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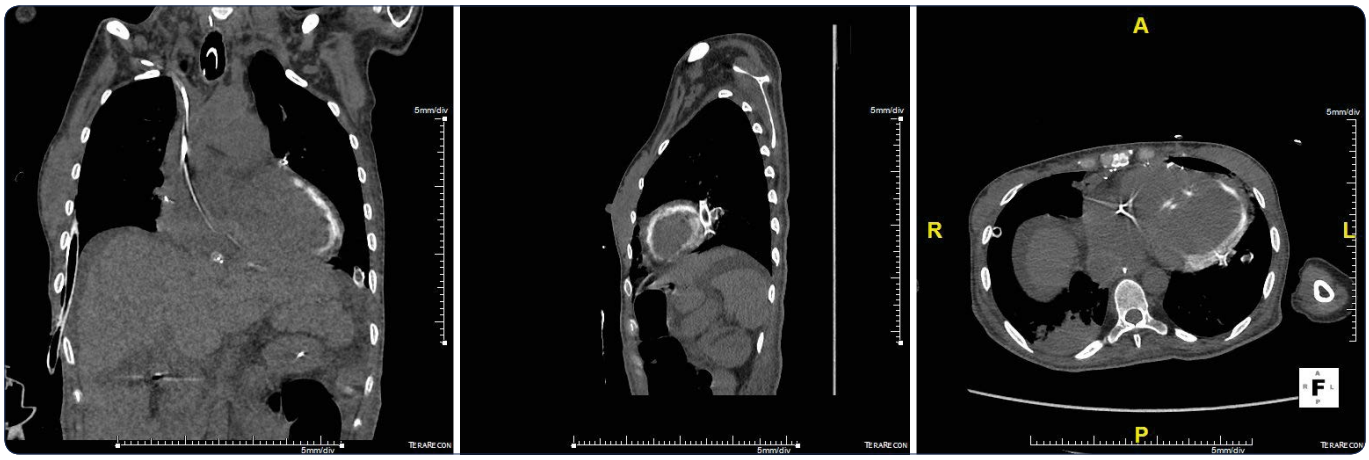

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JOURNAL OF BRAZILIAN SOCIETY OF CARDIOLOGY - Published since 1943

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Risk Factors for In-Hospital Mortality in Infective Endocarditis

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Abstract

Background: **Infective endocarditis (IE) is associated with severe complications and high mortality. The assessment of mortality rates and predictors for fatal events is important to identify modifiable factors related to the pattern of treatment, in order to improve outcomes.**

Objectives: **We sought to evaluate clinical outcomes of patients with IE and to determine predictors of in-hospital mortality.**

Methods: **Retrospective single-center study including patients with IE admitted during a 10-year period (2006-2015). Data on comorbidities, clinical presentation, microbiology and clinical outcomes during hospitalization were evaluated. Risk factors of in-hospital death were analyzed. A p-value < 0.05 was considered significant.**

Results: **A total of 134 cases were included (73% males, mean age of 61 ± 16 years-old). Half of them had previous valvular heart disease. Healthcare-associated IE and negative blood-cultures occurred in 22% and prosthetic IE in 25%. The aortic valve was the one most often affected by infection. Staphylococcus aureus was the most commonly isolated microorganism. Forty-four (32.8%) patients underwent cardiac surgery. The in-hospital mortality rate was 31.3% (42 patients). The identified risk factors for in-hospital mortality were Staphylococcus aureus etiology (OR 6.47; 95% CI: 1.07-39.01; p = 0.042), negative blood-cultures (OR 9.14; 95% CI: 1.42-58.77; p = 0.02), evidence of valve obstruction in echocardiography (OR 8.57; 95% CI: 1.11-66.25; p = 0.039), clinical evolution with heart failure (OR 4.98; 95%CI: 1.31-18.92; p = 0.018) or septic shock (OR 20.26; 95% CI: 4.04-101.74; p < 0.001). Cardiac surgery was a protective factor of mortality (OR 0.14; 95% CI 0.03-0.65; p = 0.012).**

Conclusion: **The risk factors for in-hospital mortality were clinical (heart failure, septic shock), evidence of valve obstruction in echocardiography, Staphylococcus aureus etiology or negative blood cultures. Invasive treatment by surgery significantly decreased the mortality risk. (Arq Bras Cardiol. 2020; 114(1):1-8)**

Keywords: **Endocarditis, Bacterial/mortality; Hospitalization; Comorbidity; Shock Septic; Heart Failure; Risk Factors; Echocardiography/methods; Cardiac Surgery.**

Introduction

Infective endocarditis (IE) is associated with severe complications and high mortality, despite the improvements in its medical and surgical management.[1,2]

The diverse nature and evolving epidemiological profile of IE ensure that it remains a diagnostic challenge.[2] The presentation and evolution of IE is highly variable, depending on host factors (such as existence of previous cardiac disease, prosthetic valves or implanted cardiac device, as well as factors that modulate the immune response), the microorganism involved and the adequacy of the provided treatment (antibiotics, heart failure medical treatment, surgery).[2]

The interplay of these factors results in an in-hospital mortality rate of patients with IE ranging from 15% to 30%.[3-9]

The assessment of mortality rates and predictors for fatal events is important to identify modifiable factors and the pattern of treatment in order to further improve the outcomes. This approach identifies the patients at highest risk of death for whom the level of care should be stepped-up.

Therefore, we aimed to evaluate the clinical outcomes of patients with IE and to determine predictors of in-hospital mortality.

Methods

A retrospective single-center study was performed, including all consecutive adult patients during a 10-year period (January.2006 to December.2015), in a Portuguese public tertiary general hospital, without on-site cardiac surgery department. The protocol was approved by the institutional review board and local ethics committee.

The population of interest was all cases of definite or possible IE according to the modified Duke criteria,[10] including those corresponding to patients that had more than one IE episode. For diagnosis purposes, cultural criteria consider as positive cultures during an extended incubation time for blood cultures of up to 21 days, according to the local protocol for IE suspicion. The cases were all identified

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by hospital discharge codes. The patients were followed until discharge or death (including hospitalization at the surgical center).

Demographic and clinical characteristics, type of endocarditis (native valve, prosthetic valve or device-associated), echocardiographic and microbiological findings, as well as surgical procedure and hospitalization outcomes were retrieved. The sample was characterized using basic descriptive statistic measures.

Patients that died during hospital stay were compared with those that survived regarding their demographic and clinical features, microbiological and echocardiographic findings and hospitalization outcomes.

The primary outcome was all-cause in-hospital mortality. The other adverse outcomes of interest were heart failure (defined as the presence of typical symptoms and signs caused by a structural and/or functional cardiac abnormality, resulting in a reduced cardiac output and/or elevated intracardiac pressures), septic shock (characterized by the presence of Systemic Inflammatory Response Syndrome to an infectious process, with sepsis-induced organ dysfunction or tissue hypoperfusion and persistently arterial hypotension, despite the administration of intravenous fluids), evidence of locally uncontrolled infection or periannular complication (valve destruction or perforation, increasing vegetation size, abscess formation, pseudoaneurysm, valve aneurysm and intracardiac fistula) and embolic events (ischemic stroke, hemorrhagic stroke, mycotic aneurism, myelitis/meningitis, peripheral ischemia and splenic, pulmonary or hepatic infarction or abscesses, diagnosed through computed tomography and/or magnetic resonance imaging, performed according to the clinical suspicion of embolism).

Healthcare-associated IE was defined as IE manifesting more than 48 hours after hospital admission or IE acquired in association with an invasive procedure performed in the 6 months before diagnosis during hospital stay and/or manipulation in a hospital setting.

Valve regurgitation detected at echocardiography included both significant valve regurgitation in native valve IE cases and significant intra and paraprosthetic leaks in prosthetic IE cases.

Statistical analysis

Categorical variables were presented as frequencies and percentages and were compared using the chi-square test. Continuous variables were expressed as means and standard deviations (SD) and were compared using the independent-samples t-test, after normal distribution was checked using the Kolmogorov-Smirnov test or skewness and kurtosis. Continuous variables with skewed distributions were presented as medians and interquartile ranges (IQR) and a non-parametric method (Mann Whitney U test) was employed.

In order to identify predictors of in-hospital mortality, variables with a p value < 0.1 in the univariate analysis were included in a logistic regression using an enter stepwise method. Two models were performed; one model included all Streptococcal Species and the other included the microorganism *Streptococcus gallolyticus*, since they are variables that are not independent of each other and both had a p value < 0.1 in the univariate analysis. The model predictive performance was tested by assessing its discrimination and its calibration. Discrimination was measured with the area under receiver operating characteristic curve (AUROC) and calibration was measured by using pseudo-R^2 (Nagelkerke R^2). The final model defined was that with the highest predictive performance according to the AUROC and pseudo-R^2.

All reported p values were two-tailed, with a p value < 0.05 indicating statistical significance. The statistical analyses were performed using IBM SPSS Statistics software, version 22.

Results

Population characteristics

Between January 2006 and December 2015, 134 cases of infective endocarditis were hospitalized in our center: 101 cases had definite IE and the remaining corresponded to possible IE cases, according to the modified Duke criteria. About 73% of these patients were males, the mean age was 61 ± 16 years. The main clinical characteristics, namely the comorbidities, clinical presentation, microbiology and clinical outcomes of IE cases are summarized in Table 1.

About half of the patients had previous arterial hypertension and valvular heart disease and 13.4% were intravenous drug users. Regarding the 13.4% of patients with Human Immunodeficiency Virus (HIV) infection, only 44% of these patients were on antiretroviral therapy at the time of the IE diagnosis; CD4 cells counts were obtained in 13 patients, with a median level of 130 ± 391 CD4 cells. About 12% of the IE cases corresponded to patients with chronic renal disease, and 31% of these were on hemodialysis.

The majority of the cases were related to native valves (71.6%), while the remaining were associated with prosthetic heart valves (25.4%) and device-related IE (3%).

Healthcare-associated infective endocarditis cases occurred in 22.4% of the patients.

About 22% of the cases had negative blood cultures. Antibiotic administration previous to blood culture collection was described in 72% of these cases. In 1 case, the IE diagnosis was made at the autopsy and blood samples were not obtained.

The most commonly isolated microorganisms were *Staphylococcus aureus* (22.4%) and Viridans Group Streptococci (12.7%).

A transthoracic echocardiography was performed in all patients, while a transesophageal study was carried out in 118 (88%) patients, with a mean time between admission and test performance of 10 ± 9.5 days (range 0-54 days). The main echocardiographic finding observed was the presence of vegetations (79.1%).

Valve regurgitation was observed in 69 cases, with 4 patients having reduced left ventricle ejection fraction (LVEF). Only 11 cases reported the LVEF and the median LVEF was 61% (IQR 18%). Systolic pulmonary artery pressure (SPAP) was reported in 15 cases, with a mean SPAP value of 41 mmHg (SD 27 mmHg).

Table 1 – Population characteristics of infective endocarditis cases (n = 134) and p value of univariate analysis of predictors of in-hospital mortality

Variable	IE Survivors (n = 92)	IE Non-Survivors (n = 42)	Total IE cases (n = 134)	p value
Male gender – n°. (%)	70 (76.1%)	28 (66.7)	98 (73.1%)	0.254
Age – yrs.				
mean ±SD	60 ± 17	64 ± 14	61 ± 16	0.177
Min – max	22 - 89	31 - 88	22 – 89	
> 75 yrs. – no. (%)	25 (27.2)	9 (21.4)	34 (25.4)	0.478
Comorbidities – n°. (%)				
Arterial Hypertension	47 (51.1)	21 (50)	68 (50.7)	0.907
Valvular heart disease	42 (45.7)	24 (57.1)	66 (49.3)	0.217
Heart Failure	18 (19.6)	16 (38.1)	38 (25.4)	0.022*
Hepatic Disease	24 (26.1)	8 (19)	35 (23.9)	0.413
Diabetes	14 (15.2)	8 (19)	22 (15.8)	0.579
Pulmonary Disease	15 (16.3)	6 (14.3)	21 (15.7)	0.766
Coronary Artery Disease	12 (13)	7 (16.7)	19 (14.2)	0.577
Intravenous drug users	13 (14.1)	5 (11.9)	18 (13.4)	0.763
HIV	12 (13)	6 (14.3)	18 (13.4)	0.804
Chronic Renal Disease	9 (9.8)	7 (16.7)	16 (11.9)	0.254
Intracardiac device	7 (7.6)	3(7.1)	10 (7.5)	1.000
Clinical Presentation – no. (%)				
Fever	71 (77.2)	24 (57.1)	95 (70.9)	0.018*
Systemic symptoms (weight loss, anorexia, tiredness)	52 (56.5)	28 (66.7)	80 (59.7)	0.165
Heart murmur	57 (62)	23 (54.8)	80 (59.7)	0.431
Anemia	35 (38)	17 (40.5)	52 (38.8)	0.789
Embolization symptoms	17 (18.5)	12 (28.6)	29 (21.6)	0.188
Number of episodes of IE– n°. (%)				
1	84 (91.3)	38 (90.5)	122 (91)	
2	6 (6.5)	1 (2.4)	7 (5.2)	0.816
3	2 (2.2)	3 (7.1)	5 (3.7)	
Type of IE– n°. (%)				
Native valve	67 (72.8)	29 (69)	96 (71.6)	0.653
Prosthetic valve	21 (22.8)	13 (31)	34 (25.4)	0.316
<1yr after cardiac surgery	8 (8.7)	2 (4.8)	10 (7.5)	0.251
Device-Related Infective Endocarditis	4 (4.3)	0 (0)	4 (3)	0.309
Valves affected - n°. (%)				0.378
1 valve	70 (76.1)	32 (76.2)	111 (82,8)	
2 valves	12 (13)	6 (14.3)	18 (13.4)	
3 valves	1 (1)	0 (0)	1 (0.7)	
Aortic valve	53 (57.6)	24 (57.1)	77 (57.5)	0.960
Mitral valve	30 (32.6)	17 (40.5)	47 (35.1)	0.376
Right-sided valves	16 (17.4)	3 (7.1)	19 (14.2)	0.115
Type of infection – n°. (%)				
Community-acquired endocarditis	72 (78.2)	32 (76.2)	104 (77.6)	0.790
Healthcare-associated IE	20 (21.7)	10 (23.8)	30 (22.4)	

Continuation

Microbiology – n°. (%)				
Blood culture-negative infective endocarditis	16 (17.4)	13 (31)	29 (21.6)	0.077
Staphylococcal species	25 (27.2)	17 (40.5)	42 (31.3)	0.124
Staphylococcus aureus	15 (16.3)	15 (35.4)	30 (22.4)	0.012*
Staphylococcus epidermidis	5 (5.4)	1 (2.4)	6 (4.5)	0.665
Other coagulase-negative *Staphylococci*	4 (4.3)	1 (2.4)	5 (3.7)	1.000
Streptococcal Species	34 (37)	7 (16.7)	41 (30,6)	0.018*
Viridans Group *Streptococci*	14 (15.2)	3 (7.1)	17 (12.7)	0.193
Streptococcus gallolyticus	12 (13)	1 (2.4)	13 (9.7)	0.063
Streptococcus milleri	2 (2.2)	1 (2.4)	3(2.2)	1.000
Enterococcal species	12 (13)	4 (9.5)	16 (11.9)	0.560
Gram-negative bacteria	2 (2.2)	3 (7.1)	5 (3.7)	0.177
Fungi	2 (2.2)	1 (2.4)	3 (2.2)	1.000
HACEK group	1 (1)	0 (0)	1 (0.7)	1.000
Echocardiographic Findings – n°. (%)				
Vegetation	74 (80.4)	32 (76.2)	106 (79.1)	0.776
Valve regurgitation	50 (54.3)	19 (45.2)	69 (51.5)	0.539
Valve destruction	19 (20.7)	7 (16.7)	26 (19.4)	0.722
Valve obstruction	3 (3.3)	5 (11.9)	8 (6)	0.05*
Abscess	8 (8.7)	10 (23.8)	18 (13.4)	0.009*
Pseudoaneurysm	5 (5.4)	0 (0)	5 (3.7)	0.320
Valve Aneurysm	3 (3.3)	0 (0)	3 (2.2)	0.554
Intracardiac Fistula	4 (4.3)	2 (4.8)	6 (4.5)	1.000
Treatment – n°. (%)				
Only medical treatment	52 (56.5)	38 (90.5)	90 (67.2)	< 0.001*
Cardiac Surgery	40 (43.5)	4 (9.5)	44 (32.8)	

** Statistically significant variable. IE: infective endocarditis; SD: standard deviation.*

Valve obstruction was diagnosed in 8 cases (5 cases of prosthetic IE and 3 cases in native valves) and was related to degenerated prosthesis in 4 patients, to large vegetations causing valve obstruction in 3 patients and in 1 case due to severe valvular aortic stenosis.

18F-fluorodeoxyglucose positron emission tomography/computer tomography (^{18}F-FDG PET/CT) was performed in 1 patient, detecting signs of abnormal activity around the site of the prosthetic valve implantation (surgery performed more than 1 year before). None of the diagnosis was made by radiolabeled WBC single-photon emission computed tomography/Computed Tomography (SPECT/CT).

The median length of hospital stay was 41 ± 23 days (range 1-112 days). Forty-four (32.8%) patients underwent cardiac surgery. The main indication for surgery was heart failure (n = 33; 75%), followed by uncontrolled infection (n = 11; 27.3%) and prevention of embolism (n = 6; 13.6%). One patient was referred to surgery for pacemaker lead extraction. The mean time between the first day of hospitalization and surgical procedure was 26 ± 18 days, the mean time between IE diagnosis and the surgical procedure was 21 ± 16 days and the mean time between the indication for surgery and surgical procedure was 14 ± 12 days.

Adverse outcomes during hospitalization

The in-hospital mortality rate was 31.3% (42 patients). Septic shock was the cause of death for one third of the patients (n = 14), 10 (23.8%) patients died due to heart failure, 9 (21.4%) due to embolic complications and 1 (2.4%) patient died due to cardiac tamponade. The cause of death was uncertain in 8 patients (19%).

Most of these patients (73.8%, 31 patients) were not candidates for cardiac surgery. The reasons for these patients not being candidates for cardiac surgery are described in table 2.

Eleven patients (26.2%) were candidates for surgery but 4 died before the intervention (2 patients due to embolic events occurrence, 1 due to septic shock and 1 patient due to heart failure); 3 patients were refused for surgery by the surgical team (2 patients due to the presence of an ischemic

Table 2 – Reasons for patients not being candidates for cardiac surgery (31 patients)

Cause	Patients (n)
Significant comorbidities:	21
Dementia and cognitive impairment with dependence in activities of daily living	5
Ischemic stroke with significant post-stroke sequelae in patients with advanced age or multiple comorbidities	5
Advanced age with substantial associated comorbidities	4
Noncompliant HIV patients with poor general clinical conditions	4
Active intravenous drug user with poor general clinical conditions	1
Malignant tumor with poor prognosis	1
Severe alcoholism with significant organ damage	1
Hemorrhagic stroke (1st month after the event)	3
Active bacteremia in association with an active extracardiac infectious focus	3
Death nearly after the diagnosis (the physicians did not have the chance for surgical referral)	3
Post-autopsy diagnosis	1

stroke with hemorrhagic transformation and one was an HIV patient with three IE episodes that was previously submitted to 2 cardiac surgeries due to IE and with significant associated comorbidities); 4 patients died after the intervention (2 patients due to septic shock, 1 due to cardiac tamponade and in 1 the cause of death was uncertain), resulting in a surgery-related mortality rate of 9%.

The other adverse outcomes during hospitalization are described in Table 3.

Of the 65 patients that evolved with heart failure, left ventricle systolic dysfunction was observed in 5 patients in the transthoracic echocardiography performed during hospital stay. None of the patients had previously known left ventricular systolic dysfunction.

Predictors of in-hospital mortality

In the univariate analysis, previous heart failure, apyrexia, *Staphylococcus aureus* etiology, non-isolation of Streptococcal Species, evidence of paravalvular abscess or valve obstruction in echocardiography, incident heart failure or septic shock and absence of cardiac surgery were significantly and positively associated with in-hospital mortality (Tables 1 and 3).

In the multivariate analysis, the significant risk factors of in-hospital mortality identified in the final model were *Staphylococcus aureus* etiology, blood-culture negative endocarditis, evidence of valve obstruction in echocardiography and clinical evolution with heart failure or septic shock. Cardiac surgery was a protective factor of in-hospital mortality (Table 4).

The model 2 that included *Streptococcus gallolyticus* organism had a numerically lower predictive performance and is described in table 5.

Discussion

The factors associated to increased risk of in-hospital mortality in our cohort were: development of heart failure or septic shock, valve obstruction in echocardiography, *Staphylococcus aureus* etiology, blood-culture negative endocarditis and absence of surgical treatment.

The in-hospital mortality rate observed was 31.2%, which is slightly higher that the reported in the literature (15-30%).[3-9]

It is recognized that one of the main protective factors of mortality is cardiac surgery and it was significant in our cohort.[3,7,11-13] Differently from other studies in which 40–50% of patients undergo cardiac surgery,[4,6,8,11,13,14] in our center only 32.8% underwent cardiac surgery. This can be partially justified by the absence of Cardiac Surgery Department in our center, which can difficult and delay the appropriate discussion with cardiac surgeons, and subsequently it may negatively influence the in-hospital mortality rates.

The association of mortality with other factors, such as septic shock and heart failure found in our cohort is well known and expected.[3,5,8,13]

The microbiological factors that increased the risk of in-hospital mortality were the expectedly *Staphylococcus aureus*-related endocarditis[8,15] and blood-culture negative endocarditis[14] (possibly due to the difficulty in the diagnosis and administration of timely and directed therapy in the latter group of patients).

Valve obstruction was associated with higher mortality and in half of the patients was related to prosthesis degeneration, followed by the presence of large vegetations. In both etiologies, valve obstruction could contribute to clinical patient worsening, namely with heart failure, with congestive symptoms or low cardiac output, that could lead to multiple organ dysfunction and death.

The aortic valve was the most affected (57.5%), differently to other series in which the mitral valve was the most affected.[9] Right-sided IE was observed in 14.2%, a value higher than the 5–10% reported.[11,16] This could be due to the higher incidence of drug users (13.4%), compared to other series,[3,7-9,17] which could be justified by the cultural and social characteristics of our population, and could also contribute to the higher mortality rate observed.

Table 3 – Adverse Outcomes during hospitalization and P value of univariate analysis of predictors of in-hospital mortality

Variable	IE Survivors (n = 92)	IE Non-Survivors (n = 42)	Total IE cases (n = 134)	p value
In-hospital death – no. (%)			**42 (31.3)**	
Adverse Outcomes during Hospitalization – no. (%)				
Heart failure	38 (41.3)	27 (64.3)	65 (48.5)	0.014*
Locally uncontrolled infection/ periannular complication	39(42.4)	16 (38.1)	55 (41)	0.639
Embolic events	30 (32.6)	21 (50)	51 (38.1)	0.054
Septic shock	8 (8.7)	19 (45.2)	27 (20.1)	< 0.001*

** Statistically significant variable. IE: infective endocarditis.*

Table 4 – Multivariable logistic-regression model of predictors of in-hospital mortality – Final Model (including all Streptococcal Species)

Variable	Odds ratio (OR)	95% CI	p	Nagelkerke R^2
Previous Heart Failure	3,88	0.90-16.70	0.069	0.622
Fever	0.41	0.17-1.45	0.167	
Staphylococcus aureus	6.47	1.07-39.09	0.042*	
Streptococcal Species	2.96	0.40-21.72	0.286	
Negative blood cultures	9.14	1.42-58.77	0.02*	
Valve obstruction in echocardiography	8.57	1.11-66.25	0.039*	
Abscess in echocardiography	4.14	0.89-19.21	0.07	
Heart failure	4.98	1.31-18.92	0.018*	
Septic shock	20.26	4.04-102.74	< 0.001*	
Embolic events	1.98	0.53-7.36	0.309	
Cardiac surgery	0.14	0.03-0.65	0.012*	
AUROC	< 0.001	0.88-0.97	0.926	

** Statistically significant variable. CI: confidence interval.*

Table 5 – Multivariable logistic-regression model of predictors of in-hospital mortality - Model 2 (including *Streptococcus gallolyticus* organism)

Variable	OR	95% CI	p	Nagelkerke R^2
Previous heart failure	3.48	0.80-15.13	0.097	0.614
Fever	0.46	0.13-1.56	0.211	
Staphylococcus aureus	4.05	0.87-19.00	0.076	
Streptococcus gallolyticus	0.94	0.05-17.76	0.965	
Negative blood cultures	5.32	1.14-24.92	0.034*	
Valve obstruction in echocardiography	11.97	1.27-112.91	0.030*	
Abscess in echocardiography	3.73	0.84-16.62	0.085	
Heart failure	4.80	1.27-18.23	0.021*	
Septic shock	16.03	3.59-71.53	< 0.001*	
Embolic events	1.90	0.51-7.05	0.340	
Cardiac surgery	0.17	0.04-0.72	0.017*	
AUROC	< 0.001	0.88-0.97	0.923	

** Statistically significant variable. CI: confidence interval.*

Prosthetic valve endocarditis occurred in 25%, in the range described in literature (10–30%).[3,7,8,13,14]

Healthcare-associated IE represents up to 30% of IE cases[8,13] and in this study occurred in 22.4%. Agents from Staphylococcal and Streptococcal species were the most isolated microorganisms (around 30%), like expected.[3,7,8,15] Negative-blood culture IE occurred in 21.6%, a proportion that overlaps the data found in the literature (2.1-35%).[8,14,18]

Transesophageal echocardiography (TEE) was performed in 88%. The remaining patients did not have clinical conditions to undergo a TEE or died before TEE performance. The two main echocardiographic findings were vegetations (79.1%) and valve regurgitation (51.5%).

Due to lack of ^{18}F-FDG PET/CT scan and radiolabeled WBC SPECT/CT availability in our center, only 1 patient performed PET ^{18}F-FDG PET/CT scan (in other center) and none performed radiolabeled leukocytes SPECT/CT.

Expectedly, heart failure was the main adverse event observed during hospitalization (48.5%).[3,8]

Complications, length of hospital stay, and mortality remain high in IE[1] and our data highlight these facts.

This study identified the high-risk features on endocarditis patients in our cohort. The early identification of these patients might be helpful in outcome improvement by managing more closely and delivering early cardiac surgery when indicated.

These results are important not only for clinicians, once they highlighted the risk factors of death, but also to cardiac surgeons, given that they showed the good impact in prognosis of cardiac surgery.

It is important to continue with further investigations to identify other factors that could minimize the mortality levels of IE on top of the best-known management.

Limitations

This study had a retrospective design and the information was limited to medical records. The absence of systematically collected data (such as echocardiographic measures) derived from the study design, prevented the possibility of further estimating the impact of IE in other important healthcare variables.

This study was also performed in a single center without on-site cardiac surgery and the regional variation in the diagnosis, treatment, local microbiology of IE could have influenced results and preclude the robustness of the conclusions. The sample size is unlikely to be adequately powered to assess the in-hospital mortality and risk factors. The referral bias, particularly in patients not accepted for cardiac surgery needs to be acknowledged as a limitation.

Conclusions

According to our data, the risk factors for in-hospital mortality were the development of heart failure or septic shock, evidence of valve obstruction in echocardiography, *Staphylococcus aureus* etiology or blood-culture negative endocarditis. Invasive treatment by surgery significantly decreased the mortality risk. These results are important for all participants and emphasize the importance of having a multidisciplinary Endocarditis Team (with specialists in Internal Medicine, Cardiology, Microbiology, Infectious diseases, Cardiac Surgery) in order to address all the features associated to increased mortality.

Author contributions

Conception and design of the research: Cruz I, Broa AL; Acquisition of data: Marques A, Cruz I, Alegria S, Gomes AC, Broa AL; Analysis and interpretation of the data: Marques A, Cruz I, Gomes AC, Broa AL; Statistical analysis: Marques A, Caldeira D, Broa AL; Writing of the manuscript: Marques A, Caldeira D, Alegria S; Critical revision of the manuscript for intellectual content: Caldeira D, João I, Pereira H.

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Potential Conflict of Interest

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

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Study Association

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

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Hospital Garcia Orta under the protocol number 31/2017. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013.

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Infective Endocarditis: Still a Deadly Disease

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Short Editorial related to the article: Risk Factors for In-Hospital Mortality in Infective Endocarditis

The important issue of in-hospital mortality in infective endocarditis (IE) is discussed by Marques et al.[1] In-hospital mortality in the International Collaboration in Endocarditis (ICE) cohort (2000-2005) was 18%,[2] similar to the 17% in the large European cohort recently published,[3] both unacceptably high, considering that most patients included were from developed countries and voluntary registries.

In the present article, in-hospital mortality was 42/134 (31.3%), higher than expected. The identified risk factors for in-hospital mortality were *Staphylococcus aureus* etiology, negative blood-cultures, evidence of valve obstruction in echocardiography, heart failure secondary to IE and septic shock. Cardiac surgery was protective for mortality. To me, the most important message is "surgery was protective for mortality". This has been shown in several studies.[1-6]

Surgical treatment is required in approximately half of the patients with IE because of severe complications, of which heart failure (acute or acute on chronic) is the most frequent, occurring in 40-60%.[7] It represents the most common indication for surgery in left- sided native valve IE. Surgery may need to be performed on an emergency (within 24 h) or urgent (within a few days, 7 days) basis, irrespective of the duration of antibiotic treatment, or maybe delayed 1 or 2 weeks of antibiotic treatment.[7] Although it is not clear which is the best timing,[6,8] surely before the onset of acute heart failure seems a good time.[9]

A systematic review and meta-analysis evaluated papers where early versus late surgical intervention or medical management for IE were done.[5] The definition used for early valve surgery in this publication was performance of surgery at 20 days or less of diagnosis of IE or during initial hospitalization. All-cause mortality was mentioned in 21 studies, and in the group that had early surgery, it was significantly lower than in the group without early surgical intervention (OR 0.61, 95% CI 0.50 to 0.74, $p < 0.001$). Heterogeneity was high among the included studies. However, regarding in-hospital mortality, a total of 11 studies reported on it and there was no significant difference between the early surgery and conventional therapy groups.[5]

Keywords

Heart Failure/physiopathology; Endocarditis/complications; Endocarditis/surgery; Hospital Mortality; Comorbidity; Septic shock; Echocardiography/methods.

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Wang et al.[8] addressed the issue of timing of surgery in patients with definite, left-sided IE according to the modified Duke criteria who underwent cardiac surgery during the index hospitalization.[8] This was a prospective cohort from the ICE -PLUS study and involved 485 patients who were operated during the same admission. Notably, cases of device-related IE were excluded from the analysis, as were hemorrhagic stroke before surgery, nosocomial IE, and surgery performance more than 60 days from admission. A multivariable logistic regression model was fit to calculate a propensity score (probability) for early surgical treatment. The median time to surgery was 7 days ([IQR] 2-15). Patients who underwent earlier surgery had a lower percentage of preexisting heart failure (before IE diagnosis) but a higher rate of acute heart failure; no difference in 6-month survival across the quartiles (Quartile 1, surgery day 0 or 1; Q2, day 2 to 6; Q3 day 7 to 15; Q4 more than 15 days) of surgical timing was found. The risk of 6-month mortality was highest for patients who underwent surgery within the initial 2 days after admission or transfer. The authors concluded that the routine use of very early surgery for any indication is not supported by current data.[8]

The EURO-ENDO study involved a prospective cohort of 3116 adult patients (2470 from Europe), years 2016 to 2018 with a diagnosis of probable or definite IE.[3] Cardiac surgery was indicated in 2160 (69.3%) patients but finally performed in only 1596 (73.9%) of them. In-hospital death occurred in 532 (17.1%) patients and was more frequent in prosthetic valve IE.[9] Independent predictors of mortality were Charlson index, creatinine > 2 mg/dL, congestive heart failure, vegetation length > 10 mm, cerebral complications, abscess, and failure to undertake surgery when indicated. Indications for surgery were hemodynamic in 46.3% of cases, embolic in 32.1%, and infectious in 64.2% (the latter a very percentage, which is different from other large series of IE). Surgery was performed emergently in 6.7%, urgently in 24.8%, beyond the 1st week in 32% and electively in 36.5%. Having an indication for surgery and not performing surgery was the group with the highest mortality in the study and figured as the take home message. Importantly, the main reason for not performing surgery was death before surgery (53%) of patients.[3]

It seems clear that referring early for surgical evaluation by a team experienced in treating endocarditis and performing surgery in a timely manner is important. The timeframe between surgical indication and operation was 2 weeks in the article by Marques et al.,[1] only a third of the patients were operated on, and 2/3 of patients did not have surgery indicated due to significant comorbidities.[1]

In a prospective observational study on IE from multiple sites, surgical treatment for IE was performed in 733 patients, which represented 57% of all patients and 76% of patients with a surgical indication.[6] The median age was 57 years for patients

who underwent surgery, statistically different compared with 68 years for those who did not undergo surgery. Patients who underwent surgery were more likely to have new moderate or severe mitral or aortic regurgitation, valve perforation or abscess and embolization. In contrast, patients who did not undergo surgical treatment for IE were more likely to have medical comorbidities such as coronary artery disease, previous heart failure, diabetes mellitus and moderate/severe renal disease (findings on comorbidities are similar[3]) and to have infection caused by *S. aureus*. In-hospital mortality was 26% vs 14.8% and 6-month mortality 31.4% versus 17.5% among patients who did not undergo surgery compared with those who did, respectively. The reasons for lack of surgery for those who had surgical indications were having a poor prognosis regardless of treatment (33.7%), hemodynamic instability (19.8%), death before surgery (23.3%), stroke (22.7%), and sepsis (21.0%). Sepsis was the single factor associated with nonsurgical management of *S. aureus* IE compared with other microbiological causes and median STS-IE score for *S. aureus* patients was higher (32) compared with 24 in non–*S aureus* patients, with statistical significance.

In the study by Marques et al.,[1] as expected, septic shock was associated with mortality, with an OR of 20. Sepsis remains a challenge, with very high mortality rates worldwide, especially when associated with shock.[10] Main therapeutic measures are dealt with in the Surviving Sepsis Campaigns, of which the most recent version reinforces speediness in starting intravenous fluids, collecting blood cultures, starting appropriate antibiotics soon after this, measuring lactate, and importantly, starting vasoactive drugs readily (within 1 hour) if intravenous fluids fail to improve blood pressure and normalize lactate levels.[11]

Despite the benefits in the survival of surgery, many deaths occur after surgery, and prognostic scores for valvular surgery in IE have been debated in recent years. Mortality rates in the EUROENDO study[3] shows that in hospital post-cardiac surgery mortality was 170/532 (32%) overall, 74/187 (39.6%) if it was prosthetic IE and 79/286 (27.6%) if native valve IE. A recent small study from our team included 154 patients operated for IE from 2006-2016; they were mostly male (66.9%), and mean age was 42.7±15 years.[12] Rheumatic valvulopathy was present in 31.2%; the most frequently isolated microorganisms were *viridans* group streptococci (29.9%), followed by negative cultures in 26.6% of the patients. The main surgical indication was heart failure (65.6%), and in-hospital mortality was 17.5%. On multivariate analysis, variables found to be statistically significant for death were atrioventricular block, cardiogenic shock, insulin-dependent diabetes mellitus, non-HACEK Gram-negatives as the etiology of IE and inotropic use. The calculated sensitivity for this was 88.9% and specificity was 91.8%; AUC was 0.97. This was dubbed INC-Rio score, and an app for Android was created (endocarditeinc.org).

In the present study[1] IE with negative blood cultures was associated with mortality; a publication from our group showed that, although there was no difference in mortality for blood culture positive IE and blood culture-negative IE, the latter was associated with more heart failure, which is the main factor associated with death in IE and the main reason to indicate cardiac surgery in most series.[13]

In conclusion, the manuscript by Marques et al, despite limited in its inferences due to the retrospective, single-center nature of the study, is important as it brings to the cardiologists' attention the issue of the very high mortality associated with IE, especially in a center with no cardiac surgery. The important message is conveyed: left-sided IE is very often a surgical disease, and an endocarditis team is more expedite in recognizing and better treating this condition, especially with respect to indicating surgery, hopefully at its most appropriate moment.

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Determinants of Aortic Prosthesis Mismatch in a Brazilian Public Health System Hospital: Big Patients or Small Prosthesis?

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Abstract

Background: Prosthesis-patient mismatch (PPM) is associated with worse outcomes.

Objective: Determine the frequency and evaluate preoperatory variables independently associated with severe PPM in a tertiary hospital focused on Public Health Care.

Methods: A total of 316 patients submitted to aortic valve replacement, who had echocardiography performed within the first 30 days after surgery, were retrospectively analyzed. The indexed effective orifice area (iEOA) of the prosthesis was used to classify the patients into three groups, according to PPM, considering body mass index (BMI): severe PPM (iEOA) < 0.65 cm²/m²), mild to moderate PPM (iEOA, 0.65 cm²/m² – 0.85 cm²/m²) and without PPM (iEOA > 0.85 cm²/m²) for a BMI < 30 kg/m² and severe PPM (iEOA) < 0.55 cm²/m²), mild to moderate (iEOA, 0.55 cm²/m² – 0.70 cm²/m²) and without PPM (iEOA > 0.7 cm²/m²) for a BMI > 30 kg/m². Statistical significance was considered when p < 0.05.

Results: iEOA was obtained in 176 patients. The frequency of severe and moderate PPM was 33.4% and 36.2%, respectively. Severe PPM patients were younger and had larger BMI, but smaller left ventricular outflow tract diameter (LVOTD). The independent variables used to predict severe PPM were male gender, BMI > 25 kg/m², age < 60 years, LVOTD < 21 mm, and rheumatic etiology with an area under the ROC curve of 0.82.

Conclusion: The frequency of severe PPM is high in a Brazilian population representative of the Public Health System, and it is possible to predict PPM from preoperative variables such as rheumatic valvular disease, gender, BMI, age and LVOTD. (Arq Bras Cardiol. 2020; 114(1):12-22)

Keywords: Heart Valve Prosthesis/surgery; Size Perception; Body Mass Index; Preoperative Care; Postoperative Care; Echocardiography/methods.

Introduction

The concept of prosthesis-patient mismatch (PPM) after aortic valve replacement (AVR) occurs when the indexed effective orifice area (iEOA) of the inserted prosthesis is too small in relation to patient body size.[1] PPM was first described in 1978,[2] and its negative impact on morbidity, mortality and left ventricular reverse remodeling has been established.[3-6] Transprosthetic gradients in patients with PPM varies with cardiac output, which in turn is determined by body surface area (BSA), and the relation of iEOA and pressure gradient is curvilinear. Therefore, iEOA smaller than 0.85 cm²/m² generates higher gradients with possible consequences to the left ventricle (LV).[2]

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The incidence of PPM is variable and ranges from 20-70% for moderate and 5-20% for severe PPM.[2,3] Severe PPM has been associated with a 1.8-fold increase in mortality.[3] Many studies have reported an impact of PPM on early[7,8] and late mortality,[5-8] especially in patients with pre-existing LV dysfunction.[5,7] PPM was also associated with reduced functional capacity, less regression of LV mass and accelerated bioprosthetic valve degeneration.[6]

Several factors were associated with the occurrence of severe PPM, including: advanced age,[3] female gender,[4] large body surface area (BSA) and body mass index (BMI), presence of diabetes, hypertension, small aortic valve annulus (< 21 mm),[5] and bioprosthesis implantation.[6]

There are few studies on the incidence and impact of PPM in Brazil. Oliveira *et al.* observed that 17% of patients with EOA < 0.75 cm²/m² showed no increased mortality during a 10-year follow-up.[9] There are some interesting features specific to the Brazilian population, such as the higher prevalence of rheumatic fever, a large proportion of patients with a small BSA, and implantation of prosthesis with iEOAs not reported according to the normal reference values provided by the medical society guidelines and recommendations.[1,10] Furthermore, the analysis of preoperative factors that predict the occurrence of PPM is essential for its prevention.[11,12]

The objective of this study was to assess the frequency of PPM in a representative population treated in the Brazilian Public Health System and to identify the preoperative factors that are associated with the occurrence of PPM.

Methods

In this cross-sectional retrospective study, performed from January 2011 to July 2016, we included patients older than 18 years who underwent AVR. Patients who died prior the first postoperative echocardiography or with incomplete clinical and echocardiographic data were excluded. Informed consent was obtained from each patient and the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee.

All subjects underwent surgical AVR and transthoracic echocardiogram (ETT) within 30 days after surgery. Three hundred and sixteen (316) patients met the inclusion criteria. However, data of indexed EOA (iEOA) to determine the degree of PPM was available only in 176 patients. These data were not found in the echocardiogram report, nor were the values for calculation in images available at the hospital imaging server in 140 patients. After the publication of the European prosthetics guidelines[1] there was mandatory standardization for calculation of iEOA in our Echocardiogram Laboratory.

The echocardiographic evaluation was performed following the recommendations of the American Society of Echocardiography Guideline, obtaining two-dimensional, pulsed and continuous Doppler and M mode images with Philips HDI 5000, HD 7, iE33 or GE E9 ultrasound systems with 2-5 Hz multifrequency transducer. The left atrial volume and ejection fraction (EF) were measured by Simpson's method (for LVEF $< 53\%$) or Teicholz (for LVEF $\geq 53\%$). LV mass was obtained by the Devereux formula (measured from M or 2-dimensional mode) and indexed to the BSA.[13] LV diameters were obtained by M or bi-dimensional mode.[13] LV outflow tract (LVOT) was evaluated at the plane before the aortic valve,[1,10,14] the peak and mean gradients, the velocity time integrals (VTI) ratio of the LVOT and aortic prosthesis and the calculation of EOA were performed according to the ASE recommendations. EOA = (LVOT area × LVOT VTI)/Aortic flow VTI).[1,10] The calculation of EOA was indexed to BSA estimated by the Dubois and Dubois formula: BSA = ($Weight^{0.425} \times Height^{0.725}$) × 0.007184 and was used to identify the degree of PPM.[1,5]

Definitions of PPM

Definition #1: PPM was defined as severe if iEOA was < 0.65 cm²/m², moderate if iEAO was between 0.65 cm²/m² and 0.85 cm²/m² and absent if iEOA > 0.85 cm²/m².

Definition #2: We also used the definition of PPM adjusted for high BMI as recommended by European recommendations.[1] For BMI < 30 mg/kg, moderate PPD is considered if iEOA is < 0.70 cm²/m² and severe if iEOA < 0.55 cm²/m². Definition #3: Severe PPM was also defined on the basis of the mean transprosthetic gradient > 20 mmHg.

We tested three different definitions for PPM in this study population to check which of them would identify better variables associated with mismatch.

Statistical analysis

Continuous variables with normal distribution were presented as mean and standard deviation and categorical variables in absolute numbers and percentages with confidence intervals, when necessary. Means of the three PPM groups were compared with one-way ANOVA after the Shapiro-Wilk normality test and Tukey's post hoc test. For categorical variables, a Chi-square test was use to compare proportions and frequencies. The association between preoperative variables and occurrence of severe PPM was assessed using the Poisson regression with robust variance model. In the univariate analysis, the association between each independent variable and the occurrence of PPM was assessed, and those that presented $p < 0.1$ were selected for entry into the multivariable analysis. The multivariable models were built by the consecutive exclusion of one variable from each complete model that presented the highest value of p of the Wald test, as described by Hosmer and Lemeshow. Data for multivariable models were complete for 148 patients.

A receiver operating curve (ROC) analysis was performed to assess the predictive value of the multivariable model for the prediction of severe PPM. ROC analysis was performed only for the PPM definition with more independent variables in the study, i.e., Definition #2.

The analyses were conducted using the SAS 9.4 software and $p < 0.05$ was considered significant.

Results

Frequency and Comparison of PPM Groups

Severe and moderate PPM occurred in 33.4% and 36.2% of patients, respectively. Tables 1 and 2 compare baseline clinical and echocardiographic characteristics of the 3 PPM groups. Even though 19% of the patients (34 patients out of 176 with PPD data) had rheumatic etiology, few presented significant mitral valve disease and underwent concomitant valve surgery (Table 1). There was loss of iEOA data in 140 patients with an average gradient of 18.7 ± 7 mmHg and a peak of 32.1 ± 5 mmHg. Patients with severe PPM were younger and had larger BSA and BMI, smaller LVOT diameter, and higher prevalence of rheumatic heart disease. There was low incidence of aortic root enlargement at the time of surgery in all groups. Table 3 shows the types and numbers of implanted prostheses and was presented in a descriptive way according to the type, number and category of PPD. There was a wide range of types and sizes of prostheses used in the AVR, which makes it impossible to analyze the association between prosthesis type, prosthesis number and degree of PPD. The data in Table 3 is too sparse to allow for any statistical model. Saint Jude bioprosthesis was implanted in 58% of patients (it is the most frequent), but cannot be tested as a determinant of PPM.

Table 1 – Baseline clinical characteristics of the PPM groups (176 patients Definition #2)

	No PPM 30.4%(54)	Moderate PPM 36.2% (64)	Severe PPM 33.4% (58)	p
Age (years)	55 ± 17†	60 ± 15†*	52 ± 16*	0.0335
Female/male gender %	11/19	15/21.2	14/20.4	0.78
BSA (m^2)	1.70 ± 0.24	1.71 ± 0.17*	1.8 ± 0.21*	0.016
BMI (kg/m^2)	25 ± 3.37†	26 ± 4.42†*	27 ± 5.17*	0.03
SBP (mmHg)	120 ± 15†	117 ± 18†*	111 ± 15*	0.03
DBP (mmHg)	72 ± 14†	66 ± 11†	68 ± 13	0.028
HR bpm	83 ± 14	83 ± 14	87 ± 13	0.26
Hypertension%	17.6	22.1	17.6	0.54
Diabetes%	2.8	5.1	4.6	0.77
CABG%	6.3	8	4	0.25
Renal Disease	1	2	1	0.4
Aortic Root enlargement %	1.7	1.1	3.4	0.27
Mitral valve surgery %	0	1.14	0.57	0.63
Valve disease Etiology (%)				0.003
Rheumatic	4(9.5)	8(14.55)†	22(43.1)†	
Degenerative	21(50)	29(52.8)	19(37.3)	
Congenital (Bicuspid)	11(26.2)	10(8.2)	7(13.7)	
Aortic Root Dilation	6(14.3)	8(14.6)	3(5.9)	
Type of Prosthesis Biop./Mech. %	24/6.4	31/5.2	31.4/2	0.27

† *p < 0.05 between no PPM and moderate PPM. * p < 0.05 between moderate and severe PPM. BSA: body surface area; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate; CABG: coronary bypass graft; Biop.: biological; Mech: mechanical.*

Preoperative Determinants of Severe PPM

Determinants of severe PPM according to Definition #1 (indexed EOA< 0.65 cm^2/m^2)

In univariate analysis (Table 4), there was an association between severe PPM and the following variables: age < 60 years, BSA > 1.74 m^2, rheumatic heart disease as the etiology of aortic valve disease and not performing aortic root enlargement. Multivariable analysis (Table 4) revealed that preoperative variables independently were the same as in univariate analysis, except for not performing aortic root enlargement. The tolerance indicator for multicollinearity was 0.78, indicating that there is no strong multicollinearity among the independent variables.

Determinants of severe PPM according to Definition #2 (indexed EOA < 0,65 cm^2/m^2 for patients with BMI < 30 kg/m^2 and EOA < 0.55 cm^2/m^2 for BMI > 30 kg/m^2

In addition to the independent variables described in the analysis above using the cut-off value of < 0.65 cm^2/m^2 for severe PPM, we found that male gender is an independent determinant of PPM when BMI is considered as a parameter for reclassification of severe PPM to iEOA ≤ 0.55 cm^2/m^2. However, BSA was not an independent variable within this new model. Univariate and multivariate analysis are shown in Table 5.

Determinants of severe PPM according to Definition #3 (mean prosthesis gradient ≥ 20 mmHg and iEOA ≤ 0,65 cm^2/m^2)

With this definition, only age < 60 years (PR: 3.33; IC 95%: 1.56-7.12) and LVOT diameter < 2.1 cm (PR = 1.68; IC 95%: 0.87-3.21) were independently associated with severe PPM. Complete analysis is described in Table 6.

Accuracy and Mathematical model for Prediction of Severe PPM with preoperative variables

We tested the accuracy of the predictive model for severe PPM using *Definition # 2,* for its precision in identifying more independent variables compared with the other definitions. The area under the ROC curve was 0.82 (Figure 1).

In addition, to calculate the individual risk of a patient to develop severe PPM, we built a mathematical model summarized by a formula based on multivariate logistic regression analysis (Table 7). With this formula, it is possible to calculate the individual risk of PPM for each patient before surgery (Table 7).

Discussion

One of the main findings of this study is that frequency of severe PPM is high after AVR in patients treated in the Brazilian Public Health System in a representative tertiary center.

Table 2 – Postoperative Doppler-Echocardiographic Data According to PPM Groups (176 patients- Definition# 2)

	No PPM 30.4% (54)	Moderate PPM 36.2% (64)	Severe PPM 33.4% (58)	p
LVEF %	57 ± 14%	60 ± 14%	58 ± 14%	0.75
Vmax Ao cm/s	273 ± 15	306 ± 25	335 ± 18	< 0.002
Peak Gradient (mmHg)	30 ± 14†	37 ± 14†*	45.1 ± 20*	< 0.0001
Mean Gradient (mmHg)	18 ± 8†	21 ± 8†*	28 ± 13*	<0.0001
EOA cm²	1.78 ± 0.43†	1.3 ± 0.2†*	0.52 ± 0.1*	< 0.0001
EOA/BSA cm²/m²	1.05 ± 0.17†	0.73 ± 0.06†*	0.51 ± 0.1*	< 0.0001
VTI LVOT/VTI Ao valve	0.49 ± 0.1†	0.41 ± 0.07†*	0.33 ± 0.08*	< 0.0001
LVOT diameter (cm)	2.15 ± 0.3†	2.02 ± 0.24†*	1.92 ± 0.22*	0.04
LV mass index g/m²	115 ± 42	119 ± 38	117 ± 35	0.84
LA index volume ml/m²	32 ± 12	33 ± 10	33 ± 12	0.72
Ascending Aorta cm	3.6 ± 0.72	3.6 ± 0.74	3.5 ± 0.56	0.29

† *p < 0.05 between no PPM and moderate PPM. * p < 0.05 between moderate and severe PPM. LVEF: left ventricle ejection fraction; EAO: effective orifice area; BSA: body surface area; VTI: velocity time integral; LVOT: left ventricle outflow tract; Ao: aortic; LV: left ventricle; LA: left atrium. NA: not available.*

The prevalence of severe PPM in this study was 33% compared to up to 20% previously described.[6,15] Oliveira et al. described lower prevalence of PPM in Brazilian patients with small aortic annulus (16.8%). However, their cutoff points for definition of PPM was different from the present study.[9] Another significant finding is that degenerative aortic stenosis is the main cause of aortic valve disease in our study (50%), but rheumatic etiology remains high, compared to data reported in developed countries (19%).[5,7] In addition, rheumatic etiology is independently associated with the risk of severe PPM.

PPM Characteristics

Similarly to other studies,[15,16] patients with severe PPM had larger BSA and BMI [15] and smaller LVOT diameters.[6,15] Patients with severe PPM in our study were younger compared to those in previous studies and mostly males.[5,7,8,15] This finding could be explained by the inclusion of aortic regurgitation in our study, to explain male gender as an independent variable, and by the significant proportion of patients with rheumatic etiology, to explain the predominance of younger individuals with PPM.[18,19]

Determinants of Severe PPM

A very important application of our findings is in the identification of independent preoperative variables which determine the risk of severe PPM. From these variables we built a predictive model that enables the identification of individual risk for development of severe PPM. This model can be used to identify patients at high risk for severe PPM prior to AVR and to implement preventive strategies.[18,19]

A larger BMI (> 25 kg/m²), male gender, smaller LVOT diameter (< 2.1 cm), younger age (≤ 60 years) and rheumatic etiology were determinants of high risk for severe PPM. Based on the predictive model proposed in this study, preventive strategies should be contemplated, including aortic root enlargement and implantation of prosthetic valves with superior hemodynamic performance with surgical or transcatheter procedure[11,15,18,19] In this study population, transcatheter implantation is controversial because the procedure is approved for high surgical risk in patients, who are usually older and at a higher level of frailty. This study also raises the importance for improving the hemodynamic performance of the prosthetic valves implanted in the Brazilian Public Health System**.** However, we must consider the costs of using stentless prostheses in the public health system, which may have a negative impact cost to treat the population more comprehensively.

Potential Limitations and Strengths of the Study

This was a retrospective study with limited data available of the iEOA in part of the population. It is important to emphasize that it was possible to obtain the indexed effective orifice data - the main parameter for the differentiation of PPM - in only 55% of the study population. Hence, the 45% of patients with missing data could generate bias and increase the prevalence of severe PPM. The type of prosthesis used was not found in some patients, in spite of being exhaustively searched in medical records. No long-term echocardiographic and clinical follow-up data was available to assess the effect of PPM on outcomes. However, this is the first study to show a high frequency of PPM in AVR performed in the Brazilian Public Health System. In addition, our study was able to build a mathematical model to predict PPM and find preoperative independent variables related to the implantation of small prosthesis. Further studies are needed to apply and validate this model in other populations.

Table 3 – Type and number of implanted prosthesis

Types of Prostheses	Number	No PPM	Moderate PPM	Severe PPM
Labcor Biological	19	0	1	0
	25	5	1	0
Carpentier Edwards	19	0	0	1
	21	1	3	0
	23	3	1	2
	25	0	2	0
St Jude Biological	18	0	1	0
	19	1	1	1
	21	5	8	12
	23	8	20	21
	25	5	7	3
	27	6	1	3
St. Jude Mechanical	19	2	1	1
	21	0	3	1
	23	2	2	1
	25	1	2	1
	27	1	0	1
Non-Specific Mechanical	18	0	0	1
	19	0	0	1
	23	0	1	1
	25	2	0	0
	27	0	1	0
	28	0	1	0
Non-Specific Biological	19	0	1	0
	21	0	3	2
	23	6	2	1
	25	1	0	1
	27	0	1	1
Hancock Biological	23	0	0	2
	25	0	0	1
	27	0	0	1
Biocor Biological	23	1	0	0
Medtronic Mechanical	21	1	0	0

*Descriptive Table of aortic prosthesis implanted in the present study. * No description of prosthesis type in files or surgery report.*

Conclusion

Severe aortic PPM is frequent among patients operated in the Brazilian Public Health System. The independent preoperative determinants of severe PPM in this population were: larger BMI, male gender, smaller LVOT diameter, younger age and rheumatic etiology. We developed a mathematical model including these preoperative variables in order to predict the risk of severe PPM prior to surgery. This model may be useful to implement prospective preventive strategies in patients identified as being at risk for severe PPM. Small prosthesis in big patients should be avoided.

Author contributions

Conception and design of the research: Otto ME, Atik FA, Lima JGE, Pibarot P; Acquisition of data: Otto ME, Moreira MN, Ribeiro LCM, Mello BCR, Domingues ACPM,

Table 4 – Poisson Multivariable analysis for severe PPM (Definition #1; EOAi < 0.65 cm²/m²; n = 148 patients)

Variables	Crude RP		Adjusted RP	
	RP (CI 95 %)	p-value	RP (CI 95%)	p-value
Gender		**0.7982**		**-**
Female	1	-	-	-
Male	1.06 (0.67-1.67)	0.7982	-	-
Age		**0.0078**		**0.0134**
< 60 years	1.98 (1.20- 3.29)	0.0078	2.06 (1.16- 3.67)	
≥ 60 years	1	-	1	-
BSA		**0.0571**		**0.0176**
≤ 1.74 m²	1	-	1	-
> 1.74 m²	1.56 (0.99- 2.46)	0.0571	1.65 (1.09; 2.50)	
BMI		**0.0168**		**0.0030**
< 25 Kg/m²	1	-	1	-
> 25 Kg/m²	1.80 (1.11- 2.91)	0.0168	1.89 (1.24-2.87)	
Main Diagnosis		**0.6092**		**-**
Stenosis	1.28 (0.78- 2.12)	0.3283	-	-
Regurgitation	1	-	-	-
Balanced	1.11 (0.48- 2.55)	0.8039	-	-
Etiology of AV Disease		**0.0009**		**0.0028**
Rheumatic	3.50 (1.21-10.11)	0.0206	4.00 (1.49-10.77)	0.0060
Degenerative	1.56 (0.52- 4.67)	0.4262	2.17 (0.79-5.97)	0.1331
Congenital (bicuspid)	1.82 (0.57- 5.81)	0.3107	1.78 (0.63- 5.01)	0.2779
Aortic Root Dilation	1	-	1	-
Reoperation		**0.3379**		**-**
No	1	-	-	-
Yes	1.29 (0.76-2.19)	0.3379	-	-
Hypertension		**0.1400**		**-**
No	1.39 (0.90- 2.14)	0.1400	-	-
Yes	1	-	-	-
Diabetes		**0.4760**		**-**
No	1	-	-	-
Yes	1.23 (0.69- 2.20)	0.4760	-	-
CABG		**0.1013**		**-**
No	1.87 (0.88- 3.95)	0.1013	-	-
Yes	1	-	-	-
Type of Prosthesis		**0.1398**		**-**
Biop.	1.98 (0.80- 4.93)	0.1398	-	-
Mech	1	-	-	-
LVOT Enlargement		**0.0374**		**-**
No	1.86 (1.04- 3.34)	0.0374	-	-
Yes	1	-	-	-
LV mass index		**0.0902**		**-**
≤ 127 g/m²	1.48 (0.94- 2.32)	0.0902	-	-
> 127 g/m²	1	-	-	-
Ejection Fraction		**0.1093**		**-**
≤ 64 %	1.44 (0.92-2.25)	0.1093	-	-
> 64 %	1	-	-	-
LVOT diameter		**0.0069**		**< 0.0001**
≤ 2.1 cm	2.15 (1.23-3.74)	0.0069	2.88 (1.71-4.84)	
> 2.1 cm	1	-	1	-

EOAi: Effective orifice area index; RP: relative prevalence; CI: confidence interval; BSA: Body Surface Area; BMI: Body Mass Index; CABG: Coronary Artery Bypass Graft; LVOT: Left Ventricle Outflow Tract; LV: Left Ventricle; AV: aortic valve.

