episodes of HF decompensation is reasonably safe. Long-term and outcome data on this form of intervention, including mortality rates, are not yet available.

ACEI: angiotensin-converting enzyme II inhibitors; ARB: angiotensin II receptor blockers; ARNI: angiotensin II receptor-neprilysin inhibitors; HF: heart failure; HFrEF: heart failure with reduced ejection fraction; HR: heart rate; LV: left ventricle; LVEF: left ventricular ejection fraction; RAAS: renin-angiotensin-aldosterone system.

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7.3. Sodium-glucose Cotransport 2 (SGLT2) Inhibitors
(Table 7.3)

Table 7.3 – Recommendations for use of SGLT2 inhibitors in the treatment of HFrEF patients

Recommendations	Class	LE	Comment	Table 2018	Ref.
SGLT2 inhibitors (dapagliflozin or empagliflozin) in symptomatic HFrEF patients with diabetes or not, receiving maximum optimized tolerate dose of beta-blocker, aldosterone antagonist, ACEI/ARB or ARNI to lower cardiovascular outcomes and progression of renal dysfunction.	I	A	**NEW:** SGLT2i are useful to reduce cardiovascular death and hospitalization for heart failure.	New	95-98

In *DAPA-HF* (*Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure*), 4,744 HFrEF patients were randomly assigned to dapagliflozin or a placebo in addition to standard therapy, and 41.8% of them had DM2.[95] The primary endpoint of cardiovascular death or worsening HF was significantly lower in the dapagliflozin group (26% reduction). When analyzed separately, there was a significant reduction in both cardiovascular death (18%) and worsening HF (30%), regardless the presence of DM2. The results reveal a new therapy for HF, already approved for that purpose.

The *EMPEROR-Reduced* (*Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Reduced Ejection Fraction*) trial assessed empagliflozin vs. a placebo, in addition to standard therapy, in 3,730 patients with HFrEF, 50.2% of which had DM2.[96] Patients had more severe HF than those in *DAPA-HF*, with average LVEF of 27% vs. 31%, and over 70% of patients had LVEF under 30%, in addition to higher median NT-proBNP levels (1907 *versus* 1437 pg/mL). There was a 25% decrease in the primary endpoints of cardiovascular death or hospitalization for HF in favor of empagliflozin. When analyzed separately, there was no reduction in cardiovascular death, unlike the results from *DAPA-HF*. The benefit was once again observed regardless of the presence of DM2. The data confirm the results from *DAPA-HF* and reinforce the justification for using sodium-glucose cotransporter-2 inhibitors (SGLT2i) in HFrEF patients to reduce symptoms, improve quality of life, and lower the risk of hospitalization and cardiovascular death.

The meta-analysis using results from the *DAPA-HF* and *EMPEROR-Reduced* trials, totaling 8,474 patients, found a 13% reduction in all-cause mortality (combined HR 0.87, 95% CI 0.77-0.98; p = 0.018) and a 14% reduction in death from cardiovascular disease (0.86, 95% CI 0.76 - 0.98; p = 0.027).(94) The use of SGLT2i was accompanied by a 26% relative reduction in combined risk for cardiovascular death or first hospitalization for HF (0.74,0.68–0.82; p < 0.0001), and a 25% eduction in the composite outcome of recurring hospitalizations for HF or cardiovascular death (0.75, 0.68–0.84; p < 0.0001). The risk of composite renal outcome was also lowered (0.62, 0.43–0.90; p = 0.013). The DAPA-HF subanalysis assessed the efficacy and safety of dapagliflozin use in HFrEF patients by baseline glomerular filtration rate (GFR) as well as the effects on dapagliflozin after randomization. The effect of dapagliflozin on primary (CV death or worsening HF) and secondary endpoints did not change with GFR (< 60 and $\geq$ 60 mL/min/1.73m²). A prespecified composite renal outcome (sustained > 50% reduction in GFR, terminal kidney disease or renal death) was also analyzed, along with worsening GFR throughout the study. Though dapagliflozin did not lower the composite renal outcome (RR = 0.71, 95% CI 0.44-1.16, p = 0.17), rates of worsening GFR were lower for dapagliflozin (-1.09) as compared to the placebo (-2.87), p < 0.001, for patients with our without DM2 (interaction p = 0.92).[95] In the *EMPEROR-Reduced* trial, the annual rate of decline in GFR was slower in the empagliflozin group than in the placebo group (-0.55 vs. -2.28 mL/min/1.73 m² per year, p < 0.001), and empagliflozin-treated patients had a lower risk of serious renal outcomes, regardless of the presence or absence of DM2.[96] Data from a subanalysis of the *DAPA-HF* and *EMPEROR-Reduced* trials suggest the use of SGLT2 inhibitors is safe in patients with HFrEF and those with altered GFR, regardless of the presence or absence of DM2.

ACEI: angiotensin-converting enzyme II inhibitors; ARB: angiotensin II receptor blockers; ARNI: angiotensin II receptor-neprilysin inhibitors; DM2: type 2 diabetes mellitus; GFR: glomerular filtration rate; HF: heart failure; HFrEF: heart failure with reduced ejection fraction; LVEF: left ventricular ejection fraction; SGLT2i: sodium-glucose cotransporter-2 inhibitors.

Update

7.4. Treatment of Comorbidities in Heart Failure with Reduced Ejection Fraction

7.4.1. Type 2 Diabetes (Table 7.4)

Table 7.4 – Recommendations for use of SGLT2 inhibitors in preventing hospitalizations for HF in type 2 diabetes patients

Recommendations	Class	LE	Comment	Table 2018	Ref.
SGLT2 inhibitors (canagliflozin, dapagliflozin or empagliflozin) to prevent hospitalization for HF in patients with type 2 diabetes and cardiovascular risk factors for atherosclerosis or established atherosclerotic cardiovascular disease.	I	A	**NEW:** SGLT2i are useful to reduce hospitalization for heart failure in patients with DM2.	Item 5.2 (page 451)	99-101
SGLT2 inhibitors (dapagliflozin or empagliflozin) as initial antidiabetic medication associated or not with metformin in HFrEF patients.	I	A	**NEW:** SGLT2i are useful for diabetes treatment and reduction of cardiovascular and renal events.	New	102

The benefits of SGLT2i in type 2 diabetes (DM2) patients were first described in the *EMPA-REG OUTCOME (Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes)* trial, published in 2015, which assessed empagliflozin use in patients with DM2, established cardiovascular disease, and receiving standard treatment.[99] Among those who received the medication, there was a significant reduction in major adverse cardiovascular events (MACE = CV death, nonfatal MI or nonfatal stroke) (HR: 0.86 (CI] 95%: 0.74-0.99), and a surprising reduction in hospitalization for heart failure (HHF) (HR: 0.65 (95% CI: 0.50-0.85). The *CANVAS-Program (Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes)* trial, published in 2017, assessed canagliflozin in patients with DM2 at high risk for cardiovascular events receiving standard treatment. There was a reduction in combined primary outcomes (MACE = CV death, nonfatal MI or nonfatal stroke) and a 33% reduction in HHF (HR = 0.67, 95% CI: 0.52-0.87) as well as combined renal events.[100] The *DECLARE-TIMI 58 (Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes) trial* assessed dapagliflozin in patients with DM2 and atherosclerotic disease or multiple risk factors for atherosclerotic disease receiving standard treatment. There was no reduction in the combined primary endpoint (MACE = CV death, myocardial infarction or stroke). There was a 17 percent reduction in the combined endpoint of cardiovascular death and HHF, and 27 percent (HR: 0.73 (95% CI 0.61-0.88) for HHF.[101] Recently, the *VERTIS-CV (Cardiovascular Outcomes with Ertugliflozin in Type 2 Diabetes)* trial assessed the use of ertugliflozin (not yet commercially available in Brazil) for patients with DM2, established cardiovascular disease, and receiving standard treatment. There was no reduction in the combined primary endpoint (MACE = CV death, myocardial infarction or stroke). However, a 30% decrease in HHF was observed.[100] As a whole, the available data show the efficacy of SGLT2i in reducing the incidence of HF in groups of patients with DM2.[102]

DM2: type 2 diabetes mellitus; HHF: hospitalization for heart failure; MI: myocardial infarction; SGLT2i: sodium-glucose cotransporter-2 inhibitors.

7.4.2. Renal Dysfunction (Table 7.5)

Table 7.5 – Recommendations for use of SGLT2 inhibitors in preventing worsening of renal function in HFrEF patients

Recommendation	Class	LE	Comments	Table 2018	Ref.
SGLT2 inhibitors (dapagliflozin or empagliflozin) in patients with HFrEF to prevent worsening of renal function in patients with and without diabetes, with GFR $\geq$ 20 mL/min/1.73 m².	IIa	A	**NEW:** SGLT2i are useful to reduce progressive worsening of renal function in HFrEF.	New	95, 96, 98- 104

In the *EMPEROR-Reduced* trial, the annual rate of decline in glomerular filtration rate (GFR) was slower in the empagliflozin group than in the placebo group (-0.55 vs. -2.28 mL/min/1,73 m² per year, p < 0.001), and empagliflozin-treated patients had a lower risk of serious renal outcomes, regardless of the presence or absence of DM2.[96] The *DAPA-HF* subanalysis assessed the efficacy and safety of dapagliflozin use in HFrEF patients by baseline GFR as well as the effects on dapagliflozin after randomization.[98] In the *DAPA-HF* trial, dapagliflozin did not lead to lower composite renal outcomes (RR = 0.71, 95% CI 0.44-1.16, p = 0.17).[95] However, in a subanalysis, rates of worsening GFR were lower for dapagliflozin (-1.09) as compared to a placebo (-2.87), p < 0.001, in patients with or without DM2. The *DAPA-CKD (Dapagliflozin in Patients with Chronic Kidney Disease)* trial randomized 4,304 patients with chronic kidney disease, GFR 25-75 mL/min/73 m², and urinary albumin-creatinine ratio 200-5,000. Dapagliflozin led to lower rates of primary endpoints (consisting of sustained reduction in GFR of at least 50%, terminal kidney disease or CV or renal death) (9.2% with dapagliflozin vs. 14.5% with a placebo; [RR = 0.61, CI = 9%, 0.51-0.72; p < 0.001]. Death occurred for 101 members (4.5%) of the dapagliflozin group vs. 146 (6.8%) of the placebo group (RR = 0.69, 95% CI = 0.53-0.88, p = 0.004). Dapagliflozin lowered cardiovascular death or hospitalization for HF (0.67, 0.40-1.13 vs. 0.70, 0.52-0.94, respectively, P-interaction = 0,88). The results were consistent, both with and without DM2.[104] Data from *EMPEROR-Reduced*, *DAPA-CKD* and the subanalysis of *DAPA-HF* suggest the use of SGLT2 inhibitors is safe in HFrEF and GFR alterations, regardless of the presence of DM2. They also show that SGLT2i may decrease renal function impairment in HFrEF patients.

DM2: type 2 diabetes mellitus; GFR: glomerular filtration rate; HFrEF: heart failure with reduced ejection fraction; SGLT2i: sodium-glucose cotransporter-2 inhibitors.

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7.4.3. Iron Deficiency (Table 7.6)

Table 7.6 – Recommendations for use of intravenous iron in HFrEF patients

Recommendation	Class	LE	Comments	Table 2018	Ref.
Intravenous ferric carboxymaltose replacement in patients with HFrEF and iron deficiency (serum ferritin below 100 ng/mL or between 100-299 ng/mL with transferrin saturation below 20%), even in the absence of anemia, to increase physical exercise capacity, improve quality of life, and reduce hospitalization rates.	IIa	A	2018 recommendation remains current.	Item 11.11 (page 470)	See 2018
Intravenous ferric carboxymaltose replacement in patients with HFrEF hospitalized for decompensated HF with iron deficiency (serum ferritin below 100 ng/mL or between 100-299 ng/mL with transferrin saturation below 20 percent) after clinical stabilization to reduce hospital readmission rates.	IIa	B	**NEW:** A multicenter randomized trial supports the recommendation.	New	105

In patients with chronic HF and iron deficiency, the use of intravenous ferric carboxymaltose led to improvements in symptoms, quality of life and hospitalization rates in previous meta-analyses and randomized trials.[106-108] More recently, the multicenter, randomized, placebo-controlled *AFFIRM-AHF* trial assessed the effect of intravenous ferric carboxymaltose in 1,132 patients with HFrEF and iron deficiency (stable after an episode of HF decompensation and with iron deficiency — ferritin < 100 ng/mL or serum ferritin between 109 and 299 ng/mL associated with transferrin saturation below 20 percent) and found it to be safe and to reduce hospitalization for HF (217 vs. 294 hospitalizations; RR = 0.74; 95% CI 0.58-0.94, p = 0.013), though it had no direct impact on decreasing cardiovascular mortality.[105,109]

HF: heart failure; HFrEF: heart failure with reduced ejection fraction.