Table 5 – Poisson Multivariable analysis for severe PPM (Definition #2: indexed EOA < 0.65 cm²/m² for BMI < 30 kg/m² and < 0.55 cm²/m² for BMI ≥ 30 kg/m²; n = 148 patients)

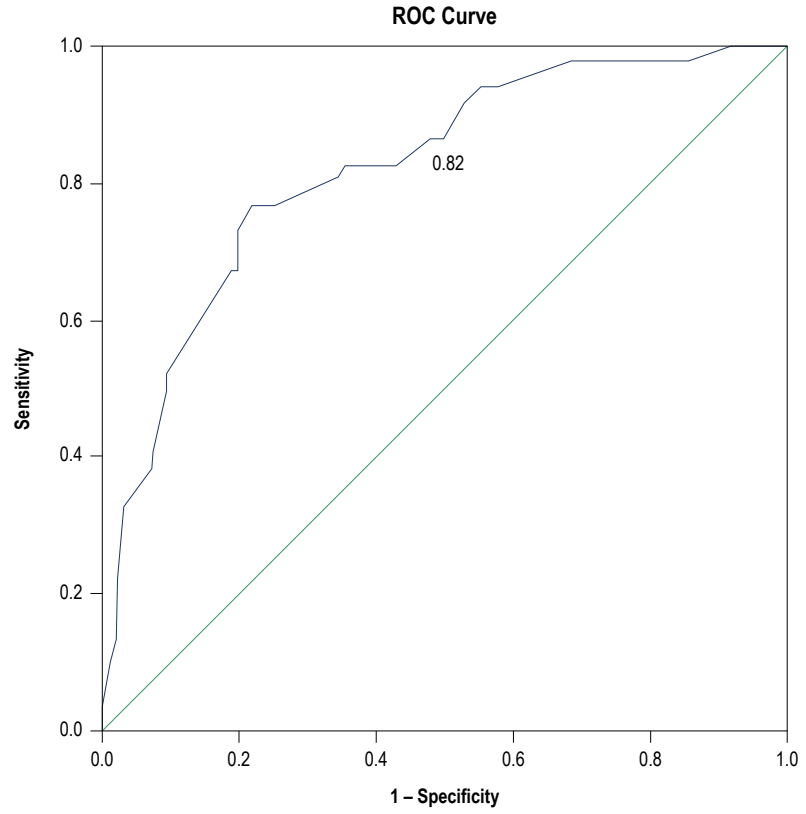
Variables	Crude RP		Adjusted RP	
	RP (CI 95 %)	p-value	RP (CI 95%)	p-value
Gender		**0.6856**		**0,0255**
Female	1	-	-	-
Male	1.10 (0.68-1.79)	0.6856	1,67 (1,06-2,61)	
Age		**0.0057**		**0.0025**
< 60 years	2.17 (1,25- 3.75)	0.0057	2.6 (1.4- 4.84)	
≥ 60 years	1	-	1	-
BSA		**0.2015**	**-**	
≤ 1.74 m²	1	-	-	-
> 1.74 m²	1.36 (0.85- 2.19)	0.2015		-
BMI		**0.0657**		**0.0034**
< 25 Kg/m²	1	-	1	-
> 25 Kg/m²	1.59 (0.97- 2.61)	0.0657	1.95 (1.25-3.06)	
Main Diagnosis		**0.7166**		**-**
Stenosis	1.25 (0.73- 2.13)	0.4152	-	-
Regurgitation	1	-	-	-
Balanced	1.19 (0.51- 2.76)	0.6850	-	-
Etiology of Aortic Valve Disease		**0.0010**		**0.0030**
Rheumatic	3.33 (1.15-9.67)	0.0267	3,29 (1.22-8.92)	0.0190
Degenerative	1.56 (0.52- 4.67)	0.5545	1.95 (0.69-5.50)	0.2079
Congenital (bicuspid)	1.82 (0.57- 5.81)	0.4244	1.32 (0.44- 3.98)	0.6245
Aortic Root Dilation	1	-	1	-
Reoperation		**0.1909**		**-**
No	1	-	-	-
Yes	1.43 (0.84-2.44)	0.1909	-	-
Hypertension		**0.0820**		**-**
No	1.51 (0.95- 2.39)	0.0820	-	-
Yes	1	-	-	-
Diabetes		**0.9325**		**-**
No	1	-	-	-
Yes	0.97 (0.48- 1.97)	0.9325	-	-
CABG		**0.0815**		**-**
No	2.1 (0.91- 4.82)	0.0815	-	-
Yes	1	-	-	-
Type of Prosthesis		**0.1993**		**-**
Bio	1.82 (0.73- 4.53)	0.1993	-	-
Mec	1	-	-	-
LVOT Enlargement		**0.0186**		**-**
No	2.03 (1.13- 3.68)	0.0186	-	-
Yes	1	-	-	-
LV mass index		**0.2952**		**-**
≤ 127 g/m²	1.29 (0.80; 2.06)	0.2952	-	-
> 127 g/m²	1	-	-	-
Ejection Fraction		**0.0517**		**-**
≤ 64 %	1.61 (1.00; 2.60)	0.0517	-	-
> 64 %	1	-	-	-
LVOT diameter		**0.0042**		**< 0.0001**
≤ 2,1 cm	2.45 (1.33-4.52)	0.0042	3.58 (2.01-6.39)	
> 2,1 cm	1	-	1	-

EOAi: Effective orifice area index; RP: relative prevalence; CI: confidence interval; BSA: Body Surface Area; BMI: Body Mass Index; CABG: Coronary Artery Bypass Graft; LVOT: Left Ventricle Outflow Tract; LV: Left Ventricle; AV: aortic valve.

Table 6 – Poisson Multivariable analysis for severe PPM (Definition #3: mean transprosthetic gradient > 20 mmHg ; n = 148 patients)

Variables	Crude RP		Adjusted RP	
	RP (CI 95 %)	p-value	RP (CI 95%)	p-value
Gender		**0.5995**		**-**
Female	1	-	-	-
Male	1.17 (0.65-2.13)	0.5995	-	0.0004
Age		**0.0019**		**0.0004**
< 60 years	3.33 (1.56- 7.12)	0.0019	3.94(1.85- 8.39)	
≥ 60 years	1	-	1	-
BSA		**0.7720**	**-**	
≤ 1.74 m^2	1	-	-	
> 1.74 m^2	1.09 (0.62- 1.92)	0.7720		
BMI		**0.2905**		**-**
< 25 Kg/m^2	1	-	1	-
> 25 Kg/m^2	1.37 (0.76-2.47)	0.2905	-	-
Main Diagnosis		**0.4620**		**-**
Stenosis	1.54 (0.77- 3.06)	0.2178	-	-
Regurgitation	1	-	-	-
Balanced	1.48 (0.53- 4.14)	0.4531	-	-
Etiology of Aortic Valve Disease		**0.0035**		
Rheumatic	4.00 (1.04-15.43)	0.0441		
Degenerative	1.35 (0.33- 5.55)	0.6728		
Congenital (bicuspid)	2.12 (0.5- 9.07)	0.3087		
Aortic Root Dilation	1	-	-	-
Reoperation		**0.4442**		**-**
No	1	-	-	-
Yes	1.31 (0.65-2.63)	0.4442	-	-
Hypertension		**0.1297**		**-**
No	1.55 (0.88- 2.73)	0.1297	-	-
Yes	1	-	-	-
DM		**0.7270**		**-**
No	1	-	-	-
Yes	0.85 (0.34- 2.13)	0.7270	-	-
CABG		**0.1715**		**-**
No	1.95 (0.75- 5.08)	0.1715	-	-
Yes	1	-	-	-
Type of Prosthesis		**0.5560**		**-**
Bio	1.32 (0.52- 3.35)	0.5560	-	-
Mec	1	-	-	-
LVOT Enlargement		**0.0427**		**-**
No	2.19 (1.03- 4.66)	0.0427	-	-
Yes	1	-	-	-
LV mass index		**0.7019**		**-**
≤ 127 g/m^2	1.12 (0.63-1.97)	0.7019	-	-
> 127 g/m^2	1	-	-	-
Ejection Fraction		**0.0409**		**-**
≤ 64%	1.87 (1.03-3.4)	0.0409	-	-
> 64%	1	-	-	-
LVOT diameter		**0.1198**		**0.0138**
≤ 2,1 cm	1.68 (0.87-3.21)	0.1198	2.2 (1.17-4.14)	0.0138
> 2,1 cm	1	-	1	-

Legend: BSA: Body Surface Area; BMI: Body Mass Index; CABG: Coronary Artery Bypass Graft; LVOT: Left Ventricle Outflow Tract; LV: Left Ventricle.



Area Under the Curve

Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
0.824	0.037	0.000	0.751	0.897

Figure 1 – *ROC curve: accuracy of the multivariable model for prediction of severe PPM (Definition #2:)*

Table 7 – Formula for individual risk and coefficient of each variable for severe mismatch probability calculation (Definition #2)

Parameter		Estimate
Intercept		-5,54
Age	< 60	1,75
Male gender		0,79
LVOT Diameter	≤ 2.1	2,25
BMI	≥ 25 Kg/m^2	1,12
Etiology of Aortic Valve Disease	Congenital (bicuspid)	0,41
Etiology of Aortic Valve Disease	Degenerative	1,10
Etiology of Aortic Valve Disease	Rheumatic	2,15

$$\text{Probability of severe PPM} = \frac{1}{1 + e^{(-5.54 + 1.75\ \text{age} + 0.79\ \text{male} + 2.25\ \text{LVOT diam} + 1.12\ \text{BMI} + 0.41\ \text{Etiol Cong} + 1.1\ \text{Etiol deg} + 2.15\ \text{Etiol Rheum})}}$$

Legend: PPM patient prosthesis mismatch; BMI: Body Mass Index; LVOT Diam: Left Ventricle Outflow Tract Diameter; Etiol Cong: Etiology Congenital; Etiol Deg: etiology degenerative; Etiol Rheum: Etiology Rheumatic.
Observation: To determine the probabilities based on the above equation, one must use the design matrix on Table 6, if the variable present. For example: if a patient is < 60 years old, one must replace the variable age by the value 1 and multiply it by the value of its coefficient. If it is older than or equal to 60, one should replace the variable age by zero.

Calzada RP, Schloicka LL, Ribeiro MS, Jreige Jr. A; Analysis and interpretation of the data: Otto ME, Atik FA, Moreira MN, Mello BCR, Domingues ACPM, Calzada RP, Schloicka LL, Pibarot P, Ribeiro MS, Jreige Jr. A; Statistical analysis: Otto ME, Atik FA, Ribeiro LCM, Lima JGE, Calzada RP, Ribeiro MS, Jreige Jr. A; Obtaining financing: Otto ME; Writing of the manuscript: Otto ME, Atik FA, Pibarot P; Critical revision of the manuscript for intellectual content: Otto ME, Atik FA, Moreira MN, Ribeiro LCM, Mello BCR, Lima JGE, Domingues ACPM, Calzada RP, Schloicka LL, Pibarot P.

Potential Conflict of Interest

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

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Study Association

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

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Instituto de Cardiologia do Distrito Federal under the protocol number 061/2010. 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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Prosthesis-Patient Mismatch Following Aortic Valve Replacement: Finding Predictors for Prevention

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Short Editorial related to the article: Determinants of Aortic Prosthesis Mismatch in a Brazilian Public Health System Hospital: Big Patients or Small Prosthesis?

Mismatch between the size of an aortic bioprosthesis and the patient (prosthesis-patient mismatch - PPM) is a poorly studied entity, and can be associated with adverse postoperative results, with quality of life impairment and a worse prognosis among those with severe PPM.[1]

The impact of prosthesis-patient mismatch

Nowadays, the main indication for valve surgery, in patients with anatomically important aortic valve disease, occurs at the onset of symptoms, given the presumed benefit of reduced morbidity and mortality associated with this procedure in this context.[2-4] Thus, the presence of PPM following surgical implantation of an aortic bioprosthesis interferes in the expected reduction of symptomatology and mortality rates, thus minimizing the benefits that such invasive procedure could bring to the patient.[5] Therefore, we need tools to predict the risk of PPM and thus implement strategies that can prevent such entity. This scenario was evaluated by Otto et al.[6] in the current issue of the *Arquivos Brasileiros de Cardiologia*.

PPM is defined echocardiographically by an indexed effective orifice area (EOA) ≤ 0.85cm²/m² and considered severe if ≤ 0.65 cm²/m².[7] Since this parameter is indexed by body surface area, individuals with body mass index ≥ 35 kg/m² have lower reference values (≤ 0.70 cm²/m² and ≤ 0.55 cm²/m², respectively) to avoid overestimation of anatomical severity in these patients.[8] Its reported prevalence varies greatly: up to 70% in the case of moderate PPM and 20% in the case of severe PPM.[5]

The current study

In this study, the authors showed a 33.4% incidence of severe PPM in a representative population treated by the Brazilian Unified Health System (SUS), which is significantly greater than that described in other studies.[5] This fact can be justified by the study design, but also because it deals with a characteristically different population, with prevalence of young patients and with rheumatic etiology.

Furthermore, the authors created a model for prediction of severe PPM, containing the following parameters: age, male sex, LV outflow tract diameter ≤ 2.1 cm, body mass index and etiology of valve disease. A specific score for this prediction, composed by preoperative factors, is extremely relevant to identify patients in need for differential interventions and to avoid PPM. In elderly patients with degenerative aortic stenosis, a transcatheter aortic valve implantation (TAVI) may be beneficial. There is evidence that the incidence of PPM in patients who underwent TAVI is lower compared with patients undergoing conventional surgery, especially among those with a small aortic annulus.[9] Currently, to test this hypothesis, there is a multicenter randomized trial (Transcatheter Aortic Valve Replacement Versus Surgical Aortic Valve Replacement for Treating Elderly Patients With Severe Aortic Stenosis and Small Aortic Annuli: A Prospective Randomized Study - The VIVA Trial; NCT03383445) comparing TAVI and conventional surgery in elderly patients with a small aortic annulus (average diameter of the aortic annulus < 22 mm).[9]

On the other hand, for young patients with rheumatic disease, like those in this study, there are surgical therapeutic alternatives, such as aortic annulus enlargement, implantation of supra-annular prostheses, sutureless prostheses and stentless prostheses. However, the literature is still scarce on this issue and randomized studies are expected to determine the best treatment among them.[10]

This study has some limitations. The retrospective cross-sectional design and the exclusion of about half of the initial population due to data loss may have resulted in overestimation of the prevalence of PPM, which reiterates the need for prospective studies on the issue.

Conclusion

Predicting PPM is important and continues to be a dilemma. The study carried out by Otto et al.[6] brings relevant information on this entity in a selected population of the Brazilian Unified Health System (SUS). New prospective studies are needed for a better understanding of PPM and also for validation of the proposed score.

Keywords

Aortic Valve/surgery; Heart Valve Prosthesis/adverse effects; Size Perception; Quality of Life; Echocardiography/methods.

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Synergistic Effect of Disease Severity, Anxiety Symptoms and Elderly Age on the Quality of Life of Outpatients with Heart Failure

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Abstract

Background: **Heart failure (HF) is a multifactorial syndrome with repercussions on quality of life (QoL).**

Objectives: **To investigate the main interacting factors responsible to worsen quality of life of outpatients with HF.**

Methods: **Cross-sectional observational study with 99 patients of both genders, attending a HF outpatient clinic at a university hospital, all with a reduced ejection fraction (<40%) by echocardiography. They were evaluated using sociodemographic and clinical questionnaires, the Minnesota Living with Heart Failure (MLwHF), and the Hospital Anxiety and Depression scale (HADS). QoL was the outcome variable. Two multivariate models were used: the parametric beta regression analysis, and the non-parametric regression tree, considering $p < 0.05$ and $0.05 < p < 0.10$ for statistical and clinical significance, respectively.**

Results: **Beta regression showed that depression and anxiety symptoms worsened the QoL of HF patients, as well as male sex, age younger than 60 years old, lower education level, lower monthly family income, recurrent hospitalizations and comorbidities such as ischemic heart diseases and arterial hypertension. The regression tree confirmed that NYHA functional class III and IV worsen all dimensions of MLwHF by interacting with anxiety symptoms, which influenced directly or indirectly the presence of poorer total score and emotional dimension of MLwHF. Previous hospitalization in the emotional dimension and age younger than 60 years in general dimension were associated with anxiety and NYHA functional class, also worsening the QoL of HF patients.**

Conclusion: **HF with reduced ejection fraction was associated with poorer MLwHF. Anxiety symptoms, previous hospitalization and younger age were also associated with worsened MLwHF. Knowledge of these risk factors can therefore guide assessment and treatment of HF patients. (Arq Bras Cardiol. 2020; 114(1):25-32)**

Keywords: **Heart Failure; Anxiety/diagnosis; Hospitalization; Quality of Life; Age; Systolic Volume.**

Introduction

Heart failure (HF) is the leading cause of heart disease morbidity and mortality and is more common among people aged 60 or older.[1] HF deeply affects the health of an individual, and has physical, psychological and social consequences. HF is a syndrome that severely impairs quality of life (QoL), predisposing patients to recurrent hospitalizations,[2] and high morbidity and mortality rates, as observed in the Framingham's study.[3]

In a study[4] of 204 HF outpatients, the authors found that 46% of the outpatients had depressive and anxiety symptoms at baseline. After a five-year follow-up, even after controlling for disease severity and other risk factors, depressive symptoms were still associated with outcomes such as hospitalization and death.[5] When analyzing patients who had difficulty in taking medication, the authors pointed out that these patients had more severe HF symptoms and worse quality of life, which can be partially explained by the coexistence of depression and psychological distress such as dysphoria and anxiety.[6]

The association between depression, physical symptoms and QoL in HF patients was observed by Bekelman et al.[7] in a cross-sectional study with 60 outpatients. It was more common to see patients with depression and anxiety after they suffered dyspnea (OR 5.28, $p < 0.05$), and those who exhibited more symptoms of depression presented more HF symptoms ($p < 0.0001$) and poorer quality of life. Another study with patients who had been diagnosed with HF concluded that depression was associated with a worse health status at the baseline, and was a strong predictor of hospitalization, and worse HF symptoms, functional status and QoL.[8]

Physical symptoms are affected by depression and anxiety, as reported in a study[9] that showed that psychological variables could affect QoL as much as physical symptoms of HF. In a multiple regression analysis, physical symptoms, age, employment status and anxiety at baseline were the best QoL predictors after a three-month follow-up. Depression, perceived control of HF, employment status

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and younger age were predictors of physical symptom status after three months. The great unanswered question is how these variables interact to worsen patients' QoL, and how much they compromise the therapeutic approach in the various degrees of impairment of ventricular function.

Thus, we collected sociodemographic, clinical variables, anxiety and depression symptoms, medications in use, previous hospitalization and left ventricular ejection fraction (LVEF) to investigate which factors are associated and interact to get worse quality of life of outpatients with heart failure.

Methods

This study was approved by the Ethics Committee of the Hospital Universitário Clementino Fraga Filho under the protocol number 104/2010. The patients signed a consent form to participate in this study, which included an observational, cross-sectional and descriptive series of consecutive cases. Patients allowed to participate had HF with reduced LVEF < 40[10] and New York Heart Association (NYHA) functional class I to IV and they were aged ≥ 20 years. Patients with HF caused by valvular dysfunction or reversible causes, and patients who were unable to be interviewed due to psychiatric syndromes, cognitive impairment assessed clinically, and hearing loss were excluded. All participants were recruited at the HF outpatient clinic of the Cardiology Department of the Federal University of Rio de Janeiro from March 2011 to September 2012. One hundred and twenty patients were interviewed individually and a sample of 99 patients of both sexes met the criteria for inclusion.

All participants sociodemographic and clinical questionnaires, the Brazilian version of the Minnesota Living with Heart Failure Questionnaire (MLwHF),[11,12] and the Hospital Anxiety and Depression Scale (HADS).[13,14]

The sociodemographic questionnaire considered age, sex, monthly family income (dollar), education (years) categorized in illiterate, education 1 (<5 yrs), education 2 (6-12 yrs), education 3 (>12 yrs), marital status (married) and family support. The clinical questionnaire considered NYHA functional class, comorbidities such as atrial fibrillation, chronic renal failure, diabetes mellitus and arterial hypertension; current use of drugs such as betablockers, spironolactone, angiotensin-converting-enzyme inhibitor (ACE), angiotensin AT1 receptor blocker (ARB), nitrate, hydralazine; previous hospitalization and LVEF.

The MLwHF is a structured QoL questionnaire for patients with HF and it has been translated and validated for the Brazilian population.[11,12] The questions are related to how the patient felt during the 30 days before completing the questionnaire. The MLwHF is made up of 21 questions that address the perception of the *physical* (strongly correlated with dyspnea and fatigue), *emotional* (correlated with emotional and social aspects) and *general well-being* (correlated with financial issues, the side effects of medication and lifestyle), and their scores vary from 0 to 40, 0 to 25 and 0 to 40, respectively. A higher score reflected a worse QoL.

The HADS was developed specifically for use in medically ill populations. It is based on mood, depression and anhedonia and excludes physical symptoms such as sleep disturbance, fatigue and body pain, which can be confused with symptoms of other diseases. The HADS is made up of 14 questions, each with four possible answers, and consists in two subscales – anxiety and depression – of seven items each. The responses refer to how the patients felt in the last seven days, and the sum of each subscale varies from 0 to 21. It has been translated and validated in a Brazilian version, using a cutoff of ≥ 8 in samples of medically ill patients.[13,14] For the analysis, this cutoff was used as an indication of depression and anxiety, which are referred to in this study as "depression and anxiety symptom". This variable was dichotomized into "possible anxiety" (8 to 11) and "probable anxiety" (12 to 21), and the same for "possible depression" and "probable depression".

The outcome variables were the MLwHF dimensions, namely, total score, physical, emotional and general welfare. The independent variables were the sociodemographic variables, clinical variables, anxiety symptoms, depression symptoms, current drugs, previous hospitalization and LVEF.

Statistical analysis

The continuous variables were presented as mean ± standard deviation (variables normally distributed); or median, first quartile and third quartile (non-normal variables). Data normality was tested using the Shapiro-Wilk normality test. The comparison between the NYHA I/II and NYHA III/IV groups was made using unpaired t-Student test, for normal continuous variables, Wilcoxon rank sum test, for non-normal continuous variables, and Exact Binomial Test, for categorical variables.

Total score, physical, and the emotional and general dimensions of the MLwHF were the outcome variables. The association of the variables described above with the outcomes and dimensions of QoL were evaluated using a parametric beta regression model and a non-parametric regression tree.[15] Beta regression is a new model recently developed by the Brazilian authors Silvia Ferrari and Francisco Cribari, used when the outcome is a continuous variable that varies in the interval (0,1). The regression tree, apart from its predictive power and its easy visual interpretation, is also extremely useful to find possible interactions between predictive variables, including in situations of unexpected interactions, as in our case. Its final nodes result in the boxplot[16,17] of the outcome variables. The Betareg package[18] of the R software[19] was used. Values of $p < 0.05$ and $0.05 < p < 0.10$ were considered statistically significant and clinical significance, respectively.

Data of 99 patients were analyzed; two did not have the LVEF data, and three did not have data of monthly family income. The missing data were imputed considering the MCAR (missing completely at random) as the missing mechanism of these data.[20] To facilitate the reading of the figures, the MLwHF scales were adjusted to vary from 0 to 100 (0, 1) and the scores were inverted so the highest scores would be equivalent to better QoL.

Results

Table 1 describes the characteristics of the sample dichotomized according to the NYHA functional class. Lower LVEF and lower MLwHF, in all dimensions, were

Table1 – Characteristics of the sample dichotomized by NYHA functional class

	Total	NYHA = I /II	NYHA = III/IV	p *
Number of patients	99 (100%)	59 (59.60%)	40 (40.40%)	0.0699
Age				
Average ± SD	61.05 ± 10.88	59.85 ± 10.65	62.83 ± 11.11	0.1829
Monthly family income				
Median (1st Qu.; 3rd Qu.)	914.28 (594.61; 1294.61)	892.3 (594.61; 1564.10)	923.07 (602.56; 1102.56)	0.3978
Ejection Fraction				
Average ± SD	35.58 ± 9.18	37.27 ± 8.7	33.1 ± 9.4	0.0258*
MLwHF Total score				
Median (1st Qu.; 3rd Qu.)	27 (10.5; 47.0)	17 (5; 32.5)	45 (31.5; 55.0)	< 0.0001***
MLwHF Physical				
Median (1st Qu.; 3rd Qu.)	14 (3; 21)	6 (2; 17.5)	20 (15; 25)	< 0.0001***
MLwHF Emotional				
Median (1st Qu.; 3rd Qu.)	6 (2; 13)	3 (0.5; 10.5)	10.5 (5.75; 15.25)	0.0001***
MLwHF General				
Median (1st Qu.; 3rd Qu.)	7 (3.0; 14.5)	4 (1; 8)	11 (8; 19)	< 0.0001***
Male	61(100%)	38 (62.30%)	23 (37.70%)	0.0722
Schooling				
Illiterate	6 (100%)	3 (50.00%)	3 (50.00%)	1.0000
Education (< 5 years)	37 (100%)	24 (64.86%)	13 (35.14%)	0.0989
Education (6-12 years)	52 (100%)	31 (59.62%)	21 (40.38%)	0.2116
Education (> 12 years)	4 (100%)	1 (25.00%)	3 (75.00%)	0.6250
Married	64 (100%)	39 (60.94%)	25 (39.06%)	0.1034
Family support	82(100%)	51 (62.20%)	31 (37.80%)	0.0352*
Employed	19 (100%)	12 (63.16%)	7 (36.84%)	0.3593
Ischemic Etiology	39(100%)	21 (53.85%)	18 (46.15%)	0.7493
Absence of atrial fibrillation	82(100%)	51 (62.20%)	31 (37.80%)	0.0352*
Absence of chronic renal failure	84(100%)	52 (61.90%)	32 (38.10%)	0.0375*
Absence of diabetes mellitus	57(100%)	38 (66.67%)	19 (33.33%)	0.0163*
Arterial hypertension	69(100%)	39 (56.52%)	30 (43.48%)	0.3356
Absence of previous hospitalization	63(100%)	44 (69.84%)	19 (30.16%)	0.0022
Probable anxiety	15(100%)	10 (66.67%)	5 (33.33%)	0.3018
Possible anxiety	35(100%)	19 (54.29%)	16 (45.71%)	0.7359
Probable depression	11(100%)	7 (63.64%)	4 (36.36%)	0.5488
Possible depression	27(100%)	15 (55.56%)	12 (44.44%)	0.7011
Current use of betablockers	96 (100%)	57 (59.38%)	39 (40.62%)	0.0822
Absence of spironolactone	38(100%)	28 (73.68%)	10 (26.32%)	0.0051**
Current use of ACE inhibitor/ARB	94(100%)	57 (60.64%)	37 (39.36%)	0.0495*
Absence Nitrate/Hydralazine	63(100%)	43 (68.25%)	20 (31.75%)	0.0052**
Absence Furosemide	25(100%)	18 (72.00%)	7 (28.00%)	0.0433*
Optimized treatment	87(100%)	50 (57.47%)	37 (42.53%)	0.1980

*p < 0.001***; p < 0.01**; p < 0.05 *. * P-values were calculated using unpaired t-Student test (for normal continuous variables); Wilcoxon rank sum test (for non-normal continuous variables); and Exact Binomial Test (for categorical variables). MLwHF: Minnesota Living with Heart Failure; NYHA: New York Heart Association; ACE: Angiotensin-converting enzyme inhibitor; ARB: Angiotensine1 receptor blocker; SD: Standard deviation.*

significantly more common in NYHA III and IV. On the other hand, family support, absence of comorbidities such as diabetes mellitus, atrial fibrillation, chronic renal failure and the non-use of spironolactone, nitrate or furosemide were significantly more frequent in NYHA I and II.

Results of the beta regression analysis are shown in Table 2. It is noteworthy that the predictor variable NYHA functional class has a statistically significant association with all outcome variables, showing that patient's QoL is affected in all its dimensions by physical symptoms of HF. Anxiety symptoms were also associated with all outcomes except the general well-being dimension. Depression symptoms were associated with the emotional well-being dimension, showing that psychological symptoms affected patients' QoL in this sample. Previous hospitalization worsened the QoL of outpatients with HF regarding emotional and physical aspects. The current use of medications as betablockers, ACE and furosemide were associated with poor MLwHF in different dimensions. The general well-being dimension of MLwHF decreased with lower monthly family income of the patients. It is worth mentioning that all beta regression models showed a coefficient of determination R2 of about 50% (Figure 1: A-50, B-48, C-56, D-44), which means that the prognostic variables explain 50% of the variation of the outcome or dependent variables.

The regression tree, the nonparametric model, also evaluated the association of the set of predictor variables with each outcome variable (Figure 1). The results of this model are consonant with the beta model seen in Table 2 and give further information about interactions between the independent variables. Figure 1 illustrates the negative effects of a worse NYHA functional class in all MLwHF dimensions. Anxiety symptoms contributed directly or indirectly to lower total score and poorer emotional well-being in MLwHF. The same was observed for previous hospitalization variable in the emotional well-being dimension, indicating an interaction with NYHA functional classes I and II. In the general well-being dimension, the NYHA classes I and II were associated with poorer MLwHF if patients were younger than 60 years old. Due to inversion of the score system, the interpretation of the regression trees considers that higher values, for each outcome variable, correspond to a better QoL. In other words, we could exemplify that the best quality of life was observed in: NYHA functional class I patients without anxiety symptoms (Figure 1A: total score, 14 patients, 14.1%), NYHA functional class I patients (Figure 1B: physical well-being dimension, 19 patients, 19.2%), NYHA I or II patients with no anxiety symptoms or previous hospitalization (Figure 1C: emotional well-being dimension, 27, 27.3%), and NYHA I or II patients older than 59 years old (Figure 1D: general well-being dimension, 32 patients, 32.3%). We have created a pseudo-coefficient of determination R2 for the regression tree resulting in coefficients around 30% and 40% (Figure 1 A 42% , B 29%, C 44%, D 29%).

Discussion

The originality of the study consists of the research methods applied to the research question. The regression tree is a nonparametric regression, useful for prediction, and to obtain data not only from the relevant variables, but also from the relevant interactions between these variables. In the usual regression, we can obtain the relevant variables, but we must define what interactions we consider relevant. In the tree of regression, the Data Mining (Machine Learning) algorithm verifies, from the existing data, which variables and which interactions are the most important, providing a better understanding of the complex relationships observed in clinical practice.

This study found an association of ventricular function (represented by NYHA functional class), anxiety symptoms, male sex, age younger than 60 years old, lower education level, lower monthly family income, recurrent hospitalization and comorbidities (such as arterial hypertension and ischemic heart diseases), current use of medications (such as betablockers, ACE and furosemide) with poorer QoL of HF outpatients.

One study[21] explored the perceptions of QoL in HF patients to assess limitations in their daily lives caused by symptoms, happiness, and relationships, and pointed out that QoL was affected not only by negative physical, psychological, social, and economic status, but also by positive physical, psychological and social status, and behavior, although it was not modified by education combined with self-management intervention. The present study revealed the association of the predictor variable NYHA functional class III-IV with all outcome variables, and of anxiety and depression symptoms with two of the three outcome variables in the beta model. Also, our study shows that even a lower NYHA functional class (I-II), associated with anxiety symptoms and previous hospitalization, may worsen the QoL in the total score and emotional well-being dimension.

HF may be the most devastating chronic disease, as it affects people's QoL in several dimensions. In fact, other authors have provided evidences that improvements in self-management skills may enhance outcomes of HF patients.[22]

The awareness of one's own diagnosis has a profound impact on the patients. Mulligan et al.[8] showed that, addressing patients' mood and beliefs about their illness and its treatment, improved physical and emotional dimensions of MLwHF and promoted an improvement by 55% and 43% in anxiety and depression symptoms, respectively, assessed by HADS, in the early period after the diagnosis of HF. Reduced anxiety symptoms were associated with reduced perception of the severity of HF and of control due to the treatment of the disease. Reduced depression symptoms was attributed to the improvement of NYHA functional class, reduction in symptoms and perceived severity of HF, and increased confidence in the treatment. The present study confirms these findings that depression and anxiety symptoms contribute to a worsening of QoL related to physical symptoms of HF. It also confirms the fact that when HF patients are less symptomatic and have no anxiety symptoms and recurrent hospitalizations, patient's QoL is better.

In another study,[23] less social support and greater depressive symptoms independently predicted poorer QoL. Also, patient's perspective on family functioning and autonomy support, along with family knowledge about HF, influenced psychological outcomes of depressive symptoms and emotional QoL of patients with HF.[24] These studies corroborate our results, since married people with family

Table2 – Beta regression analysis MLwHF and predictor variables

MLwHF QoL Dimensions	Predictor Variables	Estimate (CI 95%)	p
Total score	Education (< 5 years)	0.734 (0.101; 1.366)	0.023 *
	Education (6-12 years)	0.589 (-0.033; 1.211)	0.063
	Education (> 12 years)	0.755 (-0.210; 1.720)	0.125
	Monthly family income	0.000 (0.000; 0.001)	0.019 *
	NYHA II	-0.695 (-1.162; -0.229)	0.003 **
	NYHA III	-1.416 (-1.904; -0.928)	< 0.001 ***
	NYHA IV	-1.404 (-2.066; -0.742)	< 0.001 ***
	Arterial Hypertension	0.585 (0.239; 0.931)	0.001 ***
	Previous hospitalization	-0.553 (-0.898; -0.207)	0.002 **
	Anxiety symptoms	-0.593 (-0.997; -0.190)	0.004 **
	Depression symptoms	-0.402 (-0.828; 0.025)	0.065
	Current Use of Betablocker	0.908 (0.064; 1.752)	0.035 *
Physical	Education (< 5 years)	1.078 (0.223; 1.934)	0.013 *
	Education (6-12 years)	1.077 (0.233; 1.921)	0.012 *
	Education (> 12 years)	1.369 (0.124; 2.614)	0.031 *
	NYHA II	-1.087 (-1.658; -0.516)	< 0.001***
	NYHA III	-1.789 (-2.411; -1.167)	< 0.001***
	NYHA IV	-2.439 (-3.326; -1.552)	< 0.001***
	Arterial Hypertension	0.755 (0.307; 1.203)	0.001 ***
	Previous hospitalization	-0.867 (-1.345; -0.389)	< 0.001***
	Anxiety symptoms	-0.967 (-1.404; -0.529)	< 0.001***
	Current Use of Betablocker	2.018 (0.847; 3.190)	0.001 ***
	Current Use of Furosemide	0.520(0.031; 1.010)	0.037 *
Emotional	Male	0.538 (0.145; 0.932)	0.007 **
	Education (< 5 years)	0.725 (-0.088; 1.539)	0.080
	Education (6-12 years)	0.747 (-0.042; 1.535)	0.063
	Education (> 12 years)	1.135 (-0.099; 2.369)	0.071
	Ischemic etiology	0.561 (0.132; 0.990)	0.010 **
	NYHA II	-0.229 (-0.78; 0.322)	0.416
	NYHA III	-1.234 (-1.818; -0.65)	< 0.001 ***
	NYHA IV	-0.727 (-1.537; 0.083)	0.079
	Previous hospitalization	-0.606 (-1.059; -0.152)	0.009 **
	Anxiety symptoms	-1.104 (-1.614; -0.595)	< 0.001***
	Depression symptoms	-0.879 (-1.420; -0.338)	0.001 ***
	Current Use of ACE	-1.424 (-2.312; -0.536)	0.002 **
General	Male	-0.342 (-0.708; 0.025)	0.068
	Age	0.030(0.013; 0.047)	< 0.001***
	Monthly family income	0.001 (0.000; 0.001)	0.001 ***
	NYHA II	-0.717 (-1.249; -0.184)	0.008 **
	NYHA III	-1.717 (-2.259; -1.176)	< 0.001***
	NYHA IV	-1.895 (-2.627; -1.162)	< 0.001***
	Current Use of Betablocker	1.280(0.323; 2.237)	0.009 **

*p < 0.001***; p < 0.01**; p < 0.05*. MLwHF: Minnesota Living with Heart Failure; NYHA: New York Heart Association; ACE: angiotensin-converting enzyme inhibitor.*

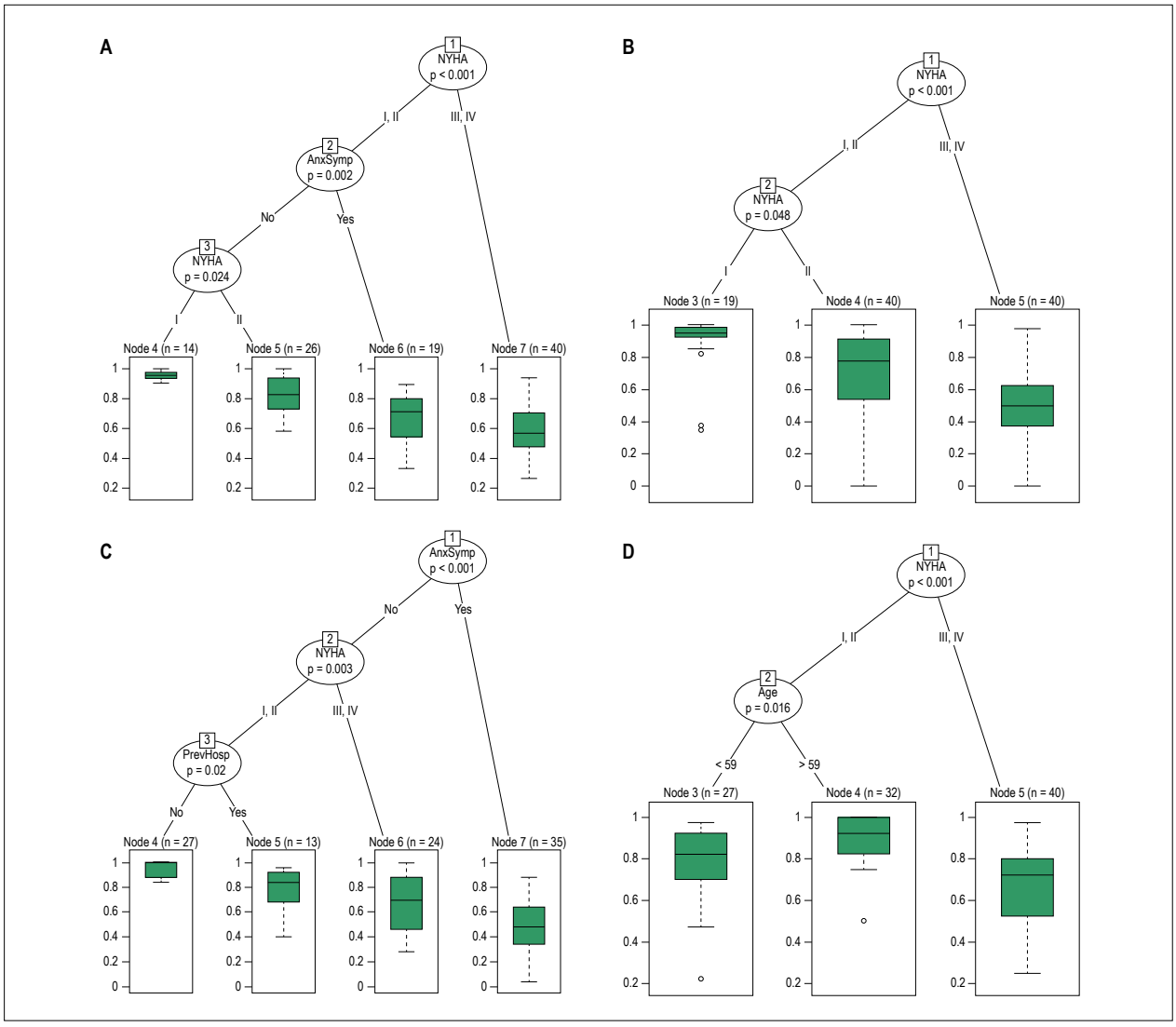

Figure 1 – *Regression tree (A- Total Score, B- Physical Dimension, C- Emotional Dimension, D-General Dimension) illustrating that advanced NYHA (New York Heart Association) functional class worsened all dimensions of MLwHF (Minnesota Living with Heart Failure). Anxiety symptoms influenced directly or indirectly the presence of poorer total score and emotional well-being dimension of MLwHF. The same was observed for previous hospitalization in the emotional well-being dimension, demonstrating an interaction with functional class NYHA I and II. In the general well-being dimension, the NYHA functional classes I and II were associated with poorer MLwHF in patients younger than 60 years old.*

support had positive perception of HF control, and anxiety and depression symptoms directly and negatively affected HF-related physical symptoms, which, in turn, interfered with QoL of these patients.

A meta-analysis concluded that somatic/affective depression symptoms were more strongly and consistently associated with mortality and cardiovascular events in patients with heart disease compared with cognitive/affective symptoms.[25] Another study[26] with 55 congestive HF patients also showed that somatic/affective depressive symptoms, but not cognitive depression symptoms and anxiety symptoms, were associated with poor health-related QoL and behavioral functional capacity, independent of age, clinical functional status and comorbidities.[26] Our study disagreed with these results because NYHA functional class III and IV worsened all dimensions of MLwHF, and anxiety symptoms, combined with age under 60 years, influenced directly or indirectly the presence of poorer score.

A willing attitude toward following a low sodium diet, and an increased social support were significantly associated with higher levels of perceived control and better QoL.[27] A recent study[28] pointed out that depressive symptoms exerted a negative effect on medication adherence related to the complexity of medication regimen commonly prescribed to HF patients. In the present study, we also observed that the current use of medications as betablockers, ACE and furosemide were associated with poor MLwHF in different dimensions, suggesting that it could be a barrier to reach medication adherence by HF patients.

How and by what mechanisms such associations are given are not clear. Probably physiological and behavioral factors including endothelial dysfunction, platelet abnormalities, inflammation, autonomic nervous system dysfunction, and reduced engagement in health-promoting activities, may link depression and anxiety with adverse cardiac outcomes and poorer QoL in HF.[29,30]

This study has some limitations. This was a single-center study, although it can encourage future studies in other specialized centers. Also, its cross-sectional design made it difficult to assess possible changes in patients' QoL and what factors contributed to such changes and to make speculations that would only be possible with a longitudinal design. Thus, generalizations must be made with caution.

Conclusion

Based on these findings, it is possible to conclude that a reduced LVEF is associated with many factors that compromise the QoL of HF outpatients, even in clinically less severe cases, like in NYHA functional class I or II . These findings may aid in the full approach of patients with HF, suggesting the diagnosis and treatment of anxiety symptoms, especially those with multiple hospitalizations and younger than 60 years.

Author contributions

Conception and design of the research: Figueiredo JHC, Oliveira GMM, Xavier SS; Acquisition of data: Figueiredo JHC, Oliveira GMM, Garcia MI; Analysis and interpretation of the data and Writing of the manuscript: Figueiredo JHC, Oliveira GMM, Pereira BB, Figueiredo AEB, Nascimento EM, Garcia MI, Xavier SS; Statistical analysis: Pereira BB, Figueiredo AEB, Nascimento EM; Critical revision of the manuscript for intellectual content: Oliveira GMM, Pereira BB, Figueiredo AEB, Nascimento EM, Garcia MI, Xavier SS.

Potential Conflict of Interest

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

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Study Association

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Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Hospital Universitário Clementino Fraga Filho under the protocol number 104/2010. 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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Quality of Life in Heart Failure: An Important Goal in Treatment

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Short Editorial related to the article: Synergistic Effect of Disease Severity, Anxiety Symptoms and Elderly Age on the Quality of Life of Outpatients with Heart Failure

Brazil is the country with the highest prevalence of anxiety disorders, according to the World Health Organization and ranks 5th regarding the prevalence of depression.[1] Mood disorders, which include anxiety and depression, are often neglected in clinical practice,[2,3] and their diagnosis in patients with heart failure (HF) is even more challenging, given the overlap of several symptoms, such as fatigue, weight loss and sleep disorders.[4,5]

In this issue of the Archives, the cross-sectional study by Figueiredo et al.[6] evaluated, in a population of 99 patients with HF and reduced ejection fraction, which clinical, sociodemographic and psychological variables most correlated with the quality of life assessed by the Minnesota Living with Heart Failure Questionnaire. The main factors associated with poorer quality of life were dyspnea advanced functional class (New York Heart Association III and IV), previous hospitalization and anxiety symptoms. Depression was not independently associated with reduced quality of life, but several other studies have found this association.[7,8] The study also shows an alarming prevalence of anxiety symptoms in these patients, of 50%, when compared to 9.3% in the overall population.[1]

The interaction between cardiovascular disease and mood disorders occurs in a bi-direction manner.[9] Recently, it was described that optimism is associated with lower risk of cardiovascular events and mortality from any cause.[10] The risk of developing HF in patients with depression is 1.5 to 2.6-fold higher than in the overall population.[11] In individuals diagnosed with HF, depression indicates a worse prognosis and is associated with higher hospitalization and mortality rates.[11] Possible mechanisms to explain this association involve lower adherence to pharmacological and non-pharmacological treatment in patients with depression and greater tendency towards having unhealthy lifestyles.[12,13] The more advanced the dyspnea functional class, the worse the symptoms of depression and the quality of life.[8,11]

Regarding anxiety disorders, affected individuals also seem to have a higher risk of developing HF throughout life.[14] In those diagnosed with HF, the presence of anxiety is associated with poorer quality of life;[15] however, the correlation with increased mortality is not as well established.[16,17]

Evidence is limited for the treatment of mood disorders in HF patients. Cognitive behavioral therapy was tested in a randomized study of 158 patients diagnosed with major depression and heart failure.18 Psychotherapy was associated with remission of depression (46% vs. 19%, NNT = 3.8), in addition to improvement in quality of life, anxiety and fatigue.

The pharmacological treatment of choice for mood disorders consists in selective serotonin reuptake inhibitors.[19,20] For patients with HF and reduced ejection fraction, two prominent randomized trials tested these therapies in individuals with major depression: 1) MOOD-HF,[21] which included 372 patients to receive escitalopram or placebo for 3 months, and 2) SADHART-CHF,[22] which included 469 patients to receive sertraline or placebo for 18 months. Both were negative for the primary outcome, showing no benefit of pharmacological therapies in the treatment of depression in HF patients.

A structured and multidisciplinary HF management education and care program implemented in 350 patients in our service has shown a reduction in unplanned hospitalizations[23] and improved quality of life, especially in the emotional domain,[23,24] suggesting that this approach may be beneficial for patients with mood disorders.

The study by Figueiredo et al.,[6] suffers from the usual limitations of a single-center, cross-sectional and observational assessment, and the small number of patients prevents more robust conclusions. The assessed primary outcome was quality of life, but it remains to be prospectively seen whether anxiety has an impact on clinical outcomes, such as hospital admissions or mortality.

In conclusion, the present article by Figueiredo et al.[6] reinforces the importance of a holistic approach for HF patients, by demonstrating that neglected factors such as anxiety disorders are very prevalent in this population and may have an impact on quality of life. The field of treatment for mood disorders has been little explored and deserves further attention in future randomized trials.

Keywords

Heart Failure; Anxiety/diagnosis; Hospitalization; Quality of Life; Aged; Stroke Volume.

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Clinical Competence in ST-segment Elevation Myocardial Infarction Management by Recently Graduated Physicians Applying for a Medical Residency Program

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Abstract

Background: A significant reduction in the morbidity and mortality related to ST-segment elevation myocardial infarction (STEMI) has been achieved with the development of reperfusion therapies. Early diagnosis and correct initial management are important to ensure this benefit. In Brazil, recent graduates in medicine are responsible for a large part of the initial care provided for these patients.

Objective: To assess the clinical competence in the diagnosis and initial treatment of STEMI by newly graduated physicians applying for a medical residency program.

Methods: We assessed the performance of 771 applicants for the direct entry selection process of the FMRP-USP Clinical Hospital Medicine Residency Program, performed in a simulated setting of STEMI, with professional actors and medical evaluators, using a standardized checklist following the recommendations of the Brazilian Guidelines for the management of this disease.

Results: The general performance score presented a median of 7 and an interquartile range of 5.5-8.0. In relation to the items assessed: 83% required ECG monitoring, 57% requested the insertion of a peripheral venous access catheter, 95% administered acetylsalicylic acid, 80% administered a second antiplatelet agent (p2y12 inhibitor), 66% administered nitrate, 71% administered morphine, 69% recognized the diagnosis of STEMI, 71% assessed the pain duration, 63% recognized the need for immediate transfer, 34% showed adequate communication skills and only 25% insisted on the transfer even in case of non-availability of beds.

Conclusions: The initial diagnosis and management of STEMI need to be improved in medical undergraduate courses and inserted into the reality of the hierarchical network structure of the Brazilian Unified Health System (SUS). (Arq Bras Cardiol. 2020; 114(1):35-44)

Keywords: ST Elevation Myocardial Infarction; Medical Staff, Hospital; Education, Medical; Clinical Competence; Internship and Residence.

Introduction

Over the last decades there has been a great development in the treatment of ST-segment Elevation Myocardial Infarction (STEMI) with an important reduction in its morbidity and mortality, especially with the emergence of fibrinolytic therapy and primary angioplasty procedures which allow for immediate recanalization of the involved coronary artery.[1]

However, to reap these benefits, it is important to make an early diagnosis of STEMI, using a resting ECG and to organize the referral of these patients to tertiary centers capable of carrying out reperfusion therapy.[2]

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Inside the Brazilian Unified Health System (SUS), which is categorized into levels of care, this patient is usually assisted in Emergency Care Units (UPAs). Because of the lack of professional doctors dedicated exclusively to emergency care, a great deal of this healthcare is provided by recently graduated physicians.[3] The lower clinical experience of these professionals can compromise the diagnosis and initial management of these patients in this critical period, in which agility makes all the difference.[4]

The objective of this study was to assess the clinical competence for the diagnosis and initial management of STEMI by recently graduated physicians applying for a medical residency program.

Methods

This is a single-centered cross-sectional study, which used simulation with professional actors, organized within the objective structured clinical examination system, better known as OSCE, as the evaluation method to verify the clinical competencies of recently graduated physicians in

STEMI management. [5] A scenario of initial patient treatment in an emergency care unit (UPA) was set up. This scenario was designed both for research data collection and as one of the practical exam stations of the direct entry public selection process of the Ribeirão Preto Medical School Clinics Hospital of the University of São Paulo (HC-FMRP-USP), for admission of first-year residency physicians to different specialties, in 2016. The practical exam to which this study refers was performed only by the applicants approved in the first-stage written exam, consisting of multiple choice questions, at a rate of 4 candidates per vacancy (except for the Infectology and Neurosurgery fields, where the proportion was of 5 candidates per vacancy). A total 1,841 candidates applied for the first-stage exam, out of whom 1,622 performed the written exam (first stage), 863 applicants were approved for the practical exam (second stage) and 771 applicants actually took the practical exam in the STEMI station (Figure 1).

The scenario organization

Before beginning the treatment, the applicants were informed that they would assist an adult patient in a UPA. The scenario was organized as a standard doctor's office, where a properly trained actor (Appendix B)* was lying on a stretcher and the evaluator was sitting at a table connected to a computer which displayed the checklist of predetermined competencies and attitudes. Inside the room, there was a printed instruction on the wall (Appendix A)* saying that the patient in question had been admitted with a complaint of chest pain, and that the nurse prioritized his care and traced a 12-lead ECG. An ECG with typical tracing for anterior wall STEMI was provided for the applicant (Appendix F)*. Some history and physical exam data were previously provided (severe retrosternal pain with an intensity 8/10 of sudden onset, associated with nausea, no irradiation and other associated symptoms, no other health problems, no use of medication in the previous 24 hours, physical examination revealed an oxygen saturation level of 98% on room air, a blood pressure of 130/80 mmHg and a heart rate of 88 bpm and no need for physical examination, considering the other data were normal). On the printed instructions, there were two tasks to be performed by the applicants: first, to define the main diagnosis for the evaluator; second, to provide the most adequate clinical management for the patient. The applicant was given a deadline of five minutes to execute these tasks. Time was clocked using an automated system. The actor was trained to ask the applicant two active questions in a row, only when the applicant suggested the need for a transfer to a hospital or Cardiology Center: "Doctor, why do I need to go to a hospital?". And after 10 seconds: "Doctor, what if there is no room?".

In the consulting room, there was a list with all the medications and procedures available in that UPA (Appendix E)*, and there were no fibrinolytic therapy and coronary angioplasty available on site. A total of 11 simulated doctor offices were organized, which worked simultaneously during the evaluation.

The evaluators' training for filling out the checklist

Sixteen evaluators, all experienced doctors, were trained to fill out the checklist electronically , using a computer available in the scenario, simultaneously with the execution of the tasks by the applicants. The evaluators were instructed not to communicate with the applicants, who should only follow the written instructions. The instructions used in the evaluators' training are available in Appendix C* of the supplementary appendix. Each applicant was evaluated by only one examiner. To reduce heterogeneity between the examiners a training was performed immediately before the beginning of the practical station, when each item of the checklist was reviewed in terms of possible answers. There was an external evaluator who was positioned in the access passage to all simulated consulting rooms and centralized any interpretation doubts concerning the applicants' answers. This external evaluator's opinion was always accepted in cases of doubtful interpretation on the part of the evaluators.

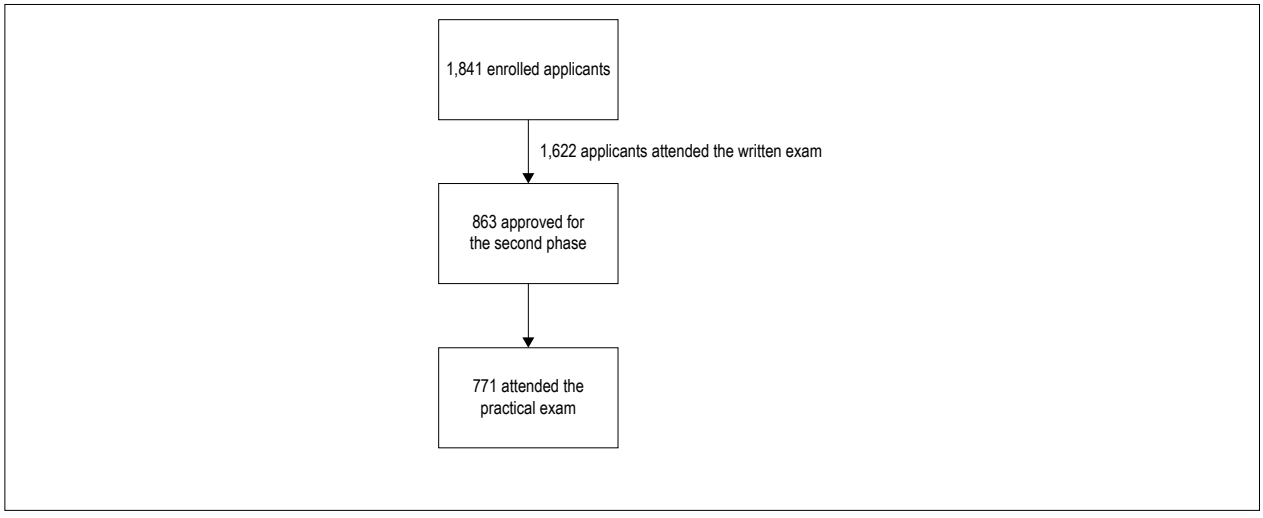

Figure 1 – *Flowchart with the number of applicants in the different phases of the medical residency selection process.*

The development of the checklist

The checklist was developed by a cardiologist with experience in treating STEMI patients following the V Guideline of the Brazilian Society of Cardiology on Acute Myocardial Infarction Treatment with ST-Segment Elevation and revised by other five experienced physicians.[6] The checklist included 12 different items, six of which were directly concerned with the treatment (0.5 points each, with a total of 3.0 points): requirement of ECG monitoring, insertion of a peripheral venous access catheter, acetylsalicylic acid administration, administration of a second antiplatelet agent (p2y12 inhibitor), sublingual nitrate administration and morphine administration (it was not necessary to specify the correct dosage of these medications, but only to mention them). And the six remaining items were directly associated with the diagnosis and transfer management: recognition of the diagnosis of STEMI (2.0 points), assessment of pain duration, which is an important aspect in the determination of the therapeutic conduct in this case (1.0 point), recognition of immediate need for patient transfer (2.0 points) in order to perform reperfusion therapy (thrombolytic or primary angioplasty), one item related with communication skills towards the patient, explaining the disease and the treatment using simple and objective language (1.0 point) and one item related with reinforcing the need to transfer the patient for a tertiary service, even in case of non-availability of beds (1.0 point), defined as "zero vacancy", according with the Resolution 2077/14 of the Federal Medicine Council (CFM) for urgencies and emergencies. Finally, there was one item of negative evaluation, which consisted of delaying treatment to wait for myocardial necrosis markers (a two-point reduction in the score). More details on the checklist can be found in Appendix C* of the supplementary appendix. The score ranged from 0 to 10 points, being directly proportional to the clinical competence observed in the simulated scenario approach. According to the organization of the checklist, the most important items were: identification of STEMI diagnosis (2.0 points) and immediate transfer to reperfusion (2.0 points). In relation to the correct diagnosis, it was necessary to specify ST-segment elevation, because electrocardiographic criteria for this diagnosis are quite well defined. We considered as a partial answer the identification of infarction with no reference to ST-segment elevation, since, even in such case, the applicant could initiate the recommended therapeutic conduct. Other drug therapies were included as adjuvant therapy and had the same value (0.5 points), since all of them were classified as Class-I recommendation in the most recent Brazilian guidelines for initial management of STEMI.

Demographic and education data

These data were obtained from the application form filled out by the candidates: age, sex, graduation year, state of origin, medical school of origin. Data related to the performance in the evaluation, obtained through the electronic checklist, were exported to Excel spreadsheets from a system exclusively developed to carry out this practical assessment. This project was approved by the Ethics Committee in Research of our institution under protocol number 838/2017.

Statistical Analysis

Sample size corresponded to all the applicants who performed the station practical exam of the selection process for the medical residency program of the HC-FMRP-USP, in 2016. Normality of distribution was checked using the Shapiro-Wilk test. Quantitative variables with normal distribution were expressed as mean (standard deviation) and the other quantitative variables as median and interquartile range. Categorical variables were expressed as percentage. Student-t test was used to compare two quantitative variables with normal distribution and Mann-Whitney test was used for comparison between two quantitative variables not normally distributed. The Chi-square test was used to compare two categorical values. A two-tailed p-value < 0.05 was considered significant. Data analyses and graphic building were performed by STATA 13.1 for Windows (STATA software, College Station, TX, USA).

Results

The demographic characteristics of the 771 applicants who performed the tasks in this simulated station are shown in Table 1. The median age was 25 years (24-27 years), and the majority of the applicants were males (58%). Most applicants were newly formed physicians (90%), among whom 71% had graduated less than a year before and 19% had graduated between 1-2 years before. Most candidates had come from a public university (66%) in the Southeast region (65%).

Regarding the general performance of the applicants, a median of 7.0 (interquartile range: 5.5-8.0) and a mean of 6.74 with a standard deviation of 1.93 were observed (Figure 2).

In relation to each item of the checklist directly associated with the treatment, the following result was observed: 83% of the applicants requested ECG monitoring, 57% oriented the insertion of a peripheral venous access device, 95% administered acetylsalicylic acid, 80% added a second antiplatelet agent (P2Y12 inhibitor), 66% administered sublingual nitrates e 71% administered intravenous morphine for pain relief (Figure 3).

The following proportion was observed in relation to the checklist items concerning with the diagnosis and transfer management: 69% of the applicants identified the diagnosis of STEMI and 28% identified the diagnosis of infarction, but did not mention ST-segment elevation. The duration of pain was verified by 71% of the applicants. The majority of the applicants recognized the need for transfer to perform the reperfusion procedure (63%) and 19% recognized this necessity, however they did not specify the reason for the transfer (reperfusion therapy), 18% did not raise the need for transfer. Communication skills were considered adequate in 34% of the applicants (they provided adequate explanation on disease and treatment), 32% explained only one of these items (disease or treatment) and 34% did not approach any of the two items with the patient. Only 25% of the applicants insisted on the transfer to a tertiary center even in case of non-availability of beds after the actor's intervention. A total of 4% of the applicants kept waiting for the markers of myocardial necrosis in order to define the therapeutic conduct (Figure 4).