7.5. Treatment Algorithm for Heart Failure with Reduced Ejection Fraction (Table 7.5)
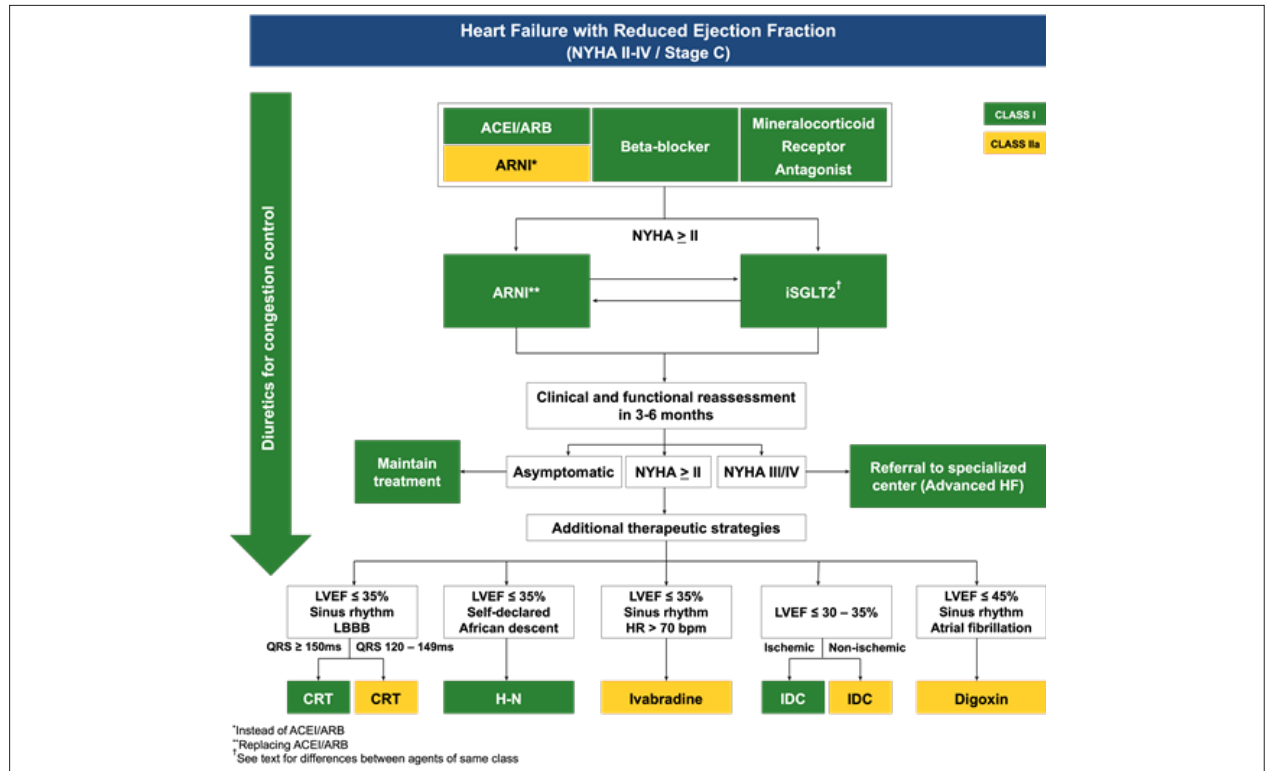
Figure 7.5 – *Treatment algorithm for heart failure with reduced ejection fraction*
**Em substituição a iECA /BRA.
ACEI: angiotensin-converting enzyme inhibitors; ARB: angiotensin II receptor blockers; ARNI: angiotensin receptor-neprilysin inhibitor; CRT: cardiac resynchronization therapy; HF: heart failure; H-N: hydralazine-nitrate; ICD: implantable cardiac defibrillator; LBBB: left bundle branch block; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association; SGLT2i: sodium-glucose cotransporter-2 inhibitors.

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8. Innovations in Other Areas Related to Heart Failure

8.1. Biomarkers in Heart Failure with Reduced Ejection Fraction (Table 8.1)

Table 8.1 – Recommendations for the use of biomarkers in HFrEF patients

Recommendations	Class	LE	Comment	Table 2018	Ref.
Measurement of BNP or NT-proBNP when HF diagnosis is in question and as a screening test in primary care.	I	A	2018 recommendation remains current.	Item 4.3 (page 451)	See 2018
Measurement of BNP or NT-proBNP for prognostic stratification in patients with HF.	I	A	2018 recommendation remains current.	Item 4.3 (page 451)	See 2018
Measurement of BNP or NT-proBNP as a complement to physical examination to assess response to treatment in HF patients in case of questions about their clinical status.	IIa	B	**MODIFIED:** Two recent studies, one randomized, the other observational, support that indication.	Item 4.3 (page 451)	84, 110
Serial measurements of BNP or NT-proBNP to guide treatment, with biomarker targets.	IIb	B	**MODIFIED:** A recent meta-analysis, including data from the *Guide-IT* trial, support that indication.	Item 4.3 (page 451)	111, 112

Natriuretic peptides may be used to assess patient response to a given treatment. In terms of strategy, the treatment is clinically directed and the biomarker is measured before and after with no specific target. New studies have come up to confirm what had already been shown by a subanalysis of the *PARADIGM-HF* trial, where patients who had lowered their NT-proBNP to below 1000 pg/mL after the initiation of enalapril or sacubitril-valsartan had lower mortality and fewer hospitalizations for HF.[113] In the *PIONEER-HF* trial following up on patients hospitalized for HF after discharge, sacubitril-valsartan produced a greater decrease in NT-proBNP than enalapril after 4 weeks (46.7 vs 25.3 percent), leading to a smaller number of events from sacubitril-valsartan use.[84] In the *Prove-HF* trial, where chronic HF patients used sacubitril-valsartan, there was a significant decrease in NT-proBNP after the medication had been used for 14 days. The NT-proBNP decrease was associated with reverse remodeling during the 12 months of follow-up and had a smaller event rate.[110] Conversely, the use of peptides to guide treatment (with natriuretic peptide targets) is controversial. Though the strategy was not superior to conventional management in the *Guide-IT* trial, previous surveys have found different results.[112] Another trial, *Protect*,[114] NT-proBNP-guided therapy was superior to standard of care, with reduced event rates, improved quality of life, and favorable effects on cardiac remodeling. The *Time-CHF*[115] and Battlescarred[116] trials found the strategy led to decreases in mortality in patients under the age of 75. In addition, a recent meta-analysis including 4,554 patients and incorporating patients from the *Guide-IT* trial found lower hospitalization rates and all-cause mortality from natriuretic peptide-guided treatment.[111]

HF: heart failure; NT-proBNP: N-terminal portion of B-type natriuretic peptide.

8.2. Immunizations in Heart Failure (Table 8.2)

Table 8.2 – Recommendations for immunizations for HFrEF patients

Recommendations	Class	LE	Comment	Table 2018	Ref.
Influenza vaccine to prevent influenza-related morbidity and mortality in HF.	I	B	**MODIFIED**: New retrospective studies have shown benefits in reducing mortality rates.	Item 6.7 (page 454)	117-120
Pneumococcal vaccine to prevent pneumococcal-related morbidity and mortality in HF.	I	C	2018 recommendation remains current.	Item 6.7 (page 454)	See 2018

Until recently, there was no data on the impact of influenza on outcomes for patients with HF. However, recent population-based studies have shown the relationship between seasonality and a higher number of hospitalizations for HF, evident on four consecutive periods.[117] In a subanalysis of the *Paradigm* trial, 21% of participants were vaccinated against influenza, leading to a 19% decrease in overall mortality after adjusting for propensity.[118] A Danish cohort study of 134,038 HF patients receiving ≥1 vaccinations between 2003 and 2015, resulted in an 18% decrease in all-cause mortality; more importantly, greater cumulative number of vaccinations was associated with an 28% reduced risk in total mortality and a 29% decrease in cardiovascular mortality.[119] A database study of 6,435 HF patients, out of which 695 had been vaccinated before or during the 2017/2018 winter seasons, found a 22% decrease in total mortality and a 17% decrease in cardiovascular death or hospitalizations for HF. The benefits from vaccination on total mortality were greater for patients over the age of 70, with an over 25% decrease.[120] There are no studies on the impact of pneumococcal vaccines on outcomes. Several prospective studies are currently recruiting patients

HF: heart failure.

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8.3. Indications for Genetic Assessment in Cardiomyopathies and Heart Failure (Table 8.3)

Table 8.3 – Recommendations for genetic assessments for patients with cardiomyopathies and HF

Recommendations	Class	LE	Comment	Table 2018	Ref.
Genetic counseling for patients and family members with inherited cardiomyopathies and previously identified mutations.	I	C		New	121-125
Screening test to 1st degree relatives of patients with inherited cardiomyopathies.	I	C	**NEW:** Advances in molecular genetic assessment techniques enable the early identification of inherited cardiomyopathies, supporting the subclassification of clinical syndromes and individualized treatment.	New	121-125
Sequencing of the transthyretin gene in patients diagnosed with transthyretin cardiac amyloidosis.	I	C		New	121-125
Molecular genetic assessment to investigate the etiology and evaluate the prognosis of patients with inherited cardiomyopathy phenotype.	IIa	C		New	121-125
Routine molecular genetic assessment for HF patients.	III	C		New	121-125

The incorporation of next-generation sequencing has increased the sensitivity of genetic testing, allowing for early early diagnosis for future interventions.[121] Consequently, molecular assessments have allowed routine genetic testing for patients with inherited cardiomyopathies, such as hypertrophic, restrictive and/or dilated arrhythmogenic cardiomyopathies, and non-compacted myocardium, due to its potential to provide more individualized and precise counseling for patients with these conditions as well as for their family members.[122] One clear example of this need is the distinction between wild-type and inherited transthyretin cardiac amyloidosis (ATTR) as cascade genetic testing allows at-risk relatives to be definitively identified. It should be highlighted that current therapies for ATTR are particularly beneficial when initiated during the early stages of the disease, as described in item 2, Table 2.4.[123] Advances in prognostic assessment involving genes with high arrhythmogenic potential have also been described for dilated and arrhythmogenic cardiomyopathies.[124,125] Thus, it is important to pursue more efficient uses of genetic information, especially in family counseling, leading to safe and sustainable results in the care of these patients and their family members.

HF: heart failure.

9. Perspectives in Heart Failure – New Molecules

9.1. Guanylate Cyclase Stimulators (Table 9.1)

Table 9.1 – Guanylate cyclase stimulators for the treatment of HFrEF patients

Notes	Comment	Table 2018	Ref.
Vericiguat in patients with LVEF lower than 45%, NYHA II – IV to reduce morbidity, especially in patients with frequent hospitalizations despite optimized guideline-directed medical therapy.	**POTENTIAL:** The observations described herein reflect data from recent studies on this new class of drug. However, it has not been approved by Anvisa for use in Brazil yet.	New	126, 127

Vericiguat acts by supplying the relative deficit of cyclic GMP production in HF patients[126] and was assessed in a multicenter, randomized, double-blind, placebo-controlled trial with HFrEF patients, the *VICTORIA (Vericiguat in Patients with Heart Failure and Reduced Ejection Fraction) trial*. In the *Victoria*, 5050 patients with HFrEF, with LVEF lower than 45%, NYHA II-IV, were randomized to receive vericiguat 10 mg/day orally or placebo, in addition to guideline-directed medical therapy. The primary endpoint was cardiovascular death or first hospitalization for HF. In an 11-month period, the primary endpoint occurred in 35.5% of the vericiguat group and 38.5% of the placebo group, which represents a number needed to treat (NNT) of 24 to save one life over 11 months. The benefit of the composite outcome was primarily attributed to the reduction in hospitalization rates, with no statistically significant impact on cardiovascular or overall mortality.[127] The drug could potentially join the set of medications acting on symptoms and readmissions for HFrEF patients, representing an additional option: for patients who undergo frequent hospitalizations despite optimized therapy; who have impaired kidney function, since patients eligible for the trial had GFR above 15%; or who are intolerance to other medications. It should be stressed that this medication class is contraindicated in combination with nitrates.

GFR: glomerular filtration rate; HF: heart failure; HFrEF: heart failure with reduced ejection fraction; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association.