Table 1 – Demographic characteristics of the recently graduated physicians who took part in the practical examin on STEMI medical care

Characteristics		n = 771 individuals
Age (years); median (19)		25 (24-27)
Male sex; n(%)		444 (58)
Years from graduation; n(%)		
	< 1 year	549 (71)
	≥ 1-2 years	145 (19)
	≥ 2-3 years	44 (06)
	≥ 3-4 years	12 (01)
	≥ 4 years	21 (03)
Institution where graduated; n(%)		
	Public	509 (66)
	Private	254 (33)
	Foreign	8 (01)
Region of origin; n(%)		
	Southeast	499 (65)
	Northeast	173 (22)
	South	48 (06)
	Central-West	33 (04)
	North	10 (01)
	Abroad	08 (01)

When comparing the applicants who performed best (general score > 7) with those with a lower performance (general score ≤7), no differences were observed in relation to the age, mean time of graduation and geographic region of origin. However, a higher prevalence of males was observed in the group with lower performance (63% vs. 52%; p = 0.003) and a higher prevalence of graduates from public universities in the group with greater performance (71% vs. 61%; p = 0.0016). When comparing their performance in each of the 12 items of the checklist, the first group presented superior results in all items. Nevertheless, the greatest differences between the groups occurred with regard to diagnosis aspects, transfer management and communication skills. The prevalence of identification of immediate transfer need was 100% vs. 31%; p < 0.0001, the percentage of adequate communication skills was 55% vs. 15%; p < 0.0001, the identification of the diagnosis of STEMI was 89% vs. 51%; p < 0.0001 and the persistence to organize the transfer even in case of non-availability of beds was 45% vs. 8%; p < 0.0001 (Table 2).

When comparing the 90 candidates from our institution with all the other applicants from the remaining institutions, the following results were found: ECG monitoring requirement (86% vs. 83%; p = 0.50), insertion of peripheral venous access device (81% vs. 54%; p < 0.0001), pain duration assessment (63% vs. 71%; p = 0.11), accurate STEMI diagnosis (76% vs. 68%; p = 0.20), acetylsalicylic acid administration (100% vs. 94%; p = 0.01), second antiplatelet agent administration (80% vs. 76%; p = 0.004), nitrate administration (72% vs. 65%; p = 0.16), morphine administration (82% vs. 70%; p = 0.01), immediate transfer requirement (82% vs. 61%; p < 0.0001), adequate communication skill (49% vs. 32%; p = 0.001), transfer requirement even in case of non-availability of beds (38% vs. 23%; p = 0.003).

Discussion

This study shows the need to enhance training, during undergraduate courses, on the identification of STEMI and, especially, to increase knowledge of the assistance flow in the care line of this disease.

According with report data on medical demography in Brazil, in 2016, there were 18,753 new registrations in Regional Medical Councils, most of them from the Southeast region (50% of the registrations).[7] Thus, every year, there is a great number of young doctors graduating from several medical colleges in Brazil. Many of them begin medical practice by choice, or due to difficulties to enter residency programs, and even concomitantly with these programs to complement their earnings. Due to lack of professionals exclusively dedicated to emergency care, newly graduated doctors usually take shifts in the emergency department.

In Brazil, about 50% of STEMI patients are treated with reperfusion therapy,[8] reaching a percentage of 20% in public hospitals of certain regions.[9] In a Brazilian registry of acute coronary syndrome, in which 2,453 patients were included, high rates of acetylsalicylic acid use (97.6%) and P2Y12 inhibitor (89.5%) were observed in the first 24 hours, similar to the rates found in this study, but among STEMI patients, only 35.9%

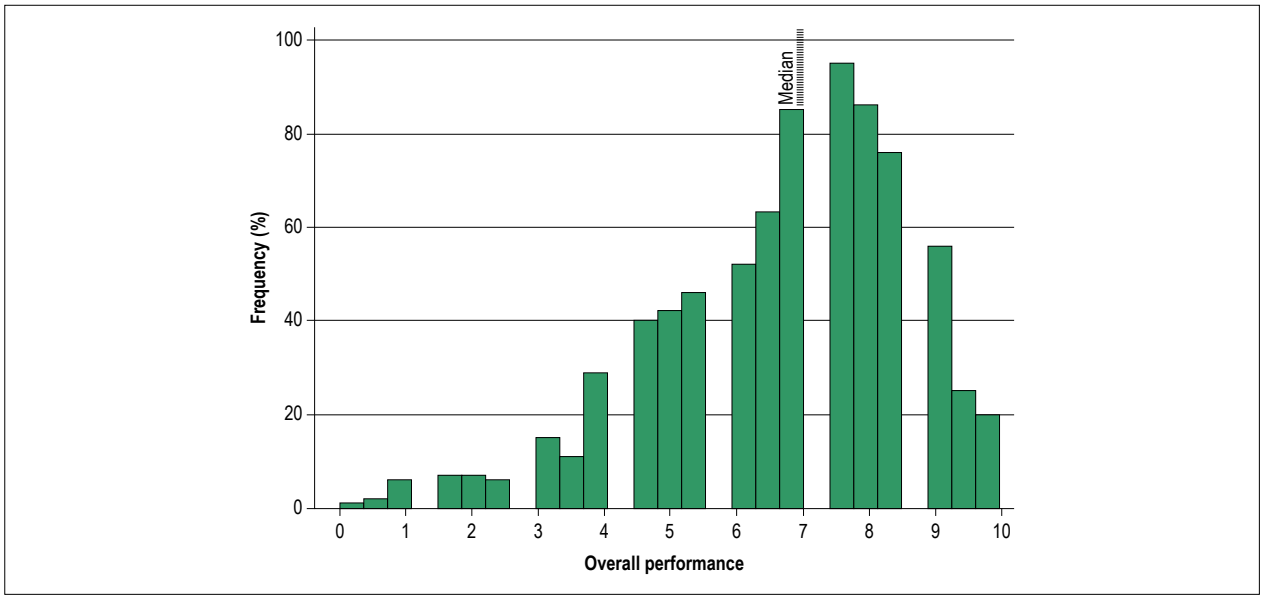

Figure 2 – *Frequency histogram showing the general score distribution obtained by the recently graduated physicians during practical assessment in the simulated station of STEMI medical care.*

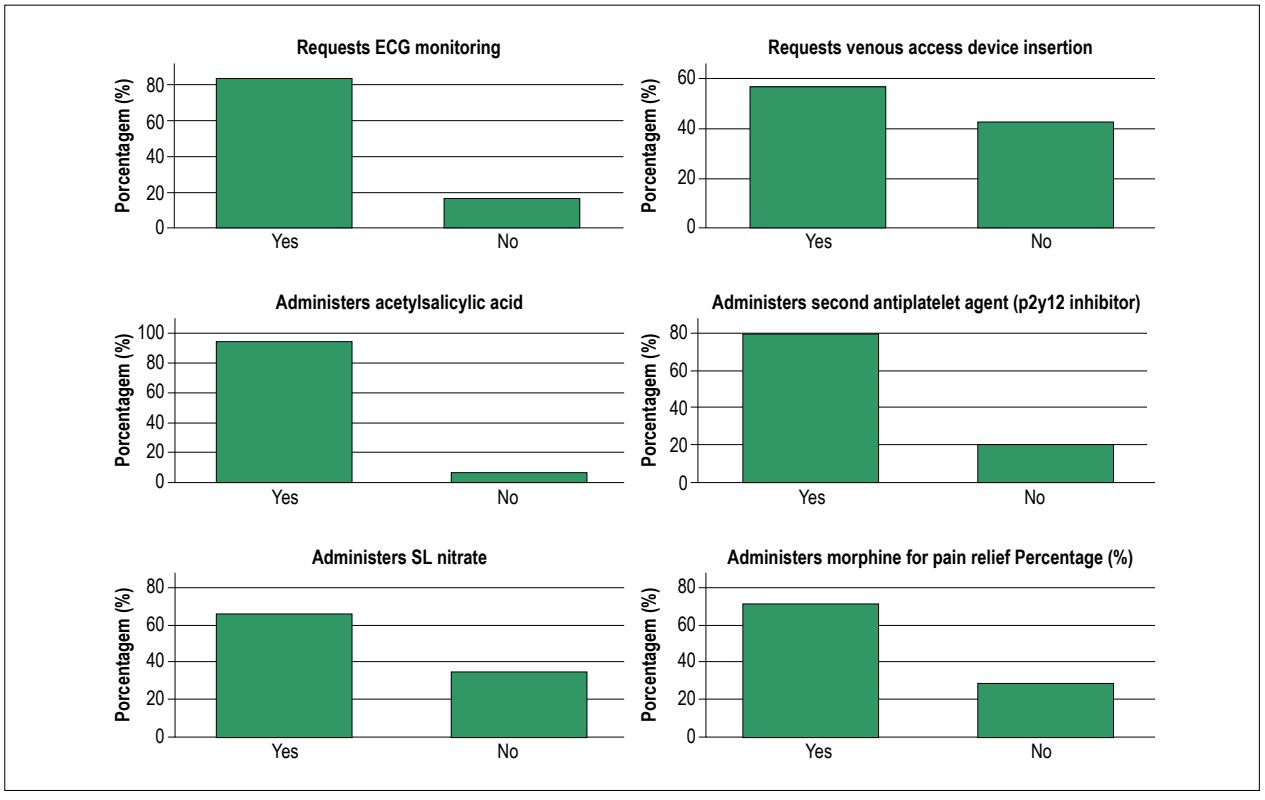

Figure 3 – *Bars graphic showing the performance of the recently graduated physicians in each of the six items of the cheklist related directly to the treatment during practical assessment in the simulated station of STEMI medical care.*

received primary angioplasty and 25.3% received fibrinolytic therapy.[10] Several factors contribute to this reduced number of patients who receive reperfusion therapy in Brazil. However, one of these factors refers to the lack of recognition and inappropriate management by newly graduated physicians in primary care. It is unlikely that a STEMI will not be identified by a cardiologist, but a less experienced doctor may have difficulties. On the other hand, a patient with STEMI is more likely to be assisted

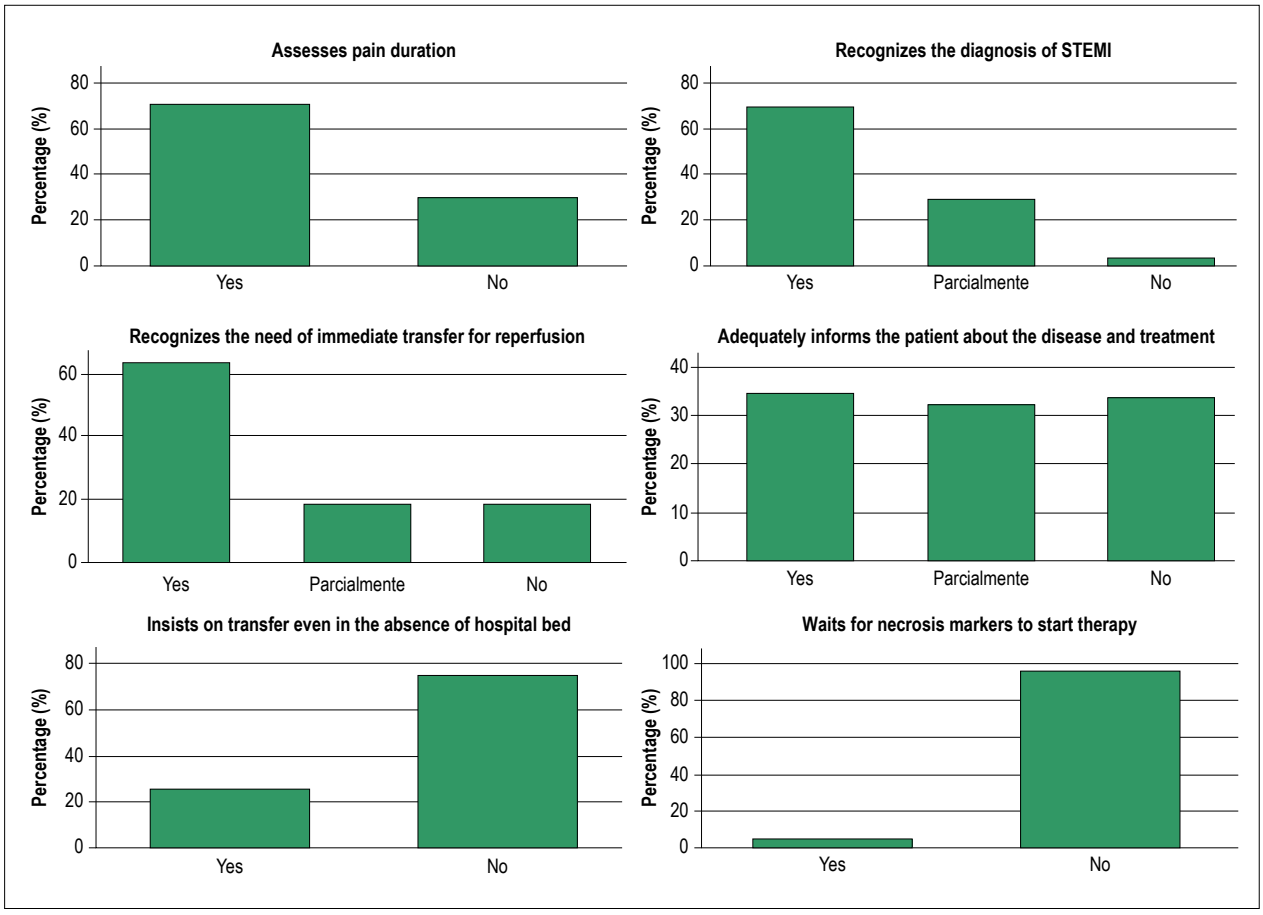

Figure 4 – *Bars graph showing performance of recently graduated physicians in each of the six items of the checklist directly related to diagnosis and management of the patient's tranfer during practical evaluation in the simulated station of STEMI medical care.*

in an Emergency Care Unit of the Brazilian National Health System (SUS) by a recently graduated doctor than by a specialist in the field. Therefore, in order to increase the proportion of patients with STEMI receiving reperfusion therapy in Brazil, it is necessary to encourage and improve the teaching of this disease during undergraduate courses in medicine.

Another study carried out in Brazil, in which 97 patients victims of acute myocardial infarction were interviewed, found that only 33% managed to get immediate hospitalization, whereas 67% of the patients went through up to five units until they could be admitted. Among the main reasons for the lack of hospitalization was the fact that the physician referred the patient back home due to no identification of this diagnosis.[11] Ghanem et al.,[12] using standard questionnaires applied to medical students, found that only 22% of them knew how to aid patients with myocardial infarction.[12] Little et al.[13] showed that only 61% of the students in the last year of medical training recognized the electrocardiographic diagnosis of inferior wall STEMI.[13]

Realistic simulation was the methodology employed in this assessment. This is an important assessment tool of health professionals, because it enables the performance of different evaluations within the same systematic framework, ensuring uniformity, which would be impracticable in a real scenario. On the other hand, it tries to reproduce directly the environment where this assistance usually occurs, allowing for knowledge, skills and attitude assessment.[14] We consider this simulation as highly reliable, since it was performed inside a hospital environment, with duly trained professional actors and the psychological aspect of the emotional stress involved in the performance of an evaluation, similar to that found in a real situation of emergency assistance. Therefore, the use of this methodology is a strong point of this study which deserves to be highlighted, because it presents greater validity, when compared with the application of standard questionnaires, for instance.

This methodology is widespread worldwide and employed in most Brazilian medical schools. Thus, most applicants are familiar with this type of evaluation, which is not a particularity of our institution. In spite of the greater performance in some items, the answer pattern of the applicants graduated in our institution was quite similar to that of the remaining applicants.

Simulation is an active learning methodology. In this study, it was used to evaluate the applicants, but it can also be used in medical teaching. We find it important to develop a realistic simulation standard scenario of STEMI assistance, adjusted to

Table 2 – Comparison between the groups with greater performance (general score > 7) and lower performance (general score ≤ 7) in the simulated practice regarding STEMI medical care

Characteristic	General score		Relative difference	p-value
	> 7 n = 363	≤ 7 n = 408		
Demographic				
Age, mean ± DP	26 ± 7	26 ± 5		0.99
Age, years; median(19)	25 (24-27)	25 (24-27)		
Male sex, n(%)	189 (52)	255 (63)	-11%	0.0034
Medical Graduation				
Time from conclusion, years; median(19)	0 (0-1)	0(0-1)		> 0,05
Private institution, n(%)	99(27)	155(38)	-11%	0.0016
Public institution, n(%)	259(71)	250(61)	+10%	0.0032
Region of origin, n(%)				**0.792**
Southeast	245(67)	254(62)	+5%	
Northeast	72(20)	101(25)	-5%	
South	24(07)	24(06)	+1%	
Central-West	16(04)	9(02)	+2%	
North	3(01)	7(02)	-1%	
Checklist Items, yes; n(%)				
Recognizes need for transfer	363(100)	125(31)	+69%	< 0.0001
Adequately informs the patient	201(55)	63(15)	+40%	< 0.0001
Recognizes STEMI	323(89)	207(51)	+38%	< 0.0001
Insists on tranfer in the absence of bed	162(45)	31(08)	+37%	< 0.0001
Requests venous access insertion	245(67)	193(43)	+24%	< 0.0001
Assesses pain duration	300(83)	244(60)	+23%	< 0.0001
Administers SL nitrate	274(75)	232(57)	+18%	< 0.0001
Administers IV morphine	293(81)	258(63)	+18%	< 0.0001
Administers P_2Y_{12} inhibitors	318(88)	298(73)	+15%	< 0.0001
Requests ECG monitoring	318(88)	323(79)	+9%	0.0018
Administers acetylsalicylic acid	355(98)	377(92)	+6%	0.0006
Waits for necrosis markers to start therapy	00(00)	32(08)	-8%	< 0.0001

SD: standard deviation; ECG: electrocardiogram; STEMI: ST-segment elevation myocardial infarction; SL:sublingual; IV: intravenous.

the particularities of the Brazilian health system, as performed in this study, because it can be reproduced in other medical schools and used in the teaching process when approaching this major cardiac disease.

An important issue that should be highlighted during the education of graduate students concerns the insertion of patients within the hierarchical network of the SUS because, in addition to establishing the adequate pharmacological treatment available in the place of care, it is important to promote an integration with the urgency and emergencies network for the prompt transfer of these patients to reference centers capable of performing the reperfusion therapy. Most students remembered to administer antiplatelet agents but, on the other hand, a significant proportion did not reinforce the need for the patient's immediate and adequate transfer, as expected in these situations.

The lack of well-organized assistance networks[14] to refer STEMI patients from emergency care units to reference hospitals, makes the primary service doctor to have a central role in this transfer management. Only 25% of the applicants insisted on the transfer even in the non-availability of hospital bed. Therefore, it is important to raise the discussion about integrated clinical scenarios with management aspects, such as the Resolution N°. 2,077/14 of Federal Medicine Council on urgencies and emergencies, which addresses the concept of "zero vacancy". It is extremely important that graduate students in Medicine courses understand that the treatment of this disease is time-dependent, and that it is possible to change the natural history, when treatment is set up early and, for this reason, they must insist on transfer of patients suffering from this disease to a center capable of providing reperfusion therapy, even in the absence of hospital beds.

The use of telemedicine can solve difficulties of ECG interpretation by newly graduated physicians, but this will be useless if they do not have enough knowledge on how to speed up the patient's transfer according with the assistance flow established for each region.[15]

Simulation has already been used to assess the performance of medical students in emergency scenarios, such as STEMI assistance in other countries. However, to our knowledge, no other Brazilian study has used a similar research method.

The study showed that undergraduate students' performance in treating simulated cases of STEMI are worse compared with other situations in which the patient is stable. For a total of 143 medical school fourth-year students, the total percentage of correct actions was 47.8% in the STEMI station, which was significantly lower in relation to the other stations ($p<0.001$).[16] This fact can be observed in practice, since during the undergraduate course they end up having more contact with stable patients, while more severe patients are treated by resident physicians. Thus, simulation is considered an interesting alternative for improving emergency competencies and abilities during the undergraduate course.[17]

In an interesting study comparing simulation in small groups combined with traditional learning activities and traditional learning activities alone in 291 medical school fourth-year students for STEMI patients management, a significant improvement was observed in the performance of students in the simulation group (53.5 ± 8.9% vs. 47.4 ± 9.8%; $p < 0.001$), especially in relation to physical examination (48.5 ± 16.2% vs. 37.6 ± 13.1%; $p < 0,02$) and to diagnosis (75.7 ± 24.2% vs. 64.6 ± 25.1%; $p < 0.02$).[18]

Another important aspect that should be emphasized with the undergraduate student is the improvement of communication skills. A small number of applicants (34%) showed effective communication with the patient concerning the disease and the recommended treatment. This issue is often neglected in emergency care, but it is a major stage, because the patient has a right to know what is happening and the treatment strategies proposed. Besides, access to information can decrease the level of anxiety and emotional tension during an acute episode.

We highlight some limitations of this study. First, since only the applicants who were approved in the first phase of the selection process (written test) were submitted to practical evaluation, the presence of a selection bias should be considered. This may have overestimated the performance of the applicants in the selected sample and if the same evaluation had been applied to a general sample, probably the performance would have been lower than that observed. However, since in some less competitive specialties, almost all enrolled applicants were approved for the practical examination, this may have minimized this effect. Secondly, it was an evaluation applied in a single center (unicentric), but there were representatives from different regions of the country, although there was a predominance of the Southeast and Northeast regions, without an adequate sample distribution proportional to the number of graduates from different medical schools around the country. Therefore, their results cannot be extrapolated to all Brazilian territory. Thirdly, it was clarified that the fibrinolytic agent was not available in the service unit, as in the majority of these units in Brazil. Thus, immediate transfer to reperfusion therapy is indicated even in the absence of hospital beds. We agree that some differences can be observed according with the organization of the line of treatment for STEMI in each region of Brazil, like, for example, the availability of fibrinolytic agents in some of these Emergency Units. In such case, we suggest that the item *Recognizes the need of immediate transfer for reperfusion therapy* should be divided into two sub-items: administers the fibrinolytic agent and requests immediate transfer to a hospital, because either way, this patient will have to be transferred to a center capable of performing coronary intervention[19] and, in fact, no UPA in Brazil provides this resource. Fourth, the drug heparin was not included in the checklist. This fact occurred because, during initial care in a UPA the reperfusion strategy to be adopted for the patient (fibrinolytic therapy or primary angioplasty) is unknown and, depending on the strategy assigned, the type of heparin and the dosage prescribed as first option are different and, most of the times, this medication is delayed in order to be administered in the hospital service where the reperfusion therapy will be implemented. Although they integrate the treatment, the medications, beta blockers, statins and the angiotensin converting enzyme inhibitors, have not been included, because these drugs do not need to be prescribed immediately and can be introduced throughout the first twenty-four hours. Fifth, due to restricted time for each evaluation (5 minutes), the evaluators selected some topics that they considered more relevant, such as diagnosis and therapeutic treatment, at the expense of others related with clinical history and physical examination, which is understandable, since, most of the times, few alterations are observed in the physical examination of these patients. And, finally, this tool needs external validation in other training centers.

Conclusion

STEMI approach needs to be improved during medical undergraduate courses, highlighting practical aspects such as temporality for starting treatment and the assistance flows of these patients inside the Brazilian Unified Health System. Realistic simulation can be an adequate tool to improve these competencies.

Author contributions

Conception and design of the research, Acquisition of data, Analysis and interpretation of the data and Critical revision of the manuscript for intellectual content: Aimoli US, Miranda CH; Statistical analysis, Obtaining financing and Writing of the manuscript: Miranda CH.

Potential Conflict of Interest

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

Sources of Funding

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Study Association

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

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the HC-FMRP-USP under the protocol number 838/2017. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013.

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***Supplemental Materials**

For additional information, please click here.

Evaluation of Clinical Competence for a Cardiology Residency Program

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Short Editorial related to the article: Clinical Competence in ST-segment Elevation Myocardial Infarction Management by Recently Graduated Physicians Applying for a Medical Residency Program

In the past decades, medical education, especially in cardiology gratuate programs (CGP), has undergone profound changes, including restrictions on hours of service.[1] In the reference article "To Err Is Human",[2] the Institute of Medicine suggests that nearly 100,000 patients die annually from preventable errors in hospitals, with another one million people with sequelae. This report turned the spotlight on the importance of patient safety with regard to healthcare.[3] At about the same time, technological progress has outweighed curriculum innovations of EMPGs. As we were trained on the job, the method "see one, do one, and teach one" was common for all services, but as training progresses, procedures become extremely complex, with consequently higher risks. Most cardiology residents remember the first time they performed resuscitation maneuvers, placed transvenous pacemakers, and passed their first Swan-Ganz.[4] Fortunately, most of these events were completed without complications. However, the level of concern and anxiety experienced regarding patient safety and their competence to perform these tasks is probably as vivid now as the day the procedure was performed. Despite the scarcity of evidence supporting the traditional training learning model,[5,6] most reviews discussing the potential of simulation-based education (SBE) for healthcare assess evidence that SBE is equivalent to or better than this traditional model.[7-9]

Nowadays, for the recent graduates and candidates for Medical Residency, assessment of clinical skills is an essential step and should be started in their education as a medical student, and should be done by the professor through direct observation of their performance in real situations.[10] This formative and summative assessment takes different forms, as it assesses students' clinical competences and quantifies the evolution of their performance based on real-life situations.[11,12] The study published in this issue, entitled "Clinical Competence in ST-segment Elevation Myocardial Infarction Management by Recently Graduated Physicians Applying for a Medical Residency Program"[13] aims to analyze the following: skills seen in the interview, physical examination skills, professionalism (ethics), clinical reasoning, orientation skills, efficiency and general clinical competence, pointing out their flaws and successes, making it a good weapon in formative assessment. Simulation training has also been widely adopted in other "high risk" industries. Although comparisons between medicine and aviation are frequent, it is important to recognize that the work performed by doctors differs a lot from that of pilots, so the nature of simulation must also be different. There is considerable focus on medical emergencies and practical procedural skills, but with scope to expand to other areas of care. The contribution of human cognitive performance to patient outcomes is well recognized; possessing the necessary knowledge and technical skills remains essential, but in addition to them, non-technical skills, such as situational awareness and the ability to synthesize information, making decisions and effectively communicating with team members during times of stress and distraction are also essential. And this study was important for this reason.

Keywords

ST Elevation Myocardial Infarction; Simulation; Internship and Residence; Hospitals; Programs; Medical Competence.

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Evaluation of Lipid Profiles of Children and Youth from Basic Health Units in Campinas, SP, Brazil: A Cross-Sectional Laboratory Study

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Abstract

Background: **Among dyslipidemias, hypercholesterolemia is considered the main risk factor for cardiovascular diseases in adults. In childhood and adolescence, elevated total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) are positively associated with atherosclerosis markers, however, systematic screening for dyslipidemias in these groups is a controversial topic.**

Objective: **To characterize the frequencies, types and severity of dyslipidemias in children and adolescents attended at the Basic Health Units managed by SUS in Campinas/SP.**

Methods: **After an agreement with the Municipal Health Department of Campinas, consecutive results of serum lipid profiles (n = 312,650) of individuals of both sexes (n = 62,530) aged between 1 day old and 19 years were obtained, from 2008 to 2015. Age groups and dyslipidemias were classified according to recommendations in the literature. The statistical significance level adopted was the probability value (p) of 0.05 or less.**

Results: **The observed frequencies of increased TC, triglycerides (TG), LDL-C and non-HDL-C (NHDL-C) were 33%, 40%, 29% and 13% respectively, and of reduced high-density lipoprotein cholesterol (HDL-C) the frequency was 39%. The frequencies, in general, were greater in females and in the southwest and south regions of the city, whose populations are more vulnerable from the socioeconomic point of view; on the other hand, in children and adolescents, the frequencies of TG and HDL-C prevailed, respectively.**

Conclusions: **The high frequency and regionalization of dyslipidemias in children and adolescents indicate the need for specific actions in the handling and treatment of such diseases by the public health system of Campinas. (Arq Bras Cardiol. 2020; 114(1):47-56)**

Keywords: **Cardiovascular Diseases; Dyslipidemias; Hypercholesterolemia; Child; Young Adult; Unified Health System; Adolescent; Laboratory Test.**

Introduction

Cardiovascular diseases (CVD) represent one of the main causes of morbidity and mortality in Brazil and worldwide. According to the World Health Organization (WHO), in 2015 CVD accounted for 31% of deaths worldwide.[1] In Brazil, 29% of deaths were due to CVD according to the Brazilian Society of Cardiology.[2]

Dyslipidemias play a well-established role in cardiovascular risk in adults, and so do hypertension, diabetes mellitus, early family history of coronary artery disease and smoking. Often these clinical situations are associated with comorbidities such as overweight, obesity, poor eating habits and physical inactivity,[1,3] with serious consequences for the individual and the public health system.[4]

Children and adolescents account for 34% of the Brazilian population, an absolute contingent of 57,1 million people.[5] There is evidence that high levels of total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) in childhood and adolescence are associated with atherosclerotic outcomes in young adults. In this context, Napoli et al.[6] demonstrated fatty streaks in the intrauterine life span, being more noticeable in pregnant women with hypercholesterolemia.

Unlike the Brazilian Dyslipidemia Directive (DBD) Update, universal lipid screening over two years of age as compared to that of children with risk factors[3] was recommended, based on other studies, by Zachariah and Johnson[7] for having a greater diagnostic sensitivity by 30% to 60%. In Brazil, there are few population studies involving dyslipidemias in childhood and adolescence.[8] In addition, the Study of Cardiovascular Risks in Adolescents (ERICA) stands out, with a national approach and covering a population of 80,000 young people between 12 and 17 years old.[8]

A previous study in our laboratory characterized severe dyslipidemias in the juvenile population in a public hospital

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segment in Campinas.[9] However, there are still gaps regarding their characterization in regional terms. Thus, this study was designed to characterize the frequencies, types and severity of dyslipidemias in children and adolescents attended at the Basic Health Units (UBS) in Campinas, SP.

Methods

This is a retrospective cross-sectional study based on monthly lipid profile databases, which were periodically sent to the Lipid Laboratory of the School of Medical Sciences of UNICAMP through an academic agreement with the Municipal Health Department of Campinas.

Between 2008 and 2015 312,650 results of serum laboratory tests were obtained from 62,530 individuals of both sexes, aged between one day and 19 years who visited UBS in the city of Campinas, SP, for medical outpatient care. The UBS are distributed over five regions or health districts of the city.

Only individuals with measured serum lipid profile were included in the study, with the following parameters: TC, triglycerides (TG), LDL-C, high-density lipoprotein cholesterol (HDL-C) and non-HDL-C (NHDL-C). These analyses were performed by enzymatic-colorimetric and/or direct homogenous methods for LDL, according to the quality control standards of the Brazilian Society of Clinical Pathology, including the blood collection stage in the UBS. NHDL-C was calculated.[10] A single chemical analyzer, Modular® Analytics Evo (Roche Diagnostics, Burgess Hill, West Sussex, UK), and reagents from Roche Diagnostics® (Mannheim, Germany) were used during the study period.

Dyslipidemias were classified biochemically in consonance with the cut-off values for age advocated by the current DBD[3] as: isolated increases of LDL-C, TG, NHDL or reductions of HDL-C; mixed dyslipidemias, defined as lipid combinations of increased LDL-C and TG and/or increased LDL-C and reduced HDL-C and/or increased TG and reduced HDL-C.

We used the reference values of Kwiterovich PO[11] for infants (children from one day to 23 months of age), once there are no DBD recommendations for this age group, except for TG in the 0-9 years of age group. For NHDL-C in all age groups, also absent in DBD recommendations, the desirable and undesirable values (<123 and ≥144) of Kwiterovich PO were used as well.

In order to determine the groups of children (2-11 years of age) and adolescents (12 to 19 years of age) we followed the Brazilian Child and Adolescent Statute definitions (Law n°. 8.069/90 updated with Law no. 12.010 of 2009), with adaptation of the upper limit for adolescents because of DBD, and the recommendations therein, between two and 19 years of age.[3] The cut-off values (mg/dL) used as desirable and undesirable are shown in Table 1.

Lipid profiles were also evaluated for LDL-C ≥ 190 mg/dL, without concomitant hypertriglyceridemia, for laboratory characterization of possible cases of Familial Hypercholesterolemia (FH).[10]

The city of Campinas is a Sao Paulo inland city that has approximately 1.1 million residents,[12] with 63 UBS distributed over five health districts: East (E), Northwest (NW), North (N), Southwest (SW) and South (S).[13]

Statistical analysis

The variables, either continuous or categorical, were analyzed using descriptive and comparative tests in software SPSS 24.0 (SPSS Inc., USA) and SAS 9.4 (Inc, Cary, NC, USA). Since there was only one lipid profile available for some individuals and for others several were available during the study, only a single and first lipid profile per year were used in the study period (2008-2015).

Tests were performed to verify the normality of data distribution (Kolmogorov-Smirnov). The groups were then compared by the Mann-Whitney and Kruskal-Wallis tests with Bonferroni post-test, with data presented as median and interquartile ranges for the continuous variables, and chi-square (X^2) test with the post-test for multiple comparisons in contingency tables based on permutations for categorical variables. Values of $p < 0.05$ were considered significant.

Results

Figure 1 shows the distribution of the five health districts of Campinas with the respective numbers observed for

Table 1 – Reference values for lipids and lipoproteins in children and adolescents

Lipidic variables	Values (mg/dL)		
	Desirable	Undesirable (1 day to 23 months)	Undesirable (2 to 19 years)
TC	< 170	≥ 200	≥ 170
LDL-C	< 110	≥ 130	≥ 110
NHDL-C	< 123	≥ 144*	-
TG			
0-9 years	< 75	≥ 100	≥ 75**
10-19 years	< 90	≥ 130	≥ 90
HDL-C	> 45	< 35	≤ 45

*Reference values for 1 day to 23 months old: *NHDL-C ≥ 144 1 day to 19 years old.**TG ≥ 75 according to current DBD. TC: total cholesterol; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; NHDL-C: non high-density lipoprotein cholesterol; TG: triglycerides.*

Figure 1 – *Corresponding area to the health districts in the map of the city of Campinas. Source: Campinas Health Department.*[13]

test results, of individuals evaluated and their percentage frequencies: East: 41,075 and 8,215 (13%); Northwest: 61,900 and 12,380 (20%); North: 52,975 and 10,595 (17%); Southwest: 79,305 and 15,861 (25%) and South: 77,395 and 15,479 (25%). Half of the tests came from the southwest and south regions.

Table 2 summarizes the demographic characteristics of subjects, including the origin of clinical laboratory calls.

The results of the descriptive and comparative analyses are shown in Tables 3 and 4.

Table 3 shows that in all the age groups, TC, TG, LDL-C and NHDL-C were higher for infants. TG was similar in children and adolescents, and the median of HDL-C levels was higher in children than in the others. In relation to sex, the female group had higher values.

In the comparison by age group, the results also showed significant differences for the parameters evaluated in both sexes.

Table 4 clearly shows that there were higher results for TC in the eastern region than in the other regions. LDL-C levels were higher in the eastern region than in the northwest, southwest and south; NHDL-C values were also higher in this region than in the south and lower in the northwest region than in the others.

In the eastern, north, and southwestern regions, triglyceridemia was higher than in the northwestern region, and in the eastern and southwestern regions, it was higher than in the south. HDL-C in the southwestern region was lower than in the other ones and higher in the eastern region than in the south.

Table 5 shows the frequencies of dyslipidemia and their ratios by sex.

The most frequent dyslipidemias were isolated increases in TG and reduction of HDL-C. By sex, dyslipidemia frequencies were higher in females.

Figure 2 shows the frequencies of dyslipidemia by age. Infants presented higher frequencies of increased TG and NHDL-C and isolated dyslipidemias, as well as a higher prevalence of the combination of increased LDL-C and TG.

As for children, higher levels of TC and LDL-C were observed, as well as the combination of increased TG and reduced HDL-C; there was also a higher frequency of at least one type of mixed dyslipidemia. On the other hand, adolescents showed a higher number of reduced HDL-C results.

Figure 3 shows the frequencies of dyslipidemia by regions of Campinas.

Dyslipidemias were more frequent in the southwestern region of Campinas than in the other regions.

Table 2 – Demographic characteristics of all subjects and by sex and age

Features	Number of individuals	Total frequencies total (%)
Total	62,530	100
Sex		
F	34,932	56
M	27,598	44
Age		
Infants	660	1
F	399	0.6
M	261	0.4
Children	25,501	41
F	13,219	21
M	12,282	20
Adolescents	36,369	58
F	21,314	34
M	15,055	24

N: number; F: female; M: male.

Table 3 – Lipid profiles: medians and interquartile ranges for all subjects and stratified by sex and age

Groups	Lipids (mg/dL)	Total	Female	Male	p*	p†
	TC	156 (137-178)	158 (139-179)†	154 (135-176)		0.000
	TG	76 (57-103)	78 (59-105) †	73 (54-100)		0.000
All	LDL-C	95 (78-114)	96 (79-114)†	93 (77-112)		0.000
	HDL-C	49 (41-57)	49 (42-57)†	48 (41-57)		0.000
	NHDL-C	106 (88-127)	107 (89-128)†	104 (86-125)		0.000
	TC	172 (151-202) *	177 (153-206)†	167 (147-193)	0.000	0.019
	TG	91 (67-131) *	94 (68-132)	87 (64-119)	0.000	0.068
Infants (I)	LDL-C	108 (88-132) *	110 (88-134)	105 (88-128)	0.000	0.138
	HDL-C	46 (39-56)	47 (39-58)	45 (38-53)		0.063
	NHDL-C	125 (101-150)*	128 (101-153)	119 (102-147)	0.000	0.108
	TC	162 (143-182)	162 (143-182)	161 (143-182)		0.901
	TG	75 (56-103)	79 (60-109)†	71 (53-97)		0.000
Children (C)	LDL-C	99 (83-118)	100 (84-118) †	99 (83-117)		0.013
	HDL-C	50 (42-58) *	49 (41-57)	51 (43-60)†	0.000	0.000
	NHDL-C	110 (93-130)	111 (94-131)†	109 (92-129)		0.000
	TC	153 (133-174)	155 (136-177) †	147 (128-168)		0.000
	TG	76 (57-102)	76 (58-103)†	74 (56-102)		0.000
Adolescents (A)	LDL-C	91 (75-110)	93 (77-111)†	88 (72-107)		0.000
	HDL-C	48 (41-56)	49 (42-58)†	46 (39-54)		0.000
	NHDL-C	102 (84-123)	105 (86-125)†	99 (82-120)		0.000

F: female; M: male; (†) Mann-Whitney, F vs. M; p < 0.05. (*) Kruskal Wallis Post-hoc Bonferroni, I vs C vs A = TC, LDL-C, NHDL-C - I>C>A; TG - I>C=A; HDL-C - C>A>I, p < 0.05; Continuous variables appear as medians and interquartile ranges. TC: total cholesterol; TG: triglycerides; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; NHDL-C: non high-density lipoprotein cholesterol.

Table 4 – Lipid profiles: medians and interquartile ranges for all subjects and by regions of campinas

Lipids (mg/dL)	East (E)	Northwest (NO)	North (N)	Southwest (SO)	South (S)	p
TC	158 (139-179) *	155 (136-177)	157 (138-178)	156 (136-177)	156 (137-177)	0,000
TG	77 (58-105) *	74 (56-101)	76 (57-103)	77 (58-105) *	75 (56-103)	0,000
LDL-C	96 (79-115) *	94 (77-113)	95 (79-114)	94 (78-113)	95 (78-113)	0,000
HDL-C	49 (42-58)	49 (41-57)	49 (42-57)	48 (41-56) *	49 (41-57)	0,000
NHDL-C	107 (89-128) *	104 (86-125)	106 (88-127)	106 (88-127)	105 (88-126)	0,000

(*) Kruskal-Wallis Post-hoc Bonferroni, TC: E > others; N > NW/SW; TG: E/N/SW>NW; E/SW>S; LDL-C: E>NW/SW/S; N>NW; HDL-C: E>S; SW < others; NHDL-C: E>S; NW<others; p < 0.05. Continuous variables appear as medians and interquartile ranges. TC: total cholesterol; TG: triglycerides; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; NHDL-C: non high-density lipoprotein cholesterol.

Discussion

The development of atherosclerotic plaques is directly associated with an increase in NHDL-C lipoproteins, and evidence suggests that childhood cardiovascular risk factors such as dyslipidemia may contribute to atherosclerotic disease in childhood and adolescence, as well as in adulthood.[14]

In this sense, the ongoing International Childhood Cardiovascular Cohort (i3C) Consortium[15] aims to evaluate the association of the presence of risk factors in childhood with the outcomes of CVD morbidity and mortality in adults. Preliminary results showed that pediatric dyslipidemia predicts dyslipidemia[16] and greater carotid intima-media thickness[17] in adults. In addition, the presence of risk factors developed from the age of nine was predictive of subclinical atherosclerosis in adults.[18]

In the present study, 67% of lipid profile results indicated the presence of at least one type of biochemically classified dyslipidemia. This percentage is greater than the one reported in other national studies: one of them, for example, carried out in the northeastern region of Brazil between 2011 and 2012,

Table 5 – Frequencies of isolated and mixed dyslipidemias in all subjects and by sex

Dyslipidemias	N	All (%)	N	F (%)	N	M (%)	Frequency ratios (%) (F/M)	p
Isolated dyslipidemias	41,689	67	23,572	38*	18,117	29	1.3	0.000
TC↑	20,759	33	12,213	19*	8,546	14	1.4	0.000
TG↑	24,703	40	14,527	23*	10,176	16	1.4	0.000
LDL-C↑	18,299	29	10,594	17*	7,705	12	1.4	0.000
HDL-C↓	24,210	39	13,120	21*	11,090	18	1.2	0.000
NHDL-C↑	7,847	13	4,665	8*	3,182	5	1.5	0.000
Mixed dyslipidemias	20,205	32	11,682	19*	8,523	14	1.4	0.000
LDL-C↑and TG↑	10,903	17	6,485	10*	4,418	7	1.5	0.000
HDL-C↓ and TG ↑	12,978	21	7,270	12	5,708	9	1.3	0.692
HDL-C↓ and LDL-C↑	6,960	11	3,901	6	3,059	5	1.3	0.742

F: female; M: male; Chi-square test (X^2); F vs M; p < 0.05. TC: total cholesterol; TG: triglycerides; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; NHDL-C: non high-density lipoprotein cholesterol.

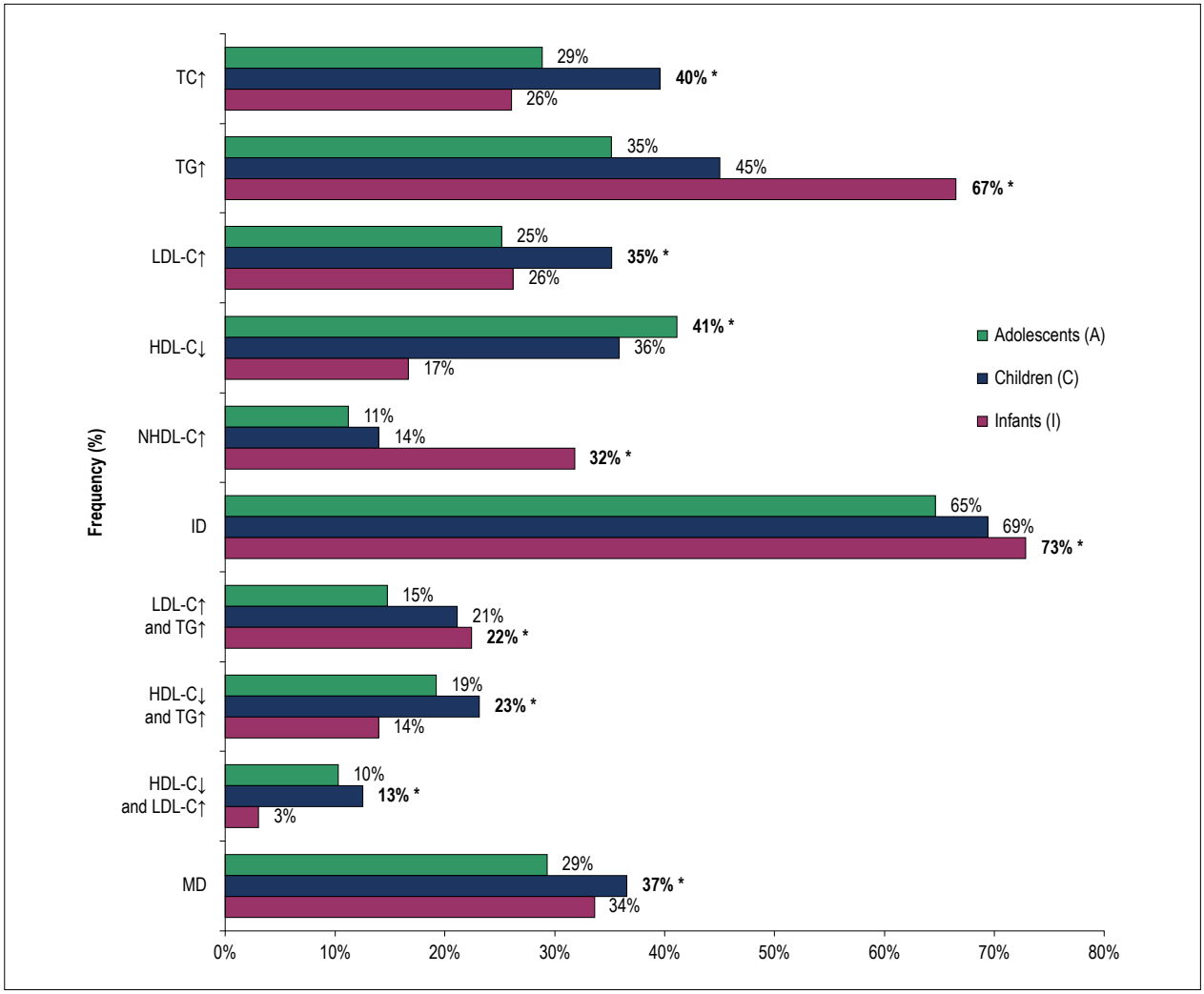

Figure 2 – *Frequencies of isolated and mixed dyslipidemias by age; ID: Isolated dyslipidemias; MD: Mixed dyslipidemias; *Chi-Square test (X^2); I vs C vs. A; p <0.05; Post-test for multiple comparisons in contingency tables based on permutations: TC↑: LDL-C↑ - C > A = I; TG↑: NHDL-C↑ - I> C > A; HDL-C↓ A> C> I; HDL-C↓ and TG↑ and HDL-C↓ and LDL-C↑ - C> A> I; ID, LDL-C↑ and TG↑: MD-A <C = I; p <0.05. TC: total cholesterol; TG: triglycerides; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; NHDL-C: non high-density lipoprotein cholesterol.*

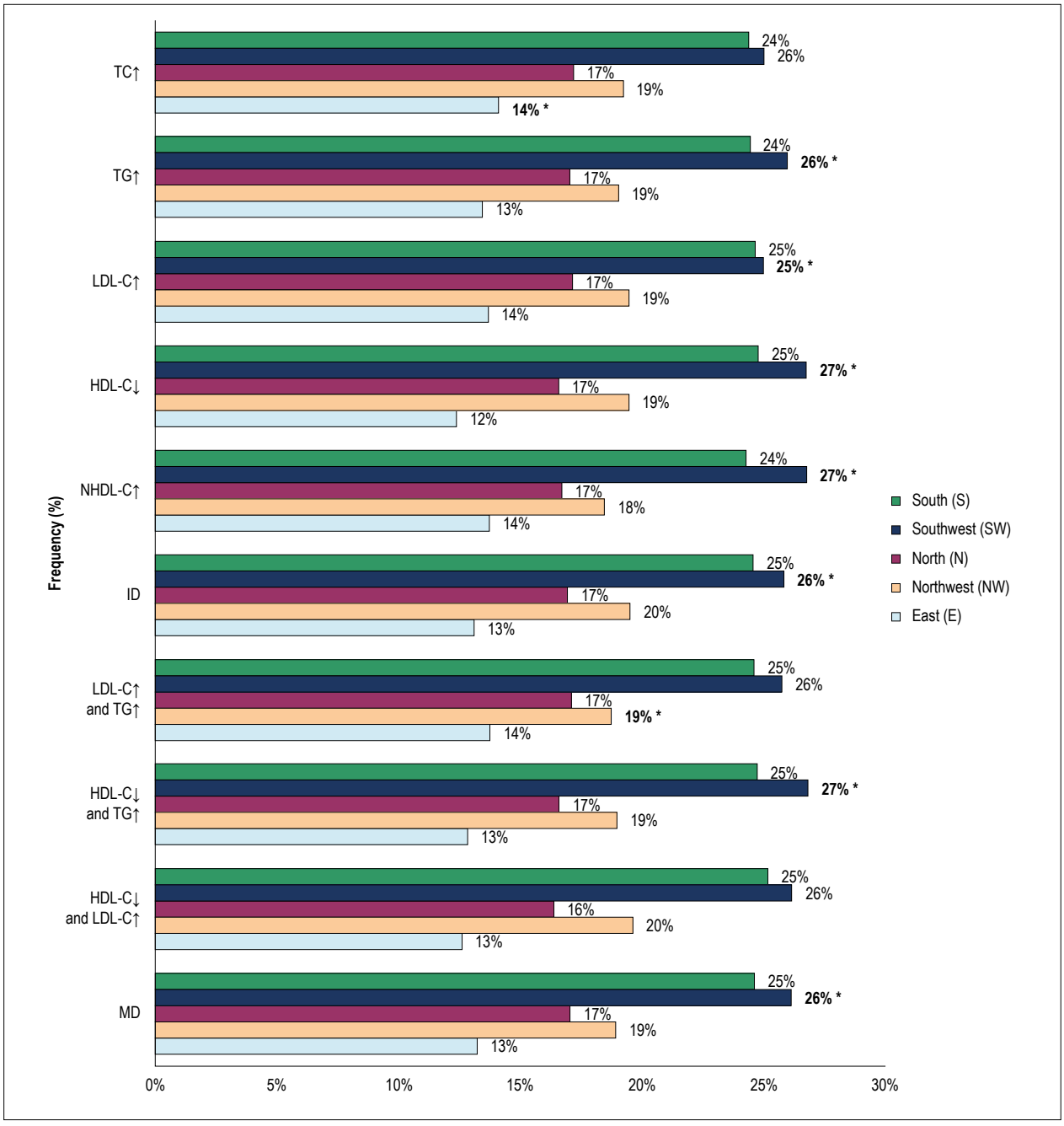

Figure 3 – *Frequencies of isolated and mixed dyslipidemias by regions of campinas; ID: Isolated dyslipidemias; MD: Mixed dyslipidemias; *Chi-Square test (X2); E vs NW vs N vs SW vs S; p <0.05; Post-test for multiple comparisons in contingency tables based on permutations: TC↑ = E <others; TG↑, NHDL-C↑ = SW> NW> E; LDL-C↑ = SW > E <NW; HDL-C↓ = SW> others, S> E; ID = NW <SW> S; LDL-C↑ and TG↑ = - NW> L; HDL-C↓ and TG↑ = SW> NW> N> E; MD = SW > NW, p < 0.05. TC: total cholesterol; TG: triglycerides; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; NHDL-C: non high-density lipoprotein cholesterol.*

involving children and adolescents (6-18 years old), found the frequency of 62% for dyslipidemias with increases in TC and/or TG and/or LDL-C and/or reductions in HDL-C.[19] Another study in Londrina/PR with adolescents (11-16 years old) showed that 61% of the subjects had dyslipidemia (elevated TC and/or TG and/or LDL-C and/or reduced HDL-C).[20] Also, in 2007 a study of schoolchildren (10-14 years old) from Recife/PE described at least one type of dyslipidemia in 63.8% of the sample.[21]

Other works performed in North and South American countries showed lower frequencies. In the United States[22] between 2011 and 2014, in individuals aged 6 to 19 years, the reported frequency of dyslipidemia was 21% (increased TC and/or NHDL-C and/or reduced HDL-C).

In Santiago, Chile[23] (2009-2011) in 2,900 individuals aged 10 to 14 years, the frequency of dyslipidemia was 32% (elevated TC and/or TG and/or LDL-C and/or reduced HDL-C). The higher prevalence in the present study may have been caused in part by the lower cut-off values used by the national guideline[3] when compared to the international guidelines.[19,20]

In the analyses performed to evaluate the effect of sex, dyslipidemias were more frequent for all lipid parameters in females, and these results are consistent with national[24] and international studies.[25] In fact, variations in serum lipoprotein levels are inherent to these individuals in the developmental stages and, consequently, to variations in sex hormones.[26]

Some studies indicate that estrogens increase HDL-C in part due to their action in reducing hepatic lipase (HL) activity and increasing ATP-binding cassette transporter A1 receptors (ABCA1).[27] In addition, they decrease LDL-C[27] levels by positively regulating LDL receptors, thus exerting a beneficial effect on the lipoprotein profile.[28]

On the other hand, androgens increase HL activity, leading to an inverse effect:[27] HDL-C is reduced while LDL-C is increased. In contrast, Zhang et al.[29] indicated that testosterone may be associated with changes in SR-B1 receptor and HL activity, facilitating the selective uptake of HDL and playing an antiatherogenic role.[29]

Comparisons by age groups revealed that infants presented higher levels of TG, NHDL-C and combination of LDL-C and TG as well as a high frequency of individual dyslipidemias; few studies report this data up to two years of age due to the difficulty of blood collection and metabolic instability in this phase of rapid growth before 24 months of life.[30] In addition, the high frequency of hypertriglyceridemia would occur through lactation and lack of food fasting. The current DBD defines the cut-off value of TG without fasting for the 0-9 years of age range as ≥ 85 mg/dL. Evaluating this interference, we applied that cut-off value, and the results showed a lower frequency, 56% instead of 67% (≥ 75 mg/dL, with fasting).

In this context, it is also worth noting that according to the national guidelines,[10] it is recommended to determine the lipid profile in children and adolescents when: i) grandparents, parents, siblings and first cousins present dyslipidemia, mainly severe or with manifestation of premature atherosclerosis; ii) in the presence of clinical signs of dyslipidemia; in the presence of other cardiovascular risk factors; iii) with involvement of other pathologies, and iv) in the use of contraceptives, immunosuppressants and other drugs that may lead to dyslipidemia.[31] Therefore, it is expected that other factors, not collected here, would potentially justify these variations.

As for children, elevated TC and LDL-C were 40% and 35%, respectively. This increase in TC is close to that of a 2009 study with 217 individuals (84 obese), aged 2-9 years in Campina Grande/PB, ranging from 37% to 46%.[32] Moreover, this result of TC in children is consistent with data from the National Health and Nutrition Examination Survey (NHANES) of individuals aged 4-19 years, where elevations of TC levels were observed in the 9-11 years age group, decreasing later along the pubertal development.[33]

Ramos et al. (2011)[32] reported that the increase in LDL-C ranged from 14% to 14.8% in children (non-obese and obese), a finding that is lower than that of our study (35%). However, the cut-off value we used is lower than that of the referred population. In addition, similar results were observed in a study in Mexico with children from 2 to 10 years of age: 30% of subjects presented LDL-C ≥ 110 mg/dL.[34]

As for adolescents, there was a high frequency of low HDL-C (41%), a value close to the one reported in the ERICA study, which was 47% among 38,069 schoolchildren,[8] results aligned with those of this study, even considering the different methodological approaches of the two studies.

Other national studies have shown important data. A study conducted in the Northeast, with individuals aged 6 to 18 years, showed a low HDL-C frequency of 41%,[19] and another one carried out in Natal, RN, with students aged between 10 and 19 showed that 50% of the sample had this type of dyslipidemia.[35] Another study conducted in the metropolitan region of Guadalajara, Mexico with 132 individuals aged 5 to 15 years showed a lower prevalence (38.7%), but not very different from our findings.[36] The high frequency of reduced HDL-C in adolescents may be associated with young people's lifestyle, which involves inappropriate eating habits, overweight and physical inactivity.[37]

It is worth mentioning that in this study, 349 individuals presented serum phenotype with LDL-C ≥ 190 mg/dL, that is in 0.56% (1:200) the results were suggestive for FH.[10]

In relation to the regions of Campinas, the frequency of dyslipidemias was higher in the south and southwest than in the other regions. According to unpublished reports from the City Hall of Campinas, these regions have the highest number of records (25.7% and 27.6%, respectively)[38] in the *Cadastro Único*, a platform of the Federal Government that characterizes low-income families. In fact, according to Johansen et al.,[12] they make up the so-called "poverty mountain range", where there is a socioeconomic homogeneity not observed in the other regions.[39] Additionally, they are the ones that have a greater number of SUS users, accounting for 50% of the test results in this study.

Socioeconomic asymmetry can compromise the lifestyle of populations with direct repercussions on morbidity and mortality indicators. According to the WHO, currently three-quarters of deaths from cardiovascular disease are occurring in low and middle-income regions.[1]

The ERICA study showed significant increases in dyslipidemias in the north and northeast regions of the country (regions reportedly with the highest poverty indices in Brazil);[40] also, ERICA suggests that regional differences in dyslipidemias occur through the process of epidemiological transition, that is, regions may be at different stages.[8]

This study evaluated the second most populous city in the state of São Paulo, located in the southeastern region of Brazil, where urban sprawl occurred without adequate planning and culminated in the expansion of occupation areas with the consequence for the population of inappropriate access to urban services.[12]

Limitations of the study

One of the limitations concerns the fact that the evaluated database is of secondary origin, with possible inaccuracies in the insertion of demographic data throughout all the processes. We are aware of the continued use of the quality control standards of the Brazilian Society of Clinical Pathology by the Municipal Laboratory of Campinas, which supplies the laboratory data.

In addition, since it was a cross-sectional study, it was not possible to evaluate the incidence of cases of dyslipidemia.

Conclusion

This study shows the high frequency of atherogenic dyslipidemias in adolescents, children and infants attended in Campinas, with a greater distribution in the less favored socioeconomic regions, indicating the need for a regionalized focus during the development of public health programs for the prevention of early and adulthood CVD, including proper handling and treatment of dyslipidemias.

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Author contributions

Conception and design of the research, Acquisition of data and Obtaining financing: Faria EC; Analysis and interpretation of the data: Gomes EIL, Faria EC; Statistical analysis: Gomes EIL; Writing of the manuscript and Critical revision of the manuscript for intellectual content: Gomes EIL, Zago VHS, Faria EC.

Potential Conflict of Interest

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

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Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Unicamp under the protocol number CAAE: 86627418.3.0000.5404 Nº do parecer: 2.662.289. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013.

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High Prevalence of Dyslipidemia in Children and Adolescents: Opportunity for Prevention

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Short Editorial related to the article: Evaluation of Lipid Profiles of Children and Youth from Basic Health Units in Campinas, SP, Brazil: A Cross-Sectional Laboratory Study

Cardiovacular diseases are a major cause of morbidity and mortality. According with the World Health Organization (WHO), worldwide, one third of ischemic heart diseases are attributable to high cholesterol, which causes 2.6 million deaths per year.[1] Atherosclerosis begins in childhood and evolves in an insidious process which can last decades from the first artery injuries to the clinical outcomes (death, myocardial infarction or strokes). This process is speeded up by risk factors such as cholesterol, smoking, obesity and hypertension.[2]

The multicenter study Pathological Determinants of Atherosclerosis in Youth (PDAY) revealed the presence of atherosclerosis injuries in all aortas and in 50% of right coronary arteries in 1.532 necropsies of individuals aged from 15 to 19 years.[3] When the role of risk factors was assessed in individuals between 15 and 34 years of age, it was found that the aortic injuries were positively correlated with LDL and VLDL levels, glucose intolerance, smoking, hypertension, obesity, but negatively associated with HDL levels.[4] Similar findings were described by the Bogalusa Heart Study, which associated the presence of fatty streaks in the aorta with higher total and LDL cholesterol levels, in addition to an inverse association with HDL-C.[5] There was also greater severity of atherosclerosis injuries in the presence of multiple concomitant risk factors (body mass index, blood pressure, cholesterol and triglyceride concentration).[6]

In agreement with the evidence that increased cholesterol levels promote atherosclerosis, Mendelian randomized studies demonstrate that exposure to genetically lower cholesterol levels since childhood is associated with a reduction in the risk for coronary artery disease (CAD). It was estimated that for each 1 mmol/l (38.7 mg/dl) reduction in LDL, there is a 54.5% (95% CI 48.8%-59.5%) in CAD risk.[7] Such reduction is threefold higher than that achieved with the use of statins in more advanced age.[7]

Cholesterol metabolism can be analysed by dosing serum non-cholesterol sterols, cholesterol synthesis and absorption markers. In 1 to 10-year-old children, absorption prevails over synthesis.[8] This finding shows the importance of dietary as a cholesterol-reduction tool among this age group.

In this issue of the *Arquivos Brasileiros de Cardiologia*, Gomes, et al.[9] assessed the prevalence of isolated and combined dyslipidemias in 62,530 children and adolescents, aged between 1 day and 19 years, attended at the Basic Health Units network in Campinas/SP. They found biochemically classified changes in 67% of the lipid profiles analysed. The prevalence of increased total cholesterol, triglycerides, LDL and HDL-C levels were, respectively, 33%, 40%, 29% and 13%. The presence of low HDL-C was observed in 39% of the cases.[9] Although the number of individuals analysed is a strength of this study, the exclusive analysis of the lipid profiles prevents any other conclusions besides the frequency of abnormalities in this population.

The risk factors present in childhood and adolescence will probably remain until adulthood. This period of life represents a window of opportunity to initiate effective measures aiming at the prevention of atherosclerosis and clinical outcomes in adulthood. Therefore, it is necessary to trace and treat abnormalities in the lipid profile of children and adolescents, particularly of those with other risk factors.

Thus, the *Updated Cardiovascular Prevention Guideline of the Brazilian Society of Cardiology – 2019* recommends the universal lipid screening between ages 9-11 and for children aged 2 years or older when other risk factors are present. The adoption of healthy eating habits, the practice of regular physical activity and weight control are the pillars of the treatment of dyslipidemia in this age group. The use of medication, predominantly statins, should be restricted to more severe cases (such as genetic dyslipidemias) and after unsuccessful non-pharmacological treatment.[10]

Keywords

Cardiovascular Diseases; Dyslipidemias; Hypercholesterolemi; Child; Young Adult; Unified Health System; Adolescent; Laboratoty Test.

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Left Ventricular Remodeling Patterns in Primary Healthcare

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Abstract

Background: **Left ventricular remodeling (LVR) is related to both non-fatal and fatal outcomes.**

Objective: **To describe the geometric patterns of the LV and their associations.**

Methods: **A total of 636 individuals between the ages of 45 and 99 years in Rio de Janeiro, Brazil, were submitted to clinical evaluation, laboratory tests, electrocardiogram, and tissue Doppler echocardiography (TDE). The difference between categories was tested with Kruskall-Wallis with post hoc tests, once all variables studied are non-normally distributed and Pearson's Qui-square (categorical variables). Gross and adjusted ORs were estimated by logistic regression. The level of significance was 5% for all tests. Subjects had LVR characterized as: normal geometry (NG), concentric remodeling (CR), concentric hypertrophy (CH), and eccentric hypertrophy (EH).**

Results: **The prevalence of altered patterns was 33%. Subjects presented NG (n = 423; 67%); EH (n = 186; 29%); CH (n = 14; 2%); and CR (n = 13; 2%). The variables of gender, age, level of education and albumin/creatinine ratio (A/C), showed a relationship with the chance of EH even after adjustment.**

Conclusion: **Approximately one third of the studied individuals had LVR and were at risk for developing heart failure. Altered A/C in urine was associated with EH, indicating an early relationship between cardiac and renal dysfunction. (Arq Bras Cardiol. 2020; 114(1):59-65)**

Keywords: **Cardiovascular Diseases/physiopathology; Ventricular Remodeling; Hypertrophy, Left Ventricular; Heart failure; Renal Insufficiency; Risk Factors/complications; Comorbidity.**

Introduction

Ventricular remodeling is a continuous process of responses to the various injuries to the myocardium. Changes in left ventricular (LV) geometry, in its various patterns, are related to the incidence of non-fatal cardiovascular outcomes and long-term mortality, which are well-known markers of poor prognosis in various cardiovascular and systemic diseases.[1-6] Changes in ventricular geometry are considered target organ lesions on the heart and make individuals with these lesions classified as being in stage B of heart failure (HF) as it is proposed by the American College of Cardiology Foundation and American Heart Association (ACCF/AHA).[7]

The pathophysiological mechanisms of ventricular remodeling vary according to the determining etiology. The diseases lead to pressure overload with increased systolic wall stress, gene activation, or direct myocardial injury followed by cell proliferation, fibrosis, collagen deposition, apoptosis, and remodeling of the ventricular geometry. The conditions that occur with volume overload lead to increased diastolic wall stress with linear stretching of cardiomyocytes, proliferation in parallel, and increased cavity diameters.[8]

Epidemiological data on the prevalence and incidence of changes in ventricular geometry in population seen in primary care are scarce and knowledge of different remodeling patterns may assist in the implementation of strategies for risk stratification in this population. The aim of this study was to describe the geometric patterns of the LV in the population aged ≥ 45 years assisted in primary care, and to examine the association between ventricular remodeling and demographic and clinical variables.

Methods

This study is part of the *Digitalis trial* that aimed to determine the prevalence of HF in the population studied.[9]

Procedures for random sample selection and patient inclusion

We selected 26 primary care units in the city of Niterói, Rio de Janeiro, Brazil, between July 2011 and December 2012. The selection of units was done by a computer-generated random sequence program, in which the weight of each unit was proportional to the number of individuals assisted. In each unit, 50 subjects were randomly selected, including

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30 individuals for participation and 20 for replacement in case of negative response. The selected total population was 1050. Nine hundred forty-two individuals confirmed the presence and 666 individuals attended the scheduled visit. Inclusion criteria were age between 45 and 99 years old and informed consent. Five individuals who did not complete the questionnaire were excluded, 6 did not perform the tissue Doppler echocardiography (TDE), and 20 did not perform the measurement of B-type natriuretic peptide (BNP). At the end of the study, 636 patients completed the necessary requirements: structured questionnaire, physical examination, anthropometric data, BNP, electrocardiogram (ECG) at rest and TDE.

Definitions

All individuals selected for the study were subjected to an assessment carried out in a single day and consisting of the following elements: clinical evaluation, laboratory tests, including BNP levels, ECG, and TDE.

TDE tests were performed according to the recommendations for the quantification of chambers of the *American Society of Echocardiography* and the *European Association of Echocardiography*. (LANG, 2015). Indexing was performed by body surface area. The left ventricular mass (LVM) was estimated by Devereux et al. (DEVEREUX, 1986) and relative wall thickness (RWT) by the formula where RWT is equal to twice the diastolic posterior wall divided by the diameter of the LV. RWT values ≥ 0.42 and indexed LV ≥ 115 g/m² for men and ≥ 95 g/m² for women were considered abnormal. The subjects were grouped into four remodeling models: normal geometry, concentric remodeling, concentric hypertrophy, and eccentric hypertrophy, according to the Guidelines of the American Society of Echocardiography.[10]

Patients were classified in stages of chronic kidney disease (CKD) according to estimated glomerular filtration rate (eGFR) calculated by KDIGO formula (Kidney Disease: Improving Global Outcomes). Stage 1: eGFR >90 mL/min; stage 2: eGFR 60-89 mL/min; stage 3: eGFR 30-59 mL/min; stage 4: eGFR 15–29 mL/min; and stage 5: eGFR <15 mL/min.

Individuals with BMI ≥ 30 kg / m2 were considered obese. Diabetic patients were defined by previous history of diabetes. The study classified as hypertensive individuals those who reported being hypertensive, were on medication to treat hypertension or had a mean systolic blood pressure (SBP) ≥ 140 mmHg or mean diastolic blood pressure (DBP) ≥ 90 mmHg.

Statistical analysis

Statistical analysis was performed using SPSS v 21.0 (Chicago, Illinois, USA). Continuous variables were expressed as median and interquartile range (50 %(25-75%)). Categorical variables were expressed in absolute numbers and/or percentages. For comparison between groups, the qui-square test was employed. All continuous variables were tested for normality with the Shapiro-Wilk test with pos-hoc test and for all of them the Ho (null hypothesis) of equality was rejected, that is, none of them had normal distribution. To that extent, the difference between those variables and the phenotypes was tested with the Kruskall-Wallis test. We estimated crude and adjusted odds ratios by logistic regression. In all comparisons, bilateral tests were utilized, and p values < 5% were considered statistically significant.

Ethical considerations

This study was conducted in accordance with the principles set out in the Declaration of Helsinki revised in 2000 (Scotland, 2000). The study was previously approved by the Universidade Federal Fluminense under n° CAAE: 0077.0.258.000-10, and informed written consent was provided by all participating patients.

Results

The study evaluated 636 individuals of 59.5 ± 10.3 years old (62% women, 63% non-whites). The subjects were classified according to the geometry of the LV: normal geometry in 423 (67%); eccentric hypertrophy in 186 (29%); concentric hypertrophy in 14 (2%); and concentric remodeling in 13 (2%). Demographic data of the subjects are listed in Table 1. The variables of age, gender, level of education, high blood pressure, pulse pressure, albumin/creatinine ratio, and the sodium/creatinine ratio in urine were statistically significant between the remodeling patterns. Hypertension and diabetes mellitus were the most prevalent comorbidities in patients with concentric hypertrophy, while coronary artery disease and obesity occurred more frequently in the group with concentric remodeling (Table 1). Table 2 lists the main echocardiographic changes.

Table 3 presents the crude and adjusted *odds ratio* of eccentric hypertrophy versus normal geometry, the only remodeling pattern with sufficient prevalence to achieve adequate power for conducting a multiple analysis. The variables of gender, age, level of education and albumin/creatinine ratio showed a relationship with the risk of eccentric hypertrophy even after adjustment.

Figure 1 shows the distribution of the patterns of left ventricular remodeling in patients without changes in renal function (A); in patients with subclinical changes demonstrated by microalbuminuria (B); and in those with established kidney disease (C).

Discussion

In the present study, with individuals assisted in primary care aged 45 years or more, the main pattern of ventricular geometric changes was eccentric LVH. The change was more prevalent in women, older patients, patients with lower educational levels, and patients with hypertension and renal dysfunction.

The differences observed in this study compared to other studies in Europe and the United States can be explained by reasons similar to those reported in the study by Schvartzman et al.[3] The stature of Brazilians is lower than that of Europeans and North American Caucasians, impacting the LV mass indexed by the body surface.

Table 1 – Demographic and clinical characteristics of the selected individuals characterized by left ventricular remodeling patterns

Variables	Normal geometry n = 423	Eccentric hypertrophy n = 186	Concentric hypertrophy n = 14	Concentric remodeling n = 13	p-value (*)
Age (years)	56 (50-64)	58 (47-70)	63 (55-71)	61 (53-71)	< 0.0001
Female (%)	57.4	71.5	78.6	53.8	0.005
Non-white (%)	63.5	63	57	61.5	0.812
SBP (mmHg)	133.7 (121-147)	133(115.5-134.9)	144.5 (126-175)	135.6 (120.2-156)	0.148
DBP (mmHg)	82.3 (74.3-90.0)	76 (73.5-91)	83.5 (75.9-91.5)	80 (72-90)	0.385
PP (mmHg)	517 (42-60)	51 (36-59)	60 (47-59)	55 (46-67)	0.004
HR (bpm)	70 (63-78)	72 (65-80)	74 (64-83)	69 (61-77)	0.468
BMI (kg/m^2)	27.2 (24,5-30.6)	28.6 (19.4-35.8)	26.8 (23.4-30.6)	27.7 (24.3-30.7)	0.881
Glycemia (mg/dL)	101 (92-113)	107 (92-125)	104 (92-125)	100 (92-115)	0.734
GFR (mL/min)	83.4 (71.7-96.1)	84.1 (74.6-92.8)	67.7 (53.6-85.0)	82.3 (67.2-94.1)	0.021
Uric acid (mg/dL)	5.2 (4.3-6.4)	4.5 (3.8-5.9)	4.6 (3.9-5.9)	5.0 (4.1-6.1)	0.266
Cholesterol (mg/dL)	214 (188-243)	201 (157-221)	208 (184-250)	215 (185-245)	0.507
Alb/Creat (mg/g)	9.3 (5.5-18.7)	8.0 (5.2-170.1)	16.2 (9.9-42.9)	11.8 (6.2-38.9)	0.018
sod/creat in urine	120.9 (77-160)	108.3 (48-200)	145.4 (77-235)	126.2 (89-185)	0,205
BNP (pg/mL)	14 (10-25)	17 (11-41)	35 (14-120)	21 (11-42)	< 0.0001
Albuminuria (mg)	10.5 (5.4-20.8)	8.5 (4.4-65.4)	13.7 (5.8-30.8)	12.8 (7-34.5)	0.049
Hypertension (%)	54.6	63.4	71.4	53.8	0.150
Diabetes (%)	24.3	23.7	50.0	30.8	0.159
CAD (%)	8.7	7.5	14.3	15.4	0.657
Obesity (%)	28.7	32.3	28.6	46.2	0.488

SBP: systolic blood pressure; DBP: diastolic blood pressure; PP: pulse pressure; HR: heart rate; BMI: body mass index; GFR: estimated glomerular filtration rate; Alb/Creat: albumin/creatinine ratio; sod/creat: sodium/creatinine ratio; BNP: type B natriuretic peptide; CAD: coronary artery disease; (*) p = difference between the patterns of remodeling performed with the Kruskall-Wallis test 1-way ANOVA for multiple comparisons (all pairs) and Pearson's chi-squared test for differences of proportion.

Table 2 – Echocardiographic parameters of the selected individuals characterized by left ventricular remodeling patterns

Variables	Normal geometry n = 423	Eccentric hypertrophy n = 186	Concentric hypertrophy n = 14	Concentric remodeling n = 13	p-value (*)
LVEF (%)	61 (58-65)	63 (58-64)	59 (50-64)	60 (56-63)	0.01
LVMi (g/m^2)	82.8 (72.2-92.0)	84 (70.7-93.4)	120 (105.6-150.71)	116.3 (102.4-127.3)	< 0.0001
LAVi (ml/m^2)	20.8 (17.1-24.5)	18 (14-22.3)	23.6 (19.2-33.1)	22.6 (19.2-27.5)	< 0.0001
EDVi (ml/m^2)	60.1 (51.8-67.2)	41.7 (36.4-49.4)	60.5 (52.1-75.9)	74.7 (67.7-83.2)	< 0.0001
E'(cm/s)	10(8-12)	12(7.5-13)	7.7(6-10.6)	9(7-11)	< 0.0001
E (cm/s)	64 (54-76)	70(52-93)	68(51-75)	63 (52-78)	0.532
A (cm/s)	65 (53-81)	76(59-99)	69(56-98)	71 (57-86)	0.242
E/A ratio	1.0 (0.7-1.3)	1.1 (0.6-1.3)	0.9 (0.7-1.1)	0.8 (0.7-1.2)	0.003
E/E' ratio	6.4 (5.3-7.7)	7.1 (4.7-8.7)	8.0 (5.7-10.0)	7.1 (5.7-8.4)	0.008
SWT (mm)	8(7-8)	9(8-10)	10(10-12)	9(8-9)	< 0.0001
LVDD (mm)	47 (44-50)	40 (34.5-41.5)	43.5 (41.7-47.8)	52 (49-54,2)	< 0.0001
PWT (mm)	8(7-8)	9(8-10)	10(10-12)	8(8-9)	< 0.0001

LVEF: left ventricular ejection fraction; LVMi: indexed left ventricular mass; LAVi: indexed left atrial volume; EDVi: indexed end-diastolic volume; E´: mitral annular early diastolic velocity; E: early mitral inflow velocity; A: peak mitral inflow velocity at atrial contraction ; LVDD: LV diastolic diameter; SWT: septal wall thickness; PWT: posterior wall thickness (*)= p value - the difference between the patterns of remodeling performed with Kruskall-Wallis test 1-way ANOVA for multiple comparisons (all pairs).

Table 3 – Crude and adjusted odds ratios of eccentric hypertrophy versus normal geometry

Variables	OR (IC 95%)	ORa (IC 95%)
Gender		
Female	1.80 (1.25-2.60)	1.75 (1.17-2.61)
Male	1	1
Age range		
70-99 years	2.33 (1.54-3.52)	2.04 (1.28-3.26)
45-69 years	1	1
Skin color		
Black	1.20 (0.812-1.774)	
Non-black	1	
Level of education		
≤ Elementary school	1.86 (1.32-2.62)	1.59 (1.07-2.34)
> Elementary School	1	1
Per capita income		
≤ 1 MW	1.52 (1.00-2.30)	
> 1 MW	1	
Smoking in life		
Smoker or ex-smoker	0.91 (0.65-1.28)	
Never smoked	1	
Alcohol consumption - risk drinker		
Yes	0.57 (0.29-1.10)	
No	1	
Physical activity		
Sedentary and irregular	0.82 (0.57-1.92)	
Active or very active	1	
Obesity		
Yes (BMI ≥ 30 kg/m^2)	1.16 (0.81-1.68)	
No (BMI < 30 kg/m^2)	1	
Hypertension		
Yes	1.69 (1.13-2.52)	1.23 (0.79-1.92)
No	1	1
Type 2 diabetes		
Yes	0.94 (0.63-1.41)	
No	1	
Uric acid altered		
Yes	1.04 (0.68-1.59)	
No	1	
Coronary artery disease		
Yes	0.78 (0.41-1.47)	
No	1	
Albumin/creatinine ratio		
≥ 30 mg/g	1.82 (1.19-2.76)	1.64 (1.05-2.57)
< 30 mg/g	1	1
Sodium/creatinine ratio in urine		
> 10.39 g/dL	1.64 (1.08-2.47)	1.34 (0.86-2.09)
≤ 10.39 g/dL	1	1
Chronic kidney disease (CKD)		
Stages 3,4,5	1.43 (0.84-2.43)	
Stages 1,2	1	

OR: odds ratio; Ora: odds ratio adjusted; CI: confidence interval; MW: minimum wage; BMI: body mass index; Uric acid altered: male > 7.0 mg/dL and female > 6.0 mg/dL; CKD: chronic kidney disease estimated by glomerular filtration rate (KDIGO) stages 1, 2, 3, 4, and 5

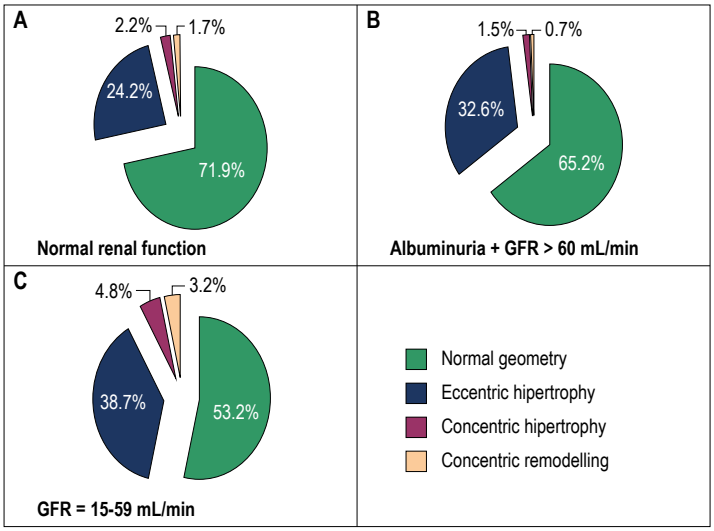

Figure 1 – *A, B, and C: Evaluation of parameters of renal function in different patterns of left ventricular remodeling.*

Ventricular remodeling throughout life occurs as an adaptive response to aging, exposure to risk factors for cardiovascular disease and myocardial injury.[11] A study carried out in the community with 4492 participants (mean age 51 years and 59% women) showed that 64% had normal geometry, 18% had concentric remodeling, 13% had eccentric hypertrophy, and 5% had concentric hypertrophy. Our data are similar to the population with normal geometry (64 vs. 67%), but different in relation to remodeling standards, especially regarding concentric remodeling (18% vs. 2%) and eccentric hypertrophy (13% vs. 29%). These differences can also be explained by the greater number of hypertensive and diabetic patients observed in our study in relation to the trial of Lieb et al.[11]

A study conducted in the community by Teh et al.[12] assessed the prevalence of the four remodeling models in 108 patients aged >70 years, in which 56% were women, 84% had hypertension, and 20% had diabetes.[12] Although the data of Teh et al.[12] were obtained in an older population, they are similar to ours in relation to the higher prevalence of eccentric hypertrophy observed in the sample (26% vs 29%), showing that there seems to be an increased prevalence of eccentric remodeling in older individuals and those with more comorbidities.

Aging is directly related to the progression of cardiac remodeling, most likely due to exposure to multiple cardiovascular risk factors. This finding was present in our study as well as in the literature.[13]

We observed an association between female gender and the presence of LV eccentric hypertrophy after adjusting for other variables (OR, 95% CI, 1.75 [1.17 to 2.61]). There are differences in cardiac structure and function in relation to gender, and these differences appear to be more pronounced in the presence of risk factors for HF with preserved ejection fraction (HFpEF), and they can be explained by sexual dimorphism.[14] A study evaluating changes in LV stiffness in 1,402 individuals in the community observed an increase in stiffness with aging, which is increased in women more frequently than in men.[15] A study involving 318 healthy adults from the Framingham Heart Study who underwent MRI to determine the reference values of LV parameters observed a greater increase in the linear dimensions of the LV after adjustment for body surface area in women than in men ($p < 0.001$).[16]

Our data showed that low educational level had an association with eccentric hypertrophy. Such a result can be explained by greater exposure to risk factors, less understanding about self-care, and less adherence to drug treatment.

Microalbuminuria is an important cardiovascular risk marker,[17] and the data presented here showed that individuals with changes in ventricular geometry had high levels of urinary albumin and worsening renal function assessed by GFR. Individuals with impaired renal function have a progressive increase in eccentric hypertrophy, which may reflect heart disease with concomitant loss of kidney function. Both concentric and eccentric patterns reflect hypertensive nephropathy, which progresses with structural heart disease. Studies show the existence of an association between albuminuria, remodeling, and cardiovascular disease. Increased urinary albumin excretion is associated with changes in ventricular remodeling in patients with hypertension. Patients with hypertension who have albuminuria regression disability have a higher incidence of cardiovascular disease.[18] Our data show there is a strong association between the albumin/creatinine ratio and the development of eccentric LV hypertrophy.

This study was the first in the Brazilian primary care population to specifically study the LV geometry with inclusion of RWT.

The greater inclusion of female patients is noteworthy as a limitation to the study. This was due to greater adherence of women to the study protocol. Similarly, the greater adherence

to therapy may have influenced the remodeling patterns in females, and such adherence was not measured.

Conclusion

One third of individuals attending primary care between the ages of 45 and 99 years, in the sample analyzed, had LVR and were at risk for developing HF. Altered albumin/creatinine ratios in urine was associated with eccentric hypertrophy, indicating an early relations hip between cardiac and renal dysfunction.

Author contributions

Conception and design of the research: Almeida RCM, Jorge AJL, Rosa MLG, Martins WA; Acquisition of data: Jorge AJL, Leite AR, Correia DMS, Chermont S, Lugon JR; Analysis and interpretation of the data: Almeida RCM, Jorge AJL, Mesquita ET, Martins WA; Statistical analysis: Rosa MLG; Writing of the manuscript: Almeida RCM, Jorge AJL, Rosa MLG, Chermont S, Martins WA; Critical revision of the manuscript for intellectual content: Jorge AJL, Rosa MLG, Mesquita ET, Lugon JR, Martins WA.

Potential Conflict of Interest

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

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Study Association

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Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Universidade Federal Fluminense under the protocol number CAAE: 0077.0.258.000-10. 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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Do We Need to Know the Left Ventricular Geometry Patterns of the Brazilian Population?

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Short Editorial related to the article: Left Ventricular Remodeling Patterns in Primary Healthcare

In this issue of the *Arquivos Brasileiros de Cardiologia*, Almeida et al.[1] describe the left ventricular (LV) remodeling patterns frequencies found in a Brazilian population followed at primary healthcare clinics in Niterói city, state of Rio de Janeiro. The authors found that a LV abnormal geometry was present in up to 33% of 636 studied individuals (mean age 59.5±10.3 years old; 62% women). Eccentric LV hypertrophy (LVH) was the most common abnormal LV geometry pattern (29%), followed by concentric LVH and concentric remodeling (2% each).

LV remodeling is no longer considered solely an adaptative mechanism but a response to several different stimuli that lead to gene activation, cellular hypertrophy, apoptosis, fibrosis, and, finally, LV remodeling with different degrees of LV function compromise and increase in cardiovascular risk.[2] In fact, the relation between LVH diagnosed by electrocardiogram and mortality has been long recognized.[3] LV mass is considered an independent risk factor for heart failure (HF),[4,5] stroke,[5] sudden cardiac death,[6] supraventricular and ventricular tachycardia,[7] and all-cause[8] and cardiovascular mortality.[9] Therefore, hypertension (HTN) is considered stage A HF and LVH is considered stage B HF on the American College of Cardiology/American Heart Association guidelines on HF management.[10] Surprisingly, it was not up to the study of Almeida et al.[1] that LV geometry patterns were studied in Brazilian population. We need to know exactly what are the frequency and value of LV geometry patterns in the Brazilian population and not only apply knowledge obtained with other populations.

Many different factors and stimuli influence LV geometry remodeling such as age, gender,[11] severity, duration and treatment status of HTN,[12] obesity,[13,14] metabolic syndrome,[15] and diabetes mellitus.[16] Almeida et al.[1] also showed an association between eccentric LVH and gender, age, level of education, HTN, and albumin/creatinine ratio. However, the frequencies of those factors may have a great variation between populations which shows the importance of specifically addressing the LV geometry patterns and their prognostic value in Brazilian population.

LV abnormal geometry is classified into concentric remodeling (normal LV mass with increased relative wall thickness), concentric LVH (increased LV mass and relative wall thickness), and eccentric LVH (increased LV mass and normal relative wall thickness)[17] based on M-mode echocardiography. LV geometric abnormalities are usually found in the general population. However, the distribution of the kind of LV geometry abnormalities may vary between studies. In a study with 35,602 patients with normal LV ejection fraction referred for echocardiography, concentric remodeling was identified in 35%, concentric LVH in 6% and eccentric LVH in 5%.[8] However, this prevalence increases with ageing. In elderly patients, concentric remodeling was found in 43%, concentric LVH in 8.5% and eccentric LVH in 7.4%.[18] Those results are strikingly different from the data described in the Brazilian population by Almeida et al.[1] with a higher prevalence of eccentric LVH. Such a difference may be related to the high prevalence of HTN and diabetes in the population studied by Almeida et al.[1] In fact, the most common type of LVH in patients with HTN is eccentric and not concentric LVH.[12] Nevertheless, such differences between studies underscore the importance of studies addressing the Brazilian population. For instance, eccentric hypertrophy was associated with the development of HF with reduced ejection fraction, while concentric LVH was associated with the development of HF with preserved ejection fraction.[19]

A new classification for LVH was proposed based on LV dilation and concentricity:[20] concentric non-dilated, concentric dilated, eccentric non-dilated and eccentric dilated. The importance of this new classification was demonstrated by the fact that eccentric non-dilated LVH is not associated with poor outcomes while all others had increased risk of all-cause and cardiovascular disease (CVD) mortality[21] or increased risk of HF or CVD death compared to participants without LVH.[22]

Thus, I congratulate Almeida et al.[1] for their very important research and I challenge them to pursue on their research and present the classification of LV geometry based on 4-tiered classification of LVH and, more importantly, the prognostic value of LV remodeling patterns in Brazilian population followed at primary healthcare.

Keywords

Heart Failure; Hypertension; Hypertrophy,Left Ventricular; Ventricular Remodeling; Heart Ventricles/cirurgia, Echocardiography/métodos.

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Subclinical Carotid Atherosclerosis and Reduced DAD Score for Cardiovascular Risk Stratification in HIV-Positive Patients

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Abstract

Background: **HIV-positive patients are twice as likely than the general population to have a heart attack and are four times at greater risk of sudden death. In addition to the increased risk, these individuals present with cardiovascular events on average approximately 10 years earlier than the general population.**

Objective: **To compare Framingham and reduced DAD (Data Collection on Adverse Effects of Anti-HIV Drugs Cohort) scores for cardiovascular risk assessment in HIV-positive patients and potential impact on clinical decision after evaluation of subclinical carotid atherosclerosis.**

Methods: **Seventy-one HIV-positive patients with no history of cardiovascular disease were clinically evaluated, stratified by the Framingham 2008 and reduced DAD scores and submitted to subclinical carotid atherosclerosis evaluation. Agreement between scores was assessed by Kappa index and $p < 0.05$ was considered statistically significant.**

Results: **mean age was 47.2 and 53.5% among males. The rate of subclinical atherosclerosis was 39.4%. Agreement between scores was 49% with Kappa of 0.735 in high-risk patients. There was no significant difference between scores by ROC curve discrimination analysis. Among patients with intermediate risk and Framingham and reduced DAD scores, 62.5% and 30.8% had carotid atherosclerosis, respectively.**

Conclusion: **The present study showed a correlation between the scores and medium-intimal thickening, besides a high correlation between patients classified as high risk by the Framingham 2008 and reduced DAD scores. The high prevalence of carotid atherosclerosis in intermediate risk patients suggests that most of them could be reclassified as high risk. (Arq Bras Cardiol. 2020; 114(1):68-75)**

Keywords: **Carotid Artery Diseases; HIV; Acquired Immunodeficiency Syndrome/complications; Indicators of Morbidity; Antiretroviral Therapy, Highly Active; Risk Factors.**

Introduction

Currently, about 36.7 million people are infected with HIV worldwide, and 1.8 million cases are diagnosed every year, while 1 million deaths occur.[1] In Brazil, estimates say that 813,000 people are infected with HIV, with 48,000 new cases and 14,000 deaths in 2016.[2] Over the last decades, the use of antiretroviral therapy (ART) has led to a progressive decrease in mortality caused by opportunistic diseases and, consequently, there has been a considerable increase in the survival of these patients. AIDS has become a chronic disease and permanent immune activation, caused by the HIV virus, which translates into a systemic inflammatory process with significant repercussions in various organs and systems, especially cardiovascular system, brain, kidneys and bones, which leads to premature aging.

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Cardiovascular diseases emerged as an important cause of morbidity and mortality in this group of patients. Data from the DAD study (Data Collection on Adverse Effects of Anti-HIV Drugs), published in 2014, indicate that 11% of deaths of HIV-positive patients are caused by cardiovascular diseases.[3,4] HIV-infected patients are at twice as high risk of having a heart attack than the general population and four times more likely to have sudden death.[5,6] In addition to the increased risk, people with HIV experience cardiovascular events approximately 10 years before the general population, on average.[7]

Although traditional cardiovascular risk scores, such as Framingham, have been developed for the general population, their use in HIV-positive patients is not well defined.[8] Based on the prospective multicenter DAD study, which was a collaboration of 11 cohorts of HIV-positive patients treated at 212 clinics in the United States, Europe, Argentina and Australia, algorithms were developed specifically for this population. The DAD score was first published in 2010, and considered CD4 count, use of Abacavir, and time of exposure to protease inhibitors and nucleoside reverse transcriptase inhibitors in addition to classic cardiovascular risk factors.[9] In order to simplify risk stratification of HIV positive patients and due to the difficulty of assessing previous antiretroviral therapy regimens, a modification in the DAD score was proposed and published in 2016, assessing the same clinical outcomes in 5 years, but not using the classes and time of exposure to ART.[10]

The aim of this study was to compare the Framingham and reduced DAD scores for cardiovascular risk assessment in HIV-positive patients and the potential impacts on clinical decision after evaluation of subclinical carotid atherosclerosis.

Methods

Population

Seventy-one asymptomatic HIV-positive patients on regular ART, with no previous diagnosis of cardiovascular disease, and in regular follow-up at the Infectious and Parasitic Diseases Outpatient Clinic of *Universidade Federal do Triângulo Mineiro* (UFTM), in Uberaba, Minas Gerais, were included.

Clinical assessment

Clinical, demographic and anthropometric data were obtained by clinical interview and included risk factors for cardiovascular disease, namely: age (≥ 45 years in men and ≥ 55 years in women), smoking (current use or cessation in the last 30 days), family history of early coronary artery disease (CAD) (myocardial infarction or death from CAD in first-degree relatives, if men < 55 years and women < 65 years), systemic arterial hypertension (previous diagnosis with medication for hypertension and/or blood pressure >140x90 mmHg), dyslipidemia (previous diagnosis with use of lipid lowering drugs and/or laboratory abnormalities according to current guidelines and described in the following), diabetes mellitus (previous diagnosis with use of blood glucose lowering medications and/or blood glucose monitoring > 126 mmHg). Body mass index (BMI) was calculated as the ratio between weight in kilograms and height squared in meters and considered normal from 18.5 to 24.9 kg/m^2, overweight from 25.0 to 29.9 kg/m^2 and obesity as ≥30.0. Waist circumference was measured in centimeters at the level of the umbilical scar and considered abnormal according to the International Diabetes Federation (IDF)'s metabolic syndrome standards.[11]

Blood pressure was measured during clinical evaluation at the outpatient clinic using an OMRON automatic arm blood pressure measuring device (HEM-7113), in compliance with current guidelines for systemic arterial hypertension, and the each individual's level of activity was assessed by the short version of IPAQ (International Questionnaire on Physical Activity), with those who reported performing physical activity lasting < 10 minutes per week being considered sedentary.

Laboratory assessment

All patients had 12-hour fasting peripheral venous puncture blood collection. Blood counts, blood glucose (RV = 60 to 99 mg/dL), total cholesterol, triglycerides, HDL-cholesterol, LDL-cholesterol, urea (RV ≤ 50 mg/dL), creatinine (RV = 0.4 to 1,4 mg/dL), sodium (RV = 136 to 145 mmol/L), potassium (RV = 3.5 to 5.1 mmol/L). Blood glucose, total cholesterol, LDL-cholesterol and triglycerides were considered altered if > 100 mg/dL, 200 mg/dL, 160 mg/dL and 150 mg/dL, respectively, and HDL-cholesterol was considered low when < 40 mg/dL in men and < 50 mg/dL in women.

The blood samples were processed at the Laboratory of Clinical Analysis of the UFTM Clinics Hospital. Total cholesterol, HDL-cholesterol and triglycerides were determined by colorimetric-enzymatic method in a Roche Cobas 6000 apparatus. LDL-cholesterol was calculated by the formula [(total cholesterol-HDL-cholesterol) – (triglycerides/5)].

Risk stratification

Estimates of cardiovascular risk were measured by the reduced DAD and Framingham 2008 scores. Framingham 2008 considers outcomes such as cardiovascular death, CAD, stroke, heart failure and claudication in 10 years, whereas simplified DAD includes acute myocardial infarction, stroke, coronary and carotid interventions and cardiovascular death in 5 years. According to the Framingham 2008 score, event rate was considered low risk when < 10%, intermediate risk when >10% and <20%, and high risk when >20%. For DAD, values <1% were considered low risk, 1% to 5% moderate risk, 5% to 10% high risk, and >10% very high risk.[9,12] The simplified DAD score was calculated by means of a tool available at https://www.chip.dk/Tools-Standards/Clinical-risk-scores.

Evaluation of subclinical atherosclerosis

Exams were performed at the Radiology Department of the UFTM Clinical Hospital with a Toshiba Aplio 400 ultrasound device using a 10-14 MHz linear and multifrequency probe. Patients were evaluated in supine position, in a semi-dark room, with their neck positioned at 45°. The distal portions of the right and left common carotid arteries (1 cm before bifurcation) and proximal segments (2 cm) of the internal carotids were evaluated. The medium-intimal complex (MIC) was measured by the distance between two echogenic lines, the lumen-intima interface and media-adventitia interface, on the vessel's posterior wall. The MIC was considered thickened if > 0.8 mm in the common carotid artery and the presence of plaques was established by a focal structure extending at least 0.5 mm to the vessel lumen and/or measuring more than 50% of the adjacent MIC value, and/or MIC greater than 1.5 mm.[13]

Statistical analysis

Qualitative variables were expressed by frequency distribution and quantitative variables with normal distribution, as per the Kolmogorov-Smirnov test, were expressed as mean and standard deviation, and those with non-Gaussian distribution as median and interquartile range. The correlations in which the variables had non-Gaussian distribution were evaluated by the Spearman's coefficient. Agreement between scores was assessed by Kappa index and discrimination power of scores was assessed by C-statistics, defined by the area below the ROC curve relating to the finding of subclinical atherosclerosis. The statistical software GraphPad Prism version 5 was used in the process. Statistical significance was set at $p < 0.05$.

Results

From January 2016 to July 2017, 71 HIV patients under regular treatment were evaluated. All patients had an undetectable viral load, and had been in ART for over a year, asymptomatic and with no history of cardiovascular disease. Mean age was 47.23 ± 9.36m with 53.52% of the sample

being composed of male patients, median time to HIV infection diagnosis of 12 years (6-17), and CD4 lymphocyte count of 654, 6 ± 308.3 cells/mm^3. The metabolic profile of these patients is shown in Table 1. We highlight the presence of alterations in triglycerides > 150 mg/dL or total cholesterol >200 mg/dL in 41 (57.74%) cases.

Among the classic cardiovascular risk factors evaluated, the most frequent were dyslipidemia, physical inactivity and age in 53 (74.6%), 46 (64.78%) and 30 cases (42.25%), respectively (Figure 1). Increased waist circumference was found in 51 (71.83%) cases and metabolic syndrome, as defined by the IDF criteria, was found in 32 (45.07%) cases.

Cardiovascular risk stratification was made by the Framingham 2008 and reduced DAD scores, and results are shown in Figure 2. The identification of high and very high risk was similar in both scores, differing in other categories, as Framingham 2008 showed 63,4% of low risk cases and DAD score revealed 54.9% intermediate risk cases. When the degree of agreement between scores was evaluated, an overall Kappa index of 0.318 was observed with $p < 0.001$. However, there was stronger agreement for patients classified as high risk, lower agreement for low risk patients, and no statistically significant difference for intermediate risk subjects (Table 2). Both scores showed a statistically significant and positive correlation with the medium-intimal thickening (Figure 3).

The medium-intimal thickening (highest thickness) in these patients was 0.73 ± 0.14 and there were 28 cases of subclinical atherosclerosis (39.4%). Of these, 17 (60.7%) patients presented non-significant plaque, 6 (21.4%) only thickening, and 5 (17.8%) had both plaque and thickening. In patients classified as high risk, the occurrence of subclinical atherosclerosis was 77.8% for the Framingham 2008 score and 88.2% for the reduced DAD score. In patients classified as low or intermediate risk, the rate of subclinical atherosclerosis was higher for Framingham 2008, with 20% of patients classified as low risk presenting subclinical atherosclerosis (Figure 4).

Among patients with subclinical atherosclerosis, 50% were classified as low or intermediate risk regardless of the score used. As for atherosclerosis stratified by Framingham 2008, 9/28 patients (32.1%) were classified as low risk and, by reduced DAD score, 12/28 (42.8%) were classified as intermediate risk (Figure 5).

Analysis of discrimination of scores by comparison between ROC curves targeting subclinical atherosclerosis showed no significant difference between Framingham 2008 and reduced DAD scores (Figure 6), and the predictive accuracy is shown in Table 3.

Table 1 – Main epidemiological, clinical and laboratory aspects of 71 HIV-positive patients

	n = 71
Males, n (%)	38 (53.52)
Age, years	47.23 ± 9.36
Time of HIV diagnosis (years)	12 (6-17)
Value of CD4 cells/mm^3	654.6 ± 308.3
Weight, Kg	73.14 ± 16.37
BMI, Kg/m^2	26.77 ± 5.21
Systolic pressure, mmHg	119.9 ± 15.47
Diastolic pressure, mmHg	75.97 ± 10.46
Total cholesterol, mg/dL	199.9 (171.2-244.9)
LDL, mg/dL	126.4 ± 40.27
HDL, mg/dL	47.85 ± 14.36
Triglycerides, mg/dL	169 (96-232)
Glycemia, mg/dL	100 (90.9-112.1)
Glycemia > 100, n (%)	35/69(50.72)
Triglycerides > 150, n (%)	38(53.52)
Low HDL, n (%)	26(36.61)
Triglycerides > 150 or total cholesterol > 200, n (%)	41(57.74)

HDL: high-density lipoprotein; BMI: body mass index; LDL: low-density lipoprotein; n: number of subjects.

Discussion

In this study, 71 HIV-positive patients under regular follow-up, diagnosed for more than one year, and under ART with immune reconstitution and viral suppression were evaluated. Most patients were classified as low risk by the Framingham 2008 score and intermediate risk by the reduced DAD score. There was a correlation between the medium-intimal thickening and the scores, high agreement between patients classified as high risk by both scores, although no significant difference was observed in the ROC curve score discrimination analysis. Although subclinical atherosclerosis was observed in 88% of patients classified as high risk by the reduced DAD score, subclinical atherosclerosis was found in 62.5% of patients classified as intermediate risk by the Framingham 2008 score.

Other authors have already compared risk stratification scores in HIV-positive patients,[8,14] but to our knowledge, this is the first study to apply the reduced DAD score and assess the degree of agreement with Framingham's score. Checking the accuracy and applicability of this tool is important because it has been developed for HIV-infected patients, and unlike DAD full, it does not use ART-related factors, which makes its use more feasible.

Regarding risk factors, it is important to highlight that, although diagnosis of dyslipidemia was reported in only 32.39% of patients, laboratory tests showed total cholesterol >200 mg/dL and/or triglycerides >150 mg/dL in 57.74% of the cases identifying significant difference between the diagnosis reported by the patient and the laboratory verification of changes in lipid profile. When considering dyslipidemia or changes in LDL-cholesterol, triglycerides or HDL-cholesterol, the frequency of dyslipidemia was 74.6%. These values reinforce the relevant presence of this risk factor in this population and the need for proper observation of criteria for diagnosis and treatment of these changes according to current guidelines.

The frequency of subclinical atherosclerosis reported here (39.4%) is similar to data from Falcão et al.,[15] who found 42.6% of subclinical carotid atherosclerosis.[15] Most patients evaluated were classified as low risk by

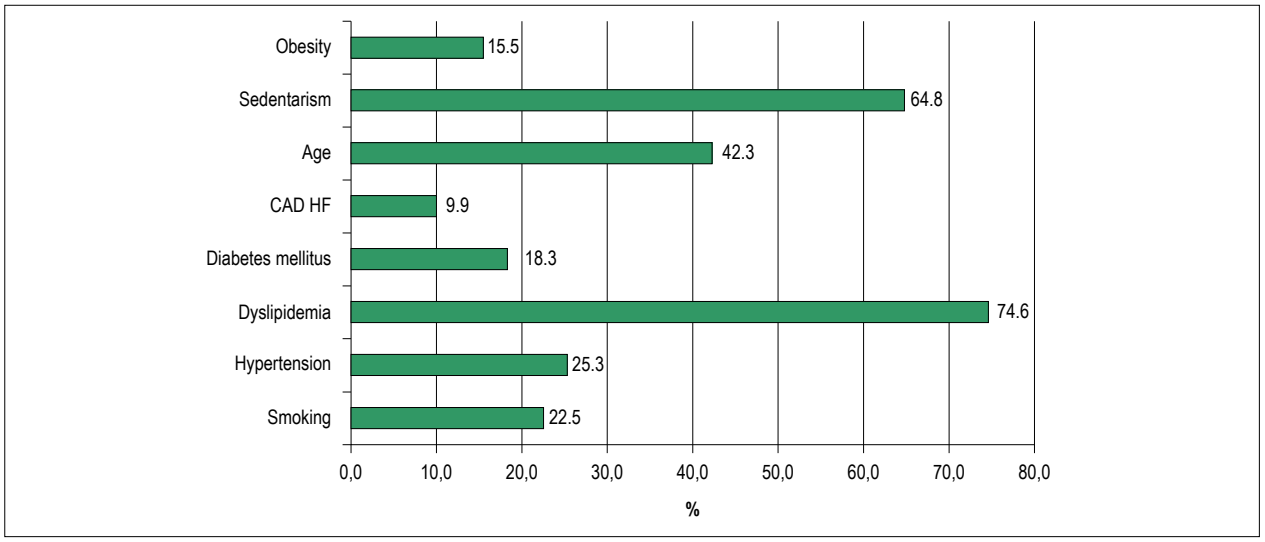

Figure 1 – *Cardiovascular risk factors in 71 HIV-positive patients.*

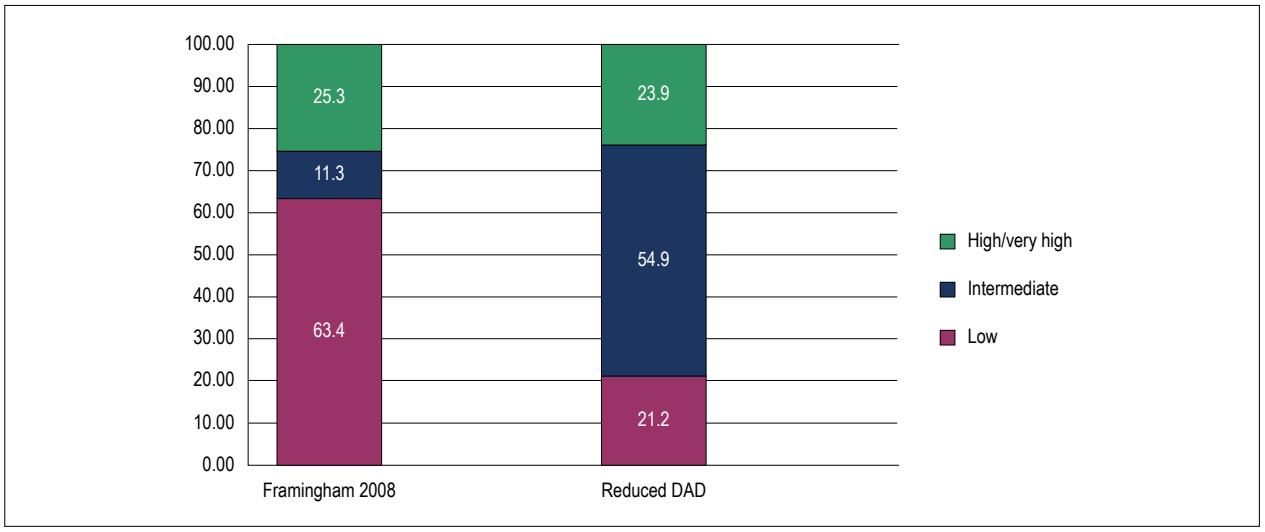

Figure 2 – *Cardiovascular risk rating in 71 HIV-positive patients according to Framingham 2008 and reduced DAD scores.*

the Framingham 2008 score and intermediate risk by the reduced DAD score, while the distribution of high risk was similar for both scores. Data from Nery et al.[14] showed most patients classified as low risk by both Framingham and DAD full scores (94% x 74.2%), respectively, and both scores had a much smaller number of patients classified as high risk (2.8% and 2.1%), respectively, than in our sample.[14]

Although these scores are not used to estimate the presence of subclinical atherosclerosis, data from Jericó et al.[16] show an increasing prevalence of subclinical carotid atherosclerosis according to cardiovascular risk category, with 26.6%, 35.3% and 76,5% for very low risk, low risk and moderate/high risk patients, respectively.[16] Similar results were found in this study, where a positive correlation between medium-intimal thickening and score value was reported. These data are important and suggest that many patients classified as low and intermediate risk could be reclassified and managed as high risk due to the presence of subclinical atherosclerosis.

According to a recent publication, the Framingham's score could underestimate cardiovascular risk in HIV-positive patients by showing a high prevalence of subclinical carotid atherosclerosis in patients sorted as low risk.[8] The same authors suggest that the use of DAD full score allows a better association between risk stratification and the presence of subclinical atherosclerosis, and that other tools such as the verification of medium-intimal thickening may bring new information that can reclassify patients and reinforce the taking of measures of greater impact to control cardiovascular risk factors.

Table 2 – Degree of agreement between cardiovascular risk scores in 71 HIV-positive patients.

	Low	Intermediate	High
Category Kappa	0.268	0.084	0.735
p-value of category Kappa	0.001	0.226	< 0.001
95%CI of category Kappa	0.11 a 0.427	-0.052 a 0.22	0.502 a 0.967

95%CI: 95% confidence interval.

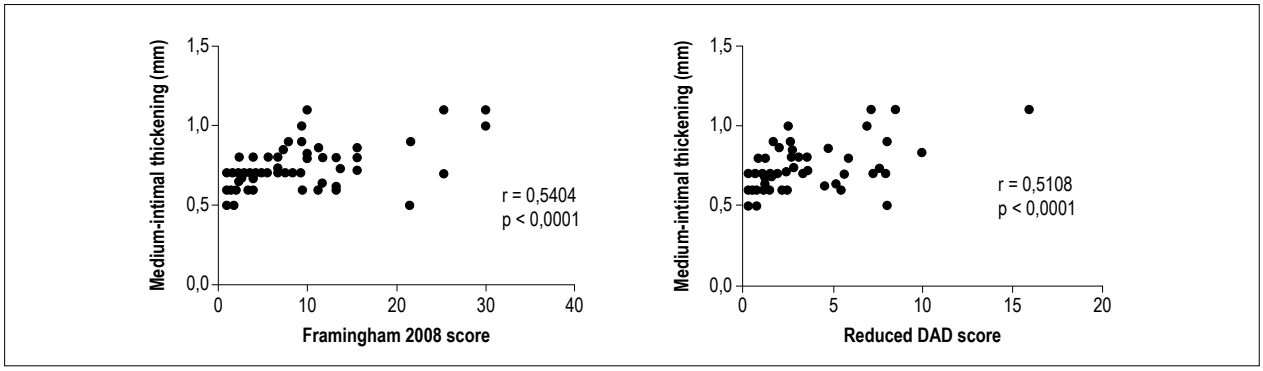

Figure 3 – *Correlation between medium-intimal thickening in 71 HIV-positive patients according to the Framingham 2008 and reduced DAD scores.*

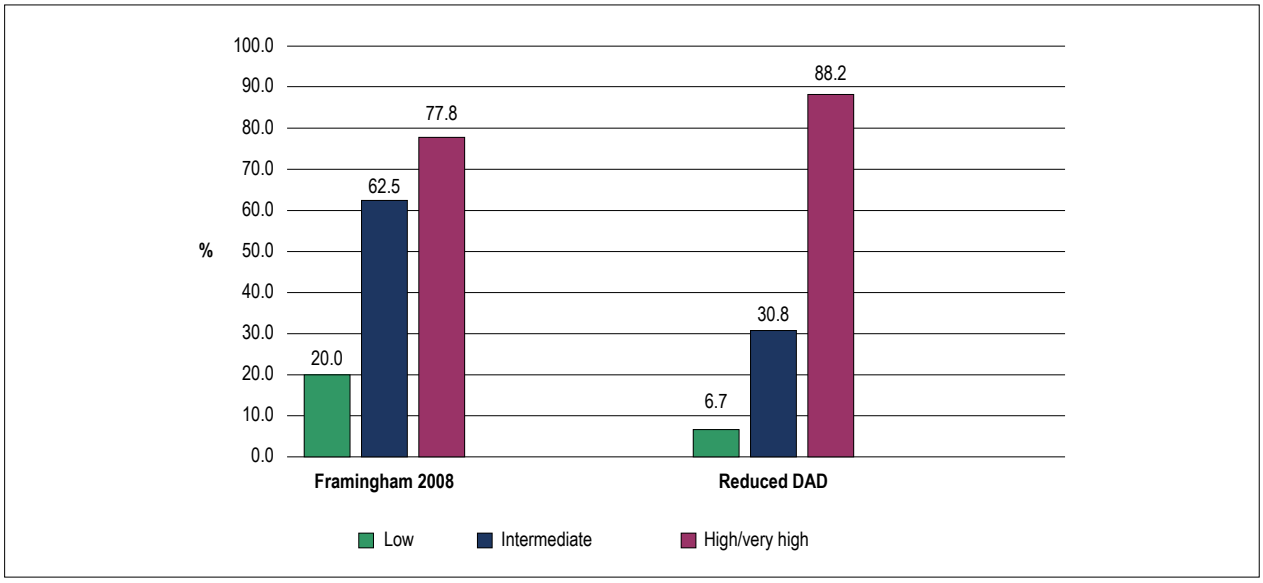

Figure 4 – *Frequency of subclinical atherosclerosis in 71 HIV-positive patients according to the Framingham 2008 and reduced DAD scores.*

In our study, aggravating factors for reclassifying the Framingham 2008 score were disregarded as some guidelines recommend, which led to a higher number of individuals in the low-risk category. The inclusion of aggravating factors could overestimate the risk in 10 years and lead to a 10-fold increase in the proportion of patients classified as intermediate risk (3.2% to 39.9%).[14]

The use of the Framingham and DAD scores in a recent study conducted with 997 HIV-positive patients concluded that the Framingham score would attribute to this population a greater cardiovascular risk than the DAD full score, and that this could lead to overtreatment of patients and increased risk.[17] Although the Framingham 2008 score underestimates the presence of subclinical atherosclerosis, in the reduced DAD score more than 50% of atherosclerosis patients are not classified as high-risk, suggesting that this score may also underestimate cardiovascular risk in HIV-positive patients. Another study evaluating 203 HIV-positive patients reported DAD score as having better performance than Framingham's, and showed that its accuracy increases when CD4 lymphocyte parameters and albumin levels are incorporated. However, the detection of subclinical atherosclerosis was underestimated by both scores.[18]

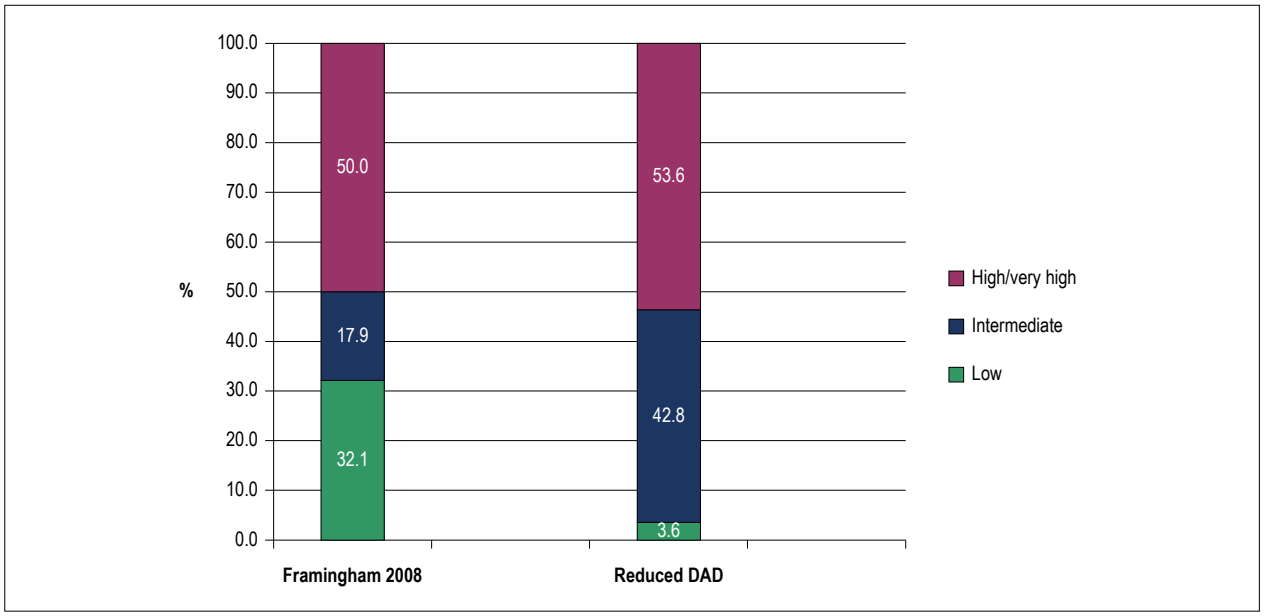

Figure 5 – *Classification of cardiovascular risk in 71 HIV-positive patients according to the Framingham 2008 and reduced DAD scores.*

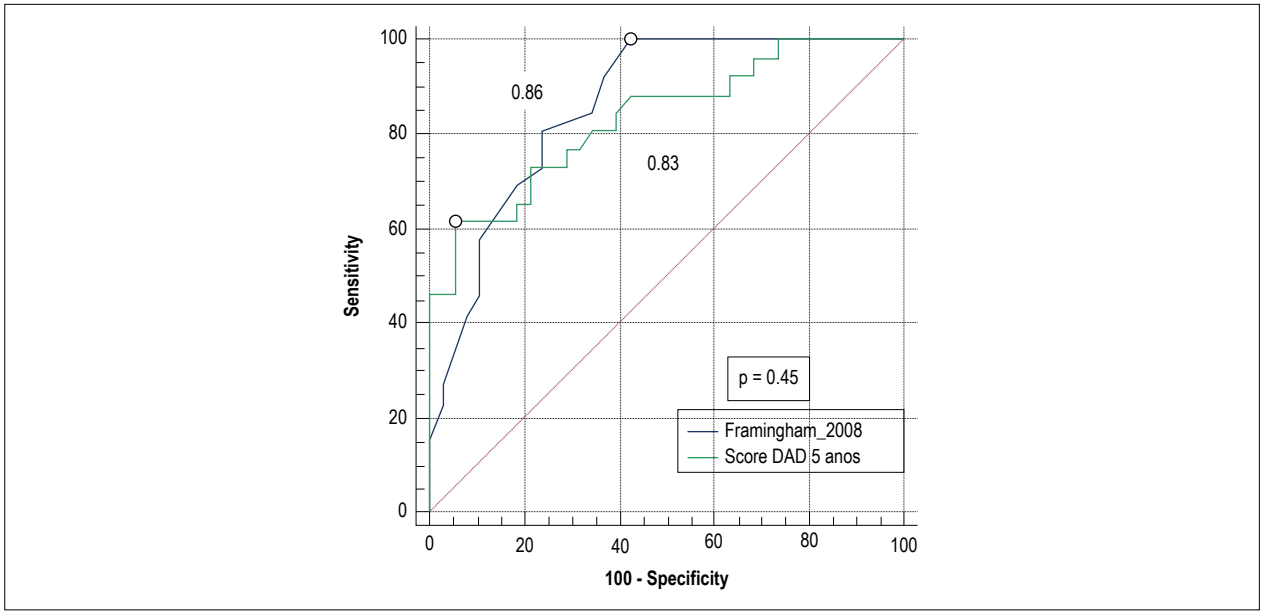

Figure 6 – *Comparison of ROC curves between Framingham 2008 and reduced DAD scores related to subclinical atherosclerosis (p = 0.46). Numbers represent the areas below the ROC curves. The circles represent the Youden Indexes of each score.*

Table 3 – Predictive accuracy of Framingham 2008 and reduced DAD scores relating to the presence of subclinical atherosclerosis

Subclinical atherosclerosis	Sensitivity (%)	Specificity (%)	C-Statistics
Framingham 2008 > 3.9	100	57.8	0.86 (0.75 - 0.93)
DAD score > 3.3	65.5	92.8	0.85 (0.73 - 0.91)

DAD: Data Collection on Adverse Effects of Anti-HIV Drugs.