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9.2. Selective Cardiac Myosin Activator (Table 9.2)

Table 9.2 – Omecamtiv mercabil in the treatment of HFrEF patients

Notes	Comment	Table 2018	Ref.
Omecamtiv mecarbil in patients with acute or chronic HFrEF.	**POTENTIAL:** The observations described herein reflect data from recent studies on this new class of drug. However, it has not been approved by Anvisa for use in Brazil yet.	New	128-131

Omecamtiv mecarbil selectively binds to cardiac myosin resulting in activation and increase in rate of ATP hydrolysis, and the transition of myosin to the strongly actin-bound force-generating state, improving impaired ventricular contraction in cases of HFrEF. Its mechanism of action is different from mechanisms of the current triple therapy, which inhibits neurohormonal stimulation. Mechanistic studies such as the *ATOMIC-AHF* (*Acute Treatment with Omecamtiv Mecarbil to Increase Contractility in Acute Heart Failure*)[128] and *COSMIC-HF* (*Chronic Oral Study of Myosin Activation to Increase Contractility in Heart Failure*)[129] trials, showed that the medication improved contractility, ejection fraction, ejected volume and cardiac output, in addition to other parameters of improved cardiac function. Studies show it promotes decreases in NT-proBNP levels. High troponin levels were also identified without clinical changes in the studies. The *Atomic-AHF* trial, however, with acute HF patients, found no reduction in dyspnea among patients in the treatment group. In the recently-published *GALACTIC-HF (Cardiac Myosin Activation with Omecamtiv Mecarbil in Systolic Heart Failure)* randomized controlled trial, patients with HFrEF who received omecantiv mecarbil had lower risk of composite outcomes from an HF event (defined as hospitalization or unplanned visits due to worsening HF) or cardiovascular death than those who received a placebo.[130,131] However, when assessed individually, there was no difference in the following secondary outcomes: all-cause mortality, cardiovascular death, first hospitalization for HF, or changes in the *Kansas City Cardiomyopathy Questionnaire* quality of life score.

HF: heart failure; HFrEF: heart failure with reduced ejection fraction.

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Update

Emerging Topics Update of the Brazilian Heart Failure Guideline – 2021	
The report below lists declarations of interest as reported to the SBC by the experts during the period of the development of these update, 2020.	
Expert	**Type of relationship with industry**
Aguinaldo F. Freitas Jr.	Financial declaration A - Economically relevant payments of any kind made to (i) you, (ii) your spouse/partner or any other person living with you, (iii) any legal person in which any of these is either a direct or indirect controlling owner, business partner, shareholder or participant; any payments received for lectures, lessons, training instruction, compensation, fees paid for participation in advisory boards, investigative boards or other committees, etc. From the brazilian or international pharmaceutical, orthosis, prosthesis, equipment and implants industry: - Novartis: Heart failure; Servier: Heart failure; Bayer: Anticoagulation.
Andréia Biolo	Nothing to be declared
Antonio Carlos Pereira Barretto	Other relationships Funding of continuing medical education activities, including travel, accommodation and registration in conferences and courses, from the brazilian or international pharmaceutical, orthosis, prosthesis, equipment and implants industry: - Novartis: Sacubitril Valsartana; AstraZeneca: Dapagliflozina, Succinato de Metoprolol, Candesartana; Servier: Ivabradina.
Antônio José Lagoeiro Jorge	Other relationships Funding of continuing medical education activities, including travel, accommodation and registration in conferences and courses, from the brazilian or international pharmaceutical, orthosis, prosthesis, equipment and implants industry: - Novartis: Entresto.
Bruno Biselli	Nothing to be declared
Carlos Eduardo Lucena Montenegro	Financial declaration A - Economically relevant payments of any kind made to (i) you, (ii) your spouse/partner or any other person living with you, (iii) any legal person in which any of these is either a direct or indirect controlling owner, business partner, shareholder or participant; any payments received for lectures, lessons, training instruction, compensation, fees paid for participation in advisory boards, investigative boards or other committees, etc. From the brazilian or international pharmaceutical, orthosis, prosthesis, equipment and implants industry: - AstraZeneca: Lectures; Novartis: Lectures; Servier: Lectures; Merck: Lectures. Other relationships Funding of continuing medical education activities, including travel, accommodation and registration in conferences and courses, from the brazilian or international pharmaceutical, orthosis, prosthesis, equipment and implants industry: - Pfizer: Travel to Congress; AstraZeneca: Travel to Symposium; Novartis: Travel to Symposium.
Carlos Eduardo Lucena Montenegro	Financial declaration B - Research funding under your direct/personal responsibility (directed to the department or institution) from the brazilian or international pharmaceutical, orthosis, prosthesis, equipment and implants industry: - FAPERJ: Clinical research; Boehringer: International Multicenter Clinical Research Participant.
Dirceu Rodrigues de Almeida	Nothing to be declared
Edimar Alcides Bocchi	Financial declaration A - Economically relevant payments of any kind made to (i) you, (ii) your spouse/partner or any other person living with you, (iii) any legal person in which any of these is either a direct or indirect controlling owner, business partner, shareholder or participant; any payments received for lectures, lessons, training instruction, compensation, fees paid for participation in advisory boards, investigative boards or other committees, etc. From the brazilian or international pharmaceutical, orthosis, prosthesis, equipment and implants industry: - AstraZeneca: ISGLT2; Bayer: ISGLT2, Vericiguat; Boehringer: ISGLT2.
Edval Gomes dos Santos Júnior	Nothing to be declared
Estêvão Lanna Figueiredo	Financial declaration B - Research funding under your direct/personal responsibility (directed to the department or institution) from the brazilian or international pharmaceutical, orthosis, prosthesis, equipment and implants industry: - AstraZeneca: Dapagliflozina; Boehringer: Empagliflozina; Pfizer: Apixabana; Novartis
Evandro Tinoco Mesquita	Other relationships Employment relationship with the brazilian or international pharmaceutical, orthosis, prosthesis, equipment and implants industry, as well as any employment relationship with health insurance companies or medical audit companies (including part-time jobs) in the year to which your declaration refers: - UnitedHealth Group.
Fabiana G. Marcondes-Braga	Financial declaration A - Economically relevant payments of any kind made to (i) you, (ii) your spouse/partner or any other person living with you, (iii) any legal person in which any of these is either a direct or indirect controlling owner, business partner, shareholder or participant; any payments received for lectures, lessons, training instruction, compensation, fees paid for participation in advisory boards, investigative boards or other committees, etc. From the brazilian or international pharmaceutical, orthosis, prosthesis, equipment and implants industry: - Novartis: Lectures; AstraZeneca: Lectures and Advisory Council; Boehringer: Advisory Council.

Fábio Fernandes	Financial declaration A - Economically relevant payments of any kind made to (i) you, (ii) your spouse/partner or any other person living with you, (iii) any legal person in which any of these is either a direct or indirect controlling owner, business partner, shareholder or participant; any payments received for lectures, lessons, training instruction, compensation, fees paid for participation in advisory boards, investigative boards or other committees, etc. From the brazilian or international pharmaceutical, orthosis, prosthesis, equipment and implants industry: - Pfizer: Tafamidis; Alnylan: Patisiran.
Fabio Serra Silveira	Financial declaration A - Economically relevant payments of any kind made to (i) you, (ii) your spouse/partner or any other person living with you, (iii) any legal person in which any of these is either a direct or indirect controlling owner, business partner, shareholder or participant; any payments received for lectures, lessons, training instruction, compensation, fees paid for participation in advisory boards, investigative boards or other committees, etc. From the brazilian or international pharmaceutical, orthosis, prosthesis, equipment and implants industry: - Novartis: Entresto; AstraZeneca: Forxiga; Servier: Procoralan. B - Research funding under your direct/personal responsibility (directed to the department or institution) from the brazilian or international pharmaceutical, orthosis, prosthesis, equipment and implants industry: - Amgen: Omecantiv mecarbil. Other relationships Funding of continuing medical education activities, including travel, accommodation and registration in conferences and courses, from the brazilian or international pharmaceutical, orthosis, prosthesis, equipment and implants industry: - Ache: Hypertension.
Felix José Alvarez Ramires	Financial declaration A - Economically relevant payments of any kind made to (i) you, (ii) your spouse/partner or any other person living with you, (iii) any legal person in which any of these is either a direct or indirect controlling owner, business partner, shareholder or participant; any payments received for lectures, lessons, training instruction, compensation, fees paid for participation in advisory boards, investigative boards or other committees, etc. From the brazilian or international pharmaceutical, orthosis, prosthesis, equipment and implants industry: - Novartis: Sacubitril/Valsartana; Pfizer: Patisiran; Merck: Vericiquat; Amgen.
Fernando Antibas Atik	Nothing to be declared
Fernando Bacal	Nothing to be declared
Flávio de Souza Brito	Financial declaration A - Economically relevant payments of any kind made to (i) you, (ii) your spouse/partner or any other person living with you, (iii) any legal person in which any of these is either a direct or indirect controlling owner, business partner, shareholder or participant; any payments received for lectures, lessons, training instruction, compensation, fees paid for participation in advisory boards, investigative boards or other committees, etc. From the brazilian or international pharmaceutical, orthosis, prosthesis, equipment and implants industry: - Novartis: Entresto; Servier: Procoralan; Merck: Concor.
Germano Emílio Conceição Souza	Financial declaration A - Economically relevant payments of any kind made to (i) you, (ii) your spouse/partner or any other person living with you, (iii) any legal person in which any of these is either a direct or indirect controlling owner, business partner, shareholder or participant; any payments received for lectures, lessons, training instruction, compensation, fees paid for participation in advisory boards, investigative boards or other committees, etc. From the brazilian or international pharmaceutical, orthosis, prosthesis, equipment and implants industry: - Novartis: Heart failure; Merck: Heart failure. B - Research funding under your direct/personal responsibility (directed to the department or institution) from the brazilian or international pharmaceutical, orthosis, prosthesis, equipment and implants industry: - Bayer: Rivaroxabana Other relationships Any economically relevant equity interest in companies in the healthcare or education industry or in any companies competing with or supplying to SBC: - Healthcare: Medical services as a legal person, assistance area - Education: Technical education company for classes and courses in the health area
Gustavo Calado de Aguiar Ribeiro	Nothing to be declared
Humberto Villacorta	Financial declaration A - Economically relevant payments of any kind made to (i) you, (ii) your spouse/partner or any other person living with you, (iii) any legal person in which any of these is either a direct or indirect controlling owner, business partner, shareholder or participant; any payments received for lectures, lessons, training instruction, compensation, fees paid for participation in advisory boards, investigative boards or other committees, etc. From the brazilian or international pharmaceutical, orthosis, prosthesis, equipment and implants industry: - Novartis: Heart failure; Roche: Biomarkers; Servier: Heart failure. C - Personal research funding paid by the brazilian or international pharmaceutical, orthosis, prosthesis, equipment and implants industry: - Roche: GDF-15