To compare scores, a correlation was made between them and medium-intimal thickness, besides the calculation of degree of agreement between them, and ROC curve discrimination analysis. Scores were shown to be correlated with medium-intimal thickening. Kappa index was statistically significant and showed 49% of total agreement between scores, but substantially between high-risk patients. The intermediate risk category did not present statistically significant agreement and the low risk category presented low agreement. There was no statistically significant difference in the ROC curve discrimination analysis between scores. Importantly, these scores present differences in time and composition of type of predicted cardiovascular events. In addition, the Kappa coefficient may have limitations, and even low coefficients may show a good degree of agreement.[19]

In the present observational, cross-sectional study with a small and random sample, we performed risk stratification and the presence of subclinical atherosclerosis was assessed by carotid Doppler ultrasonography; however, the occurrence of clinical events was not evaluated. These data suggest that HIV-positive patients classified as intermediate risk by the Framingham 2008 and reduced DAD scores could be reclassified as high risk in up to 62.5% and 30.8% of cases, respectively, due to the presence of subclinical atherosclerosis detected by carotid Doppler ultrasonography. These results are relevant because high-risk patients demand more aggressive therapeutic goals and subclinical atherosclerosis could indicate the need for other classes of drugs such as platelet antiaggregants.

More appropriate risk stratification methods are highly desirable for this population, as this group, has risk factors inherent to chronic HIV infection itself in addition to increased risk of cardiovascular events, which leads to a systemic inflammatory process, and the use of ART increases the prevalence of metabolic syndrome. In addition to more accurate scores, new diagnostic tools or biomarkers may lead to stratification that allows better identification of high-risk patients. Thus, cardiovascular prevention measures can be reinforced not only by decrease in events, but also avoiding unnecessary use of medications that could cause adverse reactions and drug interactions.

Conclusion

Although this study shows a correlation between the Framingham 2008 and the reduced DAD scores and medium-intimal thickening, as well as high agreement between patients classified as high risk, we could not find a statistically significant difference between them by ROC curve discrimination analysis. In addition, the results suggest that HIV-positive patients sorted as intermediate risk by Framingham 2008 and reduced DAD scores could be reclassified as high risk in up to 65.5% and 30.8% of cases, respectively, due to the presence of subclinical atherosclerosis detected by carotid Doppler ultrasonography.

Author contributions

Conception and design of the research and Writing of the manuscript: Silva AG, Paulo RV, Silva-Vergara ML; Acquisition of data: Silva AG, Paulo RV; Analysis and interpretation of the data and Critical revision of the manuscript for intellectual content: Silva AG, Silva-Vergara ML; Statistical analysis: Silva AG.

Potential Conflict of Interest

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

Sources of Funding

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Study Association

This article is part of the thesis of master submitted by Achilles Gustavo Silva, from Universidade Federal do Triangulo Mineiro.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Universidade Federal do Triângulo Mineiro under the protocol number 1.464.324. 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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Estimating Cardiovascular Risk in HIV-Infected Patients

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Short Editorial related to the article: Subclinical Carotid Atherosclerosis and Reduced DAD Score for Cardiovascular Risk Stratification in HIV-Positive Patients

From the initial reports of HIV infections in 1981, substantial progress in the prevention, detection and treatment have led to a marked reduction in mortality. Among them, the use of highly active antiretroviral therapy (HAART) with the combination of multiple antiretroviral drugs acting in different phases of the viral cycle resulted in impressive reductions in transmission and infectious complications. This increase in survival led to a large and growing population of persons living with HIV (PLWH) as a chronic condition in a setting where other non-infectious complications became more common.

Among those novel conditions affecting PLWH, cardiovascular complications became the leading cause of morbidity and mortality, at least in countries with adequate access to care and widespread use of HAART.[1] The increase in cardiovascular risk in PLWH is multifactorial. First, studies suggest that PLWH are more likely to be diabetics and smokers.[2] Second, those individuals are more likely to have higher triglycerides and lower HDL-C, though LDL-C and total cholesterol were also reduced. It also seems possible that HIV infection is responsible for increases in blood pressure and glucose levels by different mechanisms.[3] However, considerable evidence supports the concept that traditional risk factors do not fully account for the higher cardiovascular risk in those individuals,[4] as the changes in the cardiovascular system in PWLH is multifactorial and at least partially mediated by inflammation and immune activation, leading to endothelial dysfunction, changes in vascular elasticity, coagulation.[5]

Moreover, HIV treatment with HAART may also be responsible for a considerable increase in cardiovascular risk in this population. Previous studies suggest that longer HAART duration is associated with hypertension and lipid abnormalities, particularly for first-generation protease inhibitors and non-nucleoside reverse transcriptase inhibitors.

With such abundant evidence that the spectrum of cardiovascular risk in PLWH is not similar to the usual primary prevention patient, it should come as no surprise that the traditional risk calculators such as the Framingham risk score,[6] do not perform as expected in this population. In order to address this issue, investigators from the data-collection on adverse effects of anti-HIV drugs (D:A:D) study derived additional risk equations including HIV-related aspects such as CD4 count and type of HAART drug use to improve risk prediction in this population.[4] Since retrieval of information related to prior HAART therapies might be challenging in real practice, an updated reduced version of the D:A:D score restricting the input related to HIV to CD4 levels has but recently published.

In the present issue of the ABC Cardiol, Silva et al.,[7] further, evaluate the performance of this novel reduced D:A:D score in a Brazilian population comparing it to the traditional Framingham risk score in 71 PLWH who underwent carotid intima-media thickness (cIMT) for the evaluation of subclinical atherosclerosis.[7] The authors demonstrate that both scores correlate well with the cIMT. However, individuals with low and intermediated risk in the Framingham risk score were more likely to have documented subclinical atherosclerosis in cIMT (20% vs. 6.7% in low risk and 62.5% vs. 30.8% for intermediate risk), indicating that the use of the Framingham risk scores results in underestimation of the prevalence of subclinical disease in low and intermediate risk individuals. Those findings have important implications for practice as a substantial proportion of true high-risk individuals among PLWH would remain untreated or undertreated if the cardiovascular risk is estimated only used traditional scores such as Framingham. Although the current data cannot be interpreted as a complete validation of the D:A:D score in a Brazilian population, it certainly provides evidence to support that the concept that PLWH are of higher risk for atherosclerosis and the estimation of risk in this population is more adequately performed using the D:A:D score than other scores developed for the general population.

Keywords

Carotid Artery Diseases; Acquired Immunodeficiency Syndrome/complications; HIV; Antiretroviral Therapy, Highly Active; Risk Factors.

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Euterpe Oleracea Mart. (*Açaí*) Reduces Oxidative Stress and Improves Energetic Metabolism in Myocardial Ischemia-Reperfusion Injury in Rats

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Abstract

Background: Euterpe oleracea Mart. (*açaí*) is a fruit with high antioxidant capacity and could be an adjuvant strategy to attenuate ischemia-reperfusion injury.

Objective: To evaluate the influence of açaí in global ischemia-reperfusion model in rats.

Methods: Wistar rats were assigned to 2 groups: Control (C: receiving standard chow; n = 9) and *Açaí* (A: receiving standard chow supplemented with 5% açaí; n = 10). After six weeks, the animals were subjected to the global ischemia-reperfusion protocol and an isolated heart study to evaluate left ventricular function. Level of significance adopted: 5%.

Results: There was no difference between the groups in initial body weight, final body weight and daily feed intake. Group A presented lower lipid hydroperoxide myocardial concentration and higher catalase activity, superoxide dismutase and glutathione peroxidase than group C. We also observed increased myocardial activity of β-hydroxyacyl coenzyme-A dehydrogenase, pyruvate dehydrogenase, citrate synthase, complex I, complex II and ATP synthase in the A group as well as lower activity of the lactate dehydrogenase and phosphofructokinase enzymes. The systolic function was similar between the groups, and the A group presented poorer diastolic function than the C group. We did not observe any difference between the groups in relation to myocardial infarction area, total and phosphorylated NF-κB, total and acetylated FOXO1, SIRT1 and Nrf-2 protein expression.

Conclusion: despite improving energy metabolism and attenuating oxidative stress, açai supplementation did not decrease the infarcted area or improve left ventricular function in the global ischemia-reperfusion model. (Arq Bras Cardiol. 2020; 114(1):78-86)

Keywords: Euterpe Olerácea; Oxidative Stress; Energy Metabolism; Chemical Reactions; Myocardial Ischemia; Myocardial Reperfusion Injury; Rats.

Introduction

Although the mortality attributed to ischemic heart disease is declining in some countries, it still presents high morbidity, decreasing the quality of life and increasing healthcare spending.[1] Cardiac ischemic events may be due to partial or total tissue ischemia, with reversible or irreversible myocardial dysfunction and cell death. Ischemic periods of more than 20 minutes cause irreversible damage of the cardiomyocytes and inability to functionally recover, even with the restoration of blood flow.[2,3]

During ischemia, to meet the myocardial energy demand, cellular ATP is generated by glycolysis, leading to intracellular pH reduction.[1,4] In parallel, reduced ATP levels interrupt important active pumps in ionic homeostasis, which results in overloaded cytosolic Na^+ and Ca^{2+}, making cell repolarization unfeasible and leading to myocardial dysfunction. In addition, it is possible to observe elevated Ca^{2+} levels in cytosol, which activate enzymes (phospholipases, proteases, endonucleases and ATPases) associated with lipid peroxidation, production of reactive oxygen species (ROS), dysfunction of contractile proteins, and loss of cellular function.[4]

Although necessary to reverse ischemia, the restoration of blood flow may ultimately be more harmful than the ischemic process itself.[1,4,5] During reperfusion, ischemia damages are worsened due to an additional discharge of ROS generated in the mitochondria by the restoration of oxygen flow.[5,6] To improve myocardial protection during procedures involving reperfusion injury, attention has been focused on the research of drugs and substances that can prevent cardiac cell damage.[7] In this context, we observe great interest in the antioxidant action of natural products such as *açaí*.[8]

Açaí (Euterpe oleracea Mart.) is a typical northern Brazilian fruit recently made popular for its high antioxidant capacity related to the presence of phenolic acids, flavonoids and anthocyanins.[9-12] *Açaí* pulp compounds consist of 31% flavonoids, 23% phenolic compounds, 11% lignoids and 9% anthocyanins.[13] The main anthocyanins in *açaí* pulp are

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cyanidin-3-O-glucoside and cyanidin-3-O-rutinoside, which are responsible for the purple color of the fruit.[13] Ferulic acid, p-hydroxybenzoic, gallic, protocatechuic, ellagic, vanillic, p-coumaric acids, and ellagic acid glycoside are the most abundant phenolic compounds.[13,14]

In experimental models, *açaí* supplementation reduced pulmonary[9] and cerebral oxidative stress,[15] reduced ROS formation in polymorphonuclear cells,[11,16] decreased DNA damage, and presented anti-carcinogenic activity in bladder cancer.[10] Oral *açaí* administration was able to attenuate hypertrophy and left ventricle dysfunction in rats subjected to myocardial infarction,[17] but no studies on the effect of *açaí* in the global ischemia model or its effect on reperfusion injury were found.

The aim of our study was to evaluate the infarct area, left ventricle function, oxidative stress and the activity of enzymes involved in myocardial energy metabolism in the global ischemia-reperfusion model in rats after *açaí* supplementation.

Method

Study design

The experimental protocol of this study was approved by the Ethical Committee on the Use of Animals of the Botucatu Medical School (CEUA 1111/2014), and it is in accordance with the norms established by the National Council of Control of Animal Experimentation.

Twenty two-months-old male Wistar rats weighing 250-300 g were assigned to two groups: control (C; n = 10) and *açaí* (A; n = 10). Sample size was determined by convenience based on previous studies that used the same experimental model. Animals were kept in an environment with controlled temperature (23°C) and a 12-hour light-dark cycle in individual boxes to control feed intake. Group C received a standard chow, and the group A a standard one supplemented with 5% *açaí*[18] for six weeks. After the supplementation period, all animals were anesthetized with sodium thiopental (80 mg/kg, IP) to induce the global ischemia-reperfusion protocol, after which the heart was dissected. A sectional cut of the left ventricle was made to determine the infarct area, and the rest was stored in a freezer at -80°C for further analysis. One rat from the control group was lost due to technical problems during the ischemia-reperfusion protocol and the study was concluded with 9 rats in the control group and 10 rats in the *açaí* one.

Preparation of the chow supplemented with açaí

Commercialized *açaí* pulp (Icefruit®) was defrosted and incorporated into crushed Nuvilab chow (Nuvital®). After homogenization, the chow was pelleted again, dried at 32°C and stored in a freezer at -20°C until the moment of use. The dose used in the study was 5%, as proposed by Fragoso et al.[18]

Induction of global ischemia, reperfusion and evaluation of cardiac function

The rats were anesthetized with thiopental sodium (80 mg/kg, IP), heparinized (2,000 IU, IP) and subjected to positive pressure ventilation with 100% oxygen. Then, median sternotomy was performed, and the ascending aorta was cannulated to start retrograde perfusion with a modified Krebs-Henseleit solution (NaCl 115 mmol/L, KCl 5.4 mmol/L, $CaCl_2$ 1.25 mmol/L; $MgSO_4$ 1.2 mmol/L, NaH_2PO_4 1.15 mmol/L, $NaHCO_3$ 25 mmol/L, 11 mmol/L glucose, and 8 mmol/L mannitol). The hearts were transferred to a Langendorff apparatus (Model 830 Hugo Sachs Eletronik, Germany) with perfusion pressure at 75 mmHg. The nutrient solution was constantly oxygenated with a gas mixture of 95% O_2 and 5% CO_2, and the temperature was maintained at 37°C. A pacemaker was used to maintain controlled heart rate (250 bpm).

Left atrium was removed, and a latex balloon was inserted into the left ventricular cavity. The balloon was coupled to a pressure transducer and to a syringe, which allowed variation in the volume of the balloon. After 10 minutes of stabilization, the hearts were subjected to a 30-minute period of global ischemia followed by 30 minutes of reperfusion.[3] Global ischemia was induced by completely stopping the flow of Krebs-Henseleit solution to the heart.

After ischemia and reperfusion periods, an evaluation of left ventricular function was performed. The volume inside the balloon was progressively increased to obtain left ventricular diastolic pressure variation of 0 to 25 mmHg. In addition, for each increase in volume to the balloon, the diastolic and systolic pressure, the maximum left ventricular pressure development rate (+dP/dt) and the maximum left ventricular pressure decrease rate (-dP/dt) were recorded. Diastolic pressure-volume curves were constructed.

Analysis of infarcted myocardial area

A cross-sectional cut of the left ventricle (LV) was made – 5 mm from the apex, with a thickness of 2 mm – and incubated in phosphate buffer with 7.4 pH and 1% triphenyltetrazolium chloride (Sigma Aldrich) for 30 minutes at 37°C. After that, the sections were incubated in a 10% formaldehyde solution overnight. The ventricle sections were positioned between two glass slides and scanned to obtain the images.

Infarct area was measured through the ImageJ program by planimetry and expressed as the percentage of infarcted over total areas. In live cells the dye is reduced by dehydrogenases and appears with a dark red coloration. Dead cells lacking the enzymes are not stained and remain pale in color.[19]

Analysis of antioxidant enzymes and lipid hydroperoxide

Samples of approximately 100 mg of LV tissue were homogenized in a sodium phosphate buffer (0.01 M) with a pH of 7.4 and centrifuged for 30 minutes at -4°C; the total proteins in the samples were quantified by Bradford method. The activities of glutathione peroxidase (GSH-Px), superoxide dismutase (SOD) and catalase in the cardiac tissue were determined by spectrophotometry according to previously described methods.[20,21] Lipid hydroperoxide concentration in the cardiac tissue was measured by the oxidation of ammoniacal ferrous sulfate and determined by spectrophotometry.[22]

Evaluation of energy metabolism

Samples of approximately 100 mg of LV tissue were homogenized in a sodium phosphate buffer (0.1 M, pH 7.0) and centrifuged. The supernatant was used to determine protein concentration and activity of the enzymes β-hydroxyacyl coenzyme A dehydrogenase, phosphofructokinase, lactate dehydrogenase, pyruvate dehydrogenase and citrate synthase.[23] The pellet was re-suspended with sodium phosphate buffer (0.1 M) containing 250 mM sucrose and 2 mM EDTA and used to determine the activity of enzymatic complexes of the electron transport chain (complexes I, II and ATP synthase).[24] Readings were performed on a microplate reader with controlGen5 2.0 software, and all reagents were obtained from the Sigma-Aldrich laboratory (Saint Louis, USA).

Western blot

LV samples (80 mg) were homogenized with 1 ml of radio immune precipitation assay extraction buffer (RIPA), centrifuged, and the supernatant was collected. The protein in the samples was quantified by the Bradford method; and the samples were used to determine total and phosphorylated nuclear factor signaling pathway κB (NF-κB), sirtuin 1 (SIRT1), and forkhead box protein O1 (FOXO1) protein expression. To determine the nuclear factor erithroid 2 (Nrf-2), LV samples were extracted with Nuclear Extraction Buffer.[25] All samples were diluted in Laemmli buffer.

Protein electrophoresis was performed at 4°C on an 8 to 10% polyacrylamide gel (Mini-Protean 3 Electrophoresis Cell System, Bio-Rad, Hercules, USA). After electrophoresis, the gels were transferred to nitrocellulose membranes (Mini Trans-Blot system, Bio-Rad, Hercules, USA) in a wet transfer system followed by blocking with 5% skim milk powder solution. The membrane was washed, and primary antibodies were added (Santa Cruz Biotechnology, Inc., Europe). After overnight incubation, the membrane was washed with basal solution, and secondary antibodies were added (Santa Cruz Biotechnology, Inc., Europe). After 2 hours, the membrane was washed again in basal solution.

Immunodetection was performed with the chemiluminescence method using the SuperSignal West Pico Chemiluminescent Substrate Kit (ThermoScientific, USA). Photo documentation by ImageQuant LAS 4000 (General Eletrikcs) was used to generate images, which were analyzed in Gel-Pro 32 (Media Cybernetics, Rockville, USA). The results obtained for the target proteins were normalized by glyceraldehyde-3-phosphate dehydrogenase (GAPDH) expression, and the same control animal was included in all electrophoreses for standardization between the experiments.

Statistical analysis

Values obtained are presented as the means ± standard deviation (variables with normal distribution) or median and 25 and 75% quartile (variables with non-normal distribution). Normality was verified by the Kolmogorov–Smirnov test. Comparisons between the groups were performed with a non-pared Student's *t*-test (variables with normal distribution) or Mann-Whitney test (variables with non-normal distribution). Statistical analysis was carried out by use of the SigmaStat software, considering significance level at 5% for all analyses.

Results

General features

The animals' initial and final body weight did not differ between groups. Additionally, the left and right ventricles, liver and lung weights were similar between groups. Daily food intake was approximately 26 g for both groups (Table 1).

Infarcted myocardial area

We observed no difference in the area of myocardial infarction between groups A and C, as observed in Figure 1.

Oxidative stress and myocardial energy metabolism

Açaí supplementation promoted lower myocardial lipid hydroperoxide concentration, and greater activity of the enzymes catalase, SOD and GSH-Px in the myocardium of these rats was observed (Table 2).

Regarding myocardium energy metabolism, *açaí* pulp supplementation promoted lower activity of the enzymes lactate dehydrogenase and phosphofructokinase and higher activity of the enzymes β-hydroxyacyl-coenzyme A dehydrogenase, citrate synthase and pyruvate dehydrogenase. In addition, we observed higher activity of complex I, complex II and ATP synthase in the group supplemented with *açaí* (Table 3).

Table 1 – Morphological variables and feed intake in rats submitted to global myocardial ischemia-reperfusion

	C (n = 9)	A (n = 10)	p-value
Initial BW (g)	274 ± 15	281 ± 11	0.274
Final BW (g)	468 ± 29	448 ± 40	0.225
LV weight (g)	1.03 ± 0.09	1.02 ± 0.07	0.934
RV weight (g)	0.30 ± 0.03	0.29 ± 0.03	0.431
Liver weight (g)	14.4 ± 1.6	12.9 ± 2.6	0.154
Lung weight (g)	1.62 ± 0.03	1.54 ± 0.18	0.359
Daily chow intake (g)	26.1 ± 2.2	26.6 ± 1.8	0.246

C: control group; A: açaí group; BW: body weight; LV: left ventricle; RV: right ventricle. Values are expressed as the means ± standard deviation; p-value: t test.

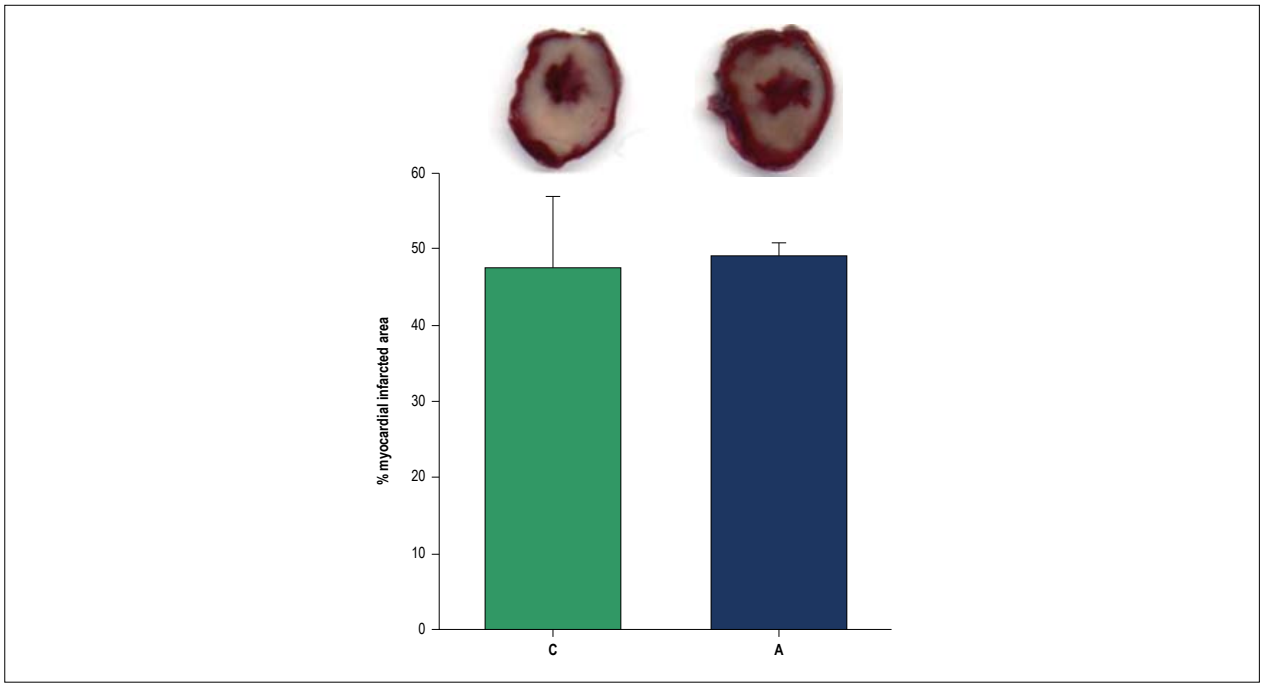

Figure 1 – *Myocardial infarcted area after global myocardial ischemia-reperfusion. Figure shows left ventricles sections stained with triphenyltetrazolium chloride 1%. White area represents the infarcted myocardium. C: control group; A: açaí group; There is no difference between groups (p = 0.710).*

Table 2 – Myocardial oxidative stress marker and antioxidant enzymes activity after global ischemia-reperfusion

	C (n = 9)	A (n = 10)	p-value
LH (nmol/g tissue)	330 ± 33	208 ± 22	< 0.001
CAT (µmol/g of tissue)	58.5 ± 6.4	70.0 ± 8.9	0.005
SOD (nmol/mg of protein)	5.7 ± 0.4	8.1 ± 0.7	< 0.001
GSH-Px (nmol/mg of tissue)	20.2 ± 3.3	32.8 ± 4.7	< 0.001

C: control group; A: açaí group; LH: lipid hydroperoxide; CAT: catalase; SOD superoxide dismutase; GSH-Px: glutathione peroxidase. Values are expressed as the means ± standard deviation; p-value: t test.

Western blot

The expression of the proteins involved in the regulation of the oxidative stress pathway is shown in Figure 2. There was no difference in the expression of total and phosphorylated NF-κB, total and acetylated FOXO1, SIRT1 and Nrf-2. Also, no differences were observed in the NF-kB phosphorylated/total or the FOXO1 acetylated/total ratios.

Isolated heart study

There was no difference between the groups regarding the initial volume of the balloon, the maximum systolic pressure reached, or +dP/dt, which represents systolic function. Group A presented worse –dP/dt than C, signifying impairment of the diastolic function in the rats that received *açaí* supplementation. The areas under the curves in the diastolic pressure-volume relationship did not differ between groups (Figure 3).

Discussion

Myocardial ischemia-reperfusion injury is one of the leading causes of death worldwide, and it remains a situation for which current clinical therapies are surprisingly deficient.[26] Irreversible myocardial injury progresses with increased duration of ischemia; therefore, rapid restoration of blood flow to the ischemic area is essential to save the viable myocardium.[1] Reperfusion, however, can induce death of cardiomyocytes regardless of the ischemic episode by a process known as reperfusion injury.[1,5,27] Decreased reperfusion injury is a key target in the battle to preserve cardiac function in patients with acute myocardial infarction.

During ischemia-reperfusion, changes such as the release of cytokines, interaction between leukocytes and endothelial cells and production of reactive nitrogen/oxygen species and free radicals (ERs)[27] occur in cellular metabolism, which can lead to oxidative damage. ERs are generated from various

Table 3 – Myocardial activity of enzymes related to energy metabolism after global ischemia-reperfusion protocol

	C (n= 9)	A (n=10)	p-value
β-hydroxyacyl-CoA dehydrogenase (nmoL/mg protein)	19.8 ± 3.3	49.8 ± 7.0	< 0.001
Phosphofructokinase (nmoL/g tissue)	181 (160 – 228)	73 (67 – 82)	< 0.001
Lactate dehydrogenase (nmoL/mg protein)	147 (145 – 167)	70 (65 - 77)	< 0.001
Pyruvate dehydrogenase (nmoL/g tissue)	114 ± 11	176 ± 19	< 0.001
Citrate synthase (nmol/mg protein)	30 (30 – 37)	100 (81 – 117)	< 0.001
Complex I (nmol/mg protein)	3.7 ± 1.0	8.0 ± 1.7	< 0.001
Complex II (nmol/mg protein)	2.1 ± 0.6	3.5 ± 0.5	< 0.001
ATP synthase (nmol/mg protein)	22.0 ± 3.9	44.5 ± 6.6	< 0.001

C: control group; A: açaí group. Values are expressed as the means ± standard deviation or median and 1st and 3rd quartile; p-value: t test or Mann-Whitney test.

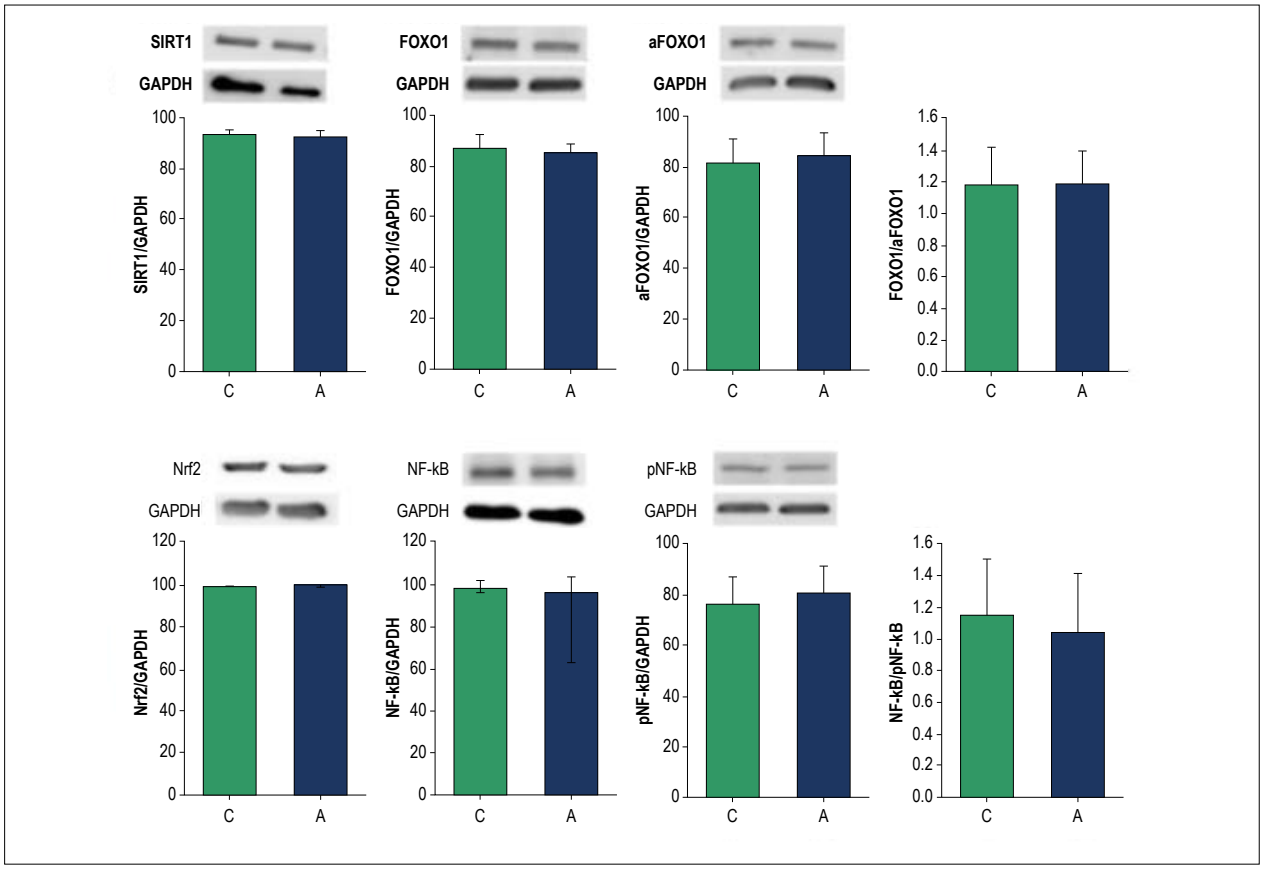

Figure 2 – *Protein expression evaluated by Western blot. C: control group; A: açaí group; SIRT1: silent information regulator 1; GAPDH: glyceraldehyde-3-phosphate dehydrogenase; FOXO1: forkhead protein 1; aFOXO1: acetylated forkhead protein 1; Nrf-2: nuclear factor erythroid 2; NF-kB: nuclear factor kappa B; pNF-kB: phosphorylated nuclear factor kappa B. All proteins expressions were normalized by GAPDH. There are no differences between groups in protein expression (p > 0.05).*

sources, and the energetic metabolism, more precisely the mitochondrial electron transport chain (ETC), is one of the most important generators of these radicals.[5]

The continuous production of ERs during metabolic processes is regulated by an antioxidant defense system, which limits the intracellular levels and controls the occurrence of cellular damage. The antioxidant defense system can be enzymatic and non-enzymatic.[6,7,28] Non-enzymatic defense system includes antioxidant compounds of dietary origin, like vitamins, mineral and phenolic compounds. Flavonoids and other compounds present in *açaí* can act as non-enzymatic antioxidant, inactivating reactive species.[29]

During ischemia, there is an increase in nicotinamide adenine dinucleotide oxidase, nitric oxide synthase, xanthine oxidase, cytochrome P450 and cyclooxygenase,[8,30] which may result in increased ER generation; likewise, ischemia is associated with a decrease in different antioxidant enzymes. All these changes may result in oxidative stress. In this study,

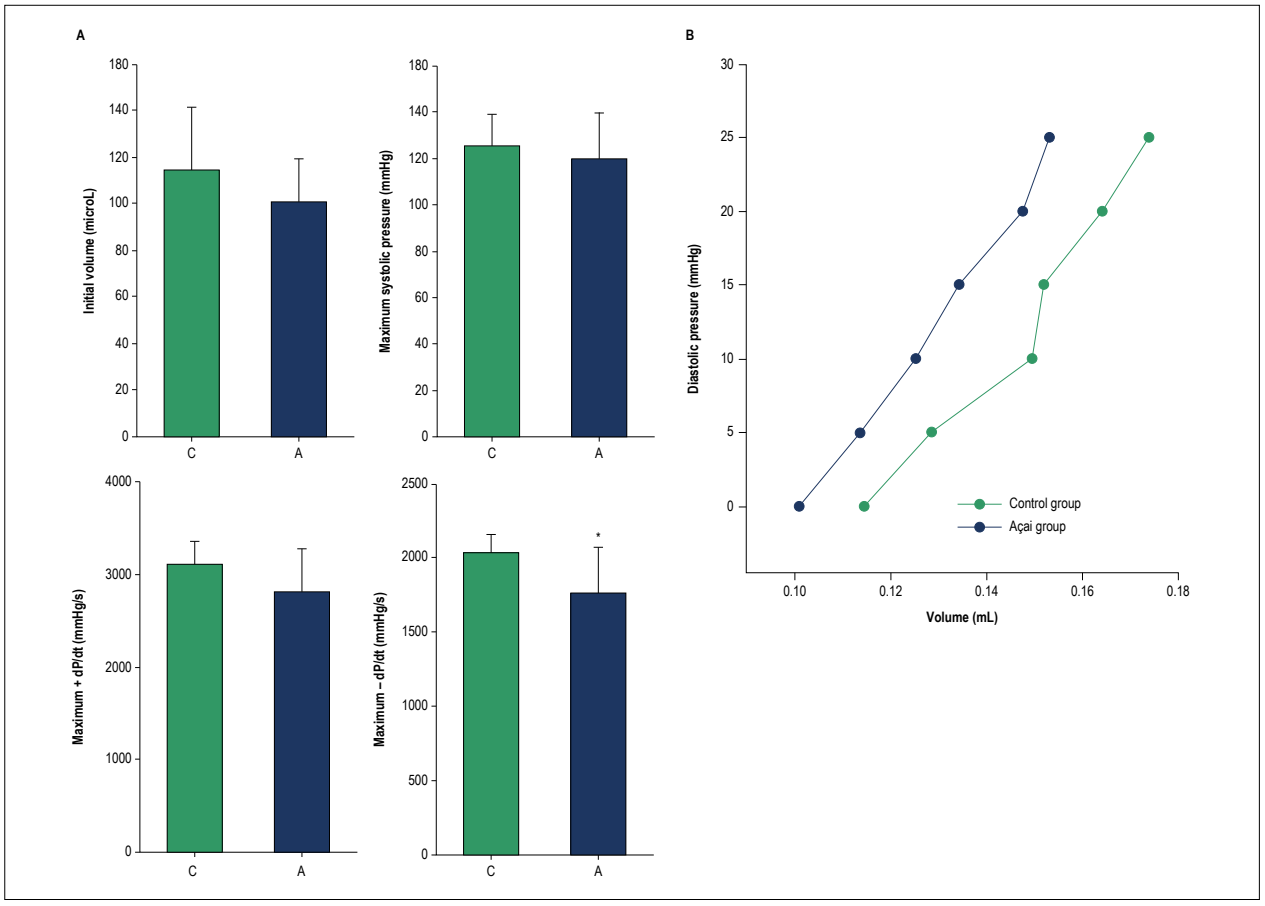

Figure 3 – *Isolated heart study after global myocardial ischemia-reperfusion. Panel A: C: control group; A: açaí group. Initial volume represents the volume inside the balloon when diastolic pressure was zero; +dP/dt: left ventricular pressure development rate; -dP/dt: left ventricular pressure decrease rate; *different from group C (p = 0.025). Panel B: Relationship between diastolic pressure and volume. The area under the curve and inclination were similar between the groups.*

group A presented higher antioxidants enzymes activity in addition to lower concentration of myocardial lipid hydroperoxide. Lipid hydroperoxide is a marker of oxidative damage and is originated from the oxidative lesion of membrane lipids. Membrane lesion can lead to disturbances in permeability, alteration of the ionic flow and DNA, and impairment of extracellular matrix components.[31]

In relation to the proteins involved in the regulation of the oxidative stress pathway, the mechanisms by which phenolic dietary compounds act in the prevention of degenerative pathologies have been partially studied. The complex interactions between these dietary molecules and their molecular targets activate signaling pathways of the cellular response, including the NF-κB, Nrf2, SIRT1, and FOXO1.[32-34]

NF-κB is considered an important transcriptional factor related to oxidative stress. *Açaí* treatment inhibited NF-kB activation in astrocytes cell culture,[35,36] inhibited NF-kB phosphorylation in microglial cells[37] and down-regulated gene expression of NF-kB in colon myofibroblasts cell culture.[38] Similarly, Nrf2 is an important regulator of antioxidant enzymes production. In response to oxidative stress, Nrf2 dissociates from the Keap1 protein and migrates to the cell nucleus, where it stimulates the production of antioxidant enzymes.[39] Myocardial ischemia promotes increased protein expression of Nrf2[40] and the effect of *açaí* on Nrf2 expression was verified in an astrocyte culture study in which the fruit reduced the protein expression of Nrf2.[41] However, in another study, also with astrocyte culture, *açaí* administration increased Nrf2 expression,[36] showing that the effects of *açaí* on Nrf2 are not completely understood.

Another cellular balance regulator is the SIRT1 protein, which can act on apoptosis, mitochondrial biogenesis, inflammation, glucose and lipid metabolism, autophagy and adaptations to cellular stress through the deacetylation of target proteins such as NF-kB and FOXO1. When acetylated by SIRT1, FOXO1 leads to increased expression of gluconeogenic genes.[33] Increased transcriptional activity of FOXO1 also increases the gene expression of catalase and superoxide dismutase.[34] To the best of our knowledge, there are no studies that evaluated the effect of açai on FOXO1 and SIRT1 protein expression.

In the normal adult heart, approximately 95% of ATP production is derived from mitochondrial oxidative phosphorylation. The adult heart normally obtains 50–70% of its ATP from fatty acid β-oxidation instead of glucose oxidation.[42] The flavin adenine dinucleotide and nicotinamide

adenine dinucleotide produced during fatty acid oxidation are used in mitochondrial ATP synthesis via oxidative phosphorylation.[43] This is critically dependent on the maintenance of an electrochemical proton gradient across the inner mitochondrial membrane generated by the extrusion of protons from the matrix to the intermembrane space by complexes I, III and IV, which form the ETC.[44]

In our study, *açaí* supplementation led to higher activity of β-hydroxyacyl CoA-dehydrogenase and citrate synthase enzymes, which can characterize higher fatty acid oxidation. Moreover, there was lower activity of phosphofructokinase, the enzyme for glycolysis. This shows that açai supplementation altered the substrate selection for mitochondrial oxidation in reperfusion from glucose to fatty acids, maintaining energy metabolism closer to a physiological situation, as showed previously in an experimental model of renal ischemia-reperfusion.[45] Additionally, *açaí* supplementation increased the activity of complexes I, II and ATP synthase by protecting the damage to mitochondrial complexes. However, fatty acid oxidation decreases the metabolic efficiency of injured hearts.

Interestingly, *açaí* pulp is composed predominantly by lipids that correspond to 48%.[46] Offering more lipids could contribute to increased β-hydroxyacyl CoA-dehydrogenase activity in the treated *açaí* group. This pattern was observed in the experimental myocardial infarction model that administered a chow rich in lipids.[47]

Regarding the infarcted area, as expected for the 30-minute period of ischemia, we observed a large infarcted area in our study, approximately 50% in both groups. Previously, supplementation of a diet rich in anthocyanins in an experimental model of ischemia-reperfusion decreased the myocardial infarcted area.[48] However, in the present study, *açaí* supplementation did not reduce infarct size.

Large infarctions usually present with important left ventricular dysfunction resulting from the impairment of cellular processes and changes in cardiac morphology. Increased oxidative stress compromises the plasma membrane permeability of myocytes, the activity of ionic pumps in the plasma membrane and in the sarcoplasmic reticulum, and intracellular calcium transit, compromising both systole and diastole.[7] It would be expected that the attenuation of oxidative stress would be followed by an improvement in left ventricular function, as showed in different myocardial damage models.[25,49,50] However, this study evidenced that the administration of *açaí* worsened the diastolic function after cardiac ischemia-reperfusion. This leads us to infer that the ventricular dysfunction observed in this model depends on mechanisms other than oxidative damage. Curiously, a study performed to investigate the effect of anthocyanin extract in global rat heart ischemia-reperfusion suggests that anthocyanin was cardioprotective in low doses and could be cardiotoxic in high ones.[51]

Additionally, the change in energetic metabolism that occurs in stress situations has a protective role in the myocardium.[42] The fact that açai supplementation prevents the use of glucose and favors the maintenance of myocardial metabolism close to normal may have negatively interfered with this adaptive protective mechanism.

Whereas ischemia induces morphological and functional alterations and reperfusion injury can exacerbate these features, the discovery of new drugs, substances or strategies that can minimize cardiac damage is essential. The quantity of *açaí* that rats took was equivalent to 600 mg for a 60 kg human,[52] which is feasible human *açaí* ingestion. Therefore, *açaí* could be a potential strategy to attenuate ischemia-reperfusion injury in clinical scenario.

However, there are some limitations that difficult the translational impact of these results. First, rats share several metabolic pathways with humans, but the organisms are quite different. Second, in this study we evaluated a global myocardial ischemia that is not the routine in clinical practice. The ischemic process in humans is the result of a long inflammatory process that can modulate completely different metabolic pathways from our model.[53]

Conclusion

Açaí supplementation did not decrease the infarcted area nor improve the left ventricular function in the global ischemia-reperfusion model despite improving cardiac energy metabolism and attenuating myocardial oxidative stress, suggesting that these mechanisms may not be the main determinants of the worsened diastolic left ventricular function observed after ischemia and reperfusion with *açaí* supplementation.

Author contributions

Conception and design of the research: Zornoff L, Paiva SAR, Polegato BF; Acquisition of data: Alegre P, Mathias L, Lourenço MA, Gonçalves A, Fernandes AA; Analysis and interpretation of the data: Alegre P, Santos PP, Gaiolla PSA, Minicucci MF, Zornoff L, Paiva SAR, Polegato BF; Statistical analysis: Minicucci MF, Paiva SAR, Polegato BF; Writing of the manuscript: Alegre P, Santos PP, Polegato BF; Critical revision of the manuscript for intellectual content: Alegre P, Mathias L, Lourenço MA, Santos PP, Gonçalves A, Fernandes AA, Gaiolla PSA, Minicucci MF, Zornoff L, Paiva SAR, Polegato BF.

Potential Conflict of Interest

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

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Ethics approval and consent to participate

This study was approved by the Animal Ethics Committee of the Faculdade de Medicina de Botucatu under the protocol number 1111/2014. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013.

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Antioxidant Effects of *Euterpe Oleracea Mart.* (Açai) on Myocardial Ischemia-Reperfusion Injury in Rats: Would it Represent a Good Way To Follow?

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Short editorial related to the article: Euterpe Oleracea Mart. *(Açaí) Reduces xidative Stress and Improves Energetic Metabolism in Myocardial Ischemia-Reperfusion Injury in Rats*

Abrupt occlusion of an epicardial coronary artery may result in acute myocardial infarction with elevation of the ST segment as the myocardium underwent an ischemic process.[1] This promotes damage to the cardiomyocytes, mainly due to metabolic disturbances in the ATP generation with subsequent cell death and myocardial necrosis. Furthermore, reduced levels of intracellular ATP leads to an overload of cytosolic Ca^{2+} and Na^{+} concentrations and heart function impairment.[2] It would be expected that restoration of blood flow to the ischemic area in the myocardium to minimize the injury, but reperfusion may also induce additional damage to the cardiac cells, a phenomenon described as ischemia-reperfusion (I/R) injury[3] which contributes to an increased infarct area and microvascular dysfunction, being sometimes lethal.[4] Myocardial I/R injury involves several features that potentiate the final damage on the heart. Morphologically, I/R lesions presents contraction bands, karyolysis, disturbance of mitochondria, sarcolemma disruption, microvascular destruction, interstitial hemorrhage, and inflammation.[5] Additionally, at reperfusion period an elevation in the production of reactive oxygen species (ROS) displays important roles for the I/R injury extent.[6] The respiratory chain and NADPH oxidases of the NOX family are major sources of ROS that trigger the opening of mitochondrial permeability pore, causing irreversible damage to the cardiomyocytes.[6] Usually, the rupture of atheroma and partial or complete obstruction of an epicardial coronary artery is followed by spontaneous or interventional reperfusion. However, reperfusion sometimes may not occur.[7] Thus, we might realize that these burdens of factors augment the final infarct size and that it is complicated to recapitulate them by using animal models considering the vast anatomic and physiological differences from the human scenario. Nevertheless, most of the current knowledge about I/R-induced myocardial damage is derived from experimental studies in animals[5] and rodent models of I/R injury can help to clarify potential pathophysiological mechanisms and identify new targets to treat this clinical condition. In this context, rat models of myocardial infarct and I/R injury have been instigating the pre-clinical research field to establish the therapeutic potential of natural agents in innumerous diseases. The antioxidant effect observed in some plant components might be useful for proposing their applicability to induce cardioprotection, and this characteristic could be, in part, proven by administrating natural products, for example, in rats with experimentally induced cardiac injury.

Euterpe oleracea Mart., popularly known as "açai," is a fruit extensively cultivated in the North region of Brazil, specifically in the Amazon. This purple fruit was chemically studied, and it was found several antioxidant substances on its composition.[8,9] Additionally, açai has anti-inflammatory and vasodilator effects.[9,10]

A recent work has been performed by Alegre et al.,[11] in which the authors address that açai supplementation prevents metabolism deregulation in an acute rat model of myocardial I/R injury. This study shows that preventive treatment with açai attenuates oxidative stress but did not decrease the infarcted area or improve left ventricular function after global I/R. The authors described a beneficial effect of açai only in the metabolism of heart cells and discuss that the reduction of oxidative stress would be followed by an improvement in the left ventricular function. However, they observed that the treatment with açai worsened diastolic function after I/R leading to infer that the left heart dysfunction depends on mechanisms other than oxidative damage. Additionally, despite the changes observed in antioxidant enzymes in this work, açai supplementation did not influence the expression of transcriptional factor NF-κB, Nrf2, SIRT1, and FOXO1, proteins related with oxidative stress, regulation of the antioxidant enzymes production and cellular balance by acting on apoptosis, mitochondrial biogenesis, inflammation, glucose and lipid metabolism. I understand that this data can be justified by the protocol used in this work, as probably there was not enough time for the I/R injury to stimulate protein transcription. But, in my opinion, the preventive treatment with açai for six weeks, should have avoided, at least partially, the higher levels of some of these markers after global I/R injury in hearts from male rats, as it acts as an antioxidant agent.

It is also addressed that açai supplementation led to a higher activity of β-hydroxyacyl-CoA dehydrogenase and citrate synthase enzymes which can characterize higher fatty acid oxidation. Moreover, there was a lower activity of phosphofructokinase, the enzyme for glycolysis.[11] The authors explain that açai supplementation altered substrate selection for mitochondrial oxidation in reperfusion from glucose to fatty acids, maintaining the energy metabolism closer to a physiological situation. In this regard, I perceived a contradictory discussion of the presented results as the authors

Keywords

Euterpe Olerácea; Oxidative Stress; Energy Metabolism; Myocardial Ischemia; Myocardial Reperfusion Injury; Rats.

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defend that açai treatment could be beneficial by altering ATP production from glycolysis to fatty acid oxidation, but later in the discussion they assume that the change in energetic metabolism which occurs in stress situations has a protective role in the myocardium and that the prevention of glucose use induced by açai supplementation may have negatively interfered with this adaptive protective mechanism.

Finally, authors comment that the amount of açai ingested by rats on their study is equivalent to 600 mg for a 60 kg human, assuming that through the data obtained in this work the quantity of açai is feasible for human ingestion, and inaccurately extrapolate their finds when, by the end of discussion, it is highlighted that açai could be a potential strategy to attenuate I/R injury in the clinical setting. How could the dose of açai administered in rats with a cardiac lesion which promoted worsening of the diastolic function be suitable for human use? This was superficially discussed by the authors when they mentioned findings from a previous work that investigated the effects of anthocyanin extract in global rat heart I/R, suggesting that this substance, which is present in the açai composition, was cardioprotective in low doses and could be cardiotoxic in high doses.[12] Howbeit, this topic of the discussion was not clear on how this argument could justify the effects of administration of a standard chow supplemented with 5% açai in rats for six weeks, as it was not measured the anthocyanin content, the treatment with açai did not promote protection against I/R injury and the authors still remained proposing that the dose of açai used in their experimental protocol could be used in humans.

Relevant points must be considered when pre-clinical experiments are developed. This was well discussed by Ibáñez et al.,[5] when they address the importance of comparing results from different models of I/R or even different laboratories. The time of the day at which the cardiac I/R injury is induced has a significative influence on the tolerance of the heart to that lesion.[5] Moreover, the season and day of the week may influence the results observed in animal models and in the response of possible new cardioprotective therapies.[5] Importantly, this is also observed in patients, as the circadian clock influences a number of cardiovascular pathophysiological processes including the incidence of acute myocardial infarction.[13]

Natural products (herbs) have in numerous substances on their composition. These compounds would interact with multiple biological targets. Thus, it is of utmost importance to identify the associations among bioactive components of herbs and their targets in the cells. Many herbal substances which are currently used have not been submitted to minacious scientific evaluations, and this might promote potential and serious toxic effects due to possible drug-to-drug interactions and/or related to the dose administrated.

Despite the important progress in pre-clinical and clinical trials evaluations of novel cardioprotective agents, it is well recognized by the cardiology field that there is a huge challenge in the development of new drugs against I/R injury, which is to perform larger phase III trials in order to elucidate clinical responses to these new substances in the context of lethal I/R. Thus, I agree that it would be worth the effort of polishing the already available therapeutic strategies instead of trying to identify new treatments for myocardial damage promoted after an episode of I/R.

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Short Editorial

Inflammatory Biomarkers and Carotid Thickness in HIV Infected Patients under Antiretroviral Therapy, Undetectable HIV-1 Viral Load, and Low Cardiovascular Risk

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Abstract

Background: People living with HIV are at increased risk of cardiovascular disease and carotid thickness, due to the inflammation caused by the virus, the antiretroviral therapy, and other risk factors. However, few studies have observed the occurrence of cardiovascular diseases and carotid thickness in HIV-positive population at low cardiovascular risk and with undetectable viral load.

Objectives: To evaluate the association between levels of inflammatory markers and carotid thickness in people living with HIV, under antiretroviral therapy and at low cardiovascular risk.

Methods: To determine low cardiovascular risk in both groups (HIV infected and non-infected individuals), the Framingham Risk Score was used. Inflammatory markers (IFN-γ, TNF-α, IL-1β, IL-6, sVCAM-1, and sICAM-1) were assessed using flow cytometry. Carotid thickness (mm) was measured using Doppler ultrasound. Level of significance was $p < 0.05$.

Results: In People living with HIV, age and smoking status were associated with carotid thickness alterations. In the non-HIV group, age, higher total cholesterol, and LDL levels were associated with increased carotid thickness. Using the multivariate analysis, a significant association between TNF-α and IL- 1β levels, and a higher chance of atherosclerosis development in HIV group were observed.

Conclusions: Both groups have a similar risk for developing cardiovascular disease, therefore our study demonstrates that HIV-positive individuals with undetectable viral load in antiretroviral therapy without protease inhibitors and with low cardiovascular risk do not present differences in carotid thickness in relation to uninfected individuals. (Arq Bras Cardiol. 2020; 114(1):90-97)

Keywords: HIV; HIV Infections; Cardiovascular Diseases; Antiretroviral Therapy; Risk Factors; Caroti Artery Diseases; Atherosclerosis.

Introduction

Increased longevity in people living with HIV (PLHIV) due to effective highly active antiretroviral therapy (HAART) has increased the incidence of chronic diseases, such as cardiovascular disease.[1] According to some studies, the virus and antiretroviral therapy (ART) are factors that favor the increase of inflammatory makers and carotid thickness.[2,3] HIV-infected individuals have high levels of C-reactive protein, which is associated with atherosclerosis and myocardial infarction. Levels of interleukin-6 (IL-6), tumour necrosis factor alpha (TNF-α), interferon gamma (IFN-γ), interleukin-1 (IL-1), intracellular cell adhesion molecule (sICAM), and vascular cell adhesion molecule (sVCAM), which rise in the progression of cardiovascular disease, are also increased in this population.[4-6]

Studies did not evaluate factors of cardiovascular disease progression in the population considered to be at low cardiovascular risk, without observing the true possible effect of the inflammation caused by the virus and the adverse effect of antiretrovirals without the interference of intrinsic factors affecting cardiovascular risk in these individuals. In addition, we have not yet studied a population in which all patients had undetectable HIV-1 RNA viral load and used only nucleoside reverse transcriptase inhibitor (NRTIs) analogues and non-nucleoside reverse transcriptase inhibitors (NNRTIs), since protease inhibitors (PIs) have high adverse effect on cardiovascular disorders.

The present study evaluated the association of inflammatory markers IFN-γ, IL-1β, IL-6, TNF-α, C-reactive protein, sVCAM-1, and sICAM-1 and carotid thickness in HIV infected peope, in use of NRTIs analogues and NNRTIs, and low cardiovascular risk. In addition, carotid intima-media thickness and inflammatory markers levels between HIV-infected and non-infected individuals stratified by age were compared.

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Method

Study subjects

Cross-sectional analytical study with 115 patients was conducted at *Hospital das Clínicas* – Federal University of Pernambuco, Northeast, Brazil. Individuals were enrolled by convenience sampling. Ninety-nine patients were infected with HIV (HIV group) and were attended at the Specialized HIV/AIDS Healthcare Service, other 16 individuals were healthy and used as control (non-HIV group); both groups were aged between ≥ 18 and ≤ 60 years. All HIV patients were under ART with two NRTIs analogues and one NNRTI started at any time from their diagnosis, had undetectable HIV-1 RNA viral load, and were not on therapy for dyslipidaemia. Healthy controls were followers of patients attending in the Urology Service of the same hospital. Low risk for cardiovascular disease was also an inclusion criterion for both groups, calculated by the Framingham Risk Score (FRS). FRS estimates the likelihood of myocardial infarction or death from coronary disease within 10 years in individuals without prior clinical atherosclerosis. Risk calculation uses parameters such as gender, age, total and HDL cholesterol levels, systolic blood pressure, and smoking status.[7]

Data collection

After patients signed the informed consent form, data were collected with standardized questionnaires, based on medical records and/or interview information as follows: age, gender, race, ART type and time, CD4+ T cells count, HIV-1 RNA viral load, and smoking and diabetes status. CD4+ T-cell counts were estimated with flow cytometry using the FACSCalibur (Becton-Dickinson, USA) and results were expressed in cells/mm^3. HIV viral load was measured using real-time polymerase chain reaction (RT-PCR) (Roche Diagnostics, Germany) with detection limit of 50 copies/mL. Afterwards, the examinations of lipidogram, the measurements of carotid intima-media thickness (CIMT), and the assessment of inflammatory biomarker levels were carried out. The moment the patient was included in the study, blood was collected for lipidogram and inflammatory biomarker determinations. Blood pressure assessment and carotid Doppler ultrasound were performed as well.

Lipidogram

Total cholesterol, HDL, and triglycerides were examined using the automated analyser CMD800i (Wiener LAB) with photometric methodology. Blood was collected without anticoagulant and was immediately sent to the laboratory for analysis. LDL and VLDL cholesterol values were obtained through the Friedwald formula.

Inflammatory markers

Inflammatory markers (IFN-γ, TNF-α, IL-1β, IL-6, sVCAM-1, and sICAM-1) were assessed using the cytometric bead array (CBA) method. Results were generated in tabular and graphical format using the BD CBA Software FCAP Array, version 3.01. Ultrasensitive C-reactive protein was measured through the latex immunoblottomymetry technique using the CMD800i automated analyzer (Wiener LAB), where it reacts with the specific antibody to form insoluble immunocomplexes. The turbidity produced by immunocomplexes is proportional to the PCR concentration in the sample.

Measurements of the carotid intima-media thickness

Measurement was performed using an ultrasound device (General Eletric, model LOGIQe BT12), which features DICOM 3.0 software and Auto IMT, with automatic and well-monitored images. Imaging exams were performed by two medical vascular surgeons. Measurements were performed on the posterior wall of the studied vessel in a plateau-free area and defined as the distance between two echogenic lines represented by the lumen-intima and media adventitia interface of the arterial wall. The mean automatic measurement of the thickened common carotid artery was defined as either right (RCC) or left (LCC). Presence of plaque was considered when intima-media thickening (IMT) > 1.5 mm was observed.[8-10]

Statistical analysis

Statistical analyses were performed using the STATA software version 11.0. Level of significance was $p < 0.05$. Variables were also analyzed stratified by age, with cutoff point at 40 years due to the distribution of N in the cases group. Qualitative variables were expressed through absolute and relative frequencies, and the quantitative ones, through descriptive statistics, such as mean, standard deviation, median, 25th and 75th percentile. Continuous variables that presented normal distribution were described through mean and standard deviation; in case of non-normal distribution, they were described through median and interquartile range. Normal distribution was observed for quantitative variables age, total cholesterol, HDL and LDL, while triglycerides, CIMT and inflammatory markers did not present normal distribution. Data normality was evaluated by the Kolmogorov-Smirnov test. Nonparametric Kruskal–Wallis and Mann-Whitney tests were used to compare medians. Student's independent *t*-test was used to compare means between groups (HIV$^+$ and HIV$^-$). Correlation analysis was performed using the Spearman coefficient. To select the most significant variables, a stepwise logistic regression was used. Variables moderately associated ($p < 0.2$) with the dependent variable were included in the model, whereas a threshold of $p < 0.05$ was adopted for the stepwise elimination of variables considered as risk factors.

Ethical considerations

The Ethics Committee of the Health Sciences Center of the Federal University of Pernambuco (No. 307087) approved this research and the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsink. All subjects signed an informed consent form.

Results

Ninety-nine HIV-positive and 16 non-infected individuals participated in the study. Individuals aged 40 years old or older

accounted for 59.6% of those infected with HIV and 75% of the control group. Comparing the characteristics of the groups, there were differences in inflammatory markers IFN-γ, IL-1, and TNF-α, with higher levels in the control group. Regarding CIMT, there was no significant difference between the groups, and distribution of gender as well as smoking and diabetes status were similar among them. The following two variables had borderline significance: levels of HDL cholesterol were higher among patients with HIV, while mean LDL was lower in this group. In the HIV-positive group, 37% of patients had less than five years of ART, 29.3% between 5 and 10 years, and 33.7% more than 10 years. Regarding CD4 levels and viral load during study admission, 90.5% of the subjects had CD4 levels above 350cells/mm^3 and all had undetectable viral load. Among the therapeutic regimens with NRTIs analogues, 98 (98.98%) of them contained lamivudine, 65 (65.65%) contained zidovudine, 32 (32.32%) contained tenofovir, and three (3.03%) contained didanosine. For NNRTIs, 93 (93.93%) used efavirenz and six (6.06%) used nevirapine (Table 1).