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Jefferson Luis Vieira	Nothing to be declared
João David de Souza Neto	Nothing to be declared
João Manoel Rossi Neto	Financial declaration A - Economically relevant payments of any kind made to (i) you, (ii) your spouse/partner or any other person living with you, (iii) any legal person in which any of these is either a direct or indirect controlling owner, business partner, shareholder or participant; any payments received for lectures, lessons, training instruction, compensation, fees paid for participation in advisory boards, investigative boards or other committees, etc. From the brazilian or international pharmaceutical, orthosis, prosthesis, equipment and implants industry: - Novartis: Lectures; AstraZeneca: Lectures.
José Albuquerque de Figueiredo Neto	Financial declaration A - Economically relevant payments of any kind made to (i) you, (ii) your spouse/partner or any other person living with you, (iii) any legal person in which any of these is either a direct or indirect controlling owner, business partner, shareholder or participant; any payments received for lectures, lessons, training instruction, compensation, fees paid for participation in advisory boards, investigative boards or other committees, etc. From the brazilian or international pharmaceutical, orthosis, prosthesis, equipment and implants industry: - Novartis: Heart failure.
Lídia Ana Zytynski Moura	Financial declaration A - Economically relevant payments of any kind made to (i) you, (ii) your spouse/partner or any other person living with you, (iii) any legal person in which any of these is either a direct or indirect controlling owner, business partner, shareholder or participant; any payments received for lectures, lessons, training instruction, compensation, fees paid for participation in advisory boards, investigative boards or other committees, etc. From the brazilian or international pharmaceutical, orthosis, prosthesis, equipment and implants industry: - Novartis: Entresto; AstraZeneca: Forxiga. B - Research funding under your direct/personal responsibility (directed to the department or institution) from the brazilian or international pharmaceutical, orthosis, prosthesis, equipment and implants industry: - AstraZeneca: Forxiga.
Livia Adams Goldraich	Nothing to be declared
Luís Beck-da-Silva	Financial declaration A - Economically relevant payments of any kind made to (i) you, (ii) your spouse/partner or any other person living with you, (iii) any legal person in which any of these is either a direct or indirect controlling owner, business partner, shareholder or participant; any payments received for lectures, lessons, training instruction, compensation, fees paid for participation in advisory boards, investigative boards or other committees, etc. From the brazilian or international pharmaceutical, orthosis, prosthesis, equipment and implants industry: - Novartis: Heart failure; AstraZeneca: Heart failure. B - Research funding under your direct/personal responsibility (directed to the department or institution) from the brazilian or international pharmaceutical, orthosis, prosthesis, equipment and implants industry: - Amgen: Heart failure.
Luis Eduardo Rohde	Financial declaration A - Economically relevant payments of any kind made to (i) you, (ii) your spouse/partner or any other person living with you, (iii) any legal person in which any of these is either a direct or indirect controlling owner, business partner, shareholder or participant; any payments received for lectures, lessons, training instruction, compensation, fees paid for participation in advisory boards, investigative boards or other committees, etc. From the brazilian or international pharmaceutical, orthosis, prosthesis, equipment and implants industry: - Astrazeneca: dapaglifozina; Novartis: Sacubitril-Valsartana; Amgen: Omecamtiv Mecarbil; Merck; Bayer.
Luiz Claudio Danzmann	Financial declaration A - Economically relevant payments of any kind made to (i) you, (ii) your spouse/partner or any other person living with you, (iii) any legal person in which any of these is either a direct or indirect controlling owner, business partner, shareholder or participant; any payments received for lectures, lessons, training instruction, compensation, fees paid for participation in advisory boards, investigative boards or other committees, etc. From the brazilian or international pharmaceutical, orthosis, prosthesis, equipment and implants industry: - Novartis: Entresto; AstraZeneca: Forxiga; Servier: Procoralan.
Manoel Fernandes Canesin	Nothing to be declared
Marcelo Imbroinise Bittencourt	Financial declaration A - Economically relevant payments of any kind made to (i) you, (ii) your spouse/partner or any other person living with you, (iii) any legal person in which any of these is either a direct or indirect controlling owner, business partner, shareholder or participant; any payments received for lectures, lessons, training instruction, compensation, fees paid for participation in advisory boards, investigative boards or other committees, etc. From the brazilian or international pharmaceutical, orthosis, prosthesis, equipment and implants industry: - Geneone - Dasa: Genetic testing; Sanofi: Enzyme replacement therapy; AstraZeneca: Forxiga.
Marcelo Westerlund Montera	Nothing to be declared

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Marcely Gimenes Bonatto	Financial declaration A - Economically relevant payments of any kind made to (i) you, (ii) your spouse/partner or any other person living with you, (iii) any legal person in which any of these is either a direct or indirect controlling owner, business partner, shareholder or participant; any payments received for lectures, lessons, training instruction, compensation, fees paid for participation in advisory boards, investigative boards or other committees, etc. From the brazilian or international pharmaceutical, orthosis, prosthesis, equipment and implants industry: - Novartis: Sacubitril/Valsartana; AstraZeneca: Forxiga
Marcus Vinícius Simões	Financial declaration A - Economically relevant payments of any kind made to (i) you, (ii) your spouse/partner or any other person living with you, (iii) any legal person in which any of these is either a direct or indirect controlling owner, business partner, shareholder or participant; any payments received for lectures, lessons, training instruction, compensation, fees paid for participation in advisory boards, investigative boards or other committees, etc. From the brazilian or international pharmaceutical, orthosis, prosthesis, equipment and implants industry: - Novartis: Entresto; AstraZeneca: Dapagliflozina. B - Research Funding Under Your Direct/Personal Responsibility (Directed To The Department Or Institution) From The Brazilian Or International Pharmaceutical, Orthosis, Prosthesis, Equipment And Implants Industry: - Amgen: Omecamtiv/Mecarbil; Beringher Ingelheim: Empagliflozina.
Maria da Consolação Vieira Moreira	Nothing to be declared
Miguel Morita Fernandes-Silva	Financial declaration A - Economically relevant payments of any kind made to (i) you, (ii) your spouse/partner or any other person living with you, (iii) any legal person in which any of these is either a direct or indirect controlling owner, business partner, shareholder or participant; any payments received for lectures, lessons, training instruction, compensation, fees paid for participation in advisory boards, investigative boards or other committees, etc. From the brazilian or international pharmaceutical, orthosis, prosthesis, equipment and implants industry: - Novartis: Heart failure C - Personal research funding paid by the brazilian or international pharmaceutical, orthosis, prosthesis, equipment and implants industry: - Amgen: Omecamtiv/Heart failure; Beringher Ingelheim: Empagliflozina.
Mônica Samuel Avila	Nothing to be declared
Mucio Tavares de Oliveira Junior	Financial declaration B - Research funding under your direct/personal responsibility (directed to the department or institution) from the brazilian or international pharmaceutical, orthosis, prosthesis, equipment and implants industry: - Torrent do Brasil: Developing forms of drugs; Sanofi Pasteur: Flu vaccine
Nadine Clausell	Nothing to be declared
Odilson Marcos Silvestre	Nothing to be declared
Otavio Rizzi Coelho Filho	Financial declaration A - Economically relevant payments of any kind made to (i) you, (ii) your spouse/partner or any other person living with you, (iii) any legal person in which any of these is either a direct or indirect controlling owner, business partner, shareholder or participant; any payments received for lectures, lessons, training instruction, compensation, fees paid for participation in advisory boards, investigative boards or other committees, etc. From the brazilian or international pharmaceutical, orthosis, prosthesis, equipment and implants industry: - Pfizer: Cardiac amyloidosis; Alnylam: Cardiac amyloidosis; AstraZeneca: Heart failure; Novartis. B - Research funding under your direct/personal responsibility (directed to the department or institution) from the brazilian or international pharmaceutical, orthosis, prosthesis, equipment and implants industry: - Pfizer: Cardiac amyloidosis. Other relationships Funding of continuing medical education activities, including travel, accommodation and registration in conferences and courses, from the brazilian or international pharmaceutical, orthosis, prosthesis, equipment and implants industry: - AstraZeneca: Heart failure; Pfizer: Heart failure.
Pedro Vellosa Schwartzmann	Financial declaration A - Economically relevant payments of any kind made to (i) you, (ii) your spouse/partner or any other person living with you, (iii) any legal person in which any of these is either a direct or indirect controlling owner, business partner, shareholder or participant; any payments received for lectures, lessons, training instruction, compensation, fees paid for participation in advisory boards, investigative boards or other committees, etc. From the brazilian or international pharmaceutical, orthosis, prosthesis, equipment and implants industry: - Novartis: Entresto; Servier: Ivabradina; AstraZeneca: Dapagliflozina; Merck: Serono. B - Research funding under your direct/personal responsibility (directed to the department or institution) from the brazilian or international pharmaceutical, orthosis, prosthesis, equipment and implants industry: - Novartis: investigacional; Eidos: AG10. Other relationships Funding of continuing medical education activities, including travel, accommodation and registration in conferences and courses, from the brazilian or international pharmaceutical, orthosis, prosthesis, equipment and implants industry: - Bayer: Rivaroxaban; AstraZeneca: Dapagliflozina.
Reinaldo Bulgarelli Bestetti	Nothing to be declared

Ricardo Mourilhe-Rocha	Financial declaration A - Economically relevant payments of any kind made to (i) you, (ii) your spouse/partner or any other person living with you, (iii) any legal person in which any of these is either a direct or indirect controlling owner, business partner, shareholder or participant; any payments received for lectures, lessons, training instruction, compensation, fees paid for participation in advisory boards, investigative boards or other committees, etc. From the brazilian or international pharmaceutical, orthosis, prosthesis, equipment and implants industry: - Boehringer: Empagliflozina; Novartis: Sacubitril/Valsartana. B - Research funding under your direct/personal responsibility (directed to the department or institution) from the brazilian or international pharmaceutical, orthosis, prosthesis, equipment and implants industry: - PROADI/SUS: Telemedicine; Boehringer: Empagliflozina.
Sabrina Bernadez-Pereira	Nothing to be declared
Salvador Rassi	Financial declaration A - Economically relevant payments of any kind made to (i) you, (ii) your spouse/partner or any other person living with you, (iii) any legal person in which any of these is either a direct or indirect controlling owner, business partner, shareholder or participant; any payments received for lectures, lessons, training instruction, compensation, fees paid for participation in advisory boards, investigative boards or other committees, etc. From the brazilian or international pharmaceutical, orthosis, prosthesis, equipment and implants industry: - Novartis: Entresto; Servier: Procoralan. B - Research funding under your direct/personal responsibility (directed to the department or institution) from the brazilian or international pharmaceutical, orthosis, prosthesis, equipment and implants industry: - Novartis: Entresto; Servier: Procoralan; Boehringer Ingelheim: Jardiance. Other relationships Funding of continuing medical education activities, including travel, accommodation and registration in conferences and courses, from the brazilian or international pharmaceutical, orthosis, prosthesis, equipment and implants industry: - Novartis: Entresto; Servier: Procoralan.
Sandrigo Mangini	Financial declaration A - Economically relevant payments of any kind made to (i) you, (ii) your spouse/partner or any other person living with you, (iii) any legal person in which any of these is either a direct or indirect controlling owner, business partner, shareholder or participant; any payments received for lectures, lessons, training instruction, compensation, fees paid for participation in advisory boards, investigative boards or other committees, etc. From the brazilian or international pharmaceutical, orthosis, prosthesis, equipment and implants industry: - Novartis: Sacubitril/Valsartan; Pfizer: Rare diseases. Other relationships Funding of continuing medical education activities, including travel, accommodation and registration in conferences and courses, from the brazilian or international pharmaceutical, orthosis, prosthesis, equipment and implants industry: - Pfizer: Rare diseases.
Silvia Marinho Martins Alves	Nothing to be declared
Silvia Moreira Ayub Ferreira	Financial declaration A - Economically relevant payments of any kind made to (i) you, (ii) your spouse/partner or any other person living with you, (iii) any legal person in which any of these is either a direct or indirect controlling owner, business partner, shareholder or participant; any payments received for lectures, lessons, training instruction, compensation, fees paid for participation in advisory boards, investigative boards or other committees, etc. From the brazilian or international pharmaceutical, orthosis, prosthesis, equipment and implants industry: - Abbott: Mitraclip; Novartis: Entresto. Other relationships Funding of continuing medical education activities, including travel, accommodation and registration in conferences and courses, from the brazilian or international pharmaceutical, orthosis, prosthesis, equipment and implants industry: - Abbott: Heartmate II e HeartMate 3
Victor Sarli Issa	Nothing to be declared

Marcondes-Braga et al.
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Update

Position Statement on Post-COVID-19 Cardiovascular Preparticipation Screening: Guidance for Returning to Physical Exercise and Sports – 2020

Development: Sports Cardiology Study Group (Grupo de Estudos de Cardiologia do Esporte – GECESP), Department of Ergometry, Exercise, Nuclear Cardiology, and Cardiovascular Rehabilitation (Departamento de Ergometria, Exercício, Cardiologia Nuclear e Reabilitação Cardiovascular – DERC) of the Brazilian Society of Cardiology (Sociedade Brasileira de Cardiologia – SBC) and the Brazilian Society of Exercise and Sports Medicine (Sociedade Brasileira de Medicina do Exercício e Esporte – SBMEE)

Norms and Guidelines Council (2020-2021): Brivaldo Markman Filho, Antonio Carlos Sobral Sousa, Aurora Felice Castro Issa, Bruno Ramos Nascimento, Harry Correa Filho, Marcelo Luiz Campos Vieira

Norms and Guidelines Coordinator (2020-2021): Brivaldo Markman Filho

Statement Coordinator: Cléa Simone Sabino de Souza Colombo

Statement Authors: *Cléa Simone Sabino de Souza Colombo,[1,2,33] Marcelo Bichels Leitão,[3,9,22] Antônio Carlos Avanza Junior,[4,5] Serafim Ferreira Borges,[6-9] Anderson Donelli da Silveira,[10,11] Fabrício Braga,[12-14] Ana Cristina Camarozano,[15] Daniel Arkader Kopiler,[16,17] José Kawazoe Lazzoli,[18-22] Odilon Gariglio Alvarenga de Freitas,[23] Gabriel Blacher Grossman,[24,25] Mauricio Milani,[26] Mauricio B. Nunes,[27] Luiz Eduardo Fonteles Ritt,[28,29] Carlos Alberto Cyrillo Sellera,[30,31] Nabil Ghorayeb[32,33]*