In HIV-infected individuals, higher HDL and LDL levels, CIMT, CD4+ T cell counts, and ART time were observed in older individuals (Table 2). The 75th percentile calculated for 115 patients was 0.61 mm. Therefore, the CIM was considered thickened if > 0.61 mm. In the HIV-positive group, CIMT ≥ 0.61 mm was detected in 51 individuals (51.51%), of whom 78.4% were aged 40 years old or older. For the non-HIV group, the presence of IMT ≥ 0.61 mm was 56.25% (nine subjects), and 88.9% of these patients were 40 years old or older. Although it was evidenced that HIV-infected individuals were aged 40 years old or older were associated with increased carotid thickness, a comparison between crude and Mantel–Haenszel odds ratios showed that the association between older age and thickness is independent of the infection status. Higher levels of total and LDL cholesterol were associated with CIMT ≥ 0.61 mm in the non-HIV group (Table 3). In the multivariate analysis, after adjustments for age, smoking status, and cholesterol level were made, a significant association with TNF-α levels was observed. Thus, increased levels of TNF-α were associated with greater chance of atherosclerosis. Individuals with increased IL1-β levels had greater chance of atherosclerosis with p-value close to significance (Table 4).

Discussion

To our knowledge, this is the first study to evaluate inflammatory biomarkers with the presence of CIMT only in individuals considered at low cardiovascular risk, with exclusive use of NRTIs and NNRTIs, and with undetectable HIV-1 RNA viral load in a population of HIV-infected patients.

In the univariate analysis, it was found that inflammatory biomarkers (IFN-γ, IL-1β, and TNF-α) were higher in the non-HIV group. These data are in contrast to the ones by Ross et al.,[2] who found that TNF-α, hs-CRP, IL-6, and sVCAM-1 were significantly higher in the HIV-infected group. Bethan et al.[11] also observed higher elevation of IL-6 and C-reactive protein in HIV-positives as compared with controls. Our study excluded patients with detectable viral load, which is a contributing factor to the increase of these markers. In contrast, the studies cited did not use detectable viral load as an exclusion criterion, and it may have been an influencing factor in the discordance of the results. Samples obtained from plasma donors before, during, and after HIV acquisition demonstrated elevations in various cytokines during viral expansion,[12] and the initiation of ART in chronic infection is associated with a decline in the circulating levels of some cytokines, including IL-1β, IL-6, and TNF-α, possibly by reduction of viral load.[13] An important limitation of the present study is the fact that the non- HIV group consisted of older individuals as compared with the infected ones. This factor may have contributed to the determination of higher levels of the abovementioned inflammatory markers and total and LDL cholesterol and consequently may have also skewed the results of the association of total and LDL cholesterol with CIMT ≥ 0.61 mm. However, it is worth noting that there is a great divergence in several studies under lipidogram changes in HIV-infected individuals[2,14]. For example, in the study by Ross et al.,[2] the HIV-infected group had lower mean HDL, but total cholesterol, triglycerides, and LDL were similar between the groups. LDL and triglyceride levels were positively correlated with CIMT. HIV-infected individuals had significantly higher triglyceride values and lower values of total cholesterol, HDL, and LDL as compared with the control group.[14,15]

It has been shown that individuals over 40 years of age presented significantly higher total cholesterol, HDL and LDL levels, and higher mean CIMT, reinforcing that older age is a factor associated with its altered thickness measurement. CIMT means showed no statistically significant difference when compared to individuals with and without HIV. Lorenz et al.[16] demonstrated higher CIMT mean in the HIV group when compared with the control one. According to Falcão et al.,[17] patients classified as having medium or high cardiovascular risk based on the Framingham score were 3.7 times more likely to present atherosclerosis than patients considered at low risk. In another study, patients with subclinical atherosclerosis had higher risk score compared to those with normal to mid-normal thickness. For every 10% increase in the FRS, the odds of having an abnormal CIMT tripled.[18] However, the low number of individuals in the control group indicates another important limitation for our results, which may explain the lack of statistical association of carotid thickness and HIV infection. Thus, in later studies, we would need a larger group of individuals to further investigate this hypothesis.

Higher mean age was associated with higher CIMT in HIV-infected and non-infected individuals. Stratified analysis, when controlling for age and CIMT by the infection status, verified that HIV infection does not interfere in the association, that is, the aforementioned relation is independent of the infection status in the analyzed population. However, a larger sample size would be necessary to give greater statistical power to the analysis, considering the wide confidence interval of the raw odds ratios and Mantel–Haenszel odds.

When evaluating the association between inflammatory markers and CIMT, a significant association with TNF-α was observed in the multivariate analysis, as the increase in IL1-β levels presented a greater chance of atherosclerosis with p-value close to significance. Ssinabulya et al.[18] found high levels of us-CRP were not associated with CIMT. However, in other studies, higher CIMT was associated with

Table 1 – Comparison between groups of HIV-infected and non-infected patients regarding demographic and clinical characteristics, risk factors for cardiovascular disease, inflammatory markers, carotid intima-media thickness measures, and risk factors for infection

Variables	Groups		p-value
	HIV+ (n = 99)	HIV- (n = 16)	
Agea (years)	42.2 ± 8.9	48.7 ± 9.1	0.007
Age group			
< 40 years old	40 (40.4%)	4 (25.0%)	0.239
40 years old or older	59 (59.6%)	12 (75.0%)	
Gender			
Female	39 (39.4%)	4 (25.0%)	0.404
Male	60 (60.6%)	12 (75.0%)	
Smoking			
Yes	12 (12.1%)	0 (-)	0.213
No	87 (87.9%)	16 (100%)	
Diabetes			
Yes	3 (3.0%)	0 (-)	1.000
No	96 (97.0%)	16 (100%)	
Lipidogram (mg/dL)			
Total Cholesterol*	184.0 ± 35.4	190.37 ± 48.9	0.528
HDL*	50.3 ± 14.2	43.6 ± 7.8	0.069
LDL*	105.3 ± 27.2	118.5 ± 38.2	0.093
Triglycerides†	116.2 (79.6; 176)	120.1 (90.1; 191.3)	0.695
CIMT (mm)			
CIMT means*	0.573 ± 0.123	0.586 ± 0.116	0.697
Inflammatory markers†			
PCR US	0.1 (0; 0.4)	0.1 (0; 0.3)	0.680
ICAM-1	0 (0; 0)	0 (0; 0)	1.000
VCAM-1($x10^{-3}$)	12.12 (11.42; 12.62)	12.94 (10.59; 13.47)	0.071
IFN	2.16 (1.98; 2.40)	2.67 (2.29; 2.91)	0.002
IL-1	2.87 (2.87; 2.87)‡	2.87 (2.87; 4.08)	0.027
IL-6	2.1 (2.1; 2.1)‡	2.1 (2.1; 2.1)‡	0.689
TNF-α	2.26 (2.26; 2.26)‡	2.26 (2.26; 7.55)	0.005
Time of ART (years)			
< 5 years	34 (37.0%)	-	-
> 5 and < 10 years	27 (29.3%)	-	
≥ 10 years	31 (33.7%)	-	
CD4+ Cells Count (Cells/mm^3)			
< 200	2 (2.1%)	-	-
200–349	7 (7.4%)	-	
≥ 350	86 (90.5%)	-	
Antiretrovirals			
Lamivudine	98 (98.98%)		
Zidovudine	65 (65.65%)		
Tenofovir	32 (32.32%)		
Didanosine	3 (3.03 %)		
Efavirenz	93 (93.93%)		
Nevirapine	6 (6.06%)		

** Mean ± SD – Independent Student's t-test was applied. †Median (P25; P75) – Kruskall–Wallis test was applied. ‡Values below the detection limit of the test. HDL: high-density lipoprotein; LDL: low-density lipoprotein; CIMT: carotid intima-media thickness; ART: antiretroviral therapy.*

Table 2 – Comparison of demographic and clinical, laboratory, mean carotid intima-media thickness, and age-related antiretroviral therapy characteristics of HIV-infected individuals

Variables	Age group		p-value
	< 40 years old (n = 40)	≥ 40 years old (n = 59)	
Gender			
Female	14 (35.0%)	25 (42.4%)	0.461
Male	26 (65.0%)	34 (57.6%)	
Smoking			
Yes	3 (7.5%)	9 (15.2%)	0.246
No	37 (92.5%)	50 (84.8%)	
Diabetes			
Yes	1 (2.5%)	2 (3.4%)	0.800
No	39 (97.5%)	57 (96.6%)	
Lipidogram (mg/dL)			
Total cholesterol*	169.3 ± 33.1	193.9 ± 33.8	0.001
HDL*	45.6 ± 9.9	53.4 ± 15.8	0.007
LDL*	97.5 ± 23.4	110.9 ± 28.5	0.002
Triglycerides†	130.5 (76; 199)	111.4 (81; 174)	0.571
CIMT (mm)*			
CIMT mean	0.521 ± 0.070	0.609 ± 0.138	< 0.001
Inflammatory markers†			
PCR US	0.2 (0; 0.4)	0.1 (0; 0.3)	0.298
ICAM-1	0 (0; 0)	0 (0; 0)	1.000
VCAM-1($x10^{-3}$)	12.06 (11.59; 12.49)	12.12 (10.42; 12.75)	0.764
IFN	2.18 (2.05; 2.42)	2.16 (1.91; 2.37)	0.255
IL-1	2.87 (2.87; 2.87)	2.87 (2.87; 2.87)	0.529
IL-6	2.1 (2.1; 2.1)	2.1 (2.1; 2.1)	0.689
TNF-α	2.26 (2.26; 2.26)	2.26 (2.26; 2.26)	0.522
Time of ART (years)			
< 5	20 (54.1%)	14 (25.5%)	0.005
5–10	11 (29.7%)	16 (29.1%)	
≥ 10	6 (16.2%)	25 (45.4%)	
CD4+ T Cells Count (Cells/mm^3)			
< 200	0 (2.1%)	2 (3.5%)	0.013
200–349	6 (7.4%)	1 (1.8%)	
≥ 350	32 (84.2%)	54 (94.7%)	

** Mean ± SD – Independent Student's t-test was applied. †Median (P25; P75) – Kruskall–Wallis test was applied. HDL: high-density lipoprotein; LDL: low-density lipoprotein; CIMT: carotid intima-media thickness; ART: antiretroviral therapy.*

higher levels of IL-2, IL-6, TNF-α, us-CRP, and sVCAM-1.[2,3] Both our studies and other ones cited have small sample size, so further investigation is needed to more accurately confirm the relationship between inflammatory markers and the occurrence of carotid atherosclerosis. Our result can be explained by careful selection of our patients. Both are attended at a referral centre for HIV treatment, with good medical follow-up. Our sample evaluates an "ideal" patient, who has undetectable viral load for probably a rather long time, since the time of ART is greater than five years in 63% and without previous or current use of protease inhibitors. In addition, the FRS calculation for cardiovascular disease is low. These data point to the importance of patient awareness among health professionals, guiding them and controlling risk factors such as smoking, diabetes, hypertension, and dyslipidaemia.

Table 3 – Risk factors related to carotid intima-media thickness, stratified according to the condition of HIV infection

Variables	HIV+			HIV-		
	< 0.61 mm	≥ 0.61 mm	p-value	< 0.61 mm	≥ 0.61 mm	p-value
Age[a] (years)	37.9 ± 7.1	46.3 ± 8.5	< 0.001	44.0 ± 9.8	52.4 ± 7.0	0.063
Age group						
< 40	29 (60.4%)	11 (21.6%)	< 0.001[b]	3 (42.9%)	1 (11.1%)	0.192[†]
≥ 40	19 (39.6%)	40 (78.4%)		4 (57.1%)	8 (88.9%)	
Gender						
Female	19 (39.6%)	20 (39.2%)	0.970	2 (28.6%)	2 (22.2%)	0.608
Male	29 (60.4%)	31 (60.8%)		5 (71.4%)	7 (77.8%)	
Smoking						
Yes	3 (6.3%)	9 (17.7%)	0.082	0 (-)	0 (-)	-
No	45 (93.7%)	42 (82.3%)		7 (100%)	9 (100%)	
Diabetes						
Yes	1 (2.1%)	2 (3.9%)	0.594	0 (-)	0 (-)	-
No	47 (97.9%)	49 (96.1%)		7 (100%)	9 (100%)	
Lipidogram (mg/dL)						
Total cholesterol[*]	178.1 ± 33.8	199.9 ± 58.3	0.395	175.7 ± 31.5	191.8 ± 37.4	0.023
HDL[*]	41.5 ± 9.8	45.2 ± 5.9	0.362	50.4 ± 17.6	50.1 ± 10.3	0.931
LDL[*]	110.9 ± 23.3	124.4 ± 47.4	0.504	98.5 ± 21.7	111.4 ± 30.2	0.020
Triglycerides[‡]	113 (72; 181)	118 (86; 174)	0.459	117 (86; 169)	122 (101; 200)	0.560
Inflammatory markers[‡]						
PCR US	0.1 (0; 0.4)	0.1 (0; 0.4)	0.966	0.1 (0; 0.6)	0.1 (0; 0.1)	0.581
ICAM-1[¥]	-	-	-	-	-	-
VCAM-1($x10^{-3}$)	12.1 (11.3; 12.6)	12.0 (11.4; 12.6)	0.931	13.0 (6.6; 13.6)	12.9 (10.8; 13.4)	1.000
IFN	2.16 (1.98; 2.37)	2.21 (1.93; 2.43)	0.481	2.91 (1.96; 3.24)	2.66 (2.32; 2.72)	0.368
IL-1	2.87 (2.87; 2.87)	2.87 (2.87; 2.87)	1.000	2.87 (2.87; 4.40)	2.87 (2.87; 3.77)	0.597
IL-6[¥]	-	-	-	-	-	0.149
TNF-α	2.26 (2.26; 2.26)	2.26 (2.26; 2.26)	0.328	2.26 (2.26; 6.75)	2.26 (2.26; 13.7)	0.634
Time of ART (years)						
≤ 5	19 (43.2%)	15 (31.2%)	0.383	-	-	-
5–10	13 (29.5%)	14 (29.2%)		-	-	-
≥ 10	12 (27.3%)	19 (39.6%)		-	-	-

**Media ± standard deviation - Independent Student's t-test was applied. † OR Crude, 5.47 (2.41–12.93); OR Mantel–Haenszel, 5.60 (2.43–12.9). ‡Median (P25; P75) – Mann–Whitney test. ¥ There is no variation (all values equal to the minimum). HDL: high-density lipoprotein; LDL: low-density lipoprotein; ART: antiretroviral therapy.*

Conclusions

HIV-positive individuals with undetectable HIV-1 RNA viral load, at low risk for cardiovascular disease, using NRTI and NNRTI presented similar carotid thickness compared with non-infected people. Inflammatory markers IL-6, hs-CRP, sVCAM-1, and sICAM-1 showed similar levels in the studied groups and IFN-γ, IL-1, and TNF-α had lower levels in the HIV population. Evaluating the association between inflammatory markers and CIMT, in the multivariate analysis, TNF-α and IL1-β were shown to be associated with a greater chance of higher carotid thickness. Our study demonstrates that HIV-positive individuals with undetectable viral load in ART without protease inhibitors and with low cardiovascular risk do not present differences in carotid thickness in relation to uninfected individuals. Control of viral load with NRTIs and NNRTI plus the maintenance of cardiovascular risk parameters under control – such as smoking, diabetes, and dyslipidaemia – possibly result in the patient with HIV having lower risk of occurrence of subclinical atherosclerosis.

Author contributions

Conception and design of the research, Statistical analysis and Writing of the manuscript: Leite KME; Acquisition of data: Leite KME, Santos Júnior GG, Godoi ETAM, Vasconcelos AF,

Table 4 – Association of factors risks related to carotid intima-media thickness, multivariate analysis stratified according to HIV infection status

Inflammatory markers‡	HIV+		HIV-	
	CIMT > 0.61 mm OR (95%CI)*	p-value	CIMT > 0.61 mm OR (95%CI)†	p-value
PCR US	1.17 (0.45–2.98)	0.747	0.31 (0.02–5.31)	0.425
VCAM-1(x10^{-3})	0.54 (0.21–1.38)	0.197	1.08 (0.07–17.4)	0.954
IFN	1. 76 (0.69–4.51)	0.238	-	-
IL-1	10.4 (0.71–151.2)	0.087	6.14 (0.24–156)	0.272
TNF-α	31.2 (2.70–361)	0.006	3.06 (0.12–79.3)	0.500

**Adjusted by age and smoking. †Adjusted by age and total cholesterol. ‡Analysis considering the median value of the markers. CIMT: carotid intima-media thickness; OR: odds ratio.*

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Potential Conflict of Interest

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

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Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Universidade Federal de Pernambuco under the protocol number 307087. 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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Cardiovascular Conditions of Patients on HIV Therapy

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Short Editorial related to the article: Inflammatory Biomarkers and Carotid Thickness in HIV Infected Patients under Antiretroviral Therapy, Undetectable HIV-1 Viral Load, and Low Cardiovascular Risk

Successful anti-infective therapy of patients submitted to contemporary HIV treatment decreased mortality between 2007 and 2017 by 51% in association with a decrease in of 17% in incidence; decrease in mortality associated with a smaller decrease in incidence means more people living with HIV disease.[1] In Brazil, annualised rate of change in mortality was -1.2% (-1.4% to -1.0%).[2] In many countries the survival rate of patients increased.[3] Therefore, other non-infectious ailments such as prevalent cardiovascular diseases came to the attention of physicians in charge for the patients.[4]

Prevention is a mainstay in the health care of patients. Patients on successful HIV treatment may incur in either asymptomatic or symptomatic conditions that may be risk factors for cardiovascular diseases[5] or demonstrate metabolic abnormalities[6] that need medical attention. Further, new technologies were studied in order to investigate in more depth vascular health either as screening, or a diagnostic tool or treatment strategies.[3]

Previous research were performed in Brazilian populations of different geographic regions. Median carotid intima-media thickness was 0.54 (0.49, 0.62) mm in 535 HIV infected patients from Rio de Janeiro, 0.58 (0.52, 0.68) mm in 88 healthy controls and 0.57 (0.49, 0.70) mm in 10943 participants of a large cohort; differences were not significant after adjustment for confounding variables.[7]

In Parana state, in a sample of 538 patients, hypertension was diagnosed in 24.4%, hypercholesterolemia in 18.2%, low HDL-cholesterol in 39.7%, hypertriglyceridemia in 51.3% and high serum glucose in 33.3%.[5] In Minas Gerais state a study of a cross-sectional sample of 133 patients compared with 20 healthy controls demonstrated that insulin resistance was more common among the infected patients, and suggested lipid accumulation product index as a new biomarker of cardiovascular risk in patients with HIV.[8]

In the current issue of *Arquivos Brasileiros de Cardiologia*, Leite et al.[9] report an additional Brazilian experience in Recife, Pernambuco State. They evaluated a convenience sample of 99 asymptomatic patients with low cardiovascular risk and undetectable plasma HIV RNA levels on HIV treatment in comparison to 16 controls for a set of inflammatory biomarkers - IFN-γ, TNF-α, IL-1β, IL-6, sVCAM-1 e sICAM-1 and carotid intima-media thickness. After multivariate analysis, they found a significant association between TNF-α and IL-1β with the risk for higher carotid-intima media thickness in HIV infected patients. They reproduced the negative findings of no difference relative to carotid intima-media thickness between the study groups. These findings add to the evaluation of patients on successful HIV therapy and re-emphasizes the achievements of the contemporary comprehensive clinical care of the patients probably including the therapeutic advice of cardiovascular risk factors such as smoking, hypertension, dyslipidemia and diabetes.

Keywords

HIV; HIV Infections; Cardiovascular Diseases; Antiretroviral Therapy; Risk Factors; Carotid Artery Diseases; Atherosclerosis; Epidemiology.

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Short Editorial

Effects of Physical Training on the Myocardium of Oxariectomized LDLr Knockout Mice: MMP 2/9, Collagen I/III, Inflammation and Oxidative Stress

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Abstract

Background: **The emergence of coronary heart disease is increased with menopause, physical inactivity and with dyslipidemia. Physical training is known to promote the improvement of cardiovascular functions.**

Objective: **To investigate the effects of aerobic physical training on the left ventricle in ovariectomized LDL knockout mice.**

Methods: **Thirty animals were divided into 6 groups (n = 5): Sedentary non-ovariectomized control; Sedentary ovariectomized control; Trained ovariectomized control; Sedentary non-ovariectomized LDL-knockout, sedentary ovariectomized LDL-knockout and trained ovariectomized LDL-knockout. We analyzed the average parameters of apparent density of collagen fibers types I and III, and metalloproteinase type 2 and type 9, were considered significant $p < 0.05$.**

Results: **The results showed that the proposed exercise protocol altered the volume of type I collagen fibers, altered collagen remodeling parameters (MMP-2), and also reduced the 8-hydroxy-2'-deoxyguanosine (8OHdG) oxidative stress parameter.**

Conclusion: **Moderate intensity aerobic training acts on collagen fiber volume, on collagen remodeling with the reduction of oxidative stress in the left ventricles of ovariectomized LDL-knockout mice. (Arq Bras Cardiol. 2020; 114(1):100-105)**

Keywords: **Coronary Artery Disease; Exercise; Menopause; Dyslipidemias; Motor Activity; Collagen; Oxidative Stress; Inflammation; Mice.**

Introduction

During the aging process, menopausal women are at increased risk of developing conditions such as dyslipidemia, hypertension, insulin resistance and changes in body composition, where lifestyle and sedentarism are associated with a higher prevalence of the development of cardiovascular disease (CD).[1,2]

The aging process is associated with increased oxidative stress resulting in damage of several cell macromolecules, partly due to decreased antioxidant capacity as well as reduced repair capacity, resulting in increased susceptibility to apoptosis.[3,4] Particularly in menopausal women, neuroendocrine alterations affect the functionality, metabolic capacity and antioxidant activity of numerous organs, especially due to the lack of estrogen, considered a female antioxidant, resulting in an additional increase of oxidative stress.[5]

Lipid metabolism is also influenced by physiological changes during menopause resulting in an increase in LDL and a decrease in HDL and contributes to the emergence of cardiovascular diseases.[6,7] When compared to men of the same age, postmenopausal women are at an increased risk of developing heart disease.[8,9] It is one of the main causes of morbidity and mortality in this physiological stage.[10]

Regular physical activity relieves the effects of aging and menopause and improves aerobic fitness, maintaining body weight index of visceral fat, plasma lipid levels, increased insulin sensitivity, increased baroreflex sensitivity and improved endothelial function, capillary wall shear stress which results in increased blood flow, stimulating nitric oxide release.[11-13] These factors promote a better health-related quality of life and prolong survival and can be considered essential non-pharmacological standards in the treatment of postmenopausal effects and other physiological and pathological conditions.[14,15]

The objective of this study is to analyze the effects of aerobic physical training on the left ventricle in ovariectomized wildtype and LDLr knockout female mice on the following

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parameters: volume density of types I and III collagen fibers, metalloproteinases type 2 and type 9 expression, in addition to COX2 and 8-OhdG expression.

Methods

Animals

Thirty female mice aged 10 months were used: 15 genetically modified female mice, with knockout of the low-density lipoprotein receptor (LDLr Knockout), and 15 female wildtype mice (C57BL/6J) obtained from the University of São Paulo vivarium. The animals were kept in a USJT vivarium at a controlled temperature (22-24°C) and lighting (12 hours of light cycle and 12 hours of dark) receiving commercial feed (NUVILAB CR1, Nuvital Nutrients LTDA, Curitiba, PR) and water "ad libitum". The animals were divided into 6 groups (n = 5): sedentary non-ovariectomized control (CS), sedentary ovariectomized control (COS); trained ovariectomized control (COT); non-sedentary ovariectomized LDL knockout (LDL-S), sedentary ovariectomized LDL knockout (LDL-OS) and trained ovariectomized LDL knockout (LDL-OT). The division of the animals in the groups was performed by convenicence.

The experimental protocol was approved by the Research Ethics Committee of Universidade São Judas Tadeu (CEP-Protocol: 058/2007) and the research was conducted according to the Principles of Laboratory Animal Care formulated by the National Institutes of Health.

Ovariectomy

At nine months of age animals underwent the ovariectomy procedure. The animals were anesthetized with a ketamine and xylazine solution (120:20 mg/Kg, im) and placed in supine position and a small incision in the lower third of the abdominal region, parallel to the line of the body, was made. The ovaries, the uterine horns, and the blood vessels were located, sectioned, and removed. After that, the musculature and the skin were sutured. Confirmation of the efficacy of the ovariectomy was determined through colpocytology of the vaginal secretion performed over four consecutive days. On the last day of analysis, euthanasia was performed on these animals.[16]

Training Protocol

Maximal training Test

A maximal training test was performed on all the groups at the beginning and at the end of the exercise training program. The test consists of placing the animal to run on an ergometric treadmill at 0.3 km/h for 3 minutes, and this workload was increased by 0.3 km/h every 3 minutes until the animal reached exhaustion. The time of the test and the speed of the last workload were noted and served to determine the mean value of aerobic capacity of each group.

Exercise training

Exercise training began 7 days after the ovariectomy surgery; the trained groups were subjected to a physical training protocol on an ergometric treadmill at low-moderate intensity (≈50% to 70% maximal running speed) for 1 hour a day, 5 days a week, for 4 weeks, with a gradual increase in speed from 0.3 to 1.2 km/h. The animals were adapted to the treadmill for 10 minutes on three days prior to beginning the training.

Euthanasia and tissue preparation

At the end of the training the animals were sacrificed by decapitation. A thoracotomy was performed in which the heart and atria were removed and the right and left ventricles were sectioned. Left ventricle samples were fixed in 10% buffered formalin for 24 hours. Afterwards, the tissue was transferred to a 70% ethyl alcohol solution, dehydrated in increasing ethanol series, diaphanized in xylol and embedded in paraffin. Non-serial, 5 μm thick cuts were performed in which each section received a total of 6 cuts. The sections were stained with the Picrosirius technique, for the analysis of collagen fibers I and III in the left ventricle and visualized by polarized light microscopy.

The volume density of collagen fibers I and III (Vv[fc]) expresses the fraction of the volume occupied by the collagen fibers in relation to the total volume of the analyzed image. For this analysis, the test system was used with a total of 475 points, which corresponds to 100% of the image, using the program Image J. (version 1.47 - National Intitutes of Health-(Collins).

Immunohistochemistry

For the immunohistochemical techniques, 3 to 4 micrometer thick cuts were made and mounted on slides previously silanized using 4% silane. After the slides were dewaxed, using a heating oven overnight set at 57ºC, after which they were immersed in xylol baths for 30 minutes. Afterwards, they were hydrated in ethyl alcohol with decreasing concentrations of 100%, 80% and 70%, each with a duration of 5 minutes, then washed in running water. In the next step, the antigenic recovery was performed in a water bath at 90°C, the slides were placed in citrate buffer for 30 minutes, then washed in running water. Endogenous peroxidase blockade was performed in H_2O_2 for 15 minutes, followed by washing in distilled running water and in PBS pH = 7.4. For each slide, a specific antibody was used, table 1, and the antibody was placed overnight in a humid chamber at 4°C. The material was washed with PBS buffer and incubated with a biotinylated secondary antibody for 30 minutes, washed again with PBS and incubated with a streptoavidin-peroxidase antibody for another 30 minutes. A chromogenic substrate, DAB (33-Diaminobenzidine) solution in the ratio of 1:1 were used for five minutes at room temperature to wash with PBS solution and to reveal the reaction. When the presence of a dark brown precipitate was observed the slides were placed in running water, after which they were counterstained with "Hematoxylin Harrys" for 2 minutes. Afterwards, they were submitted to 3 xylol baths to diafieze and to 2 alcohol baths. The slides were mounted with coverslips and Entellan®.

In all the techniques, observing the presence of a dark brown precipitate, the sample was visualized under an optical microscope. A quantitative analysis of the images was performed using the program ImageLab 2000, where the brown markers were selected and the program quantified immunoexpression intensity, figure 1.

Table 1 – Antibodies used for protein detection

Antibody	Dilution	Labeling	Function	Manufacturer
MMP2	1:250	Cytoplasm	Collagen remodelling	sc-10736, Santa Cruz®
MMP9	1:300	Cytoplasm	Collagen remodelling	sc-6840, Santa Cruz®
COX 2	1:100	Cytoplasm	Inflammation	sc-1745 P, Santa Cruz®
8-OHdG	1:100	Cytoplasm	Oxidative stress	sc-66036, Santa Cruz®

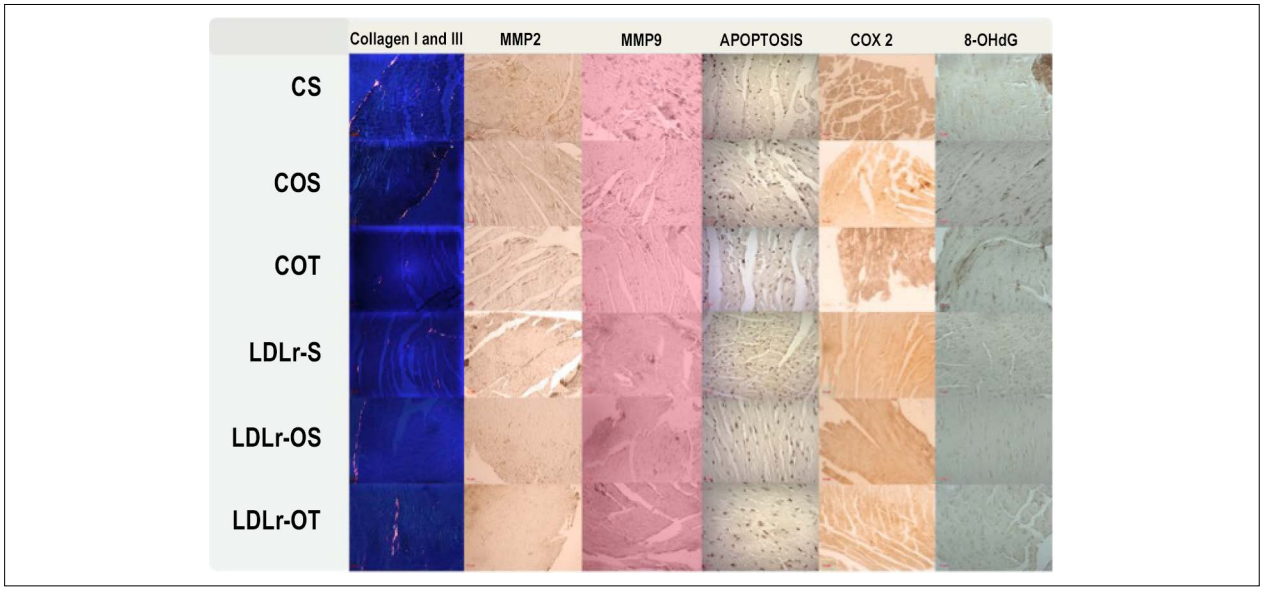

Figure 1 – *Immunoexpression of proteins. CS: sedentary non-ovariectomized control; COS: sedentary ovariectomized control; COT: trained ovariectomized control; LDLr-S non-sedentary ovariectomized knockout; LLr-OS: sedentary ovariectomized LDL knockout; LDLr-OT: trained ovariectomized LDL knockout.*

Statistical analysis

Absolute and relative values were used to describe the qualitative variables. For the quantitative variables with normal distribution (Shapiro-Wilk > 0.05), mean, standard deviation, minimum and maximum were used, and for the variables with non-normal distribution (Shapiro-Wilk < 0.05), median and percentiles were used. To study the diferences between the variables with the groups, the Kruskal-Wallis and ANOVA tests were used, complemented by the Dunn test or Bonferroni. For all analyzes, a confidence level of 95% was used. The program utilized for these analyzes was Stata version 11.0. (StataCorp. 2009. *Stata Statistical Software: Release 11*. College Station, TX: StataCorp LP.)

Results

Our data show a significant reduction in the volume density of type I collagen fibers in the ovariectomized dyslipidemic group (LDL-OS) (-51%). The LDL-OT group showed a decrease of 100% when compared to the COS group and a significant difference in relation to the COT and LDL-S groups. Table 2 shows the association of COX-2 and MMP9 expression variables and the density of type I collagen fibers in relation to the evaluated animal group.

Regarding metalloproteinase type 2 expression, in the control group (CS) there was a significant increase of 24% in the ovariectomized group (COS), when physical training (COT) was performed there was an increase of 72%, and with dyslipidemia (LDL-S), the increase was 92%. In the dyslipidemic group with ovariectomy (LDL-OS), the values decrease 27% in relation to the LDL-S group and 18% in relation to the COT group, but still above the values of the control groups by 42% in relation to the CS group and 14% in relation to the COS group. When the training was performed in the ovariectomized dyslipidemic group LDL-OT, the results obtained present a 15% increase in relation to the sedentary ovariectomized LDL-OS group and a 15% decrease in relation to the LDL-S group. When compared to the control group, there was an increase of 64% in relation to the CS group, 32% in relation to the COS group and a decrease of 5% in relation to the COT group.

When analyzing the oxidative stress data, evaluating 8OHdG expression, there was a decrease in the indexes for the control group (CS), in which there was a decrease of 33% in the group with ovariectomy (COT) and a 39% decrease in the trained group. When dyslipidemia was present (LDL-S), there was a 51% decrease in relation to the CS group, and in the dyslipidemic group with ovariectomy (LDL-OS) there was a decrease of 85% in relation to the CS group, 78%

Table 2 – Comparison of Cyclooxygenase-2, Volume Density of collagen fibers I and Metalloproteinase type 9, with the groups studied. clinical variables with groups

Variables	CS	COS	COT	LDL-S	LDL-OS	LDL-OT	p*
COX-2	35.0 (23.9; 46.3)	46.5 (44.2; 79.7)	46.1 (31.3; 47.7)	47.7 (45.8; 63.1)	87.8 (42.5; 92.4)	49.4 (49.1; 50.9)	0.232
Vv [fc I]	0.21 (0.21; 0.43)	0.43 (0.21; 0.43)	-	-	0.21 (0.0; 0.41)^{A,B,C}	0.0 (0.0; 0.21)^{A,B,C}	< 0.001
MMP9	44.7 (40.1; 44.8)	40.9 (39.8; 45.6)	53.9 (48.6; 66.2)	53.0 (38.3; 58.1)	42.2 (27.3; 53.7)	64.1 (45.5; 93.9)	0.169

**Kruskal-Wallis. Data expressed as median and 25% and 75% percentiles. COX-2: Cyclooxygenase-2; Vv [fc I]: Volume Density of collagen fibers I; MMP 9: Metalloproteinase type 9; CS: sedentary non-ovariectomized control; COS: sedentary ovariectomized control; COT: trained ovariectomized control; LDL-S: non-sedentary ovariectomized LDL knockout; LDL-OS: sedentary ovariectomized LDL knockout; LDL-OT: trained ovariectomized LDL knockout. A: statistically significant difference between the studied group and the COS group; B: statistically significant difference between the studied group and the TOC group; C: statistically significant difference between the studied group and the LDL-S group.*

Table 3 – Comparison of the variables Metalloproteinase type 2, Anti-8-Hydroxydeoxyguanosine and Volume Density of collagen fibers III (Vv [fc III]), with the groups studied.

Variables	CS	COS	COT	LDL-S	LDL-OS	LDL-OT	p*
MMP 2	28.5 (4.0)	35.3 (9.1)^{A}	49.0 (3.8)^{A}	54.8 (52.0)^{A}	40.5 (9.6)^{A,B,C,D}	46.8 (31.0)^{A,B,C,E}	< 0.001
8-OHDg	105.2 (7.6)	70.0 (10.8)^{A}	64.9 (4.7)^{A}	51.7 (0.5)^{A}	15.3 (7.5)^{A,B,C,D}	38.7 (8.4)^{A,B,C,E}	< 0.001
Vv[fc III]	0.007 (0.037)	0.003 (0.024)	0.016 (0.067)	0.015 (0.057)	0.013 (0.062)	0.009 (0.043)	0.649

**ANOVA. Data expressed as mean and standard deviation. A: statistically significant difference between the studied group and the CS group; B: statistically significant difference between the studied group and the COS group; C: statistically significant difference between the studied group and the TOC group; D: statistically significant difference between the studied group and the LDL-S group; E: statistically significant difference between the studied group and the LDL-OS group. MMP2: Metalloproteinase type 2; 8OHdG: Anti-8-Hydroxydeoxyguanosine; Vv [fc III]: Volume Density of collagen fibers III; CS: sedentary non-ovariectomized control; COS: sedentary ovariectomized control; COT: trained ovariectomized control; LDL-S: non-sedentary ovariectomized LDL knockout; LDL-OS: sedentary ovariectomized LDL knockout; LDL-OT: trained ovariectomized LDL knockout.*

in relation to the COS group, 76% in relation to the COT group and 70% in relation to the LDL-S group. When training was performed in the dyslipidemic ovariectomized group (LDL-OT), the data presented a 152% increase in relation to the LDL-OS group and a decrease in relation to the control groups, with 63% for the CS group, 45% for the COS group and 40% for the COT group. For the parameters related to volume density of type III collagen fibers, metalloproteinase type 9 and inflammation (COX2), the values obtained for the control and dyslipidemic groups do not present significant differences in any parameter, table 3.

Discussion

Physical activity is recognized as an important non-pharmacological treatment for numerous diseases and conditions, including dyslipidemia and menopause. Studies indicate that collagen fibers are present in the process of myocardial remodeling, which occur due to aging and other factors.[17,18]

Our data show that in the myocardium, the expression of type III collagen fibers did not differ between groups and parameters. In relation to type I collagen, ovariectomy and training brought a decrease in the levels presented in relation to the sedentary ovariectomized control group. Results similar to those found in our study verified the same variable in animals after a period of obesity induced by a diet rich in unsaturated fat.[19] Interestingly, the findings reported in this article have similar results only with the proposed physical activity. Another study where acute myocardial infarction was induced in rats, the gradual increase of types I and III collagen was observed at 4 weeks. The kinetics of collagen I/III increase, in combination with the decrease of the elastic fibers in the infarcted area after an MI, provided evidence that impaired cardiac function after an MI was due to healing or infarct scar formation, with increased rigidity and less flexibility of the heart.[20]

Our results suggest that the aging period in this study does not appear to interfere with the increase in the expression of collagen fibers presented in other studies.[21,22] However, when evaluating the LDL-OT groups, there is a clear reduction in the volume of type I collagen fibers. This verification was obtained using the proposed training protocol (intensity or duration).[23,24]

Metalloproteinase type 2 and type 9 also participate in the remodeling process of cardiac tissue, and are present in several pathologies such as inflammatory and cardiovascular diseases, among other injuries.[24-29] The expression of metalloproteinase type 9 did not differ between groups and parameters. Regarding metalloproteinase type 2, an increase was shown in the control group with ovariectomy and physical training even in the presence of dyslipidemia. This process explains the factor with the collagen indexes when these are not elevated, because the degradation of collagen and the extracellular matrix is peformed by the action of the metalloproteinases.[25,30-32] The elevated presence of MMPs in patients with dyslipidemias found in some studies suggest their participation in the matrix degradation process in atherosclerotic plaques and in the ruptures of these and with exposure of the nucleus[17,33] and are independent predictors for the progression of kidney disease and are independently associated with an increased risk of mortality.[34]

The expression of COX2 in our study did not present statistical significance, indicating that in all groups and parameters, there were no changes for these data. Thus, in this parameter chosen to verify inflammation, no changes are observed showing that the factors associated with the groups do not interfere in such an evaluation.

Aging, menopause and dyslipidemia are factors that also result in oxidative stress.[3-5] In our research, oxidative stress was verified through the expression of 8OHdG, and ovariectomy decreased the values of this parameter in the control and dyslipidemic groups, differing from the results obtained in other studies.[5,35] When physical training was performed, the values were decreased in the control group, but in the dyslipidemic group, they presented an increase. Interestingly, this marker seems to have no association with the groups proposed in this experimental model.

Conclusion

The data of this research indicate that physical exercise beneficially influenced the control and dyslipidemic groups in the volume density parameter of type I collagen fibers and the control group in relation to oxidative stress.

Author contributions

Conception and design of the research: Brianezi L, Maifrino LBM; Acquisition of data: Brianezi L, Ornelas E, Sousa LVA; Analysis and interpretation of the data: Brianezi L, Ornelas E, Gehrke FS, Fonseca FLA, Sousa LVA, Souza J, Maifrino LBM; Statistical analysis: Brianezi L, Gehrke FS, Fonseca FLA, Souza J; Writing of the manuscript: Brianezi L, Ornelas E, Gehrke FS, Fonseca FLA, Alves BCA, Sousa LVA, Maifrino LBM; Critical revision of the manuscript for intellectual content: Gehrke FS, Fonseca FLA, Alves BCA, Maifrino LBM.

Potential Conflict of Interest

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

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Study Association

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

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Universidade de São Judas Tadeu under the protocol number 058. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013.

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The Impact Of Exercise On Inflammation, Oxidative Stress And Remodelling In Cardiac Muscle

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Short Editorial related to the article: Effects of Physical Training on the Myocardium of Oxariectomized LDLr Knockout Mice: MMP 2/9, Collagen I/III, Inflammation and Oxidative Stress

Aging is naturally connected with a decline, in some if not all physiological functions, namely loss of bone mass density (BMD) and strength associated with the loss of muscle mass.[1-3]

This muscle loss happens mainly due to an imbalance between muscle protein synthesis and muscle protein breakdown. The increase of catabolic factors such as oxidative stress and inflammation contribute significantly to the above process. Nevertheless, the weakening of strength and muscle loss is not linear, occurring differently in all sexes. Other factors such as a decline in hormonal levels due to menopause phenomenon are thought to be also implicated in this process.[1] In fact, some authors proposed that, in females, an accelerated loss of muscle mass and strength arises at an earlier age than in males, around the time of menopause.[1] A good body of evidence supports that the decline in muscle mass may be in line with the estrogen decrease that typifies menopausal years.[3]

The present study published at *Arquivos Brasileiros de Cardiologia* by Brianezi et al.[4] proposed to investigate the aerobic exercise training on the left ventricle in low-density lipoprotein (LDL) knockout ovariectomized mice, mimicking the effects of menopause, exercise and its effects on muscles of the mouse.

It is well known that estrogen decrease contributes to the loss of BMD, as well as to the redistribution of subcutaneous fat to the visceral area, associated to an increased risk of cardiovascular disease, affecting the quality of life of females. To worsen the undesirable impact of menopause on female's health, the decrease in estrogen levels may also have a direct effect on muscle tissue.[1,3]

In order to better understand the above-mentioned effects, Ledimar et al.,[4] design the following experiment; a group of thirty animals were divided into 6 groups, each with 5 mice: non-ovariectomized sedentary control, ovariectomized sedentary control, ovariectomized trained control, non-ovariectomized sedentary LDL knockout, ovariectomized sedentary LDL knockout, ovariectomized LDL knockout trained. The animals were ovariectomized at 9 months according to the protocol described, after that the animals were exposed to two different tests, one regarding the max training test and a second one training exercises. Then animals were euthanized and parameters such as the average volume density type I and III collagen fibres, matrix metalloproteinases (MMP) 2 and 9, oxidative stress (OS) were analysed. Their results revealed that the exercise protocol altered the volume of collagen fibres in type I and collagen remodelling parameters namely MMP-2, and further reduced the OS parameter of 8-hydroxy-2'-deoxyguanosine (8-OhdG).

In females, aging of the vascular system only occurs due to a decline of ovarian function along with the decline in associated circulating hormones, in particular estrogen.[5] Although the risk factors, age and estrogen deficiency are well characterized, the mechanism of estrogen action in the vasculature compromised by aging are not well determined. Inflammation is associated with the aging of the vascular system, mainly due to the elevated levels of proinflammatory cytokines, such as tumour necrosis factor (TNF), which is also known to induce MMP. For example, MMP2 can specifically cleavage big endothelin-1, suggesting the role of this proteolytic enzyme in the vascular wall. Also, an interesting study found increased MMP2 activity in the mesenteric arteries from aged/estrogen-deficient animals, which was restored when the animals were treated with an anti-inflammatory agent targeting TNF.[6] Also, the major source of MMP-9 are leucocytes, major key players in inflammatory process, suggesting that MMPs are critical modulators of vascular disease in an aging/estrogen-deficient model.

Although estrogen replacement had been proposed for the management of cardiovascular risk associated with aging in female, its efficacy is controversial. Physical activity seems to be an effective alternative to estrogen supplementation in post-menopausal females, improving aerobic fitness and physiological adaptations of the cardiovascular system.[7-9]

There is some intriguing evidence related to the loss of estrogen in mice showing a role in muscle contractile properties. Wohlers et al.[10] studied the contractile properties

Keywords

Coronary Artery Disease; Exercise; Menopause; Dyslipidemias; Physical activity; Collagen; Oxidative Stress; Inflammation; Mice.

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of ovariectomized mice muscle, has demonstrated the lower capability of activating adenosine monophosphate kinase (AMPK) phosphorylation.[10] This protein is important for glucose uptake and lipid oxidation in muscle, being implicated in energy production, needed to produce muscle contractions.[1,11,12]

Associated to physical activity is the generation of reactive species of oxygen (ROS) that may damage cell membranes lipids, proteins as well as both mitochondrial and nuclear DNA in case of oxidative stress, that can result in serious or mortal cellular injury.[13,14]

Novais et al.[15] reported that with eight weeks of exercise training in the trained hypertensive menopausal group, aerobic training was effective in promoting an increase in superoxide dismútase (SOD) and catalase, antioxidant agents, which have a crucial role in oxidative stress modulation. Also in animal studies, Claudio et al.[16] demonstrated that eight weeks of interval training programs significantly increased SOD and catalase expression, contributing to the reduction of cardiac superoxide production in rats with ovariectomized, in this case with hypertension, which may prevent coronary heart disease in hypertensive postmenopausal women.[1,7,14]

Brianezi et al.[4] conclude that moderate-intensity aerobic training acts on the volume of collagen fibres and on the collagen remodelling, with reduced oxidative stress in left ventricles of mice ovariectomized LDLr Knockout. It is known that after menopause, different factors contribute to the decline in muscle mass, the combination of physical inactivity, protein intake and oxidative stress[16] clearly contribute the increase to this process.[16] Associated with the oxidative stress increase, characterized by the imbalance between the production and the removal of free radicals, usually due to an inadequate antioxidant system.[16,17] Oxidative stress is related to a higher ROS production from the mitochondria, which can induce cell apoptosis.[18] Meaning that the mitochondrial DNA may be damaged due to oxidative stress, affecting mitochondria capacity to produce energy, contributing to a higher susceptibility to apoptosis which finally intensifies muscle fibre atrophy or death and muscle mass decrease.[1]

Taking together, the results of Brianeziet et al.[4] conclude that physical exercise contributes positively influencing the control and dyslipidemic groups in the parameter of density and volume of collagen fibres of type I and the control group in relation to oxidative stress. The mechanisms underlying the pathophysiology of menopausal alterations are complex and implicate estrogen-MMP-metabolic deregulation with age-driven vascular changes.

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Aortic Arch Calcification on Routine Chest Radiography is Strongly and Independently Associated with Non-Dipper Blood Pressure Pattern

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Abstract

Background: **Non-dipper blood pressure (NDBP) is one of the important causes of hypertension-related target organ damage and future cardiovascular events. Currently, there is no practical tool to predict NDBP pattern.**

Objectives: **The aim of this study was to investigate the relationship between aortic arch calcification (AAC) on chest radiography and NDBP pattern.**

Methods: **All patients referred for ambulatory BP monitoring test were approached for the study participation. NDBP was defined as the reduction of ≤10% in nighttime systolic BP as compared to the daytime values. AAC was evaluated with chest radiography and inter-observer agreement was analyzed by using kappa statistics. Univariate and multivariate logistic regression analysis was conducted to assess the association of AAC and NDBP pattern. A 2-tailed p-value < 0.05 was considered statistically significant.**

Results: **A total of 406 patients (median age: 51.3) were included. Of these, 261(64%) had NDBP pattern. Overall, the prevalence of AAC was 230 (57%). Non-dipper group had significantly higher prevalence of AAC (70% vs. 33%, p < 0.0001) as compared to the dipper group. Presence of AAC was a strong and independent predictor of NDBP pattern (OR 3.919, 95%CI 2.39 to 6.42) in multivariate analysis.**

Conclusions: **Presence of AAC on plain chest radiography is strongly and independently associated with the presence of NDBP pattern. (Arq Bras Cardiol. 2020; 114(1):109-117)**

Keywords: **Thoracic, Aorta/physiopathology; Calcification; Calcinosis; Cardiomyopathies; Hypertension/imaging diagnosis; Ventricular Function,Left; Antihypertensive Agents/therapeutic use;Blood Pressure Monitoring Ambulatory; Heart Rate.**

Introduction

Hypertension (HT) is the most common cardiovascular disease and it is the leading cause of cardiovascular mortality and morbidity. Blood pressure (BP) follows a circadian pattern with a nocturnal decline of %10 or more as compared with daytime BP. Non-dipper BP (NDBP) pattern is defined as the absence of normal nocturnal decline in BP as compared to daytime measurements. NDBP pattern is associated with disease severity, left ventricular hypertrophy (LVH), proteinuria, secondary forms of HT and insulin resistance.[1-4] Several forms of HT including NDBP pattern can only be detected by ambulatory BP monitoring (ABPM). Moreover, ABPM is superior to office BP measurements in predicting cardiovascular risk.[5,6] However, utilization of ABPM to unselected population is not practical and currently, there is no practical tool to predict NDBP pattern.

NDBP pattern has shown to be associated with arterial stiffness.[4,7,8] Vascular calcification plays an important role in the development of arterial stiffness.[9,10] Accordingly, aortic arch calcification (AAC) has been shown to be closely related to arterial stiffness.[11,12] Thus, we hypothesized that AAC on chest radiography predicts NDBP pattern.

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Methods

Study population

All patients who were referred for ABPM test were approached for the study participation. Indication for ABPM test was left to physician discretion. Following inclusion criteria, we applied: 1) Age ≥ 18-years-old; 2) A valid measurement rate of >85% during the ABPM test. Nighttime workers, patients with inadequate chest x-ray, pregnancy or suspicion of pregnancy, history of moderate to severe cardiac valve disease, malignancy, cardiac or thoracic surgery, coronary artery, cerebrovascular and peripheral vascular disease were excluded from the study. Posterior-anterior (PA) chest radiography and transthoracic echocardiography were performed in all patients. Eligible subjects underwent a comprehensive assessment, including documentation of medical history, physical examination and measurement of laboratory variables. Body mass index was calculated as the weight in kilogram divided by height in square meter. Diabetes was defined as being on treatment with insulin or oral anti-diabetic drugs. HT and hyperlipidemia were defined as the use of anti-hypertensive

drugs or lipid-lowering drugs, respectively. The institutional ethics committee approved the study protocol. Patients were divided into two groups according to circadian BP pattern; non-dipper and dipper group.

Ambulatory blood pressure monitoring

ABPM studies were carried out using a Mobil-O-Graph (M-o-G; I.E.M, Germany) monitoring device. The first hour was discarded from the analysis. BP readings were obtained automatically at the 30-min interval and if >85% of the measurements were valid then it was included in the analyses. Daytime, nighttime and 24-hour BP data and the percentage of the decrease in nighttime systolic BP vs. daytime systolic BP were recorded. The default setting for daytime (07:00 to 23:00) and nighttime (23:00 to 07:00) hours were modified appropriately based on the patient's feedback. NDBP pattern was defined as the reduction of ≤ 10 % in nighttime systolic BP as compared to the daytime systolic BP.

Evaluation of AAC

All patients had chest radiography in the PA view. The standard PA chest radiograph (40 cm×40 cm; Curix HT 1.000G Plus, Agfa, Mortsel, Belgium) was acquired with the patient standing up (Thoramat, Siemens, Erlangen, Germany). The focus–patient distance was 150 cm. An automated exposure control with a fixed tube voltage of 117 kV was used. We noted the presence of calcification in the aortic knob. AAC was graded as follows: Grade 0, no visible calcification; Grade 1, small spots of calcification or thin calcification; Grade 2, one or more areas of thickened calcification, and Grade 3, circular calcification on the aortic knob[13] (Figure 1). One hundred randomly selected chest radiography for evaluation of AAC were independently evaluated by two cardiologists, who was unaware of the result of the patient's ABPM data to assess the reliability of AAC diagnosis and Kappa value was detected as 0.812 and $p < 0.001$.

Laboratory tests

A venous blood sample was collected from each participant under fasting conditions. Fasting blood glucose, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglyceride and creatinine were measured by standard laboratory methods. Glomerular filtration rate (GFR) was calculated using CKD-EPI Creatinine Equation.[14]

Echocardiographic examination

All patients were examined in the left lateral decubitus position using by a commercially available system (Vivid 4 GE Medical System, Horten, Norway) with a phased-array 3.5-MHz transducer. The conventional M-mode and B-mode parameters were measured in accordance with the American Society of Echocardiography guidelines. Left ventricular end-diastolic (LVEDD) and end-systolic (LVESD) diameters, and posterior (PWT) and septal (IVST) wall thicknesses were measured. Left ventricular ejection fraction was measured by using the Teichholz method. Left ventricular mass (LVM) was calculated using the Devereux equation: $LVM = 0.8\{1.04[([LVEDD + IVST + PWT]^3 - LVEDD^3)]\} + 0.6$.[15] Left ventricular mass index (LVMI) was calculated by dividing the LVM by body surface area. LVH was defined as LVMI > 115 g/m² for men and 95 g/m² for women.[16] Based on relative wall thickness (2 x PWT/LVEDD) and the presence or absence of LVH various types of the left ventricular geometrical pattern were defined (normal geometry, concentric LVH, eccentric LVH, and concentric remodeling).

Statistical analysis

Continuous variables were expressed as mean (standard deviation) or median (interquartile range (IQR)), and categorical variables as number (percentage). The distributions of the continuous variables across the study groups were tested with the Kolmogorov–Smirnov test. Normally distributed data were compared using the Independent Samples t-test and data with non-normal distribution were compared using the Mann-Whitney U test. Categorical data were compared using the chi-square or Fisher's exact tests when needed.

Univariate and multivariate logistic regression analyses were conducted to assess the association of AAC and NDBP pattern. In multivariate regression analysis (Enter method), the effect size was adjusted for variables with a univariate significance level of < 0.1. Adjusted odds ratios (OR), along with their 95%CIs were presented. A 2-tailed p-value < 0.05 was considered statistically significant. All statistical analyses were performed using the IBM SPSS software (IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.)

Results

A total of 406 patients (mean age 51.3 female 58%) were included. Two hundred sixty-one (64%) had NDBP pattern and classified as non-dipper group. The remaining 145 (36%) patients who had dipper BP pattern were classified as dipper group. As compared to the dipper group, the non-dipper group was older ($p < 0.001$), had higher LVMI ($p = 0.007$), prevalence of LVH ($p = 0.013$), prevalence of HT ($p = 0.049$) and higher serum triglyceride level ($p = 0.013$). GFR was significantly lower in the non-dipper group ($p < 0.0001$). Groups were similar with respect to the remaining baseline characteristics shown in Table 1.

There was no difference in daytime DBP, 24-hour SBP and 24-h DBP values between non-dipper and dipper groups. However, daytime SBP was lower in non-dipper groups ($p = 0.012$). In addition, nighttime SBP ($p < 0.0001$) and DBP ($p < 0.0001$) values were significantly higher in non-dipper group (Table 2).

Prevalence of AAC was 57% in our study population. Non-dipper group had significantly higher prevalence of AAC (grade ≥ 1) on chest radiography ($p < 0.0001$) as compared to the dipper group (Table 3).

Age, body mass index, female gender, HT, GFR, LVMI, presence of LVH, LV geometric pattern of concentric hypertrophy and AAC were associated with the presence of NDBP pattern in univariate logistic regression analysis with a p-value of less than 0.1 (Table 4). Of these; age, body mass index, female gender, HT, GFR, LVMI, presence of LVH and AAC were entered in multivariate regression model. In the multivariate regression analysis, presence of AAC on chest radiography (OR 3.919, 95%CI 2.392 to 6.421) was the only independent predictors of NDBP pattern (Table 5).

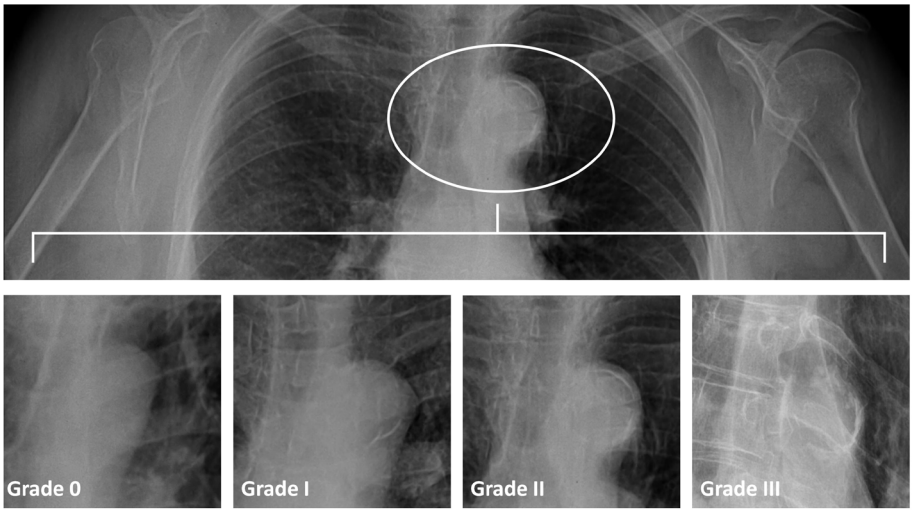

Figure 1 – *Aortic arch calcification grading.*

Discussion

NDBP pattern is one of the important causes of HT-related target organ damage and future cardiovascular events.[1,5,6] In this study, the presence of AAC on chest radiography was a strong and independent predictor of NDBP pattern.

Diagnosis of HT is generally based on daytime office BP measurements, and nighttime BP and NDBP are usually overlooked in clinical practice. However, the association of nighttime and NDBP with HT-related target organ damage is more powerful than daytime BP.[17-19] Patients with NDBP pattern are at high risk for target organ damage including myocardial infarction, LVH, carotid artery disease, chronic kidney disease and stroke.[2-4,20] In the Ohasama study, impaired nocturnal BP decline was associated with cardiovascular mortality.[21] Each 5% decrease in the decline in nocturnal BP was associated with an approximately 20% greater risk of cardiovascular mortality. Importantly, this association was observed not only in hypertensive, but also in normotensive individuals.[21] Moreover, cardiovascular mortality and morbidity can be reduced by achieving a better nocturnal BP control.[22] Thus, effective treatment of HT should include nighttime BP control as well. Currently, ABPM remains the only method for the diagnosis of nocturnal BP variations. Unfortunately, it is relatively expensive, inconvenient for routine usage and not widely available tool. Yet, it may not be practical to perform ABPM in every hypertensive patient. A practical and inexpensive tool may help the filtration of the unselected population for ABPM. Here, in this study, we have shown that AAC on plain chest radiography, an inexpensive and widely available tool, has a strong predictive ability for NDBP pattern.

There are several possible mechanisms that may explain the relationship between AAC and NDBP pattern. First, AAC was found to be strongly correlated with pineal gland calcification which may reduce melatonin secretion during sleep.[23] Melatonin plays a pivotal role in the regulation of nocturnal BP.[24-26] Autonomic nervous system activity is involved in the control of the circadian variation of BP[27,28] and impaired sympathovagal balance with increased sympathetic nervous activity and/or decreased vagal activity has been documented in non-dippers.[29,30] Melatonin shifts the balance between the sympathetic and parasympathetic system in favor of the parasympathetic system. It may also reduce nighttime BP by its direct arterial vasodilator effect.[25] Accordingly, exogenous melatonin has been shown to reduce nighttime BP.[31,32] Thus, a reduced melatonin secretion during nighttime may significantly impair nocturnal BP decline. Second, AAC is closely related with vascular stiffness and loss of arterial compliance[33] which in turn may impair arterial relaxation capacity. An impaired nocturnal decrease in BP was found to be independently associated with aortic stiffness in patients with nocturnal HT.[34] Moreover, it has been found that increased arterial stiffness is more associated with nighttime BP load than day time BP.[35] Third, the relationship between arterial BP and arterial calcifications is likely a bidirectional phenomenon. Increased arterial BP load may facilitate arterial calcification and vice versa. Non-dippers are exposed to an abnormal the nocturnal BP load which may accelerate arterial calcification and stiffness. Fourth, the underlying clinical profile of the patients with impaired nocturnal BP decline and arterial calcification are similar. Both conditions are associated with age, renal diseases, diabetes, sleep apnea, autonomic dysfunction, malignant HT and coronary artery disease.[36,37]

NDBP pattern is associated with disease severity and a higher risk of subsequent cardiovascular events. This risk can be reduced by achieving better dipping patterns and nocturnal BP levels. In clinical practice, many patients with controlled daytime BP levels are not evaluated for the nighttime BP levels. Our results may help to improve detection of NDBP pattern and nocturnal HT. Appropriate treatment of these patients by changing antihypertensive medications or administering the antihypertensive medications in the night may eventually help to improve dipping pattern and patient outcomes.

Table 1 – Baseline characteristics of the study groups

	Non-Dipper (n = 261)	Dipper (n = 145)	p-value
Age (year)	54 (13)	47 (14)	< 0.001
Weight (kg)	80 (13)	79 (13)	0.336
Height (cm)	165 (8)	166 (9)	0.084
Body surface area (m^2)	1.90 ± 0.18	1.90 ± 0.18	0.864
Body mass index (kg/m^2)	29 (5)	28 (4)	0.067
Female gender (n, %)	160 (61.3)	76 (52.4)	0.061
Obesity (n, %)	106 (40.6)	51 (35.2)	0.281
Hypertension (n, %)	135 (51.7)	60 (41.4)	0.049
Diabetes (n, %)	59 (22.6)	25 (17.2)	0.201
Hyperlipidemia (n, %)	42 (16.1)	26 (17.9)	0.634
Smoking (n, %)	45 (17.2)	34 (23.4)	0.130
ACE inhibitors (n, %)	71 (27.2)	33 (22.8)	0.326
Angiotensin receptor blockers (n, %)	27 (10.3)	16 (11)	0.829
Calcium channel blockers (n, %)	30 (11.5)	18 (12.4)	0.783
Beta blockers (n, %)	24 (9.2)	16 (11.0)	0.551
Diuretics (n, %)	29 (11.1)	21 (14.5)	0.322
Creatinine (mg/dL)	0.80 (0.20)	0.8 (0.3)	0.910
Glomerular filtration rate ($mL/min/1.73\ m^2$)	98 ± 13	103 ± 26	< 0.0001
Total cholesterol (mg/dL)	190 ± 39.5	195 ± 39.3	0.200
Triglyceride (mg/dL)	190 (40)	172 (83)	0.013
Low-density lipoprotein (mg/dL)	112 ± 32	114 (33)	0.816
High-density lipoprotein (mg/dL)	47 (11)	46 (12)	0.528
Glucose (mg/dL)	107 (31)	103 (30)	0.088
Left atrial diameter (mm)	35 (4)	34 (4)	0.070
Left ventricular ejection fraction (%)	65 ± 6	64 (5)	0.437
Left ventricular mass index (gr/m^2)	93 (20)	87 (18)	0.007
Left ventricular hypertrophy (n, %)	61 (23.4)	19 (13.1)	0.013
Left ventricular geometry (n, %)			
Normal	49 (18.8%)	30 (20.7%)	0.640
Concentric remodeling	151 (57.9%)	96 (66.2%)	0.099
Eccentric hypertrophy	19 (7.3%)	5 (3.4%)	0.117
Concentric hypertrophy	42 (16.1%)	14 (9.7%)	0.072

Continuous variables are presented as median (interquartile range) or mean (standard deviation); categorical variables are presented as number (percentage). ACE: angiotensin converting enzyme.

Both AAC and NDBP are associated with several HT-related target organ damage and future cardiovascular events in patients with HT.[1,5,6,38-40] In this study, we showed that there is also a strong association between AAC and NDBP. Further studies are needed to confirm our findings and to evaluate the potential association of AAC with other hypertensive subforms.

Study limitations

This study has several limitations. The small sample size is the main limitation. Our definition of NDBP pattern was based on systolic BP variations. Although this is the most commonly used definition of NDBP, diastolic BP values may also be used to assess NDBP. We did not study autonomic nervous system activity or vascular stiffness parameters to explain the potential mechanistic link between AAC and NDBP. Finally, we did not study the association of AAC with cardiovascular events.

Conclusion

Presence of AAC on plain chest radiography is strongly and independently associated with the presence of NDBP pattern. Routine use of this simple and inexpensive tool in clinical practice may have additional benefits in the detection and control of the

Table 2 – Ambulatory blood pressure variables of the study groups

	Non-Dipper (n = 261)	Dipper (n = 145)	p-value
Day time mean SBP (mmHg)	124 (14)	127 (13)	0.012
Day time mean DBP (mmHg)	77 (11)	79 (11)	0.407
Nighttime mean SBP (mmHg)	122 (15)	108 (12)	< 0.0001
Nighttime mean DBP (mmHg)	74 (10)	67 (10)	< 0.0001
24-hour mean SBP (mmHg)	124 (14)	121 (12)	0.108
24-hour mean DBP (mmHg)	76 (10)	75 (10)	0.127
Change in SBP (mmHg)	1.9 (7)	19 (5)	< 0.0001
Change in DBP (mmHg)	4 (8)	14 (10)	< 0.0001

Continuous variables are presented as median (interquartile range) or mean (standard deviation).SBP: systolic blood pressure; DBP: diastolic blood pressure.

Table 3 – Aortic arch calcification grades in the study groups

	Non-Dipper (n = 261)	Dipper (n = 145)	p-value
Aortic arch calcification (n, %)			
Grade 0	79 (30.3)	97 (66.9)	
Grade 1	107 (41.0)	36 (24.8)	< 0.0001
Grade 2	62 (23.8)	11 (7.6)	
Grade 3	13 (5.0)	1 (0.7)	
Aortic arch calcification grade ≥ 1 (n, %)	182 (69.7)	48 (33.1)	< 0.0001
Aortic arch calcification grade ≥ 2 (n, %)	75 (28.7)	12(8.3)	< 0.0001
Aortic arch calcification grade ≥ 3 (n, %)	13 (5.0)	1(0.7)	0.023

nocturnal BP. Moreover, this tool may help to use of ABPM devices more precisely, which may reduce healthcare cost.

Author contributions

Conception and design of the research, Statistical analysis and Critical revision of the manuscript for intellectual content: Adar A, Onalan O; Acquisition of data: Adar A, Cakan F, Akbay E, Karakaya E; Analysis and interpretation of the data: Adar A, Onalan O, Cakan F, Akbay E, Karakaya E; Writing of the manuscript: Adar A, Onalan O, Cakan F, Akbay E, Karakaya E.

Potential Conflict of Interest

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

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Study Association

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

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Abant Izzet Baysal University Clinical Researches Ethics Comitee Approval under the protocol number 2015/20. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

Table 4 – Univariate analysis for non-dipper blood pressure pattern

	β	p-value
Age (year)	0.037	< 0.0001
Body surface area (m^2)	0.098	0.864
Body mass index (kg/m^2)	0.049	0.029
Female gender (%)	-0.363	0.082
Obesity (%)	0.231	0.281
Hypertension (%)	0.417	0.046
Diabetes mellitus (%)	0.338	0.202
Hyperlipidemia (%)	-0.130	0.635
Smoking (%)	-0.385	0.131
Medications (%)		
Angiotensin converting enzyme inhibitor	0.238	0.326
Angiotensin receptor blocker	-0.072	0.829
Calcium channel blocker	-0.087	0.783
Beta blocker	-0.203	0.552
Diuretics	-0.304	0.323
Creatinine (mg/dL)	-0.241	0.512
Glomerular filtration rate ($mL/min/1.73m^2$)	-0.027	0.001
Total cholesterol (mg/dL)	-0.003	0.200
Triglyceride (mg/dL)	-0.002	0.067
Low density lipoprotein (mg/dL)	-0.002	0.608
High density lipoprotein (mg/dL)	0.005	0.587
Glucose (mg/dL)	0.005	0.219
Left atrial diameter (mm)	0.040	0.144
LV ejection fraction (%)	0.009	0.615
LV mass index (gr/m^2)	0.017	0.003
Left ventricle hypertrophy (%)	0.704	0.014
LV geometry (%)		
Normal	-0.121	0.640
Concentric remodeling	-0.356	0.099
Eccentric hypertrophy	0.788	0.125
Concentric hypertrophy	0.585	0.074
Day time mean SBP (mmHg)	-0.015	0.052
Day time mean DBP (mmHg)	-0.009	0.339
Nighttime mean SBP (mmHg)	0.080	< 0.0001
Nighttime mean DBP (mmHg)	0.071	< 0.0001
24-hour mean SBP (mmHg)	0.016	0.050
24-hour mean DBP (mmHg)	0.015	0.130
Aortic arch calcification (%)		
Grade 0	Reference category	
Grade 1	1.295	< 0.0001
Grade 2	1.935	< 0.0001
Grade 3	2.770	0.008
Aortic arch calcification grade ≥ 1 (%)	1.538	< 0.0001
Aortic arch calcification grade ≥ 2 (%)	1.497	< 0.0001

SBP: systolic blood pressure; DBP: diastolic blood pressure; LV: left ventricle; β: Regression coefficient.

Table 5 – Multivariate analysis for non-dipper blood pressure pattern

			95% CI	
	β	OR	Lower	Upper
Age	0.015	1.015	0.988	1.043
Body mass index	0.037	1.038	0.989	1.090
Left ventricular mass index	0.006	1.006	0.992	1.019
Hypertension	0.059	1.061	0.664	1.696
Triglyceride	-0.003	0.997	0.995	1.000
Presence of aortic arch calcification	1.366	3.919	2.392	6.421
Gender	-0.444	0.641	0.405	1.016
Glomerular filtration rate	0.003	1.003	0.979	1.028

CI: confidence interval; OR: odds ratio; β: regression coefficient.

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Aortic Arch Calcification on routine Chest Radiography is Strongly and Independently Associated with Non-Dipper Blood Pressure Pattern

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Short editorial related to the article: Aortic Arch Calcification on Routine Chest Radiography is Strongly and Independently Associated with Non-Dipper Blood Pressure Pattern

Arterial hypertension is the most prevalent chronic disease worldwide, and it is estimated that in Brazil, according to the Vigitel study of 2018, the Brazilian population has 24.7% of hypertensive individuals.[1] It is the most important risk factor for all cardiovascular diseases, being one of the main factors responsible for stroke, coronary artery disease, heart failure, renal failure, and so on.

Blood pressure is not simply a biological phenomenon characterized by two numbers expressed in mmHg that reflect systolic and diastolic pressure. It is a multiform event resulting from the hydrodynamic action of a complex fluid that exerts force on a compliant vascular wall, with elastic properties governed by multiple forces arising from vascular structures (muscle cells, extracellular matrix, elastic fibers, etc.). This vector wave of blood follows the laws of sympathetic and parasympathetic interaction, varying more or less depending on the conditions of each patient. Therefore, the simple measurement of blood pressure in the office does not reflect the reality of the patient's true daily life.

The several measurements obtained during the 24-hour period have a better meaning in the global context evaluation and can discriminate the blood pressure behavior in the different phases of the day and, especially, during sleep. Ambulatory blood pressure monitoring (ABPM) has a better correlation with all cardiovascular events compared to simple office measurements. The pressure varies widely during the 24-hour period, and during sleep, in individuals considered normal, there is a reduction between 10 and 20% of daytime values. In some studies, the absence of this physiological dipping during sleep, which we call "non-dipper", shows a positive association with an increase in target-organ damage and mortality.[1,2]

This concept that hypertensive individuals (as well as normotensive ones) who do not have a physiological pressure dipping during sleep (non-dipper), are subject to a worse prognosis has been a consensus for some time, well evidenced in several studies; however, the intrinsic mechanisms that lead to a higher risk are not yet fully known.[3-5] In clinical practice, hypertensive patients with the non-dipper pattern usually have some other comorbidity, leading to the suspicion of secondary causes for blood pressure elevation and/or obstructive sleep apnea.

The usefulness of ABPM is quite broad. The European guideline for hypertension very objectively suggests performing out-of-office blood pressure measurements, supplemented with in-office measurements for diagnosing hypertension.[6]

The phenomenon of white coat hypertension and the white coat effect are common and may lead to case wrong conduct and management. In the first, there is an erroneous diagnosis of hypertension and in the presence of the white coat effect, one can start the medication incorrectly, with harm to the patient. These are situations where ABPM is critical for the diagnosis.

Another important and not infrequent aspect is masked hypertension, where the patient has normal office pressure values and levels outside the office are elevated. This situation can be correctly assessed only by out-of-office measurements and represents a huge danger, as target-organ damage is more intense and occurs earlier.[7]

The assessment of out-of-office BP can also be attained by the much more inexpensive and affordable home blood pressure measurement (HBPM), which shows a good correlation with ABPM measurements. However, it does not evaluate BP during sleep, the fundamental period of the biological cycle. That is why ABPM remains the gold standard for out-of-office measurements.[8]

The assessment of sleep, of the phenomena that occur before waking up and after awakening are also very important for a more precise stratification of the risk of cardiovascular events. Kazuomi Kario was one of the pioneers in assessing the effect of arousal on cardiovascular risk, finding greater target-organ damage in those with more intense and sustained blood pressure response.[9]

Nakanishi et al.[10] found that patients who experienced BP increases during sleep rather than the physiological reduction were more subject to cardiovascular events. Studying a population of 828 patients through brain imaging tests, such as MRI, they found that elevated systolic pressure during sleep was associated with subclinical brain disease.[10]

In the study by Adar A. et al.,[11] they found that patients who had aortic arch calcification on routine chest X-ray showed an association with the non-dipper pattern in ABPM.[11] The authors started by detecting a target-organ lesion, aortic atherosclerosis, in a routine exam to look for changes in blood pressure physiology and eventually diagnose or correct other problems.

This association is important, because we can verify the entire aortic arch calcification in the search for non-dippers and, thus, better typify the behavior of arterial hypertension.

Chest X-ray, used in many clinical situations, is an inexpensive, practical exam and, when performed for some

Keywords

Thoracic, Aorta/physiopathology; Calcification; Calcinosis; Cardiomyopathies; Hypertension; Ventricular Function, Left; Antihypertensive Agents; Blood Pressure Monitoring Ambulatory; Heart Rate.

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other reason, it can also be used to screen for non-dippers, as demonstrated in this study. This may be beneficial to the patient, since secondary causes of hypertension, including obstructive sleep apnea, are frequent.

The pathophysiological justification of this association, between the aortic artery calcification and the non-dipping of pressure during sleep, remains unknown. The authors mention the association of this calcification with pineal gland calcification and melatonin reduction, which plays an important role in sleep regulation.[12] Moreover, it also participates in the autonomic regulation with greater accentuation of the parasympathetic system with direct vasodilating effects, thereby reducing blood pressure.[13]

The finding of calcification in the aortic arch allowing the diagnosis of the presence of atherosclerosis immediately changes the cardiovascular risk, wherein clinical care should be more intense and thus improve our clinical practice.

Although there are not robust clinical trials evaluating chromotherapy and the influence of antihypertensive drugs on the non-dipper pattern yet, it is sensible and intuitive that this should be done, when there is no objective cause for no reduction of blood pressure during sleep. In hypertensive patients, the change in the time of medication may change the pattern of nocturnal dipping and possibly benefit the patient.[14,15]

An adequate BP control in the early hours of the morning means the use of drugs with adequate 24-hour coverage; however, some medications do not provide this effect. Changing the time when the patient takes the drug, particularly to the afternoon, may result in a pressure behavior closer to the normal circadian rhythm.

We still have a long road ahead to assess blood pressure behavior, but some light is already emerging to unravel the mechanisms implicated in this complex web of hypertensive disease etiology.

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Pathophysiology and Treatment of Heart Failure with Preserved Ejection Fraction: State of the Art and Prospects for the Future

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Introduction

Heart failure (HF) is extremely prevalent and has a considerable impact on mortality and quality of life.[1] It affects nearly 1-3% of the adult population in developed countries, exponentially increasing with age and affecting more than 10% of the population over 70 years. Given the increase in the average life expectancy, better diagnostic methods and increased comorbidities, a greater prevalence of heart failure is expected.[2]

It is a clinical syndrome characterized by classic symptoms (such as fatigue, dyspnea) that may be accompanied by clinical signs (elevated jugular pressure, pulmonary crackles and peripheral edema). It is caused by structural and/or functional cardiac abnormalities, resulting in reduced cardiac output and/or elevated intracardiac pressures at rest or during stress.[3]

The main terminology used to describe HF is based on the measurement of the left ventricular ejection fraction (EF), differentiating patients with reduced <40% (HFrEF), mid-range 40-49% (HFmrEF) and preserved ≥50% (HFpEF) ejection fraction. This classification is important due to different underlying etiologies, pathophysiology, available treatment and its respective response.[3] HFpEF accounts for about half of the cases of HF in developed countries.[4]

Its pathophysiology is complex, heterogeneous and still poorly understood. The wide variety of phenotypes resulting from the several pathophysiological mechanisms, comorbidities and dominant clinical characteristics, make diagnosis and treatment extremely challenging.[4]

Unlike HFrEF, no treatment has unquestionably shown a reduction of morbidity or mortality in patients with HFpEF or HFmrEF. Several clinical trials evaluating drugs proven to be effective in HFrEF have failed to demonstrate prognostic benefits in these patients.[4] Current recommendations are based on symptom relief, screening, and treatment of comorbidities.[3]

New therapies are presently under research, especially directed at the pathophysiological mechanisms of the disease.[5] This review addresses the pathophysiology of HFpEF and summarizes the studies that have been carried out regarding treatment, including failures, hopes and future prospects.

For this article, we carried out a systematic search in three databases: Medline - Pubmed, ISI Web of knowledge and Scopus, using the following keywords in English and Portuguese: "Heart failure AND preserved ejection fraction", "Heart failure AND preserved ejection fraction AND physiopathology" and "Heart failure AND preserved ejection fraction AND treatment". The study was conducted between January and March of 2019. Prospective and retrospective studies were included. Clinical cases, abstracts presented at conferences (not published as articles) and studies with a sample size of less than 10 patients were excluded. The eligibility of each study was independently assessed by three researchers. The divergent opinions regarding the relevance of the articles were resolved by consensus among the authors.

Keywords

Heart Failure/physiopathology; Heart Failure/diagnosis; Heart Failure/drug therapy; Systolic Volume; Heart Failure/complications.

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Pathophysiology

The pathophysiology of the disease is complex and remains insufficiently understood. It is known that these patients are generally older, females and have multiple cardiovascular comorbidities, such as hypertension, atrial fibrillation (AF), coronary artery disease (CAD), pulmonary hypertension (PH), and non-cardiovascular diseases such as diabetes, chronic kidney disease (CKD), anemia, chronic obstructive pulmonary disease (COPD), among others. They also have a higher percentage of non-cardiovascular pathologies, with a great impact on morbidity and mortality, and a lower incidence of acute myocardial infarction (AMI) as well as sudden cardiac death or death from HF.[6]

Historically, HFpEF was exclusively associated with diastolic dysfunction, opposed to HFrEF, which was associated with systolic dysfunction. It is currently known that this is not such a clear-cut matter, as both types of HF may also show systolic and/or diastolic dysfunction. Different mechanisms are involved in HFpEF. This is thought to result from a complex variety of cardiac, vascular and systemic dysfunctions, with the contribution of several comorbidities.[4] (Figure 1)

Diastolic dysfunction is usually present and results from structural changes (cardiac fibrosis, hypertrophy and remodeling), microvascular dysfunction and metabolic abnormalities, with increased stiffness and decreased cardiac compliance. This leads not only to an increase in LV filling pressures, but also to structural and functional changes at the atrial, pulmonary and right ventricular levels, due to a rise in upstream pressures. The systolic reserve is also affected, mainly due to changes in the ventricular-vascular coupling ratio.[4]

Atrial changes, with dilatation and remodeling, favor the appearance of AF. Pulmonary hypertension, present in 53-83%

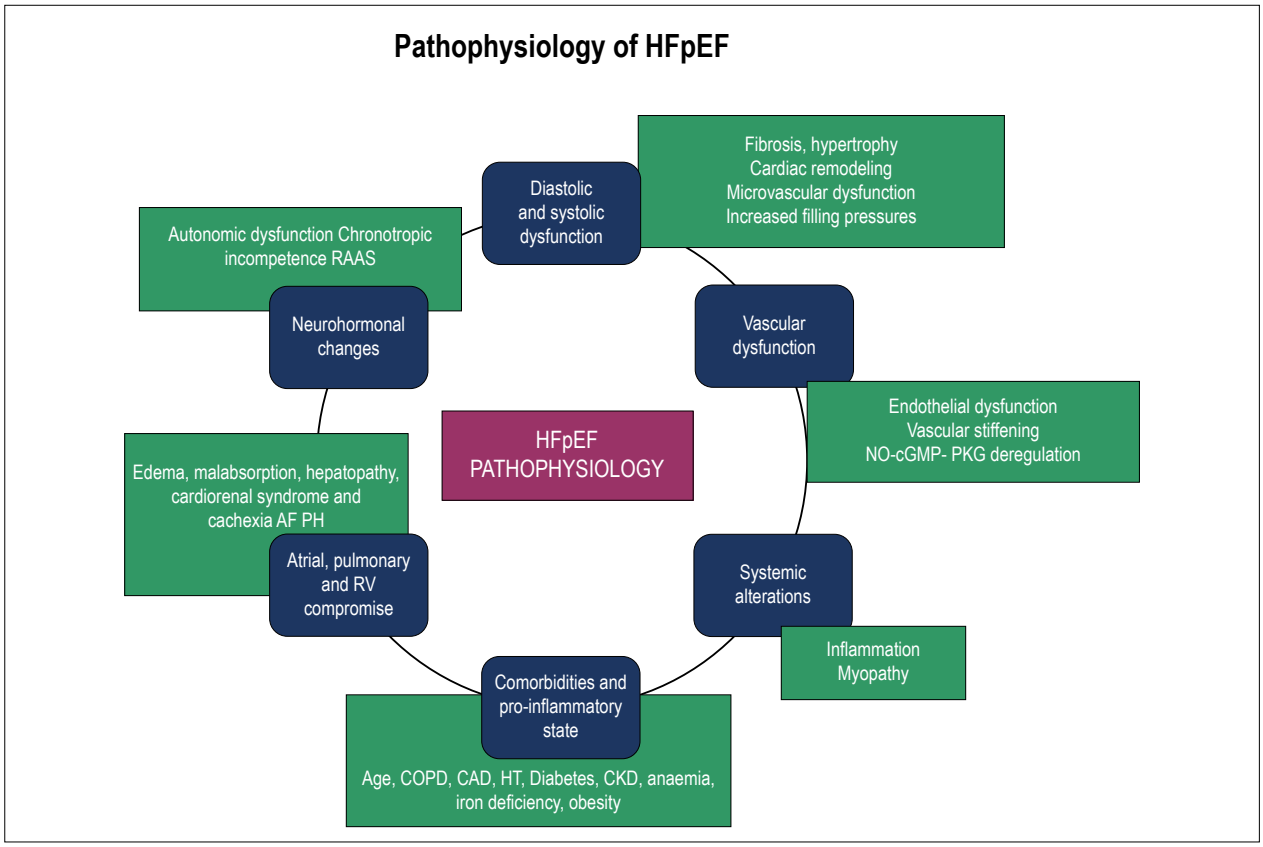

Figure 1 – *Pathophysiology of HFpEF - possible mechanisms involved. AF: atrial fibrillation; CAD: coronary artery disease; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; HFpEF: heart failure with preserved ejection fraction; HT: arterial hypertension; NO-cGMP-PKG: nitric oxide, reduced cyclic guanosine monophosphate and protein kinase G; PH: pulmonary hypertension; RAAS: renin-angiotensin-aldosterone system; RV: right ventricle.*

of the cases and associated with a worse prognosis, also seems to contribute to the disease progression.[7] The onset of right ventricular dysfunction, with systemic venous congestion, also predicts worse results, associated with edema, malabsorption, congestive hepatopathy, cardiorenal syndrome and cachexia.

Another mechanism involved is chronotropic incompetence, with inadequate heart rate (HR) variations, probably due to autonomic nervous system dysfunctions.[4] Electrical and/or mechanical, systolic and diastolic asynchronies were also observed in some patients.[7] Its magnitude is related to the extent of diastolic dysfunction and exercise capacity.[4]

Many of these changes are not apparent, nor do they entail any impairment at rest, with functional reserve limitations being evident only under stress.

Neurohormonal alterations, such as autonomic dysfunction and activation of the renin-angiotensin-aldosterone system (RAAS) are also important mechanisms involved.[4]

At the vascular level, we can observe endothelial dysfunction, systemic inflammation, increased vessel stiffness and impaired vasodilation. A potential mechanism could be the deregulation of the NO-sGC-cGMP-PKG signaling pathway (nitric oxide, soluble guanylate cyclase, reduced cyclic guanosine monophosphate and protein kinase G), which is responsible for smooth muscle relaxation, cardiac protection, gene transcription, endothelial permeability and platelet inhibition.[5] At the peripheral level, musculoskeletal changes seem to contribute to aerobic capacity reduction, with less exercise tolerance.

Both the age and the several comorbidities intensify these mechanisms and contribute to disease progression. The interaction between the various pathophysiological factors and comorbidities and the relative dominance of each of them makes this pathology complex and heterogeneous, making its diagnosis and treatment extremely difficult. A subgroup analysis with certain phenotypes can facilitate this process by allowing a more particular and direct approach.[4]

Diagnosis

The diagnosis of HFpEF is more challenging than the diagnosis of HFrEF. There have been several proposed classifications and inclusion criteria in the conducted studies, contributing to the enormous heterogeneity of patients assessed in the clinical trials.[1]

The current guidelines proposed by the European Society of Cardiology suggest the existence of 3 diagnostic criteria: symptoms and signs of HF, LVEF ≥ 50%, elevated levels of natriuretic peptides and relevant structural heart disease and/or diastolic dysfunction.[3] Notwithstanding these

recommendations, and given the clinical heterogeneity, absence of pathognomonic criteria and the multiplicity of differential diagnoses, there are several challenges and uncertainties to be faced.[5]

Treatment

Unlike HFrEF, no treatment has yet shown a reduction in morbidity or mortality. Therefore, current recommendations are based on symptom relief with diuretics, screening and treatment of comorbidities.[3] Diuretics are recommended in case of congestion, for symptom relief, regardless of the LVEF.[3] They are widely used, especially loop diuretics, even though there are no specific recommendations concerning which diuretic therapy should be followed.[8]

Several clinical trials have studied the effect of drugs proven to be effective in HFrEF for the treatment of patients with HFpEF (Table 1-A).

1. Beta-blockers (BB)

The *Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure,* the "SENIORS" trial,[9] evaluated the effect of nebivolol in patients over 70 years with a history of HFrFE and HFpEF (LVEF > 35%). Despite the reduction in morbidity and mortality, most patients had reduced LVEF (mean 36%) and a history of coronary artery disease and, thus, it was not possible to extrapolate the results to patients with true HFpEF. In a meta-analysis performed later, the BB were the only drugs able to reduce cardiovascular and all-cause mortality.[10] However, patients with different LVEF were included, so the obtained results might possibly have been due to pleiotropic effects in patients with HFmrEF. Recently, our group showed the role of BB in patients with acute coronary syndrome and HFmrEF, demonstrating a reduction of in-hospital mortality, as well as myocardial revascularization.[11]

2. Angiotensin-converting enzyme inhibitor (ACEI)/ Angiotensin receptor blocker (ARB)

In spite of the proven efficacy in patients with HFrFE, post-AMI, hypertension and/or high cardiovascular risk, the benefit in patients with HFpEF is limited.[12] The *Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction,* the "CHARM-Preserved" trial,[13] showed that candesartan, despite reducing hospital admissions, had no impact on cardiovascular mortality when compared to placebo. *The perindopril in elderly people with chronic heart failure,* the "PEP-CHF" trial[14] evaluated the impact of perindopril in patients with diastolic HF, showing no statistical benefit on long-term mortality or hospitalization. However, it appeared to improve symptoms, exercise capacity and HF hospitalization, particularly in younger patients with a history of AMI or hypertension. In addition, irbesartan showed no benefits in terms of mortality, hospitalizations or quality of life assessed in the *Irbesartan in Patients with Heart Failure and Preserved Ejection Fraction,* the "I-PRESERVE" trial.[12] Another clinical trial showed that 12 months of enalapril had no effect on exercise capacity, aortic distensibility, ventricular parameters or quality of life.[15]

3. Mineralocorticoid/aldosterone receptor antagonists (MRA)

Activation of the mineralocorticoid receptors contributes to the pathophysiology of HF through sodium and water retention, potassium loss, endothelial dysfunction, inflammation, fibrosis, and hypertrophy.[16] These patients would be expected to benefit from MRA use. The *Effect of Spironolactone on Diastolic Function and Exercise Capacity in Patients With Heart Failure With Preserved Ejection Fraction,* the "ALDO-DHF" trial,[16] showed advantages in structural reverse cardiac remodeling and improved diastolic function, but did not affect maximal exercise capacity, patient symptoms, or quality of life. The study did not have enough power to evaluate the effect of spironolactone on HF hospitalizations or mortality. The *Spironolactone for Heart Failure with Preserved Ejection Fraction,* the "TOPCAT" trial,[17] added more information and assessed the clinical impact of spironolactone on HFpEF. Although it did not significantly reduce the primary outcome (cardiovascular death, cardiac arrest or HF hospitalization), a subgroup analysis revealed benefits in patients with elevated natriuretic peptide levels. These results have led current American guidelines to consider spironolactone in selected groups of patients with symptomatic HFpFE, particularly those with high natriuretic peptide levels, aiming to reduce hospitalizations (Class IIb).[18]

4. Angiotensin receptor neprilysin inhibitor (ARNI)

Increasing natriuretic peptide levels with ARNI is expected to improve myocardial relaxation, natriuresis, vasodilation and attenuation of sympathetic and fibrotic activity, aiming to improve cardiac function and symptoms. *The angiotensin receptor neprilysin inhibitor LCZ696 in heart failure with preserved ejection fraction"*, the PARAMOUT"[19] trial: a phase II study, randomized 301 patients with HFpEF to receive either ARNI or valsartan. The primary endpoint, which was the change in NT-proBNP levels at 12 weeks, was significantly better in the sacubitril/valsartan group. At 36 weeks, there was also a reduction in left atrial (LA) volume, a marker of LV filling pressures, and an improvement in the NYHA functional class. *Angiotensin Receptor Neprilysin Inhibition in Heart Failure With Preserved Ejection Fraction, the* "PARAGON"[20] trial: a phase III study, will assess the clinical benefit and safety of this drug in chronic symptomatic patients with HFpEF.

5. Ivabradine

An elevated heart rate (HR) is a predictive factor of worse outcomes and increased mortality in patients with heart failure, including those with HFpEF. Ivabradine is a specific and selective inhibitor of the sinoatrial node, *if current*, and thereby decreases HR in patients with sinus rhythm.[21] In patients with HFpEF, short-term treatment increased exercise capacity by improving LV filling pressures.[22] As these patients are mostly symptomatic during exercise, therapies targeting hemodynamic changes during exercise may be useful. The *Effect of ivabradine in patients with heart failure with preserved ejection fraction,* the "EDIFY" trial,[21] evaluated the effect of the drug over 8 months. Unlike the previous study, there was no improvement in the evaluated parameters (diastolic function, exercise capacity and NT-proBNP reduction). Future studies may show benefits in certain subgroups.

Table 1 – A) Main studies performed in patients with HFpEF using effective drugs in the treatment of the HFrEF; B) New drugs and new approaches in HFpEF

A	Clinical Trial	Year	Intervention	Patients, n	Major inclusion criteria	Mean follow-up	Main conclusions
Beta Blockers	SENIORS[9]	2005	Nebivolol vs. placebo	2128	≥70 years, mean LVEF of 36%, 35% with LVEF > 35%, 68% CAD	1,8 years	Well tolerated and effective in reducing mortality and CV hospitalization (HR 0.86, 95%CI: 0.74–0.99; p = 0.039)
ACEI/ARB	CHARM Preserved[13]	2003	Candesartan vs. placebo	3023	>18 years, LVEF > 40%, NYHA II-IV	3 years	Tends towards a reduction in CV mortality and HF hospitalization (*unadjusted* HR 0.89 95%CI: 0.77-1.03, p = 0.118; *adjusted* 0.86 [0.74-1 0], p = 0.051)
	PEP-CHF[14]	2006	Perindopril vs. placebo	850	≥70 years, HF under diuretic therapy, diastolic dysfunction, without systolic or valvular dysfunction	2,1 years	No difference in mortality or CV hospitalization (HR 0.92 95%CI: 0.70-1.21, p = 0.545). Some improvements in symptoms, exercise capacity and HF hospitalization in the first year of follow-up (younger patients with AMI or hypertension)
	I-PRESERVE[12]	2008	Irbesartan vs. placebo	4128	>60 years, LVEF > 45%, NYHA II-IV	4.1 years	No difference in mortality or CV hospitalization (HR 95%CI: 0.86-1.05, p = 0.35)
	Enalapril[15]	2010	Enalapril vs. placebo	71	70 ± 1 years (80% women), LVEF ≥ 50%, Compensated HF and controlled Hypertension	1 year	No impact on exercise capacity (p = 0.99), aortic distensibility (p = 0.93), ventricular volume and mass (p = 1) or quality of life (p = 0.07)
MRA	Aldo –DHF[16]	2013	Spironolactone vs. placebo	422	≥50 years, LVEF ≥ 50%, NYHA II-III, diastolic dysfunction	1 year	Improved diastolic function (E/e' p < 0.001, ventricular remodeling p = 0.09 and neurohormonal activation; p = 0.03). Did not improve exercise capacity, symptoms or quality of life (p = 0.03)
	TOPCAT[17]	2014	Spironolactone vs. placebo	3445	≥50 years, LVEF ≥ 45%, Symptomatic HF, hospitalization within last 12 months or elevated natriuretic peptides	3.3 years	No reduction in CV mortality, cardiac arrest or HF hospitalization (HR 0.89, 95%CI: 0.77-1.04, p = 0.14). Some benefit in terms of natriuretic peptide levels
ARNI	PARAMOUNT[19]	2012	Sacubitril/ valsartan vs. valsartan	301	LVEF ≥ 45%, NYHA II-III and NT-proBNP > 400 pg/ml	12 and 36 weeks	Reduction in NT-proBNP at 12 weeks (HR 0.77, 95%CI: 0.64-0.92, p = 0.005); LA volume reduction (p = 0.003) and NYHA class improvement (p = 0.05) at 36 weeks
	PARAGON[20]	2019*	Sacubitril/ valsartan vs. valsartan	4300	LVEF ≥ 45%, NYHA II-IV, elevated natriuretic peptides and evidence of structural heart disease	>2 years	Evaluation of CV mortality and HF hospitalizations
Ivabradine	If- Channel Inhibitors[22]	2013	Ivabradine vs. placebo	61	LVEF ≥ 50%, diastolic dysfunction, NYHA II-III, sinus rhythm, HR ≥ 60 bpm, exercise capacity <80% for age and gender	7 days	Increased exercise capacity (p = 0.001), with improvement in hemodynamic status during the exercise (p = 0.004); improved LV filling pressure (p = 0.02)
	EDIFY[21]	2017	Ivabradine vs. placebo	179	LVEF ≥ 45%, NYHA II-III, sinus rhythm, HR ≥70 bpm, NT-proBNP ≥ 220 pg/mL (BNP ≥ 80 pg/mL	8 months	No improvement in diastolic function (HR 1.4 90%CI: 0.3-2.5, p = 0.135), exercise capacity (p = 0.882) or NT-proBNP level (HR 1.01, 90%CI: −0.86-1.19; p = 0.882)

Digoxin	DIG PEF[23]	2006	Digoxin vs. placebo	988	LVEF > 40% (mean 53%), sinus rhythm	3.1 years	No effect on natural history endpoints such as mortality and hospitalizations (HR 0.82; 95%CI: 0.63–1.07; p = 0.136)
Nitrates and Nitrites	NEAT HFpEF[24]	2015	Isosorbide mononitrate vs. placebo	110	≥50 years, LVEF ≥ 50%, evidence of HF	6 weeks	No effect on quality of life (p = 0.37) or NT-proBNP levels (p = 0.22); Reduction in daily activity level (-381 95%CI -780-17, p = 0.06) and increased symptoms of HF
	Inorganic nitrate on exercise capacity[25]	2015	NO3-rich beetroot juice vs. placebo (single dose)	17	Symptomatic HF, LVEF > 50%	12 days	Increased exercise capacity (p = 0.04) (reduction in systemic vascular resistance, increased cardiac output and increased oxygen delivery)
Sildenafil	RELAX[26]	2013	Sildenafil vs. placebo	216	LVEF ≥ 50%, NYHA II-IV, NT-proBNP > 400 pg/mL, Peak VO_2 < 60%, or elevated LV filling pressures	24 weeks	No effect on exercise capacity (p = 0.90), clinical status (p = 0.85) or diastolic function (p = 0.16). Worsening of renal function, NTproBNP, endothelin-1 and uric acid
sCG Stimulators	DILATE-1[27]	2014	Riociguat vs. placebo (single dose)	39	≥18 years, LVEF > 50% and PH; mPAP ≥ 25 mmHg and PCWP > 15 mmHg	30 days	Well tolerated; improved exploratory hemodynamic and echocardiographic parameters; No impact on mPAP (p = 0.60)
	SOCRATES-Preserved[28]	2016	Vericiguat vs. placebo	470	LVEF ≥ 45%, NYHA II-IV, elevated natriuretic peptides	12 weeks	No effect on NT-proBNP (p = 0.20) or LA volume (p = 0.37). Some potential in improving quality of life (p = 0.016), particularly with higher doses
Ranolazine	RALI-DHF[29]	2013	Ranolazine vs. placebo	20	LVEF ≥ 45%, E/E` > 15 or NT-proBNP > 220pg/mL, tau ≥ 50ms, LVEDP ≥ 18 mmHg	14 days	Despite hemodynamic improvements at 24 h, there was no effect on diastolic function parameters

B	Clinical Trial	Year	Intervention	Patients, n	Major inclusion criteria	Mean follow-up	Main conclusions
Albuterol	BEAT – HFpEF[30]	2019	Albuterol vs. placebo	30	LVEF ≥ 50%, elevated LV filling pressures, PCWP > 15 mmHg and/or ≥ 25 mmHg during exercise	-	Symptom evaluation through its effect on pulmonary vascular resistance at rest and during exercise
Shunt	REDUCE LAP-HF I[31]	2017	Interatrial septal shunt device vs. sham procedure	94	LVEF>40% and elevated PCWP	1 month	Showed to be safe and effective; Reduction of PCWP (p = 0.028) without significant increase in PAP or pulmonary vascular resistance
Monitoring	CHAMPION[34]	2014	Hemodynamic monitoring vs. control	119	LVEF > 40% (mean 50.6%), NYHA III	17.6 months	Significant reduction in HF hospitalizations (HR 0.50; 95%CI: 0.35–0.70; P < 0.0001)
Exercise	EX DHF[36]	2011	Supervised resistance training vs. usual care	64	> 45 years, LVEF ≥ 50%, NYHA II-III, diastolic dysfunction, sinus rhythm and ≥ 1 CV risk factor	3 months	It showed to be achievable, safe and effective; Improved functional capacity, diastolic function and quality of life (´p < 0.001)
Comorbidities	OPTIMIZE-HFPEF[38]	2016	Systematic screening and optimal treatment of comorbidities vs. usual care	360	>60 years, LVEF ≥ 50%, NYHA II-IV	2 years	Assessment of clinical status
Pacing	RAPID-HF[39] (NCT02145351)	2019	Dual chamber pacemaker with pacing on vs. pacing off	30*	LVEF ≥ 50%, NYHA II-III, diastolic dysfunction and chronotropic incompetence	4 weeks	Assessment of exercise capacity, symptoms and quality of life

Iron Supplementation	FAIR[40] (NCT03074591)	2019	Ferric Carboxymaltose IV vs placebo	200*	LVEF ≥ 45%, NYHA II-III, diastolic dysfunction, iron deficiency, Hb 9-14g/dL	52 weeks	Evaluation of exercise capacity, quality of life, NYHA functional class, mortality and HF hospitalizations
SGLT2 Inhibitors	EMPERIAL Preserved[46] (NCT03448406)	2019	Empagliflozin vs. placebo	300*	LVEF > 40%, NYHA II-IV, NT-proBNP > 300pg/mL, 6 min-walking distance ≤ 350 metros	12 weeks	Assessment of exercise capacity measured by the 6 min-walking distance
	Preserved-HF[47] (NCT03030235)	2019	Dapagliflozin vs. placebo	320*	LVEF ≥ 45%, NYHA II-III, NT-proBNP ≥ 225pg/mL or BNP ≥ 75 pg/mL	12 weeks	NT-proBNP evaluation
	EMPEROR-Preserved[48] (NCT03057951)	2021	Empagliflozin vs. placebo	6000*	LVEF > 40%, NYHA II-IV, NT-proBNP > 300pg/mL	38 months	Evaluation of CV death and HF hospitalization

*AMI: acute myocardial infarction; CAD: coronary artery disease; CO: cardiac output; CV: cardiovascular; HF: heart failure; HR: hazard ratio; LA: left atrium; LVEF: left ventricle ejection fraction; mPAP: mean pulmonary artery pressure; NYHA: New York Heart Association; PAP: pulmonary artery pressure; PCWP: Pulmonary Capillary Wedge Pressure; 95% CI: 95% confidence interval; * Estimated target number.*

6. Digoxin

Digoxin is also part of the therapeutic algorithm in HFrEF, although it is not the first-line therapy.[3] A potential benefit in patients with diastolic dysfunction and HFpEF could arise from its neurohormonal action. The *Effects of Digoxin on Morbidity and Mortality in Diastolic Heart Failure,* the "DIG PEP" trial,[23] showed no effect on the natural history endpoints, such as mortality and hospitalizations. Although it was associated with a trend toward reduction in HF hospitalizations, it did not affect the overall results, partly because of a non-significant increase in the risk of hospitalization for unstable angina.

7. Nitrates and Nitrites

Another pathophysiological mechanism involved in HFpEF is the deregulation of the NO-sGC-cGMP-PKG pathway. A possible therapeutic approach would consist in the use of drugs that act at this level, such as nitrates, phosphodiesterase-5 inhibitors, riociguat and vericiguat.

The *Isosorbide Mononitrate in Heart Failure with Preserved Ejection Fraction,* the "NEAT- HFpEF" trial,[24] evaluated an isosorbide mononitrate regimen, using increasing doses, for 6 weeks. In addition to the lack of improvement in quality of life or NT-proBNP levels, there was a reduction in daily activity level and increased HF symptoms. Other mechanisms eventually limit the hemodynamic benefits of organic nitrates and predispose patients to excessive hypotension and other adverse effects.

The hypothesis that the results would be better with inorganic nitrates (NO3) was tested in a pilot study that assessed exercise capacity and the impact on vasculature and skeletal muscle, using NO3-rich beetroot juice. Although the primary endpoint was not reached, the results seemed to be positive.[25] It will be important to confirm the results in larger, long-term trials.

8. Sildenafil

Inhibition of phosphodiesterase-5 seems to reverse cardiac remodeling and improve vascular, neuroendocrine and renal function, with clinical improvement in patients with idiopathic pulmonary arterial hypertension (PAH) and HFrEF. The *Effect of Phosphodiesterase-5 Inhibition on Exercise Capacity and Clinical Status in Heart Failure With Preserved Ejection Fraction,* the "RELAX" trial,[26] evaluated these parameters in patients with HFpEF, comparing sildenafil with placebo for 24 weeks. Not only was there no improvement in exercise capacity, clinical status, cardiac remodeling or diastolic function, but also the renal function and NTproBNP, endothelin-1 and uric acid levels were adversely affected. In the subgroup of patients with HFpEF and severe pulmonary vascular disease, the results might perhaps be different and more encouraging.[5]

9. sCG Stimulators (Riociguat and Vericiguat)

Pulmonary hypertension (PH) is frequently seen in patients with HF and has been shown to be a major determinant of worse outcomes, thereby representing a potential novel therapeutic target in HFpEP. Riociguat is a novel soluble guanylate cyclase (sGC) stimulator. Its vasodilatory, antifibrotic, antiproliferative and antiinflammatory effect has shown to be efficient in pulmonary arterial hypertension and chronic thromboembolic PH with LV systolic dysfunction. The *Acute Hemodynamic Effects of Riociguat in Patients With Pulmonary Hypertension Associated With Diastolic Heart Failure,* the "DILATE-1" trial,[27] evaluated its effect in patients with PH and diastolic dysfunction. It was an initial study, which assessed a small number of patients and used single doses of riociguat. Despite being well tolerated and improving exploratory hemodynamic and echocardiographic parameters, further studies with larger sample sizes and longer duration are needed to assess its long-term clinical effect.

In the *Vericiguat in patients with worsening chronic heart failure and preserved ejection fraction,* the "SOCRATES-Preserved" trial,[28] 12 weeks of treatment with vericiguat also did not change the primary endpoints, NT-proBNP levels and LA volume. Some potential to improve quality of life has been suggested, particularly at higher doses, which may be tested in further studies, possibly with higher doses, longer follow-up and additional endpoints.

10. Ranolazine

It is known that both HF and ischemic heart disease show increased late sodium current on intracellular calcium cycling, compromising cardiac relaxation. By inhibiting the late sodium channels with ranolazine, an improvement in the diastolic function would theoretically be expected.[6] The *RAnoLazIne for the Treatment of Diastolic Heart Failure in Patients With Preserved Ejection Fraction, the* "RALI-DHF" trial[29] was an exploratory study that evaluated the drug in patients with HFpEF. Despite hemodynamic improvements after 24 hours, there were no significant changes in diastolic function after 14 days of treatment.

Another Direction

The failure of clinical trials in testing proven effective drugs in HFrEF, has led to a new direction in the treatment of patients with HFpEF. Attempts were made to better understand the pathophysiological mechanism of the disease and act on those different pathways (Figure 2). New drugs have been tested and new approaches are under research. (Table 1-B)

11. Albuterol

Given the frequent lung involvement in these patients, drugs acting at this level are being tested. This is the case of albuterol, an inhaled bronchodilator. The *Inhaled Beta-adrenergic Agonists to Treat Pulmonary Vascular Disease in Heart Failure With Preserved EF,* the "BEAT – HFpEF" trial,[30] aims to assess the impact of this drug on symptoms, through its effect on pulmonary vascular resistance at rest and during exercise.

12. Interatrial septal shunt

It is known that the atrial volume and pressure overload not only contributes to the development of symptoms and exercise intolerance, but it is also a major determinant of morbimortality. Pulmonary capillary wedge pressure (PCWP) is an invasive hemodynamic parameter with prognostic value, which reflects the pressure in the LA and pulmonary veins. Based on these hemodynamic changes and in view of the limited success of pharmacological management of patients with HFpEF, an interatrial communication device was developed, which is used to reduce LA pressure. The prospective, non-randomized, open-label study, called "*A Transcatheter Intracardiac Shunt Device for Heart Failure with Preserved Ejection Fraction* "REDUCE LAP-HF"[31] evaluated the performance and safety of this device in 64 patients with HFpEF and elevated PCWP. Preliminary analyses demonstrated clinical and hemodynamic benefits at 6 months. Pressure reductions in LA resulted in improved functional capacity, at the expense of a slight increase in the right cardiac pressure and output. These benefits persisted in a long-term evaluation with sustained improvement of the hemodynamic profile, NYHA functional class, quality of life and exercise capacity at the end of one year, with no evidence of complications.[32]

Subsequently, a randomized controlled phase II trial was performed with PCWP evaluation during exercise, one month after the implantation of the interatrial septal shunt device *vs*. sham procedure. It showed to be safe and effective, with a reduction of PCWP and without a significant increase in pulmonary artery pressure (PAP) or pulmonary vascular resistance, which are possible consequences of right cardiac overload.[33] It remains unclear whether this hemodynamic effect will lead to sustained clinical improvements.

13. Monitoring

Congestive symptoms are present in the majority of patients hospitalized for decompensated HF regardless of LVEF. Changes in body volume and cardiac filling pressures are predictive of adverse events. A strategy of hemodynamic monitoring, with consequent targeted and early therapeutic intervention, may reduce the risk of hospitalization for HF. The *Wireless pulmonary artery haemodynamic monitoring in chronic heart failure*, the "CHAMPION" trial,[34] tested this hypothesis by using a microelectromechanical system pressure sensor permanently implanted during right cardiac catheterization. Through daily assessment of PAP and active reduction of filling pressures with diuretics and vasodilators, significant reductions were demonstrated in hospital admissions. The benefits persisted in the subgroup of patients with HFpEF, with reductions of 50% in HF hospitalizations after 17 months.[35]

14. Exercise

Physical exercise is beneficial in certain conditions strictly related to HFpEF, such as hypertension and metabolic syndrome. The effect of structured and supervised training on exercise capacity, diastolic function and quality of life was evaluated. The *Exercise Training Improves Exercise Capacity and Diastolic Function in Patients With Heart Failure With Preserved Ejection Fraction, the* "EX DHF" trial,[36] showed that a short-term supervised endurance/resistance training is achievable, safe, and effective in patients with HFpEF. The program maintenance in the long term and the involvement of elderly patients, at advanced stages of the disease and with multiple comorbidities, are possible limitations. Nevertheless, it seems a promising strategy with potential synergism with other pharmacological and non-pharmacological approaches. It is important to define the regimen approach, improve long-term adherence and expand availability.[37]

15. Comorbidities

Another of the proposed pathophysiological mechanisms involves the existence of a systemic proinflammatory state induced by multiple comorbidities, resulting in endothelial dysfunction, cardiac remodeling and dysfunction. It was hypothesized that by screening and treating comorbidities in a targeted manner, the overall prognosis of these patients could be improved. The *Optimizing the Management of Heart Failure with Preserved Ejection Fraction in the Elderly by Targeting Comorbidities,* the "OPTIMIZE-HFpEF" trial,[38] proposes a systematic screening and optimized treatment of comorbidities as a pathophysiological mechanism of HF, rather than the simple treatment of previously diagnosed concomitant pathologies. Although it lacks sufficient power to assess cost-effectiveness, it is a good starting point to test a new promising approach.

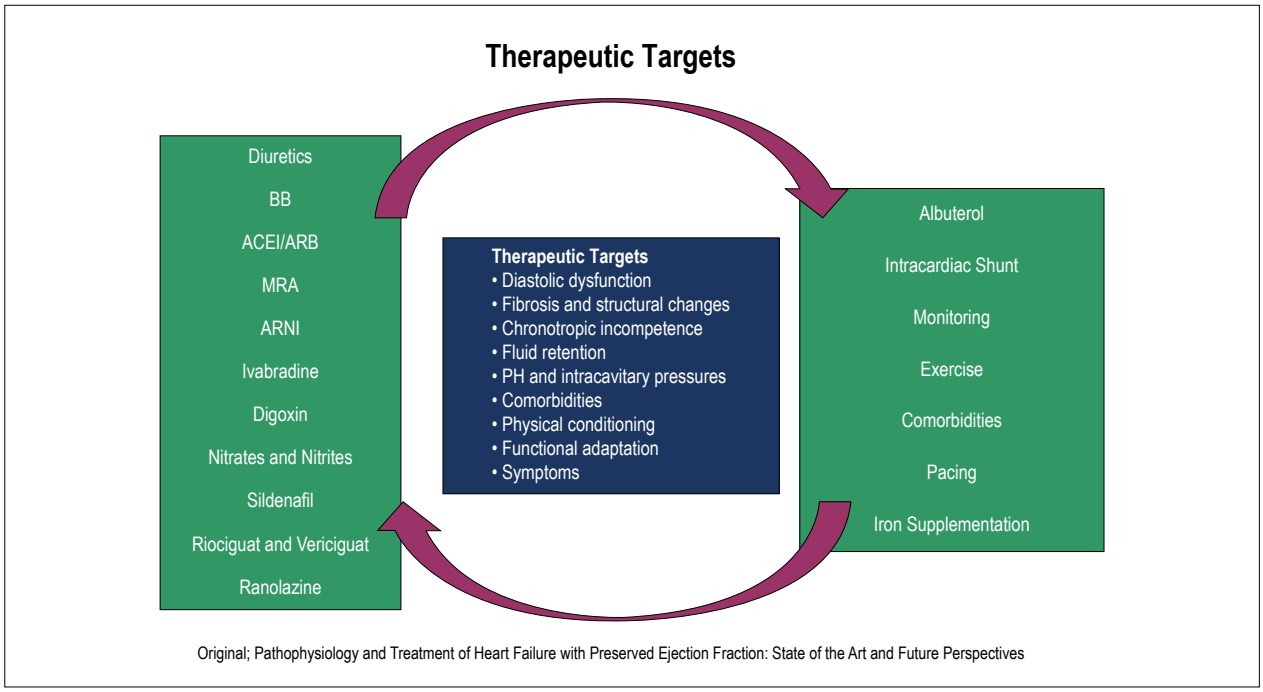

Figure 2 – *Potential therapeutic targets and drugs evaluated in HFpEF. ACEI/ARB: angiotensin-converting enzyme inhibitors/angiotensin II receptor blocker; ARNI: angiotensin receptor neprilysin inhibitor; BB: Beta Blockers; MRA: mineralocorticoid receptor antagonists; PH: pulmonary hypertension.*

16. Pacing

Patients with HFpEF and chronotropic incompetence may benefit from pacemaker devices, which may help to restore the normal HR during daily activity and exercise. The *Rate-Adaptive Atrial Pacing In Diastolic Heart Failure* (RAPID-HF) trial[39] aims to evaluate the impact of this intervention on short-term exercise capacity, symptoms and quality of life.

17. Iron Supplementation

Iron kinetics is part of the initial evaluation of patients with HF. Intravenous iron supplementation is part of the therapeutic approach in patients with HFrEF and reduced iron stores.[3] The *Effect of IV Iron Ferric Carboxymaltose (Ferinject) on Exercise Tolerance, Symptoms and Quality of Life in Patients With Heart Failure With Preserved Ejection Fraction and Iron Deficiency With and Without Anaemia, the* "FAIR" trial,[40] aims to evaluate the effect of intravenous iron on exercise capacity, quality of life, NYHA functional class, mortality and hospitalizations for HF in patients with HFpEF and iron deficiency, with or without anemia.

18. Sodium-glucose cotransporter-2 inhibitors (SGLT2i)

HF and diabetes frequently coexist, associated with an increased risk of cardiovascular mortality and HF hospitalization.[41] Several studies with SGLT2 inhibitors have demonstrated a significant reduction in HF hospitalizations in diabetic patients at high cardiovascular risk or with established cardiovascular disease (*Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes "EMPA-REG",*[42] *Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes "CANVAS",*[43] *Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes "DECLARE"*[44] trials). Given the potential benefits of this pharmacological group in improving diastolic function in patients with HF,[45] studies are underway to determine the impact of these drugs in patients with HFpEF, with and without diabetes (*A Phase III Randomised, Double-blind Trial to Evaluate the Effect of 12 Weeks Treatment of Once Daily EMPagliflozin 10 mg Compared With Placebo on ExeRcise Ability and Heart Failure Symptoms, In Patients With Chronic HeArt FaiLure With Preserved Ejection Fraction (HFpEF) "EMPERIAL – Preserved",*[46] *Dapagliflozin in PRESERVED Ejection Fraction Heart Failure "PRESERVED-HF",*[47] *EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure With Preserved Ejection Fraction "EMPEROR-Preserved"*[48]).

Conclusions

HFpEF is a common pathology, still poorly understood and without any treatment proven to be effective in reducing morbidity or mortality.

There seems to be no single cause to justify the failure of the obtained results; however, potential contributions can be identified: incomplete understanding of the pathophysiology, heterogeneity of the studied population, lack of universal diagnostic criteria with recruitment of patients without true HFpEF or at the very early stages, treatment not targeting the predominant pathophysiological mechanism, suboptimal designs or weak statistical power of the trials.

The pathophysiology of HFpEF is multifactorial, with several mechanisms and comorbidities involved, and probably different from those of HFrEF. It results from a complex interaction of

factors that culminate in the reduction of cardiac and vascular functional reserve - systolic and diastolic dysfunction, atrial reserve, heart rate and rhythm, autonomic control, vasculature and microcirculation. The interaction and relative dominance of these factors make this pathology extremely heterogeneous. The definition and division into subgroups with certain phenotypes may allow a more targeted treatment, with possible improvement of the clinical results.

Several clinical trials are being carried out, using different therapeutic approaches. It is important to remember that these patients tend to be older and have multiple pathologies. Thus, the benefit of the treatments may be better evaluated by their effect on hospitalizations, functional status, symptoms and quality of life.

Author contributions

Conception and design of the research, Acquisition of data and Writing of the manuscript: Fernandes SL; Critical revision of the manuscript for intellectual content: Carvalho RR, Santos LG, Sá FM, Ruivo C, Mendes SL, Martins H, Morais JA.

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Echoes of Telecardiology Guideline

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Echocardiography has an established role in the diagnosis, prognostic evaluation and therapeutic orientation in several cardiovascular diseases.[1] The great technological development in the last decades has allowed the digitization and standardization of medical images (DICOM), miniaturization of echocardiography equipment (portable cardiac ultrasound) and the transfer of images over the internet. In this scenario, strategies for the use of telemedicine-associated echocardiography, called tele-echocardiography, have been employed in the context of clinical research with the support of teleconsultation for remote expert review, in real time or after image storage and submission. In recognition of the demands generated by the ongoing digital transformation in health, the Brazilian Society of Cardiology recently published the Telemedicine Guideline in Cardiology.[2] The document recognizes tele-echocardiography as a strategy for early detection of congenital heart disease in newborns and screening for early detection of subclinical cases of rheumatic heart disease in children and adolescents (both recommended as indication class IIa, level of evidence B). In addition, it evokes potential application in primary health care in remote locations, where it could enable early detection of cases of heart disease and assist in prioritizing referrals to specialized care (indication class IIb, level of evidence C).[2] It should be emphasized that such recommendations are made within the conditions of regular use of the method in Brazil, which would include the need for doctors at both ends, i.e., the execution and interpretation of the exam. The text of the Guideline explicitly states the need for regulation and legal provision for the participation of other professionals in performing diagnostic procedures (in this case, obtaining echocardiographic images by non-doctors), currently not allowed by the country's legislation.