Faculdade de Medicina São Leopoldo Mandic – Campinas,[1] SP – Brazil
Sportscardio Clínica Cardiológica – Valinhos,[2] SP – Brazil
CEFIT – Centro de Estudos de Fisiologia do Exercício e Treinamento,[3] Curitiba, PR – Brazil
Universidade Vila Velha,[4] ES – Brazil
Clínica Centrocor,[5] Vitória, ES – Brazil
Clube de Regatas do Flamengo,[6] Rio de Janeiro, RJ – Brazil
Instituto Estadual de Cardiologia Aloysio de Castro,[7] Rio de Janeiro, RJ – Brazil
Imagecor Medicina Diagnóstica e do Exercício,[8] Rio de Janeiro, RJ – Brazil
Brazilian Federal Council of Medicine, Technical Committee on Sports Medicine,[9] Rio de Janeiro, RJ – Brazil
Hospital de Clínicas de Porto Alegre,[10] Porto Alegre, RS – Brazil
Universidade Federal do Rio Grande do Sul,[11] Porto Alegre, RS – Brazil
Laboratório de Performance Humana,[12] Rio de Janeiro, RJ – Brazil
Casa de Saúde São José,[13] Rio de Janeiro, RJ – Brazil
Brazilian Triathlon Confederation,[14] Rio de Janeiro, RJ – Brazil
Universidade Federal do Paraná,[15] Curitiba, PR – Brazil
Instituto Nacional de Cardiologia (INC),[16] Rio de Janeiro, RJ – Brazil
Pan American Confederation of Sports Medicine[17]
Instituto Biomédico da Universidade Federal Fluminense (UFF),[18] Niterói, RJ – Brazil
Hospital Santa Teresa/ACSC,[19] Petrópolis, RJ – Brazil
Pan American Confederation of Sports Medicine (COPAMEDE)[20]
International Federation of Sports Medicine (FIMS)[21]
Therapeutic Use Exemption Committee (CAUT) of the Brazilian Authority on Doping Control (ABCD)[22]
Minascor Centro Médico,[23] Belo Horizonte, MG – Brazil
Hospital Moinhos de Vento,[24] Porto Alegre, RS – Brazil
Clínica Cardionuclear,[25] Porto Alegre, RS – Brazil
Fitcordis Medicina do Exercício,[26] Brasília, DF – Brazil
Hospital Português,[27] Salvador, BA – Brazil
Hospital Cárdio Pulmonar,[28] Salvador, BA – Brazil
Escola Bahiana de Medicina e Saúde Pública,[29] – Salvador, BA – Brazil
Santa Casa de Santos,[30] Santos, SP – Brazil
Universidade Metropolitana de Santos,[31] Santos, SP – Brazil
Instituto Dante Pazzanese de Cardiologia,[32] São Paulo, SP – Brazil
Hospital do Coração (HCor),[33] São Paulo, SP – Brazil

Statement

Position Statement on Post-COVID-19 Cardiovascular Preparticipation Screening: Guidance for Returning to Physical Exercise and Sports – 2020

The report below lists declarations of interest as reported to the SBC by the experts during the period of the development of these statement, 2020.

Expert	Type of relationship with industry
Ana Cristina Camarozano	Nothing to be declared
Anderson Donelli da Silveira	Nothing to be declared
Antônio Carlos Avanza Junior	Nothing to be declared
Carlos Alberto Cyrillo Sellera	Nothing to be declared
Cléa Simone Sabino de Souza Colombo	Nothing to be declared
Daniel Arkader Kopiler	Nothing to be declared
Fabrício Braga	Nothing to be declared
Gabriel Blacher Grossman	Nothing to be declared
José Kawazoe Lazzoli	Nothing to be declared
Luiz Eduardo Fonteles Ritt	Financial declaration A - Economically relevant payments of any kind made to (i) you, (ii) your spouse/partner or any other person living with you, (iii) any legal person in which any of these is either a direct or indirect controlling owner, business partner, shareholder or participant; any payments received for lectures, lessons, training instruction, compensation, fees paid for participation in advisory boards, investigative boards or other committees, etc. from the brazilian or international pharmaceutical, orthosis, prosthesis, equipment and implants industry: - Pfizer: Amiloidose Other relationships Any other interest — financial or other — that should be declared considering the position taken in sbc that has not been expressly listed above: - Consultor em projeto de pesquisa junto ao Cimatec, da empresa MDI Medical
Marcelo Bichels Leitão	Nothing to be declared
Mauricio B. Nunes	Nothing to be declared
Mauricio Milani	Nothing to be declared
Odilon Gariglio Alvarenga de Freitas	Nothing to be declared
Serafim Ferreira Borges	Nothing to be declared
Nabil Ghorayeb	Nothing to be declared

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Position Statement on Post-COVID-19 Cardiovascular Preparticipation Screening: Guidance for Returning to Physical Exercise and Sports – 2020

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Content

1. Introduction

On January 30, 2020, the World Health Organization (WHO) stated that the outbreak of coronavirus disease 2019 (COVID-19) caused by the new coronavirus (SARS-CoV-2) constituted a "public health emergency of international concern" — the highest-level alert issued by the organization, as provided for in the International Health Regulations. Compared to SARS-CoV, which caused an outbreak of severe acute respiratory syndrome (SARS) in 2003, SARS-CoV-2 has greater transmission potential. The rapid increase in confirmed cases has made COVID-19 prevention and control extremely important. The Brazilian Ministry of Health received the first report of a confirmed case of COVID-19 in Brazil on February 26, 2020; on March 11, 2020, WHO declared the disease a pandemic, leading to an urgent need to seek knowledge and solutions as quickly as possible for both treatment and prevention.[1]

The pandemic led to preventive and restrictive measures worldwide, which were different across countries and continents depending on COVID-19 outcomes in each region. As infection rates decline, less strict restrictions are being implemented for sports and exercise.

COVID-19 has been associated with a significant number of cardiovascular complications, reaching approximately 16% of patients.[2] However, there is a lack of long-term data, especially on active individuals and competitive athletes. Based on the established knowledge about common viral myocarditis, it is known that there may be sequelae affecting physical performance and leading to greater occurrence of

sudden death (SCD) during exercise, as they constitute an arrhythmogenic substrate in the myocardium.[3]

This position statement aims to warn against the risk of cardiac impairment and its possible sequelae in patients with COVID-19 as well as to provide guidance on the need for post-disease cardiological evaluation before returning to sports, including proposed strategies for SCD prevention using targeted cardiovascular preparticipation screening (PPS).

2. Physical Activity and the Pandemic

In view of the lack of effective treatments in the event of a SARS-CoV-2 infection, obtaining measures that reduce the risk of contamination is essential. These include the widespread practices of social isolation, distancing, respiratory etiquette, wearing masks, and frequent hand hygiene.

However, interventions that improve the health of the population and thus allow a reduction in the risk of infection or a more efficient clinical response are also required, so that individuals have mild symptoms and good outcomes if infected with the new coronavirus. Dietary changes and vitamin supplements are among the proposed strategies. However, there is no consistent evidence in favor of any of those prophylactic measures to date.[4]

As this is a new disease, there is a lack of data on how regular exercise may affect the course of COVID-19.

Conversely, the health benefits of physical activity are well established. Overall, individuals who exercise regularly are protected against viruses, with reduced incidence of upper airway infections and better clinical outcomes with fewer complications.[5] Such evidence has been documented in different types of viral infections, including some caused by rhinovirus and some types of coronavirus.[6] Regular light-to-moderate intensity exercise improves immunity and may contribute as a potential factor for having greater resistance to develop COVID-19 and for having more favorable outcomes in an occasional infection.[7,8]

The most important benefits of regular exercise include reduced cardiovascular risk through several mechanisms, such as reduced levels of blood pressure, blood lipids, blood glucose, and inflammatory and hemostatic markers.[9] The presence of cardiovascular and metabolic diseases is associated with higher mortality in SARS-CoV-2-infected patients.

Another relevant factor is obesity, which has been described as an important risk factor for the severity of COVID-19 symptoms, especially in the young. Studies show that patients with body mass index (BMI) > 30 kg/m^2 require invasive mechanical ventilation more frequently, which may be a factor associated with a higher risk of death.[10-13]

The quarantine period, with the imposition of people's confinement, has caused an increase in binge eating and sedentary lifestyle, contributing to an increased prevalence of obesity and a loss of control over diseases such as hypertension and diabetes mellitus.

Another feature that has been documented since the beginning of the COVID-19 pandemic is the increased incidence of psychological disorders due to home confinement.

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High rates of anxiety and depression have been reported in quarantined individuals because of the pandemic, and a possible increase in suicides has been discussed.[14,15] As is the case with obesity, there is also consistent literature documenting the effects of regular physical activity on reducing depression, anxiety, and other mental health disorders.[16]

Therefore, treatment of those diseases must be continuously optimized, and exercise plays an essential role in control measures. Thus, adopting and maintaining an active lifestyle is recommended to improve several aspects of health and well-being, including reduced cardiovascular and metabolic risk and improved mental balance.

Despite the restrictions imposed by the risk of coronavirus contamination, we should primarily encourage individuals to remain physically active, regardless of whether they exercise at home or outdoors, respecting local hygiene and distancing rules.

3. COVID-19

Individuals with COVID-19 have a wide range of symptoms, with the majority showing mild-to-moderate manifestations, especially flu-like symptoms such as dry cough, sore throat, headache, and fever, as well as diarrhea, skin rash, and loss of smell and taste. A small proportion of patients develops more severe symptoms and may experience shortness of breath, chest pain, and loss of movements, requiring hospitalization and intensive support.[17]

The progression of the disease over time is divided into three pathological stages: an early infection stage, a pulmonary stage, and a severe hyperinflammation stage. The early infection stage is characterized by viral infiltration and replication. The disease then progresses to the pulmonary stage, characterized by respiratory impairment and changes in pulmonary imaging tests. An exaggerated inflammatory response, driven by host immunity, defines the hyperinflammation stage. Inflammatory markers are elevated at this stage, and damage to secondary organs becomes apparent.[18,19]

Although clinical manifestations of COVID-19 are dominated by respiratory symptoms, some patients have severe cardiovascular impairment.[20] Some patients with underlying cardiovascular disease (CVD) may also be at an increased risk of death.[21] Therefore, understanding the damage caused by SARS-CoV-2 to the cardiovascular system and the underlying mechanisms is of utmost importance so that the treatment of those patients can be timely and effective, with reduced mortality and late complications.

3.1. COVID-19 and the Heart

Based on data from countries such as China, where the pandemic began, from other countries with a large number of COVID-19 cases, such as the United States (US) and Italy, and from a meta-analysis on the disease, cardiac injury appears to be a prominent feature, affecting 20% to 30% of hospitalized patients and contributing to 40% of deaths.[22] Cardiovascular complications have been described, including myocardial injury (20% of cases), arrhythmia (16%), myocarditis (10%), and congestive heart failure (CHF) and shock (up to

5%).[23,24] In a study evaluating 138 patients hospitalized with COVID-19, 16.7% developed arrhythmia and 7.2% had acute cardiac injury (electrocardiographic or echocardiographic abnormalities). Almost 12% of patients without any previously known CVD had elevated levels of high-sensitivity troponin T (TnT) or cardiac arrest during hospitalization.[25,26] Notably, TnT was above the 99th percentile upper reference limit in 46% of nonsurvivors as opposed to 1% of survivors.[27] Its elevation was associated with other inflammatory biomarkers (D-dimer, ferritin, interleukin-6, lactate dehydrogenase), increasing the possibility that this reflects a "cytokine storm" or secondary hemophagocytic lymphohistiocytosis rather than myocardial injury alone.[27] It is unknown whether this phenomenon is the main cause of fulminant myocarditis and whether the response is purely related to inflammation, autoimmunity, or a combination of both, as seen in other types of viral myocarditis.[28]

Conversely, there are reports of patients with predominant cardiac symptoms that suggest a different pattern, such as stress cardiomyopathy and acute coronary syndrome, in which pathophysiology is unclear but may be related to a prothrombotic state associated with the disease, as seen in individuals who had pulmonary embolism and stroke.[15,24,29-31] The exact pathophysiology in severe cases of COVID-19 remains unclear, and cardiac injury is believed to result from direct or indirect mechanisms (Chart 1).[21,29,32]

Cardiac involvement with other presentations, such as cardiogenic shock and heart failure, would probably entail the same pathophysiological mechanism.

4. Cardiovascular Preparticipation Screening

Cardiovascular PPS is the main tool for SCD prevention in sports. The Guidelines for Exercise and Sports Cardiology, published by the Brazilian Society of Cardiology and the Brazilian Society of Exercise and Sports Medicine, recommend that all individuals undergo a medical evaluation before beginning to exercise.[33] Considering that most people stopped or reduced their physical training during the pandemic, it is recommended that, before resuming it, they undergo a new PPS evaluation.

It is well known that vigorous exercise may lead to SCD in susceptible individuals, ie, those who have underlying, usually undiagnosed heart disease.[34] Overall, PPS aims to identify such individuals, searching for so-called genetic cardiovascular diseases, which are relatively uncommon but represent the main causes of SCD in sports, such as hypertrophic cardiomyopathy, arrhythmogenic ventricular dysplasia, anomalous origin of coronary arteries, aortic aneurysm related to Marfan syndrome, long QT syndrome, Brugada syndrome, among others. Acquired diseases that may lead to SCD include obstructive coronary artery disease and myocarditis, especially in the young. In the current context, special attention should be given to a possible aggression to the myocardium and pericardium by SARS-CoV-2. Because COVID-19 is a new disease and relevant knowledge remains limited, a careful evaluation should be conducted to rule out the presence and/or sequela of myopericarditis, even in asymptomatic individuals who tested positive.
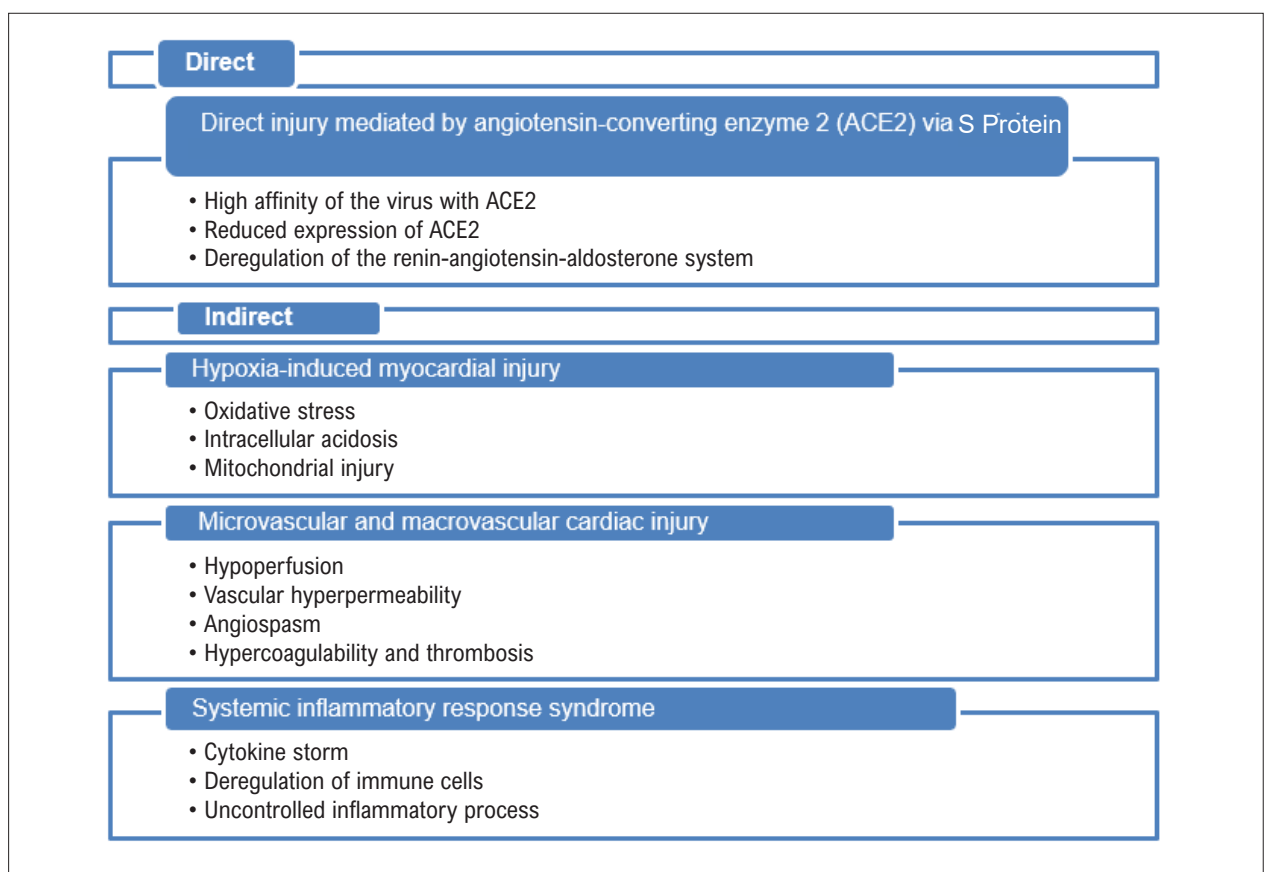
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┌─────────────────────────────────────────────────────────────────────┐
│   ┌──── Direct ────┐                                                  │
│   ┌───────────────────────────────────────────────────────────────┐  │
│   │  Direct injury mediated by angiotensin-converting enzyme 2      │  │
│   │  (ACE2) via S Protein                                           │  │
│   └───────────────────────────────────────────────────────────────┘  │
│     • High affinity of the virus with ACE2                            │
│     • Reduced expression of ACE2                                      │
│     • Deregulation of the renin-angiotensin-aldosterone system        │
│                                                                        │
│   ┌──── Indirect ────┐                                                │
│     Hypoxia-induced myocardial injury                                 │
│     • Oxidative stress                                                │
│     • Intracellular acidosis                                         │
│     • Mitochondrial injury                                            │
│                                                                        │
│     Microvascular and macrovascular cardiac injury                   │
│     • Hypoperfusion                                                   │
│     • Vascular hyperpermeability                                     │
│     • Angiospasm                                                     │
│     • Hypercoagulability and thrombosis                              │
│                                                                        │
│     Systemic inflammatory response syndrome                          │
│     • Cytokine storm                                                 │
│     • Deregulation of immune cells                                   │
│     • Uncontrolled inflammatory process                             │
└─────────────────────────────────────────────────────────────────────┘
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Chart 1 – *Proposed mechanisms for cardiac injury in COVID-19*

Therefore, we recommend that all those who had COVID-19, asymptomatic or not, undergo a medical assessment, including at least medical history and physical examination, and resting 12-lead electrocardiogram (ECG). As a higher risk of SCD is related to greater exercise intensity, the recommendations for additional PPS tests are different according to sports practice. In this document, we divided the amateur athletes into recreational and competitive, as we believe that there is an increasing number of individuals who compete as amateurs and have no professional relationships but who are exposed to high volume and intensity training, similar to the so-called professional "athletes." How those groups are defined and some important concepts for understanding them are shown in Charts 2 and 3.[33,35]

Likewise, indication for tests may also vary according to the severity of COVID-19 ilness. In the current classification proposal for COVID-19 stages, patients can be divided into mild, moderate and severe, according to the clinical presentation (Figure 1).[36]

Because information about COVID-19 in children and adolescents is limited and because they have different characteristics, this document will not address this group. The suggested recommendations are focused on the adult population.

As a criterion for positive COVID-19 testing, we considered the existence of previous reverse-transcription polymerase chain reaction (RT-PCR) (viral RNA identification) associated with suspicious symptoms or serology (IgG identification) positive for SARS-CoV-2.[37] The reason why some asymptomatic individuals remain positive on RT-PCR after clinical resolution is not well established. Recent data have shown that some individuals may have traces of SARS-CoV-2 RNA for up to 12 weeks after the infection but no viral replication, with no potential for infection.[38] Hence, repeating the RT-PCR test 3 to 4 days after symptom resolution is not indicated, and there is no need for negative RT-PCR documentation to end quarantine or to return to sports, as clearance criteria are based on clinical data.

It is worth noting that individuals who are in the acute phase and/or symptomatic cannot resume physical activity. Therefore, PPS should be conducted at least 14 days after diagnosis in asymptomatic patients or 14 days after clinical resolution in symptomatic patients.

4.1. Additional Tests

4.1.1. 12-Lead Electrocardiogram
Resting 12-lead ECG is recommended in PPS of amateur and professional athletes in the Brazilian Guidelines for Sports Cardiology to identify possible changes that correlate with

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PHYSICAL ACTIVITY

• Action allowing muscle contraction, starting from rest and then producing energy expenditure

PHYSICAL EXERCISE

• Planned activity with increasing intensity and volume cycles, with performance gain purposes

SPORT

• Exercise involving basic rules, which can be for leisure or competitive purposes

Chart 2 – *Concepts of movement. Source: Pescatello L et al.[35]*

RECREATION AMATEUR ATHLETES

• Practices exercices and sports on a regular basis, from mild to moderate intensity, but do not participate in competitive events

COMPETITIVE AMATEUR ATHLETES

• Practices exercices and sports on a regular basis, often at high intensity, occasionally competing, but has no professional relationships with the sport

PROFESSIONAL ATHLETES

• Participates in an organized team or individual sport that requires systematic training or regular competition, with professional relationships with clubs and/or sponsors of any nature. The key characteristic of athletes is the tendency to highest-intensity stimuli and training in the search for overcoming their own limits and records under intense physical and psychological stress

Chart 3 – *Definition of groups engaging in physical activities and sports. Modified from: Ghorayeb N et al.[33]*
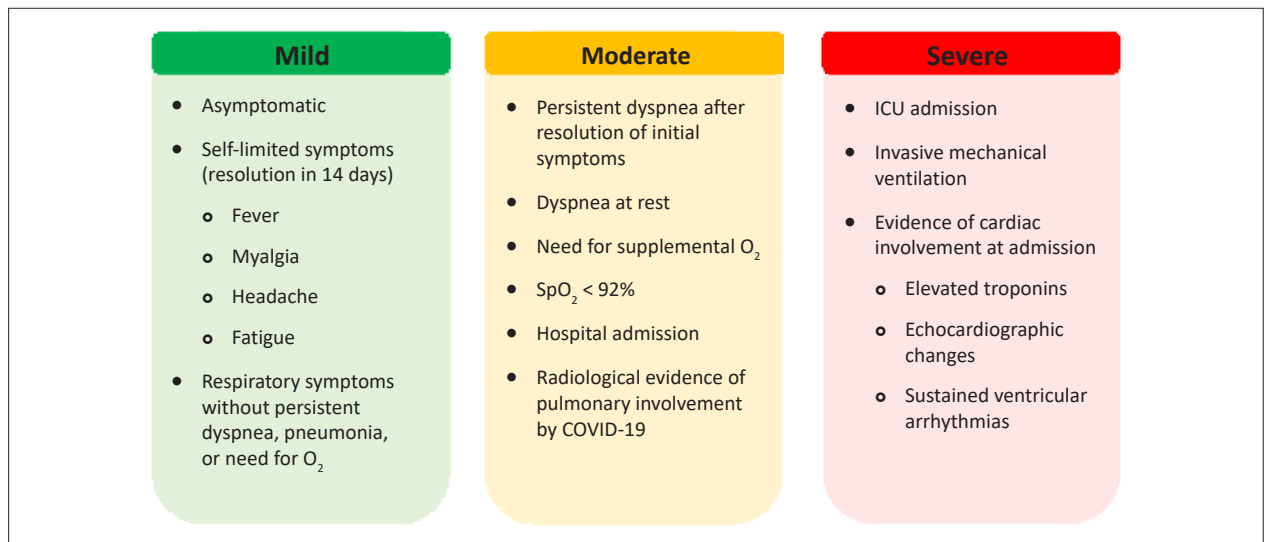
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Figure 1 – *Definition of mild, moderate and severe clinical presentation of COVID-19 ilness. Adapted from: Siddiqi HK & Mehra MR.[36]*

incipient diseases that were previously mentioned as the most common causes of SCD.[39] Particularly in individuals post COVID-19, we must be aware of changes that may be related to pericarditis or myocarditis. The most common ones are:

• ST-segment changes (usually ST-segment depression);

• T-wave inversion;

• Conduction abnormalities, especially complete left bundle branch block and atrioventricular blocks;

• Complex supraventricular and ventricular arrhythmias.[40]

An Italian study of patients hospitalized with COVID-19 associated with pneumonia showed that 26% had new electrocardiographic changes within 51 days (mean, 20 to 30 days) of symptom onset when compared to admission ECG. The most frequent findings were bradycardia (2%), atrial fibrillation (6%), and persistent ST changes (14%); in 38% of patients, increased levels of associated TnT were identified. The changes did not correlate with severity of pulmonary symptoms, sometimes appearing on the eve of hospital discharge and after a new negative RT-PCR test.[41]

It is important to point out that well-trained individuals and athletes usually have an electrocardiographic pattern different from that of the general population due to physiological cardiac adaptations secondary to exercise. Therefore, interpretation should be done preferably by a cardiologist with experience in sports or a sports medicine physician with experience in cardiology, following the current Ïnternational recommendations for electrocardiographic interpretation in athletes.[42] Additionally, comparing a post-COVID-19 ECG with a previous ECG of the athlete is extremely useful, and any new changes should be considered suspect and subject to further investigation.

4.1.2. High-Sensitivity Troponin T

High-sensitivity TnT is an important marker of myocardial injury, and its assay is used to help in the diagnosis of some

heart diseases. The association of elevated levels with changes suggestive of myocarditis on cardiac magnetic resonance imaging (MRI) is well established and has long been known. Although elevated TnT during hospitalization of patients with COVID-19 has proved to be an important prognostic marker, a direct correlation between those two findings has not been established in this disease.[43-46]

Initial data on patients at the subacute stage of COVID-19 presenting cardiac MRI changes compatible with myocarditis showed a significant increase in TnT levels (> 9.3 pg/mL), but interestingly, 71% of recovered patients had "detectable" TnT levels (> 3.0 pg/mL).[47] To date, this is the best available information on a possible association of elevated TnT with myocarditis in COVID-19.

Hence, we consider that outpatient TnT levels dosage also in the subacute stage of disease can be an important tool not only for stratifying risk but also for screening patients who should undergo cardiac MRI for further diagnostic investigation.

4.1.3. Exercise Testing

Exercise testing (ExT) has several indications in the sports field, including assessment of functional capacity (FC) and early identification and prognosis of cardiovascular diseases and arrhythmias. In athletes post COVID-19, it is important to note the occurrence of ST segment changes and arrhythmias during or after exercise, and FC assessment at the peak exercise, as well. However, in the case of FC, a cardiopulmonary exercise test (CPET) is preferable for a more accurate assessment. As in resting ECG, comparing new and previous tests of the same patient is of great importance in the interpretation of ExT findings.

4.1.4. Cardiopulmonary Exercise Testing

CPET is the gold standard for assessment of maximal FC using direct measurement of oxygen uptake. It has important advantages over conventional ExT, including measuring FC

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more accurately, providing prognostic measures of ventilatory efficiency, assisting in differential diagnosis of dyspnea, and using objective criteria for maximality.[48] CPET, in many cases, is able to elucidate the main pathophysiological mechanism of exercise limitation, helping in diagnosis and appropriate therapeutic approach. It is an important test for identifying the genesis of dyspnea suggesting pulmonary, cardiovascular, or physical deconditioning limitations, depending on results.

Little is known about the role of CPET in patients post new coronavirus infection. To date, there are no published studies on patients post COVID-19. In a study of a small sample of patients with SARS, 75% had abnormal tests — 43% due to deconditioning, 19% due to cardiovascular limitation, and 6% due to pulmonary limitation.[49]

Many athletes are returning to their activities and will occasionally be less conditioned. In the current context, as there is the possibility that athletes who contracted COVID-19, even in its mild presentation, have late cardiorespiratory complications, an available method that helps differentiate low conditioning from cardiorespiratory inefficiency can assist in the approach for those athletes.

CPET provides a range of information about ventilatory efficiency, and the relationship between minute ventilation and carbon dioxide production (VE/VCO_2 slope) is the most used parameter in patients with CHF.[50,51] There are studies showing that VE/VCO_2 slope in athletes does not change, even when there are significant variations in maximal FC.[52,53]

Because of the potential additional prognostic role, the possibility of assisting in differential diagnosis of dyspnea, and the availability of information on ventilatory efficiency regardless of maximal FC, we recommend CPET, if available, for all individuals post COVID-19 with dyspnea who had severe or moderate clinical presentation and for all competitive athletes.

4.1.5. 24-Hour Holter Monitoring

A 24-hour Holter test is useful for identifying arrhythmias, either symptomatic or not, and will be indicated for specific cases when myocardial injury with sequelae is suspected. The presence of arrhythmias is one of the criteria for prognostic evaluation and for eligibility to return to sports in patients diagnosed with myocarditis.[54]

4.1.6. Echocardiography

Echocardiography (Echo) is particularly useful in sports for evaluating data regarding adaptive physiology of athlete's heart. Echo is indicated for identification of cardiac structural changes that are often responsible for SCD in those individuals. Therefore, the use of Echo for screening high-performance athletes is of great importance to prevent tragic outcomes, since the method has high sensitivity and specificity for identifying those changes.[55]

The European Society of Cardiology PPS protocol highlights three main points: personal and family history, clinical examination, and ECG.[56] However, some structural diseases such as incipient cardiomyopathy and anomalous origin of coronary arteries may be missed by clinical examination and ECG but will be identified on Echo. It is essential to know the

characteristics and normal values of athletes' Echo measures, which differ from those of the general population, for adequate test interpretation.[57]

Particularly in individuals post COVID-19, we must be aware of cardiac changes suggestive of myopericarditis. Those changes may be more frequently present in individuals who have moderate or severe illness but, occasionally, also in those who have mild illness presenting symptoms such as chest pain and palpitation or signs of dyspnea and effort intolerance. In such cases, Echo becomes essential before returning to exercise to assess cardiac function and possible residual changes.[58] If there is a possibility of comparing new and previous Echo tests, any new change should be considered abnormal. However, changes in global or segmental contractility of the left ventricle (LV) or right ventricle (RV) (ejection fraction [EF] ≤ 50% or tricuspid annular plane systolic excursion [TAPSE] ≤ 17 mm), dilation of cardiac chambers, presence of intracardiac thrombi, and pericardial effusion are findings that may be related to myopericarditis.[57,59]

Moreover, cardiac assessment using new Echo technologies, such as two-dimensional longitudinal strain (or speckle tracking), which is a sensitive marker of myocardial deformation capable of assessing contractility in an objective, quantitative, and early manner, demonstrates a pattern of predominantly basal contractile change in the LV affected by post-COVID-19 myocarditis, which is different from conventional myocarditis. Two-dimensional longitudinal strain of the RV was able to predict higher mortality in individuals with COVID-19, stratifying those at greater risk and shorter survival, when RV strain became ≤ 20.5%; thus, this is another important analysis that can be of great help when available.[60,61] The optimal cut-off value in RV function analysis was –23%, with 94.4% sensitivity and 64.7% specificity, thus being a parameter superior to TAPSE in terms of prognostic value.[56] Finally, Echo must check if there is RV dilation, especially on the apical 4-chamber view, considering a baseline RV diastolic diameter greater than 41 mm, or if RV/LV diameter ratio is ≥ 0.9. Hypokinesia/akinesia of the RV free wall and tricuspid regurgitation are more prevalent in the presence of chamber dilation, and they are found in one third of mechanically ventilated patients or in those with pulmonary thromboembolism. The RV dilation mechanism is not completely understood and appears to be multifactorial, including thrombotic event, hypoxemia, vasoconstriction, and direct viral damage, but the presence of RV dilation is strongly associated with hospital mortality.[62]

4.1.7. Cardiac Magnetic Resonance Imaging

Cardiac MRI has emerged as an important method for assessing myocardial injury. The association of T1 and T2 mapping and late gadolinium enhancement provides the identification of signs of edema, inflammation, and myocardial fibrosis, as well as the differentiation between ischemic and nonischemic etiology. In patients with suspected myocarditis, cardiac MRI is the gold standard for noninvasive diagnosis.[63]

Although a significant percentage of patients hospitalized with COVID-19 showed increased TnT levels, the use of cardiac MRI for investigating myocarditis in the acute phase was limited because of the risk of staff contamination.

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However, initial cardiac MRI data on clinically recovered patients suggests that myocardial injury may persist after the acute phase and regardless of severity of clinical manifestations in the acute phase.

A German study used cardiac MRI in 100 participants with at least 15 days of COVID-19 symptom resolution (mean, 71 days) and negative RT-PCR tests, and reported that 78% of patients had abnormal findings, 71% had detectable TnT levels, and 5% had significant elevation (above the 99th percentile). Among the study patients, only 33% had required hospitalization and 18% had been asymptomatic.[47]

Therefore, we believe that cardiac MRI has an important role in additional PPS investigation of some athletes. However, we should consider that this is a test of limited access and high cost, not always accessible to our population.

Our indications for using cardiac MRI in individuals post acute phase of COVID-19 are described in Chart 4.

5. Recommendations for PPS in Recreational Amateur Athletes

PPS is essential for practicing exercise safely. Recreational amateur athletes account for a significant percentage of the population and belong to a wide range of age groups. In this new reality that we are living in, PPS must be adapted to amateur athletes contaminated with COVID-19.

5.1. Mild Clinical Presentation

Individuals who had mild ilness, after remaining asymptomatic for 14 days, should undergo a medical evaluation that includes medical history, physical examination, and ECG, and the possibility of measuring TnT should be considered. Based on the information we have to date, we should assume that the presence of any detectable TnT level is an abnormal finding, which may be associated with late myopericardial injury identified out of the acute phase.

If the evaluation is normal, individuals must wait at least 14 days after symptom resolution and then are free to resume light physical activities with gradual progression of intensity and training.

If any changes are detected, additional investigation should be made based on the suggested sequence for moderate illness.

5.2. Moderate Clinical Presentation

Individuals who had moderate clinical presentation should undergo, at least 14 days after disease resolution, Echo, TnT, and ExT or CPET, if available, in addition to medical history, physical examination, and ECG. Preferably, Echo should be performed first because, if there are signs of ventricular dysfunction or pericarditis, maximal effort is contraindicated. If the tests are normal, physical activities can be resumed gradually, with monitoring of symptoms. As the course of COVID-19 remains not well known, and apparently some

Detectable high-sensitivity troponin after clinical resolution with previous symptomatic respiratory disease*

New** changes in structure and global or segmental (L or R) ventricular function on echocardiogram: EF ≤ 50%; TAPSE ≤ 17 mm; presence of intracardiac thrombus or pericardial effusion

Frequent or complex ventricular arrhythmias at rest or during exercise
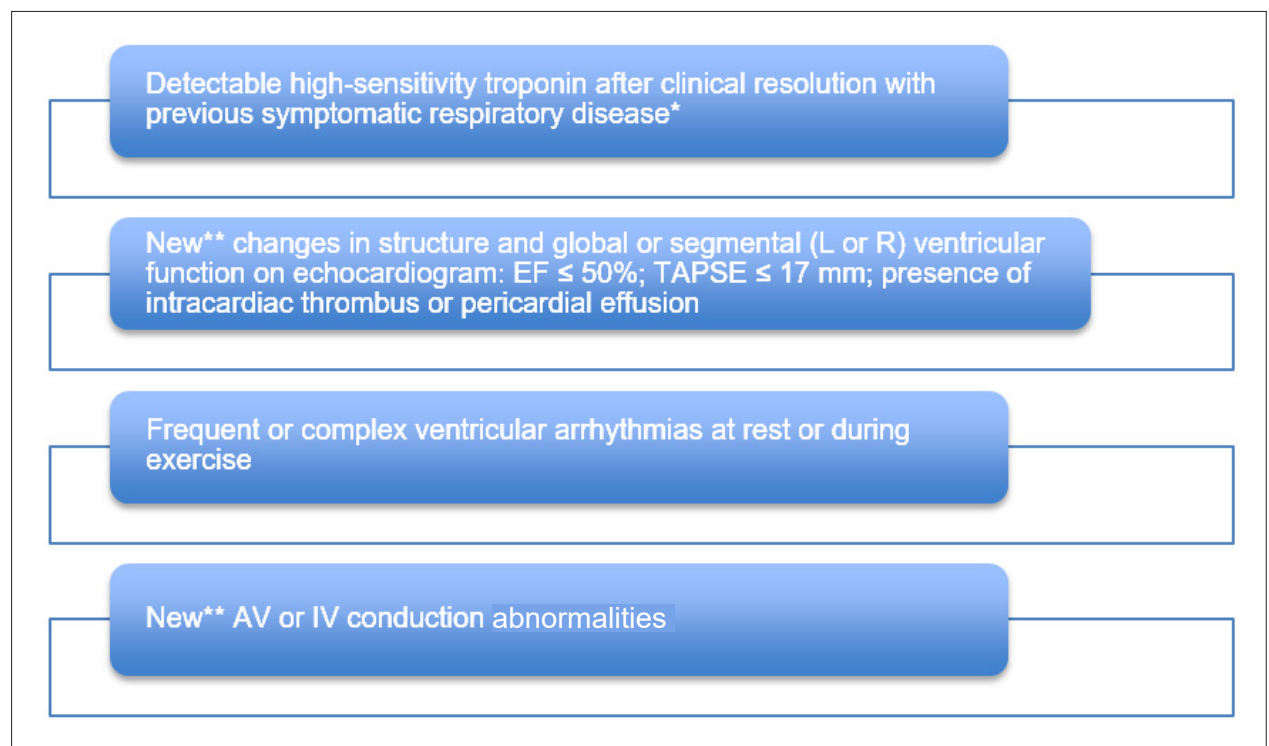
New** AV or IV conduction abnormalities

Chart 4 – *When we recommend using cardiac magnetic resonance imaging*
* Which cannot be attributed to other causes; ** Associated with the onset of diseases or whose presence is uncertain before COVID-19. L: left; R: right; EF: ejection fraction; TAPSE: tricuspid annular plane systolic excursion; AV: atrioventricular; IV: intraventricular.

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changes in the heart may occur late or even persist, we suggest a medical reevaluation in 60 days.

If abnormalities appear, investigation should continue with cardiac MRI and, in the case that myocarditis is suspected, 24-hour Holter monitoring and other required tests, according to the guidelines for cases of myocarditis.[54]

5.3. Severe Clinical Presentation

Individuals who had severe COVID-19 clinical presentation should undergo a protocol similar to that of the moderate ones; however, cardiac MRI should be considered even if all tests are normal. There have been descriptions of cases that had no changes on ECG or Echo but showed areas of late enhancement on cardiac MRI during additional investigation, especially in those who had severe ilness, in which cardiac involvement is relatively frequent. If there are changes in the tests, investigation should continue according to myocarditis guidelines, including a 24-hour Holter test, following the specific elegibility criteria to return to sports practice. The same applies to when an arrhythmia is identified on initial evaluation or functional test.

At the end of the evaluation, if results are all normal, individuals should wait two weeks without symptoms before resuming physical activities, and reappearance of symptoms should be monitored after the return. In this group, there may be a need for a more gradual return and even cardiac rehabilitation, depending on the degree of cardiac involvement in the acute phase and possible sequelae (Figure 2).

6. Recommendations for PPS in Competitive Amateur Athletes and Professional Athetes

In this group, there are individuals who usually do high-intensity training, and, at the moment, some have already resumed training and even competitions. With the return of some football clubs in some Brazilian regions, serological testing has been routinely used for screening, even in those with no history of previous disease. There are isolated reports of individuals recovering from COVID-19 and developing cardiovascular complications even in the absence of underlying cardiovascular disease as well as nonhospitalized COVID-19-positive individuals having SCD, even with mild symptoms.[64] Therefore, they must undergo strict protocols for a safe return to competitive sports. Several protocol models have recently been proposed, both nationally and internationally, in order to reach a consensus on what the best approach for athletes' PPS is, and served as a reference for the proposal of this document.[65-67]

Our aim is to guide a safe return for athletes and medical/technical staff, in an attempt to reintegrate these athletes and protect them from sequelae that would make them ineligible to continue their competitive career or even put the athlete at risk of SCD.

In competitive athletes, maintaining their skills and fitness by resuming intense training to reach the level required for competition in a short period of time generates greater physical and emotional stress, with increased anxiety.[66] Adequate medical support is important to minimize the impact of those conditions.
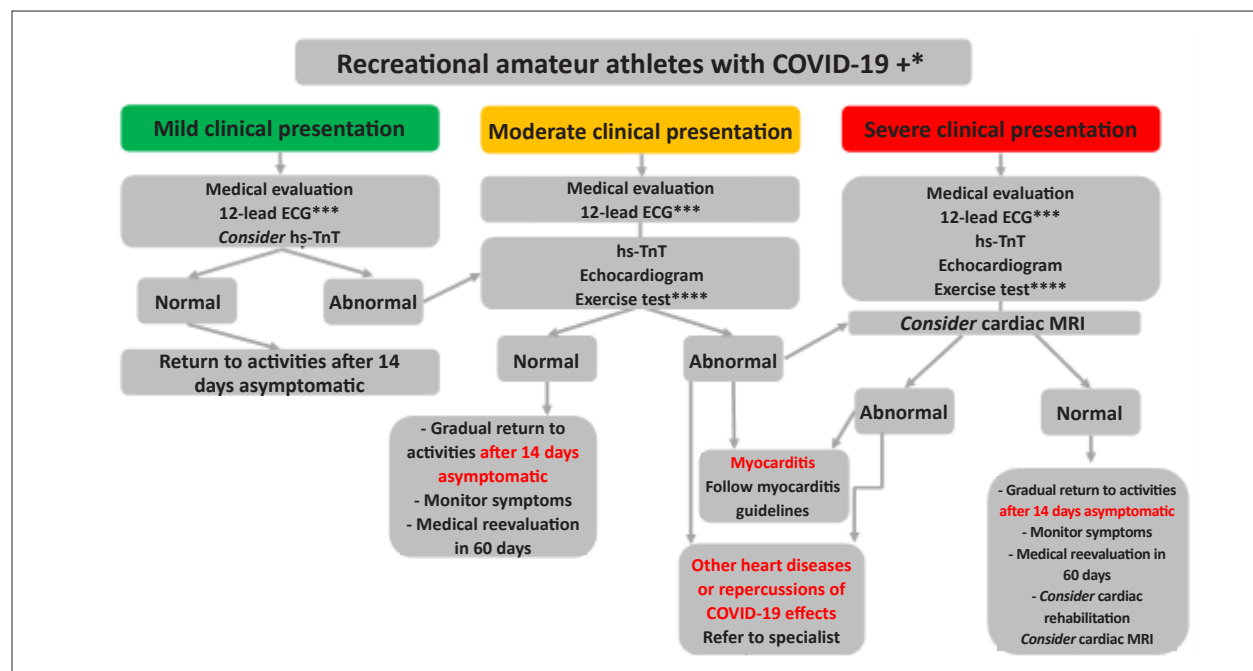

Figure 2 – Flowchart for evaluation of recreational amateur athletes
* RT-PCR or immunologic test; ** Wait at least 3 months for those diagnosed with myocarditis in the acute phase; *** Follow athlete's ECG evaluation criteria/compare with a previous test; **** If available, perform a cardiopulmonary exercise test. ECG: electrocardiogram; TnT: troponin T; MRI: magnetic resonance imaging.

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In this group of athletes, because of the history of intense training, it may be difficult to differentiate usual ECG changes from other diseases. Therefore, comparing new and previous ECGs and conducting additional tests, even in the mildest cases, are extremely important.

6.1. Mild Clinical Presentation

After remaining at least 14 days asymptomatic, all patients must undergo medical evaluation that includes medical history, physical examination, ECG, and TnT dosage. If there are no abnormalities, ExT or CPET are recommended, if available. If the test is normal, the athlete is considered fit to resume low volume and intensity exercises, progressing according to the functional protocol of each modality. Protocol laboratory examinations of each institution in an early season model can be added.

In case of abnormalities, the investigation should continue as in moderate ilness before they return to physical activities.

6.2. Moderate Clinical Presentation

The evaluation of athletes who had moderate clinical presentation should include medical history, physical examination, ECG, TnT, Echo, and ExT, preferably CPET (always at least 14 days after disease resolution). If there are changes in TnT levels, even when Echo is normal, we suggest additional investigation with cardiac MRI. If there are signs suggestive of myocarditis, the evaluation should continue according to current myocarditis guidelines, which includes

a 24-hour Holter test and other tests for risk stratification and eligibility to return to physical activities.[54]

If the evaluation is normal, the athlete is considered fit to resume low volume and intensity exercises 14 days after symptom resolution, with gradual return to greater intensity and specific training, and appearance of symptoms should be monitored. A medical reevaluation is suggested after 30 days of the initial PPS, since late cardiac manifestations may occur and new electrocardiographic changes may appear in individuals who had COVID-19 associated with pneumonia requiring hospitalization (classified in this group).[41]

6.3. Severe Clinical Presentation

For athletes who were severe clinical presentation, we suggest a comprehensive PPS evaluation, including cardiac MRI even if all other tests are normal. In case of suspected myocarditis changes, these athletes should follow the established recommendations for investigation, risk stratification, and eligibility.[54]

It is worth noting that individuals who were diagnosed with confirmed myocarditis during the acute phase must stay away from physical activities for at least 3 months before undergoing an initial PPS evaluation, following the previously mentioned recommendations.

If all tests during PPS are normal, the athlete is considered fit to return to activities at least 14 days after disease resolution, with gradual return to greater intensity and specific training as well as careful monitoring for symptoms or changes in performance. A medical reevaluation with ECG is suggested 30 days after the initial PPS evaluation. Even among athletes,
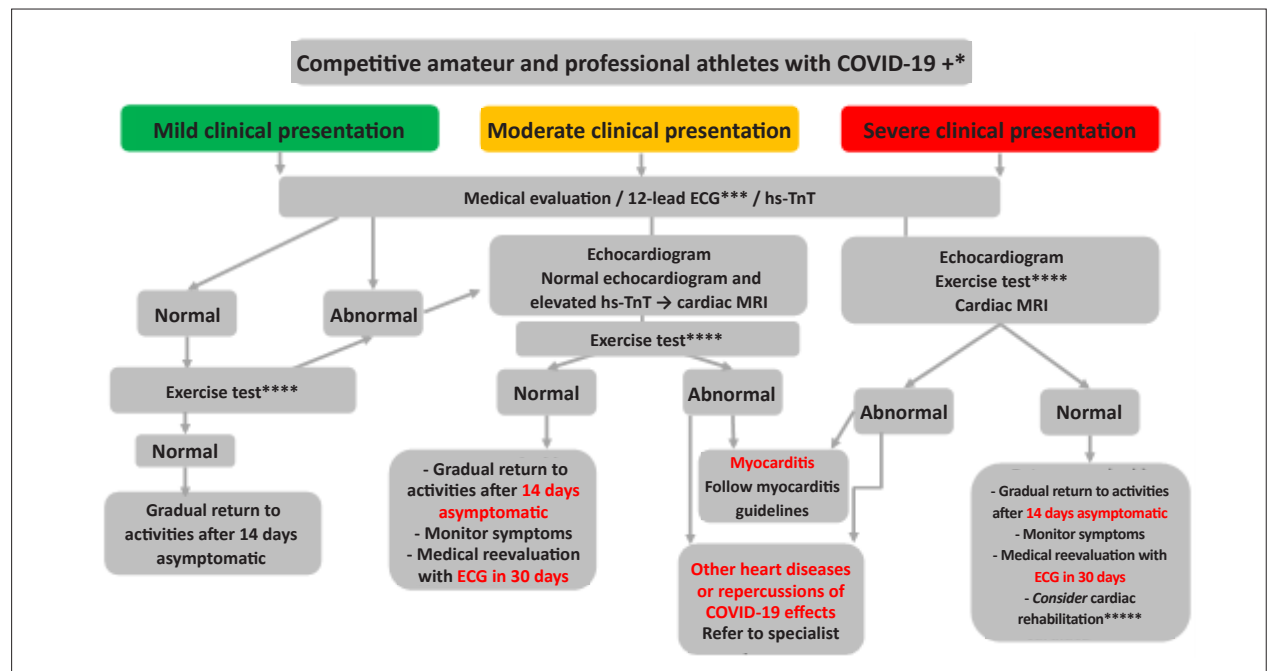
Figure 3 – *Flowchart for evaluation of competitive: amateur and profissional athletes*
* RT-PCR or immunologic test; ** Wait at least 3 months for those diagnosed with myocarditis in the acute phase; *** Follow athlete's ECG evaluation criteria/compare with a previous test; **** If available, perform a cardiopulmonary exercise test; ***** See text. ECG: electrocardiogram; TnT: troponin T; MRI: magnetic resonance imaging.

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there may be those who need to be referred to cardiac rehabilitation before returning to their usual activities because of the magnitude of injuries and possible myocardial sequelae in this high-severity group (Figure 3).

7. Conclusion

Although we still do not know the real meaning of the findings reported to date, the possibility of cardiac involvement as a COVID-19 sequela, especially myocarditis, should be considered and investigated before individuals return to sports practice, since it may constitute an arrhythmogenic substrate during effort, thus increasing the risk of SCD in athletes.

We believe that cardiovascular PPS after full recovery from COVID-19 is very important, which includes medical history, physical examination, and ECG for all patients. Further investigation such as TnT dosage, ExT or CPET, ECHO and cardiac MRI may be necessary, especially in competitive amateur and professional athletes. Individuals diagnosed with myocarditis in the acute phase must wait at least 3 months before undergoing PPS and considering the possibility of resuming exercise.

Moreover, we suggest that individuals who had COVID-19 and recovered without apparent sequelae, especially athletes, in addition to undergoing an initial PPS evaluation, should be evaluated in the medium and long term for full eligibility to compete in high-intensity sports, given the limited amount of knowledge about the late course of the disease.

Finally, the suggestions made herein are based on the information we have to date, even if there is a lack of strong evidences, since learning and discovery are still emerging about this disease. We highlight that such recommendations may be temporary and may change in the light of future knowledge about COVID-19.

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