In recent years, tele-echocardiography has extended the application of the method to individuals in geographically distant locations, such as remote rural communities[3] or even space.[4] A rural area is classified as remote when 50% of the local population needs at least 45 to 60 minutes of travel by motor vehicle to reach a population center of at least 50,000 inhabitants.[2] Several situations have been experimentally tested, with a study on focused echocardiographic by non-cardiologist physicians,[5,6] non-physicians,[3,7] or remote-operated robotic devices,[8] combined with remote interpretation by echocardiography cardiologists.

Historically, tele-echocardiography was initially employed in pediatric populations to rule out relevant congenital heart disease, with either live or offline transmission approaches, using different technologies and data rates. Taken together, these studies have suggested that tele-echocardiography assists in the diagnosis and clinical management of patients, avoiding unnecessary transport and potentially reducing costs.[9-12]

More recently, the feasibility of tele-echocardiography for mass screening of heart disease in large communities has been investigated. The exam supposedly detected significant cardiac abnormalities in 16%[3] to 35%[7] of the individuals, despite the clear limitation of the different criteria adopted to define heart disease. On the other hand, previous data indicate that focused echocardiography screening tends to overestimate the rate of heart disease in the community, which makes it imperative to validate the examination by an experienced echocardiographist to ensure an adequate level of accuracy.[13] Even employing well-trained sonographers for local echocardiographic evaluation, remote examination by experienced echocardiographers alters the diagnosis in approximately one quarter of the studies, half of which undergo major clinical changes in the final report.[13] In general, accuracy appears to be acceptable in the detection of valvular heart disease, although only modest for the diagnosis of systolic dysfunction and left ventricular hypertrophy.[3,5]

In addition to the expansion of cardiovascular imaging through telemedicine, some researchers have also described imaging acquisition through tele-robotics. A French study evaluated 41 individuals with valvular heart disease who underwent tele-echocardiography through a robotic arm operated by an echocardiographer via an internet connection in a room 10 meters away from the patient.[8] The quality of the images was lower than those obtained by conventional echocardiography, but the diagnosis was reliable in 86% of the cases.[8] An American study showed the feasibility of carotid vascular ultrasound imaging through the robotic arm and its long-distance transmission over the traditional bandwidth internet.[14] A Swedish prospective randomized study conducted in a rural community concluded that the combination of cardiologic teleconsultation and robotic arm tele-echocardiography resulted in shorter time to care and diagnosis definition compared to the usual routine referral to the nearest specialty hospital.[15] However, the number of patients evaluated was small (19 in each group), not allowing inferences regarding clinical outcomes.

Keywords

Cardiovascular Diseases; Diagnosis imaging; Echocardiography/methods; Telemedicine/methods; Telemedicine/trends; Robotics/trends; Training; Image Interpretation Computer-Assisted; Telemonitoring.

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Echocardiography as a cardiovascular imaging modality directly depends on the appropriate acquisition and interpretation of satisfactory images. There are no studies conclusively comparing image quality by tele-echocardiography and traditional echocardiography. In parallel, there is no scientific evidence to conclude that the use of tele-echocardiography in primary health care in remote locations is able to reduce morbidity and mortality in the community compared to traditional care workflow.

Obviously, the advent of digital health, which encompasses the use of telemedicine as a useful complementary tool to allow equity of access to health for all Brazilians, is a desirable novelty in the current scenario.[16] Considering the continental dimension of Brazil, we could assume that populations living in remote areas would benefit from state investment in the spread of digital health. We must welcome the changes that digital transformation can trigger in the practice of medicine, especially where the integrality of access to health is not contemplated. However, such changes should be supported by consistent scientific evidence that accredits them as real advancement, avoiding inappropriate use of new technologies.[17]

There are potential advantages of adopting tele-echocardiography in public healthcare of underprivileged populations in distant locations, but the method still lacks robust scientific validation with prospective controlled studies confirming the health benefits of patients. In addition, a broad discussion on the need for investment in digital technology infrastructure, cost-effectiveness, budgetary impact, regulation and legal certainty, among other challenges and risks, is crucial. It is important to remember that Brazilian law: (a) authorizes only physicians to perform and interpret echocardiograms in the country, and (b) recognizes echocardiography as an area of activity of cardiology and pediatrics. Regulatory debate involving authorities, professional councils and medical societies is mandatory before tele-echocardiography is incorporated into public health policies in Brazil. In the area of supplementary health, there is no legal backing for non-medical individuals, even under the supervision of physicians, to perform echocardiograms, and the use of tele-echocardiography by other health professionals would be a practice not covered by law.[18] In addition, there is currently no provision for reimbursement for any of the procedures used in Telemedicine, which are not part of the Procedures and Health Events Roll of the National Health Agency. Table 1 lists the potential advantages and challenges for the implementation of tele-echocardiography in Brazil.

Table 1 – Potential advantages and main challenges for the adoption of tele-echocardiography in Brazil

Potential advantages	Main challenges
Allow access to the method at remote locations	Lack of standardization of tele-echocardiography components and proper internet coverage
Early diagnosis and therapy guidance	Uncertainty whether image quality and diagnostic accuracy is comparable to traditional method
Potential optimization of clinical outcomes	Lack of scientific evidence proving impact on clinical outcomes
Reducing the cost of transporting human resources to geographically distant areas	Absence of scientific evidence showing cost-effectiveness; questions about budget impact and system reimbursement
Reducing the cost of transporting patients to tertiary centers	Uncertainty about adherence by local health professionals
Reduction in the number of unnecessary echocardiograms	Prohibition of Brazilian law to the performance of echocardiography by non-medical operators (sonographers)
Prioritization and organization of waiting lists in healthcare systems with limited availability of specialized exams and consultations	Lack of guidelines for operator training
	Forensic insecurity
	No current laws regarding licensing, data storage, privacy and confidentiality

Author contributions

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Extensive Myocardial Calcification in a Heart Transplant Patient

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A 33-year-old female patient underwent heart transplantation (Tx) for valvular heart disease, where the surgical procedure was uneventful. Post-Tx, she developed with acute graft dysfunction, acute renal failure (ARF) requiring dialysis and septic shock. Bloodstream infection confirmed by treatment for carbapenemase-producing *Klebsiella pneumoniae*. Non-contrast-enhanced computed tomography (CT) of the chest and abdomen was done for investigation of the infectious focus and distention of the abdomen and melena, with extensive left ventricular myocardial calcification (MC) not previously found in CT (Figures 1, 2 and 3). A diagnosis of cytomegalovirus (CMV) infection was also confirmed by upper digestive endoscopy findings with diffuse gastroduodenal ulcers and quantitative detection of positive CMV DNA, and the patient received ganciclovir. The patient became refractory to treatment and died.

MC is a rare complication that occurs in critically ill patients. It has various etiologies, and its pathophysiology is not completely elucidated. MC may involve mechanisms of metastatic calcification and dystrophic calcification, as presented in Table 1. It can be the cause of heart failure, sudden death, abnormalities in ventricular wall movement, arrhythmias and restrictive disease.[1]

The case demonstrates a correlation with others described in the literature, showing extensive MC in a young patient with anemia, ARF, septic shock,[2] exposure to extracorporeal membrane oxygenation,[3] and high mortality, with the difference being an immunosuppressed post-heart transplant patient. The true meaning of this finding and its reversibility are unknown. However, it is believed to be related to disease severity and poor prognosis, and its identification in clinical practice is important.

Keywords

Heart Transplantation/complications; Heart Valve Diseases/surgery; Renal Insufficiency/complications; Shock, Septic.

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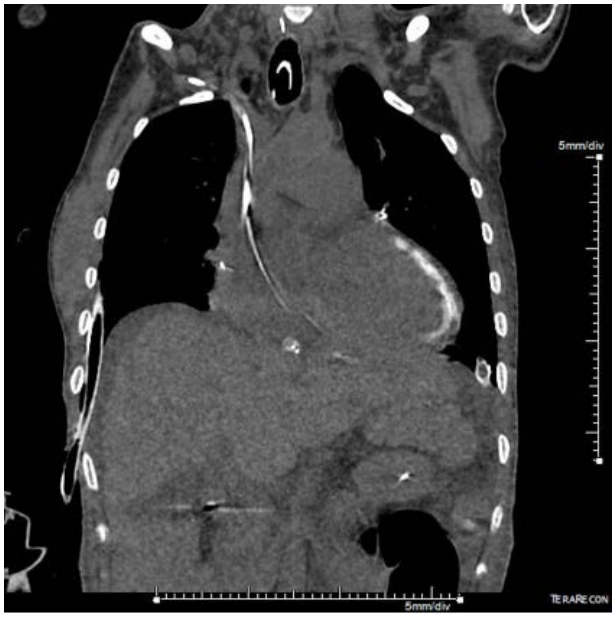

Figure 1 – *Coronary non-contrast-enhanced computed tomography scan of the chest with finding of extensive myocardial calcification in the left ventricle.*

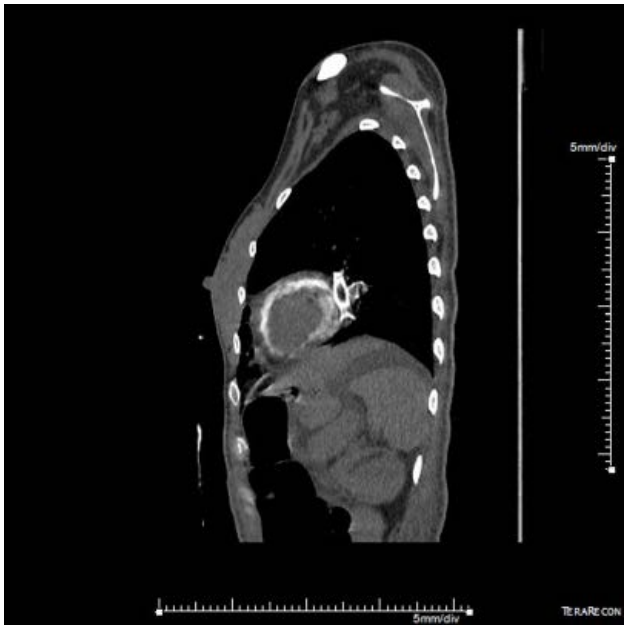

Figure 2 – *Sagittal non-contrast-enhanced computed tomography scan of the chest with finding of extensive myocardial calcification in the left ventricle.*

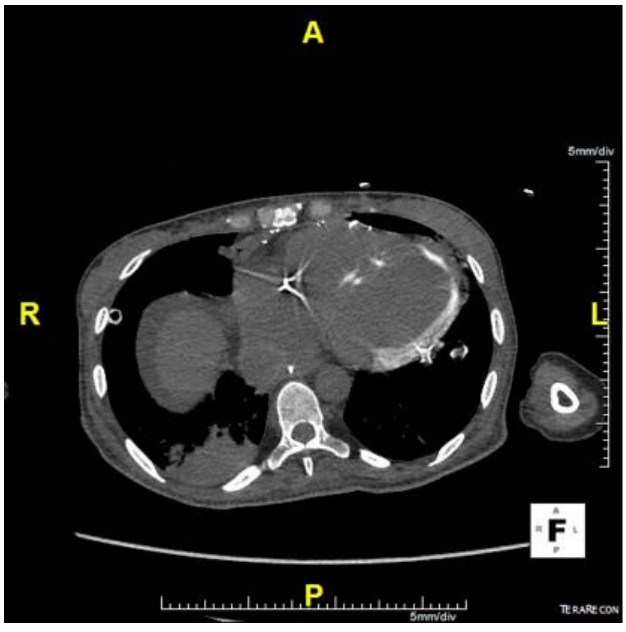

Figure 3 – *Axial non-contrast-enhanced computed tomography scan of the chest with finding of extensive myocardial calcification in the left ventricle.*

Table 1 – Possible myocardial calcification etiologies

Metastatic calcification (Altered serum calcium level)	Dystrophic calcification (Calcium accumulation in necrotic tissues, without hypercalcemia)
Chronic renal failure	Infections
Primary parathyroidism	Extracorporeal membrane oxygenation
Neoplasms	Inflammatory processes
Bone disturbances	Processes myocardial infarction
Medications	Myocarditis

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Left Ventricle Mass Index, a Confounding Variable of Global Longitudinal Strain to be Noticed

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Dear Editor,

We read with great interest the article entitled as "Strain Analysis of Left Ventricular Function in the Association of Hypertrophic Cardiomyopathy and Systemic Arterial Hypertension". In this paper, the authors evaluated the global longitudinal strain (GLS) of the left ventricle (LV) in two distinct groups: patients with hypertrophic cardiomyopathy (HCM) and patients with HCM and systemic arterial hypertension (SAH) and demonstrated that GLS was lower in the second group. This important finding may indicate greater impairment of LV function in patients with SAH and HCM.[1]

Keywords

Ventricular Function, Left; Cardiomyopathy, Hypertrophic; Hypertension; Strain; Heart Failure; Hypertrophy, Left Ventricular.

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However, despite these findings, it is important to notice the impact of the LV mass on the GLS, unfortunately not reported by the authors. A previous study by Soufi Taleb Bendiab et al.[2] showed that hypertensive patients with LV hypertrophy had a reduced GLS.[2] Moreover, in the study of Lópes-Candales et al.[3] patients with increased LV mass had a significant reduced GLS.[3] From a mechanical point of view of a physiological heart model validated by echocardiography, the volume of heart tissue is constant throughout the cardiac cycle, since it is incompressible.[4] In that way, patients with increased LV thickness would have less longitudinal myocardial deformation.[3]

Since the population of this study were patients with hypertrophic cardiomyopathy with or without hypertension, the measurement of LV mass becomes even more important to report an accurate multivariate analysis and to measure the impact of this important confounder on the study's conclusions.

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Position Statement of the Brazilian Cardiology Society and the Brazilian Society of Hemodynamics and Interventional Cardiology on Training Centers and Professional Certification in Hemodynamics and Interventional Cardiology – 2020

Development: Sociedade Brasileira de Cardiologia (SBC) and Sociedade Brasileira de Hemodinâmica e Cardiologia Intervencionista (SBHCI)

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Note: These statements are for information purposes and are not to replace the clinical judgment of a physician, who must ultimately determine the appropriate treatment for each patient.

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Declaration of potential conflict of interests of authors/collaborators of the Position Statement of the Brazilian Cardiology Society and the Brazilian Society of Hemodynamics and Interventional Cardiology on Training Centers and Professional Certification in Hemodynamics and Interventional Cardiology – 2020
If, within the last 3 years, the author/collaborator of the guideline:

Names of guideline collaborators	Participated in clinical and/or experimental studies sponsored by pharmaceutical or equipment companies related to this guideline	Spoke at events or activities sponsored by industry related to this guideline	Was (is) a member of a board of advisors or a board of directors of a pharmaceutical or equipment industry	Participated in normative committees of scientific research sponsored by industry	Received personal or institutional funding from industry	Wrote scientific papers in journals sponsored by industry	Owns stocks in industry
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Nelson Antonio Moura de Araujo	No	No	No	No	No	No	No
Raul Ivo Rossi Filho	No	No	No	No	No	No	No
Ricardo Alves da Costa	No	No	No	No	No	No	No
Silvio Giopatto	No	No	No	No	No	No	No
Viviana de Mello Guzzo Lemke	No	No	No	No	No	No	No

Content

1. Introduction

The first coronary angioplasty, performed by Gruntzig[1] in 1977, marked the beginning of a revolution in cardiovascular disease treatment. Coronary angioplasty was initially considered an alternative to myocardial revascularization. With the passing of the years, accompanied by great technical-scientific advancement, percutaneous coronary intervention (PCI) has gone on to become the modality of choice when opting for mechanistic treatment of obstructive coronary disease. In this manner, coronary obstructions, with their diverse scenarios of complexity and forms of clinical presentation, are currently preferably treated by means of percutaneous techniques. Great advances in scientific knowledge and the development of increasingly less invasive techniques have also made it possible to overcome the limits of the territory of coronary circulation. The range of interventional treatments for cardiovascular and structural heart diseases is increasingly broad, and it represents a new branch of PCI, encompassing congenital and acquired heart diseases which were previously treated by traditional surgery or not even addressed. All of these enormous advances witnessed over the past decades have expanded not only the capacity but also the responsibility of interventional cardiologists within this new model of percutaneous treatments for cardiovascular diseases. The competences attributed to interventional cardiologists have gone on to include percutaneous treatment of structural heart diseases and extracardiac arterial and venous vascular territories, which, in addition to treatment of coronary obstructions, requires a broad and sophisticated process of training and certification.

As the realm of diseases that may be treated by means of percutaneous techniques expands, the processes for training, certifying, and keeping abilities up-to-date undergo a true metamorphosis for interventional cardiologists. It is thus necessary for the Brazilian Society of Hemodynamics and Interventional Cardiology (Sociedade Brasileira de Hemodinâmica e Cardiologia Intervencionista – SBHCI) to revise the stages adopted in this complex process, with the objective of guaranteeing civil society's access to professionals with the abilities, competences, and responsibility to carry out percutaneous treatment of the diverse diseases included in this vast scenario in a proper and safe manner.

2. Objectives

This Position Paper is an update to the second chapter of the previous edition of the Guidelines on Quality and Professional Certification,[2] and its objective is to offer a guide to orient professionals, training centers, and institutions acting in the area of cardiovascular intervention (Hemodynamics and Interventional Cardiology) in relation to PCI, congenital and structural heart diseases, and intervention in the extracardiac arterial and venous vascular bed.

The recommendations contained in this document are in following with the standards established by the Brazilian Cardiology Society (Sociedade Brasileira de Cardiologia – SBC) for the elaboration of position papers, guidelines, and normalizations and they comprise recommended actions that are, generally, individualized for each specific topic covered in this document.

3. Norms for Establishing Hemodynamics and Interventional Cardiology Training Centers

The SBHCI has always been vigilant regarding the formation of new professionals in the area, elaborating norms that guarantee the quality of services provided at diverse hospitals in diverse communities.

These position papers, which are the result of consensus between members of the commission who participated in their elaboration, are intended to update the criteria for capacitating training centers acting in the area of interventional cardiology.

Existing centers and centers that may be established in the future must comply with the following criteria in order to maintain or apply for accreditation as **SBHCI Hemodynamics and Interventional Cardiology Training Centers.**[3]

3.1. Basic Requirements

3.1.1. Hospitals (Institutions)

A hospital which is a candidate to become a Training Center must apply to the SBHCI, and it must meet the following essential composition and resource requirements:

- Hemodynamics and interventional cardiology laboratory.
- Active cardiovascular surgery service.
- Intensive therapy unit or coronary unit.
- Clinical analysis laboratory.
- Hemotherapy service.
- Imaging services, comprising radiology, transthoracic and transesophageal Doppler echocardiography, preferably with 3-D reconstruction, Doppler ultrasound, computerized tomography (CT) and/or magnetic resonance (MR), digestive endoscopy.
- Hemodialysis service.
- Clinical specialties (cardiology, radiology, nephrology, neurology, gastroenterology, pneumology, hematology, and anesthesiology).
- Ventricular assist devices.

3.1.2. Hemodynamics Laboratories

To the extent that the spectrum of interventional procedures expands, in conjunction with the complexity of "old" and new procedures, catheterization laboratories must have equipment and instruments that are compatible with this new working scenario, especially in training centers.

The supplies necessary for catheterization laboratories to function and the role of nurses, radiology technicians, and other members of the interventional cardiology teams are described in the latest guidelines on professional quality, and they are in consonance with current practice.[2] The necessary requirements for structural constitution of a training center catheterization laboratories are described in Chart 1.

For Training Centers that utilize more than one catheterization laboratories in different hospitals, it is mandatory for each unit to comply with the basic minimum requirements listed in this Position Paper.

3.1.3. Medical Teams

Medical teams must be made up of preceptors and a coordinator, provided that they meet the following requirements:

Chart 1 – Necessary requirements for structural constitution of a training center catheterization laboratories

1.	A radiological device, adequately fixed to the ground or ceiling, and a motorized C-arm system
2.	Architecture that allows for axial projections with 40º angulation and oblique projections with 90º angulation, by electronic movement
3.	An examination table with capacity to support patients weighing up to 200 kg, plus 100 kg imposed during reanimation maneuvers
4.	A high-voltage X-ray generator with 80 kW minimum power, for rapid radiation emission, sufficient to obtain image contrast and sharpness
5.	An X-ray tube with minimal thermal capacity of 1,700,000 HU
6.	Pulsed fluoroscopy with rates of at least 30/15 pulses per second
7.	An image intensifier with the highest possible conversion factor or a flat-panel digital system
8.	High-quality digital imaging with a matrix of at least 512 × 512 × 8 bits at 30 frames per second
9.	Long-term (20-year) digital archiving in DICOM format
10.	Polygraph with a record of at least three electrocardiogram and two pressure channels
11.	Contrast injection pump
12.	An anticoagulation monitoring device by measurement of activated coagulation time
13.	Pulse oximetry
14.	Equipment for measurement of cardiac output by thermodilution
15.	Material for cardiorespiratory resuscitation and external pacemaker/defibrillator
16.	Intracardiac lead and temporary pacemaker generator
17.	Radiation protection equipment

- To have at least two preceptors, both titular members of the SBHCI for at least five years, with certificates in the area of hemodynamics and interventional cardiology provided by the SBHCI. Each preceptor should perform at least 75 cardiovascular therapeutic interventions annually and demonstrate maintenance of proficiency by sending a record of these interventions to the current SBHCI database.
- The program coordinator must be one of the preceptors, and he or she will responsible to the SBHCI for compliance with these recommendations.
- Perform at least 1,500 diagnostic cardiac catheterizations annually, proven by a declaration signed by the technician responsible for the service.
- Perform cardiovascular interventions, with at least 600 PCI yearly, proven by a declaration signed by the technician responsible for the service.
- Send the records of all cardiovascular interventions performed annually to the current SBHCI database.
- Follow the theoretical-practical program recommended in this Position Paper.
- The number of openings made available to candidates per team per year must comply with the following limits: for the minimum requisite of 600 annual angioplasties, up to two openings; for each increment of 200 PCI, one opening may be added. It is necessary that there be a ratio of one preceptor per trainee (Chart 2).

3.1.4. Trainees

The prerequisites and obligations of trainees include a degree in Cardiology and full-time dedication to the training program, in addition to the following:[3]

- Be duly registered with the Regional Council of Medicine (Conselho Regional de Medicina – CRM) of the state where the training center is located.
- Have completed two years of medical residency in Cardiology at a service accredited by the National Medical Residency Commission (Comissão Nacional de Residência Médica – CNRM); have completed two years of internship in Cardiology in training centers recognized by the SBC or hold the title of specialist in Cardiology issued by the Brazilian Medical Association (Associação Médica Brasileira – AMB)/SBC.
- For the interventional cardiology for congenital heart diseases program, in place of the previous items, the candidate must have completed two years of medical residency in Pediatric Cardiology at a service accredited by the CNRM and have completed two years of internship in Pediatric Cardiology in training centers recognized by the SBC or hold the title of specialist in Pediatrics acting in the area of Pediatric Cardiology issued by the AMB/SBC.
- During the formation period, the trainee must fulfill the full course load established by the theoretical-practical program.

Chart 2 – Minimum number of procedures required for formation of interventional cardiologists

Procedure	Yearly minimum for a training center	Minimum per trainee in 2 years (first operator)
Diagnostic cardiac catheterization	1,500	400
Percutaneous coronary intervention	600	200

3.1.5. The Theoretical-Practical Program

- The minimum training period is 24 consecutive months, with 30 days of vacation per year, scientific improvement, and participation in congresses and meetings related to the specialization.
- The training program must provide trainees with a complete formation, with mastery of the techniques and knowledge related to cardiovascular interventions. The first year should focus on fundamental training in radiation protection, vascular accesses, diagnostic percutaneous procedures, low complexity coronary interventions, and their complications. The second year should include and focus on training in high complexity coronary interventions, approaches to structural heart disease, extracardiac vascular procedures, and their complications.
- The direct participation of the trainee in diagnostic and therapeutic cardiovascular procedures should always take place under preceptor supervision, and all pertinent activities should be duly registered in the current SBHCI database.
- Throughout the duration of the training period, the trainee must act as first operator, under supervision, in at least:

  - 400 diagnostic cardiovascular procedures.

  - 200 PCI.

The minimum training syllabus in hemodynamics and interventional cardiology should comprehend:[3-7]

- A review of historical aspects relevant to hemodynamics and interventional cardiology.
- Basic concepts of ionizing radiation, image formation, and radiation protection (Annex 1).
- Vascular accesses (vascular anatomy; choice and techniques for arterial and venous access in multiple sites [radial/ulnar, femoral, jugular, transapical, transhepatic, carotid, subclavian/axillary, cavo-aortic]; techniques for obtaining hemostasis; and treatment of vascular complications).
- Ultrasound imaging for obtaining vascular access.
- Vascular hemostasis devices (indications, benefits, limitations, and complications).
- Manometry recordings (critical evaluation of recording quality and its functioning; and analysis of arterial and venous pressure curves in different cardiac cavities and vascular circuits under normal conditions and in pathological situations, including assessment of ventricular diastolic function).
- Determination of cardiac output by the Fick principle and the thermodilution method.

- Calculation of valve areas, vascular resistances, and arteriovenous shunts.
- Evaluation of hemodynamic response to pharmacological agents to study ventricular performance and pulmonary vascular reactivity.
- Means of contrast (types, doses, complications, prevention and treatment of adverse reactions).
- Knowledge of cardiac, coronary, and vascular radiological anatomy and the corresponding angiographic projections for proper performance of cardiovascular procedures.
- A review of cardiovascular anatomy and physiology with a focus on interventional cardiology.
- Cardiovascular pathology and physiopathology (determinants of atherosclerosis and thrombosis; systemic manifestations of atherosclerosis and risk factors that contribute to its development; established guidelines for modifying these risk factors; physiopathology, clinical manifestations, natural history, assessment, and management of other structural and functional cardiovascular diseases; prothrombotic states, encompassing hereditary and acquired disorders; and proinflammatory states that contribute to appearance of unstable coronary lesions).
- Indications and contraindications for therapeutic and diagnostic percutaneous cardiovascular procedures.
- Interpretation of images and quantitative angiography for assessment of coronary lesions, valve dysfunctions, and systolic ventricular function.
- Methods for evaluating functional significance of coronary obstructions.
- Methods for obtaining and interpreting intravascular imaging.
- Technical knowledge of materials utilized for diagnostic and interventional cardiovascular procedures.
- Recognition and management of complications of diagnostic and therapeutic cardiovascular procedures.
- Pharmacology applied to diagnostic and therapeutic percutaneous cardiovascular procedures.
- Hemodynamic and angiographic diagnoses of the main congenital and structural cardiovascular diseases in children and adults.
- Indications, contraindications, techniques, and limitations of diverse therapeutic procedures in interventional cardiology for congenital heart diseases (atrial septostomy [diverse techniques] and pulmonary and aortic valvuloplasty; angioplasty and pulmonary artery stent implantation, conduct and other arteries and veins; aortoplasty and aortic stent; occlusion techniques, embolizations and cardiac occlusion devices; and transcatheter pulmonary valve implantation [TPVI]).
- Peculiar technical aspects of all percutaneous cardiovascular intervention devices.
- Indications, contraindications, methods, techniques, and limitations of diverse therapeutic procedures in interventional cardiology (coronary and vascular interventions; utilization of distal protection devices; valvuloplasties; alcohol septal ablation in obstructive hypertrophic cardiomyopathy; embolization of coronary arteries to treat complications and other vascular beds for therapeutic purposes; and retrieval of intravascular foreign bodies by percutaneous methods).
- Indications, contraindications, techniques, and limitations of diverse percutaneous procedures employed to treat structural heart diseases, such as percutaneous aortic valve implantation (transcatheter aortic valve replacement (TAVR), transcatheter mitral valve repair (TMVR), atrial appendage occlusion, percutaneous treatment of paravalvular leaks and patent foramen ovale (PFO) closure.
- Indications and management of ventricular assist devices.
- Critical analysis of published studies, in accordance with the principles of medicine based on scientific evidence.
- Ethics and compliance in interventional cardiology.
- Writing and obtaining consent forms in interventional cardiology. Examples of consent forms suggested by the SBHCI for the most common procedures may be found in Annexes 2 to 15.
- Writing reports in interventional cardiology (Annex 16).

4. Approval, Maintenance, and Revalidation of Accredited Centers

The definition of norms for accreditation and maintenance of hemodynamics and interventional cardiology training centers will be governed by self-regulation of which the Corporate Advisory Council is in charge. Verification of compliance with the requirements established in this Position Paper is the responsibility of the SBHCI's Permanent Certification Commission (Comissão Permanente de Certificação – CPC). To this end, a Verification Committee will be designated, consisting of three members, one belonging to the Directory Board, one belonging to the Advisory Council, and one belonging to the CPC.

Training centers will be submitted to a re-registration process every four years. In the event that the requirements of these guidelines are infringed, the Verification Committee will advise the coordinator of the training center to redress the irregularities observed, by means of a report based on the corrections necessary for the training center's maintenance. Six months later, a new inspection will be carried out. In the event that the recommendations have not been met, a final opinion will be emitted by the Advisory Council, deciding on the center's loss of accreditation.

Loss of accreditation of a training center will also occur under any one of the following conditions:

- Absence of at least one trainee who has completed training within a continuous four-year period.
- Absence of at least one graduate trainee from the training center who has passed the test to obtain certification in the area of interventional cardiology and interventional cardiology from the SBHCI, over the past four years.

Formal authorization is mandatory from the technical director of the hospital where the training center will operate.

5. Annual Evaluation of Trainees and Training Centers

At the end of each year of training, the CPC, in conjunction with the SBHCI, will make a structured form (Annex 17) available on the SBHCI intranet for all trainees, who will confidentially assess whether the training center is fulfilling this Position Paper's recommendations. Each form must be forwarded to the SBHCI.

6. Percutaneous Intervention in Congenital and Structural Heart Diseases and in the Extracardiac Vascular Bed

As observed, the theoretical-practical program which is applied over the two-year period is rich and comprehensive, and it allows interventional cardiologists, following training and certification, to act with proficiency in the treatment of coronary artery disease in their most varied forms of presentation. Furthermore, during this formative period or even after the conclusion of this phase, it is possible to participate in specific training processes, which will provide interventional cardiologists with the competences necessary to act in congenital and structural heart diseases and in the extracardiac arterial and venous vascular bed. We will subsequently detail the specific processes that ensure that an interventional cardiologist has obtained competences in the areas mentioned.

6.1. Congenital Heart Diseases

The knowledge, the abilities, and the training necessary for therapeutic interventions of congenital heart disease in children and adults are different than those required for PCI. Knowledge of the natural history of diverse congenital heart diseases is a prerequisite for the procedure's safety and effectiveness. Trainees are also required to know the indications for percutaneous treatment, as well as diverse types of surgery (palliative and corrective), hemodynamic evaluation and interpretation of diverse conditions in the catheterization laboratory, study and management of pulmonary hypertension, angiography, and interpretation of reports and complementary exam images, such as transthoracic echocardiography (TTE), transesophageal echocardiography (TEE), intracardiac echocardiography, CT, and MR. In contemporary interventional cardiology practice, we also recommend that trainees develop abilities for software or computer programs dedicated to reconstruction and measurement of cardiovascular structures. This new set of abilities aims to increase the capacity for planning and carrying out highly complex procedures, with the goal of increasing efficacy and safety for patients.

Training should proceed starting with less complex procedures until the abilities have been acquired which will allow trainees to perform procedures considered more complex. Among the abilities that should be acquired, basic training, by means of supervised practice, includes handling diverse vascular accesses, guides, wires, balloons, and devices, and, especially, orientation on how to anticipate, recognize, and treat possible complications. Great effort should be put forth to disseminate precautions with ionizing radiation and rational use of different means of contrast. Concomitant to this technical formation, it is recommended that trainees participate in didactic sessions, case discussions, post-procedure follow-up of patients, outpatient clinical follow-up, research, databanks and registries, assessment of quality and results, and participation in multidisciplinary groups (heart teams). Also recommended are training and familiarity with the particularities of handling newborns and young infants.

We consider that, for a complete formation, this training should last at least two years for pediatric or adult cardiologists or at least one additional year for general interventional cardiologists. Due to the numerous procedures currently performed for congenital and structural heart disease, the minimum number of exams carried out in order to have proper qualification varies in accordance with the complexity of the condition and intervention; however, qualified centers for formation of interventional cardiologists in congenital heart diseases should perform at least 100 therapeutic procedures per year, and trainees should participate as first operators in at least 40 cases during the training period.

Subsequently, we will describe the recommendations for acquisition and maintenance of competences in interventional treatment of congenital heart diseases, which are here divided by degree of complexity.

6.1.1 Basic Interventions in Congenital Heart Diseases

6.1.1.1 Interatrial Communication Occlusion

6.1.1.1.1. Basic Knowledge

- Natural history, classification, and hemodynamic repercussion of septal atrial defects.
- Indications for intervention.
- Proper differentiation between simple and complex defects.

6.1.1.1.2. Interventional Cardiologists' Abilities

- Knowledge and proper handling of introducers, sheaths, guidewires, and catheters utilized.
- Interpretation and familiarity with different imaging tests: atrial septal characteristics; determination of defect location, number, borders, and adjacent structures by TTE, TEE, intracardiac echocardiography, and fluoroscopy.
- Invasive assessment of pulmonary vascular pressure and reactivity, including the need for temporary balloon occlusion.
- When and how to use balloons for measurement.
- In-depth knowledge of different available devices, their characteristics, sizes, and forms of release.
- Mastery of techniques necessary to remove devices in the event of device embolization.
- Patient care and recognition of immediate and late complications and long-term patient guidance.

6.1.1.2. Ductus Arteriosus Occlusion

6.1.1.2.1. Basic Knowledge

- Natural history, classification, and hemodynamic repercussions of patent ductus arteriosus (PDA).
- Knowledge of the different anatomical types of PDA.
- Proper differentiation of simple or complex PDA, associated congenital anomalies, and pulmonary hypertension.
- Indications or contraindications for intervention.

6.1.1.2.2. Interventional Cardiologists' Abilities

- Evaluation of adequate access route for patients.
- Knowledge and proper handling of introducers, sheaths, guidewires, and catheters utilized.
- Invasive assessment of pulmonary vascular pressure and reactivity, including the need for temporary balloon occlusion.
- Evaluation of characteristics of the ductus arteriosus by means of diverse imaging methods: TTE, CT, MR, and angiography.
- Techniques for crossing the ductus: anterograde and retrograde.
- In-depth knowledge of different available devices, their characteristics, sizes, and forms of release.
- Mastery of techniques necessary to remove devices in the event of device embolization.
- Patient care and recognition of immediate and late complications and long-term patient guidance.

6.1.1.3. Pulmonary Valvuloplasty

6.1.1.3.1. Basic Knowledge

- Natural history, classification and hemodynamic repercussion of pulmonary stenosis.
- Knowledge of different types and etiology of pulmonary stenosis, as well as associated anomalies.
- Indications or contraindications for intervention.

6.1.1.3.2. Interventional Cardiologists' Abilities

- Knowledge and proper handling of introducers, sheaths, guidewires, and catheters utilized.
- Hemodynamic interpretation of pulmonary stenosis in the catheterization laboratory.
- Assessment of characteristics of pulmonary stenosis by means of diverse imaging methods: TTE, CT, MR, and angiography.
- Techniques for crossing pulmonary stenosis.
- Knowledge of the different balloons available for the procedure.
- Patient care and recognition of immediate and late complications and long-term patient guidance.

6.1.1.4. Aortic Valvuloplasty

6.1.1.4.1. Basic knowledge

- Natural history, classification, and hemodynamic repercussion of congenital aortic stenosis (AoS).
- Knowledge of different types of AoS, as well as associated anomalies.
- Indications or contraindications for intervention.

6.1.1.4.2. Interventional Cardiologists' Abilities

- Assessment of vascular access: carotid, axillary, or femoral; puncture or dissection.
- Knowledge and proper handling of introducers, sheaths, guidewires, and catheters utilized.
- Hemodynamic interpretation of AoS in the intervention laboratory.
- Assessment of characteristics of AoS by means of diverse imaging methods: TTE, TEE, CT, MR, and angiography.
- Techniques for crossing the AoS.
- Knowledge of different balloons available for this procedure and their choice in relation to ring size.
- Stimulation of very high frequencies by means of a pacemaker (rapid pacing).
- Patient care and recognition of immediate and late complications and long-term patient guidance.

6.1.2. Complex Interventions in Congenital Heart Diseases

6.1.2.1. Interventricular Communication Occlusion

6.1.2.1.1. Basic Knowledge

- Natural history, localization, characteristics, and associated defects. Simple or complex interventricular communication (IVC).
- Hemodynamic repercussion and assessment of pulmonary hypertension.
- Feasibility and indications for intervention.
- Therapeutic and prognostic options. Risk of total atrioventricular block (TAB).

6.1.2.1.2. Interventional Cardiologists' Abilities

- Knowledge and proper handling of introducers, sheaths, guidewires, and catheters utilized.
- Interpretation and familiarity with different imaging exams: characteristics of the ventricular septum, determination of defect location, number, borders, and adjacent structures by TTE, TEE, CT, MR, and angiography.
- Choice of access route (superior vena cava, inferior vena cava, transapical, etc.).
- Invasive assessment of pulmonary vascular pressure and reactivity.

- Appropriate angiography for characterization of the defect.
- Techniques for crossing and releasing the device: anterograde and retrograde.
- Proper technical knowledge of different devices available, characteristics, sizes, and forms of release.
- Mastery of techniques necessary to remove devices in the event of embolization.
- Patient care and recognition of immediate and late complications and long-term patient guidance.

6.1.2.2. Angioplasty and Stent Implantation for Coarctation of the Aorta

6.1.2.2.1. Basic Knowledge

- Natural history and treatment of native coarctation of the aorta (CoA) or post-operative recoarctation.
- Knowledge of different types and etiology of simple or complex CoA and associated anomalies.
- Assessment of characteristics of CoA by means of diverse imaging methods: TTE, TEE, CT, MR, and angiography.
- Indications for intervention.

6.1.2.2.2. Interventional Cardiologists' Abilities

- Knowledge and proper handling of sheaths, guidewires, and catheters.
- Choice of adequate access route: femoral, carotid, radial, axillary; puncture or dissection.
- Hemodynamic and angiographic interpretation of CoA in the intervention laboratory.
- Techniques for crossing the coarctation: anterograde or retrograde.
- Knowledge and appropriate choice of different balloons and covered or uncovered stents available for this procedure and their techniques.
- Recognition and treatment of acute complications.
- Knowledge and techniques for utilizing different hemostasis devices.
- Long-term care.

6.1.2.3. Angioplasty and Stent Implantation for Pulmonary Artery Stenosis

6.1.2.3.1. Basic Knowledge

- Natural history and knowledge of etiology, whether congenital or acquired, isolated or multiple, proximal or distal, and associated malformations.
- Appropriate assessment of pulmonary arteries by means of diverse imaging methods: TTE, TEE, CT, MR, angiography, and scintigraphy.
- Indications for intervention.

6.1.2.3.2. Interventional Cardiologists' Abilities

- Knowledge and proper handling of sheaths, guidewires, and catheters utilized.
- Choice of adequate vascular access.
- Hemodynamic and angiographic assessment of pulmonary stenoses.
- Knowledge and appropriate choice of different balloons, stents, and covered stents available for this procedure and their techniques.
- Recognition and treatment of acute complications.
- Medium and long-term care and orientations for the patient.

6.1.2.4. Angioplasty and Stent Implantation for Pulmonary Vein Stenosis

6.1.2.4.1. Basic Knowledge

- Natural history and knowledge of etiology, whether congenital or post-operative.
- Appropriate assessment of pulmonary veins by means of diverse imaging methods: TTE, TEE, CT, MR, angiography, and scintigraphy.
- Indications for intervention.

6.1.2.4.2. Interventional Cardiologists' Abilities

- Knowledge and proper handling of sheaths, guidewires, and catheters utilized.
- Choice of adequate access route.
- Transseptal puncture: techniques (guided by fluoroscopy and echocardiography) and complications.
- Selective hemodynamic and angiographic assessment of pulmonary veins.
- Knowledge and appropriate choice of different balloons and stents available for this procedure and their techniques.
- Recognition and treatment of acute complications.
- Medium and long-term care.

6.1.2.5. Angioplasty and Stent Implantation in Surgical Conduits, Tunnels, and Homografts

6.1.2.5.1. Basic Knowledge

- Natural history of the different types of material utilized: biological or synthetic, valved or not valved.
- Knowledge of anatomical and physiological differences in intra- or extracardiac surgical conduits and tunnels.
- Appropriate understanding of the anatomy and hemodynamics of surgical procedures performed in complex heart diseases, univentricular physiology, transposition of great arteries, corrected transposition of great arteries; repercussions of ventricle pressure and volume overload.
- Appropriate assessment of anatomy and physiology by means of diverse imaging methods: echocardiography, CT, MR, angiography, and scintigraphy.
- Indications for intervention.

6.1.2.5.2. Interventional Cardiologists' Abilities

- Knowledge and proper handling of sheaths, guidewires, and catheters utilized.
- Choice of vascular access.
- Hemodynamic and angiographic assessment of surgical conduits and tunnels.
- Knowledge and appropriate choice of different balloons, stents, and covered stents available for this procedure and their techniques.
- Recognition and treatment of acute complications.
- Medium and long-term care and orientations for the patient.

6.2. Structural Heart Diseases

Structural heart diseases encompasses congenital and acquired conditions that involve major cardiovascular structures, excluding coronary atherosclerotic and peripheral vascular diseases. Formal training in structural and congenital heart diseases in adults takes place during the specialization phase, even in developed countries.[8] With the advent of percutaneous interventions for the treatment of structural defects and valve diseases, such as TAVR, TPVI, and TMVR, as well as the expansion of occlusion procedures with intra- and extracardiac shunts, among others, it is clear that there is a need to create basic requirements for training interventional cardiologists who are interested in performing these procedures.

As the complexity of the conditions increases, the level of training goes from a "basic" stage to more "advanced" levels. Training for occlusion of atrial septal defects requires less advanced abilities and tools than those that are required for mitral paravalvular leak closure, for instance. Training in formation centers should seek to hierarchize this process. In the same manner, for interventional cardiologists who are already acting in the field, the tutorial process, with the figure of an instructor or proctor, is fundamental to determining which steps to go through, from less complex to more complex scenarios.

6.2.1. Basic Interventions in Structural Cardiovascular Diseases

6.2.1.1. Catheterization of Left Chambers following Transseptal Puncture

6.2.1.1.1. Basic Knowledge

- Normal anatomy and morphospatial variations resulting from diverse conditions (right and/or left atrial dilatation, ascending aortic dilatation, dextrocardia, heterotaxy, etc.).
- Hemodynamic interpretation of pressure curves.
- Appropriate assessment and recognition of atrial septal structures by means of diverse imaging methods: TTE, TEE, intracardiac echocardiography, and fluoroscopic markers.
- Indications for intervention.

6.2.1.1.2. Interventional Cardiologists' Abilities

- Percutaneous access for transseptal puncture.
- Transseptal introducers, wires, needles, and other devices, such as radiofrequency.
- Selective puncture guided by TEE.

6.2.1.2. Aortic Valvuloplasty in Adults

6.2.1.2.1. Basic Knowledge

- Natural history and etiology of AoS.
- Hemodynamics of severe AoS with high and low gradients.
- Interpretation and familiarity with different imaging exams of the aortic valve: TTE, TEE, CT, MR, angiography.
- Knowledge of current guidelines for treatment of AoS.
- Therapeutic options and outcomes.
- Indications for intervention.

6.2.1.2.2. Interventional Cardiologists' Abilities

- Hemodynamic interpretation of AoS.
- Access choice.
- Techniques for crossing the stenotic aortic valve.
- Sheaths, wires, and catheters utilized.
- Balloon catheters for valvuloplasty.
- Stimulation of very high frequencies by means of a pacemaker (rapid pacing).
- Familiarity in managing devices for vascular suture.
- Recognition and rapid management of complications (vascular occlusions, dissections, thromboembolism, hemodynamic collapse, retroperitoneal bleeding, cardiac perforations, arrhythmias/atrioventricular blocks, coronary occlusion, etc).
- Immediate and long-term post-procedural care.

6.2.1.3. Patent Foramen Ovale Occlusion

PFO is observed in approximately 25% of the general population, and it may thus coexist, by chance, in patients with strokes or thromboembolic phenomena that are undefined in nature.[9] Epidemiological data, however, have established a clear relation between PFO and stroke of undetermined origin.[10-14] Additionally, studies have documented higher rates of systemic embolization among patients who have venous thrombosis or debris and concomitant PFO.[15-18] Many reports have also demonstrated direct evidence of thrombi adherent to the PFO.[19,20] Finally, and most importantly, randomized studies have demonstrated that PFO occlusion significantly reduces stroke recurrence in comparison with isolated medical therapy.[21-24]

Based on a document signed by several European scientific societies, PFO occlusion or closure in the scenario of stroke or paradoxical systemic embolic events of undefined causes (related to PFO) should be performed in select patients, between the ages of 18 and 65, as a form of secondary

prevention.[25] Within this same scenario, it has also been demonstrated that the cost-effectiveness relationship is favorable for PFO occlusion, in comparison with isolated medical treatment.[26]

6.2.1.3.1. Basic Knowledge

- Natural history and mechanisms of paradoxical thromboembolic events; stroke related to PFO; hemodynamic repercussion of atrial septal defects.
- Medical management of stroke related to PFO.
- Interpretation and familiarity with different imaging exams related to the atrial septum, adjacent structures, and the brain structures as well: TTE, TEE, intracardiac echocardiography, MR, CT, transcranial Doppler, and fluoroscopy.
- Knowledge of current guidelines for PFO occlusion in the scenario of paradoxical embolism (secondary prevention).
- Indications for intervention.

6.2.1.3.2. Interventional Cardiologists' Abilities

- Techniques for crossing the PFO.
- Knowledge and proper handling of introducers, sheaths, guidewires, and catheters utilized.
- Knowledge and abilities with imaging methods for guiding the procedure: TEE, intracardiac echocardiography, and fluoroscopy.
- When and how to use balloons for measurement.
- In-depth knowledge of different devices available, their characteristics, sizes, and forms of release.
- Mastery of techniques necessary to remove devices in the event of embolization.
- Recognition and rapid management of complications (vascular occlusion, dissection, thromboembolism, hemodynamic collapse, cardiac perforation, arrhythmias/atrioventricular block, coronary occlusion, etc.).
- Immediate and long-term post-procedural care.

6.2.2. Complex Interventions in Structural Cardiovascular Diseases

6.2.2.1. Transapical Ventricular Access

6.2.2.1.1. Basic Knowledge

- Normal anatomy and morphospatial variations resulting from diverse conditions (right and/or left atrial dilatation, ascending aortic dilatation, dextrocardia, heterotaxy, etc.).
- Hemodynamic interpretation of pressure curves.
- Familiarity with different imaging exams (CT, TTE, TEE, intracardiac echocardiography).
- Indications for intervention.

6.2.2.1.2. Interventional Cardiologists' Abilities

- Micropuncture needles, wires, and introducers.
- Selective puncture guided by CT, ultrasound, and fluoroscopy.
- Knowledge and techniques for utilization of different hemostasis devices.
- Immediate and long-term post-procedural care.

6.2.2.2. Transhepatic Access

6.2.2.2.1. Basic Knowledge

- Normal anatomy and morphospatial variations resulting from diverse conditions.
- Indications for intervention.

6.2.2.2.2. Interventional Cardiologists' Abilities

- Micropuncture needles, wires, and introducers.
- Selective puncture guided by ultrasound and fluoroscopy.
- Knowledge and techniques for utilization of different hemostasis devices
- Immediate and long-term post-procedural care.

6.2.2.3. Mitral and Tricuspid Valvuloplasty in Adults

6.2.2.3.1. Basic Knowledge

- Natural history and etiology of mitral and tricuspid stenosis.
- Hemodynamics of severe mitral and tricuspid stenoses.
- Interpretation and familiarity with different imaging methods related to the aortic and tricuspid valves: echocardiography, CT, MR, angiography.
- Knowledge of current guidelines for treatment of mitral and tricuspid stenoses.
- Therapeutic options and outcomes.
- Indications for intervention.

6.2.2.3.2. Interventional Cardiologists' Abilities

- Hemodynamic interpretation of pressure curves in mitral and tricuspid stenoses in the hemodynamics laboratory.
- Choice of vascular access.
- Selective transseptal puncture (for mitral stenosis).
- Techniques for crossing mitral and tricuspid stenoses.
- Sheaths, wires, and catheters utilized.
- Balloon catheters for valvuloplasty.
- Knowledge and techniques for utilization of different hemostasis devices.
- Recognition and rapid management of complications (vascular occlusions, dissections, thromboembolism, hemodynamic collapse, retroperitoneal bleeding, cardiac perforations, tamponade, arrhythmias/atrioventricular blocks, etc.).
- Immediate and long-term post-procedural care.

6.2.2.4. Balloon Pericardiotomy and Pericardiocentesis

6.2.2.4.1. Basic Knowledge

- Natural history of recurrent or malign pericardial effusion.
- Therapeutic options and outcomes.
- Pericardial sac anatomy.
- Indications for intervention.

6.2.2.4.2. Interventional Cardiologists' Abilities

- Techniques for percutaneous access to the pericardial sac.
- Puncture guided by echocardiography and fluoroscopy.
- Needles, wires, introducers, catheters, and balloon catheters.
- Immediate and long-term post-procedural care.

6.2.2.5. Post-infarction Interventricular Communication Occlusion

6.2.2.5.1. Basic Knowledge

- Natural history of post-infarction IVC (anterior and inferior infarctions).
- Management of cardiogenic shock.
- Hemodynamic repercussion and assessment of pulmonary hypertension.
- Interpretation and familiarity with different imaging exams related to characteristics of the ventricular septum, determination of defect location, number, and adjacent structures: TTE, TEE, CT, MR, and angiography.
- Feasibility and indications for intervention.

6.2.2.5.2. Interventional Cardiologists' Abilities

- Hemodynamic interpretation of post-infarction IVC in the hemodynamics laboratory.
- Choice of vascular access (superior vena cava, inferior vena cava, transapical, etc.).
- Techniques for crossing the IVC.
- Knowledge and proper handling of sheaths, guidewires, and catheters utilized.
- Knowledge of when and how to use balloons for measurement.
- Appropriate angiography for defect characterization.
- Techniques for crossing and releasing the device: anterograde and retrograde.
- Proper technical knowledge of different devices available, characteristics, sizes, and forms of release.
- Mastery of techniques necessary to remove devices in the event of embolization.
- Recognition and rapid management of complications (vascular occlusions, dissections, thromboembolism, hemodynamic collapse, cardiac perforations, cardiac tamponade, device embolism, arrhythmias/atrioventricular blocks, coronary occlusion etc.).
- Immediate and long-term post-procedural care.

6.2.2.6. Occlusion of Paravalvular Leaks

6.2.2.6.1. Basic Knowledge

- Natural history of paravalvular leaks.
- Paravalvular leaks in mechanical and biological valve prostheses.
- Recognition and clinical management of mechanical device hemolysis.
- Interpretation and familiarity with different imaging exams related to accurate localization of the leak: TTE, TEE, CT, MR, and angiography.
- Indications for intervention.

6.2.2.6.2. Interventional Cardiologists' Abilities

- Hemodynamic interpretation of paravalvular leaks in the hemodynamics laboratory.
- Choice of vascular access: retrograde, anterograde transseptal, and transapical.
- Selective transapical puncture.
- Techniques for crossing paravalvular leaks.
- Knowledge and proper handling of introducers, sheaths, guidewires, and catheters utilized.
- Proper technical knowledge of different devices available, their characteristics, sizes, and forms of release.
- Mastery of techniques necessary to remove devices in the event of embolization.
- Recognition and rapid management of complications (vascular occlusion, dissection, thromboembolism, hemodynamic collapse, cardiac perforation, cardiac tamponade, device embolism, arrhythmias/atrioventricular block, coronary occlusion etc.).
- Immediate and long-term post-procedural care.

6.2.2.7. Left Ventricular Pseudoaneurysm Occlusion

6.2.2.7.1. Basic Knowledge

- Natural history of ventricular pseudoaneurysms.
- Pseudoaneurysms as complication of mechanical and biological valve prostheses.
- Recognition and clinical management of mechanical device hemolysis.
- Management of cardiac insufficiency.
- Interpretation and familiarity with different imaging exams: accurate localization and characterization of the pseudoaneurysm by TTE, TEE, CT, MR, and angiography.
- Indications for intervention.

6.2.2.7.2. Interventional Cardiologists' Abilities

- Choice of access route: retrograde, anterograde transseptal, and transapical.
- Selective transseptal puncture.
- Selective transapical puncture.

- Techniques for entering the left ventricular pseudoaneurysm.
- Knowledge and proper handling of introducers, sheaths, guidewires, and catheters utilized.
- Proper technical knowledge of different devices available, their characteristics, sizes, and forms of release.
- Mastery of techniques necessary to remove devices in the event of embolization.
- Recognition and rapid management of complications (vascular occlusion, dissection, thromboembolism, hemodynamic collapse, cardiac perforation, cardiac tamponade, device embolism, arrhythmias/atrioventricular block, coronary occlusion etc.).
- Immediate and long-term post-procedural care.

6.2.2.8. Occlusion of Endovascular Endoleaks

6.2.2.8.1. Basic Knowledge

- Natural history and recognition of endovascular endoleaks.
- Endovascular endoleaks in different endoprosthesis types.
- Knowledge of the collateral and arterial ramifications of the aorta.
- Interpretation and familiarity with different imaging exams: CT, MR, angiography, and ultrasound.
- Indications for intervention.

6.2.2.8.2. Interventional Cardiologists' Abilities

- Choice of vascular access.
- Direct selective access.
- Knowledge and proper handling of introducers, sheaths, guidewires, and catheters utilized.
- Proper technical knowledge of different types of occlusion devices and chemical agents.
- Mastery of techniques necessary to remove devices in the event of embolization.
- Recognition and rapid management of complications (vascular occlusions, dissections, thromboembolism, hemodynamic collapse, cardiac perforations, cardiac tamponade, device embolism, arrhythmias/atrioventricular blocks, coronary occlusion, etc.).
- Immediate and long-term post-procedural care.

6.2.2.9. Aortic Pseudoaneurysm Occlusion

6.2.2.9.1. Basic Knowledge

- Natural history and etiology of aortic pseudoaneurysms.
- Interpretation and familiarity with different imaging exams related to accurate localization and characterization of the pseudoaneurysm: ultrasound, CT, MR, and angiography.
- Indications for intervention.

6.2.2.9.2. Interventional Cardiologists' Abilities

- Choice of vascular access.
- Knowledge and proper handling of introducers, sheaths, guidewires, and catheters utilized.
- Proper technical knowledge of different types of occlusion devices, chemical agents, covered stents, and endoprostheses.
- Mastery of techniques necessary to remove devices in the event of device embolization.
- Recognition and rapid management of complications (vascular occlusion, dissection, thromboembolism, hemodynamic collapse, cardiac perforation, cardiac tamponade, device embolism, arrhythmias/atrioventricular block, coronary occlusion etc.).
- Immediate and long-term post-procedural care.

6.2.2.10. Hypertrophic Cardiomyopathy and Alcohol Septal Ablation

Hypertrophic cardiomyopathy is the most common genetic cardiovascular disease, with an estimated prevalence of 0.2% in the general population.[27] Interventional cardiologists who perform this procedure should possess extensive knowledge of the results, limitations, and complications of medical therapy, surgical myectomy, dual-chamber pacemaker pacing, and alcohol septal ablation itself.[27-29]

Alcohol septal ablation should involve a multidisciplinary program that includes the contributions of a cardiac surgeon, an echocardiographist, a clinical cardiologist, and an electrophysiologist. The first procedures should be supervised by an experienced operator in training centers or in services outside of training centers under the supervision of a medical instructor (proctor).

6.2.2.10.1. Basic Knowledge

- Natural history and etiologies of left ventricular outlet obstructions.
- Hemodynamics of left ventricular outlet obstructions.
- Interpretation and familiarity with different imaging exams: TTE, TEE, CT, MR, and angiography.
- Knowledge of current guidelines for treatment of hypertrophic cardiomyopathy.
- Therapeutic options.
- Indications for intervention.

6.2.2.10.2. Interventional Cardiologists' Abilities

- Hemodynamic interpretation of left ventricular outlet obstruction.
- Choice of vascular access.
- Sheaths, wires, balloons, and catheters utilized.
- Angiographic projections for septal ablation.
- Pacemaker in the right ventricle during intervention.
- Ablative substances (alcohol, microspheres, etc.).
- Recognition and rapid management of complications (vascular occlusion, dissection, thromboembolism, hemodynamic collapse, extension of infarction, iatrogenic

post-infarction IVC, cardiac perforation, arrhythmias/atrioventricular block, coronary occlusion, etc.).
- Immediate and long-term post-procedural care.

6.2.2.11. Left Atrial Appendage Occlusion

Oral anticoagulation is indicated as a class I recommendation, level of evidence A, for prevention of thromboembolic stroke in patients with non-valvular atrial fibrillation (NVAF) and CHA_2DS_2-VASc scores ≥ 2, in both Brazilian[30] and international[31,32] guidelines. There are, however, several absolute and relative contraindications to the use of this therapy, either with the use of vitamin K antagonists or direct action oral anticoagulants[33] (Chart 3).

Based on the rationale that more than 90% of intracardiac thrombi that are formed as a result of NVAF are localized in the left atrial appendage (LAA),[34] percutaneous left atrial appendage occlusion (LAAO) has proven to be a non-inferior alternative, in relation to the occurrence of thromboembolism, and it is superior in terms of late mortality, when compared to oral anticoagulation with warfarin.[35,36] The II Brazilian Guidelines for Atrial Fibrillation recommend LAAO for patients with high risks of thromboembolic phenomena and contraindications to the use of oral anticoagulants (class IIa, level of evidence B), and for patients sustaining a ischemic stroke of cardioembolic origin occurring in the presence of adequate oral anticoagulant use (class IIa, level of evidence C).[30]

Notwithstanding its growing utilization, LAAO is not yet an intuitive procedure for interventional surgeons, which is reflected by the slower and more gradual learning curve and by the potential associated complications. In addition to technical abilities for the intervention itself, LAAO requires proficiency in several stages of management for these patients who are generally elderly and complex, including proper indication for the procedure, interpretation of cardiac angiography and pre- and trans-operative echocardiography imaging, and management of specific protocols of medication and late follow-up. In this manner, with the aim of obtaining better safety and effectiveness in the intervention, and in accordance with international propositions,[36-38] these guidelines recommend the establishment of prerequisites for institutions and professionals who wish to dedicate themselves to LAAO, in addition to a consistent model for acquiring competence in this intervention.

Chart 3 – Absolute and relative contraindications to the use of oral anticoagulation

• Previous significant bleeding
• Previous intracranial bleeding
• Symptomatic bleeding in a critical organ (e.g., ocular, pericardial, medullary)
• High risk of bleeding
• Frailty/frequent falls
• Comorbidities (e.g., intestinal angiodysplasia, renal failure, blood dyscrasia)
• Lack of adherence to treatment
• Labile INR
• Anticoagulant intolerance
• Use of double antiplatelet therapy
• Refusal to use the medication
• Occupational risk

INR: international normalized ratio.

6.2.2.11.1. Institutional Prerequisites

The institution should have an established service for structural or congenital heart diseases and/or electrophysiology equipped with an infrastructure that includes, among other things, a hybrid room or a cardiac catheterization laboratory with fixed hemodynamic equipment; it is considered not adequate performing these procedures with a C-arm.

There should be a local echocardiography service, with a capacity for performing transthoracic and transesophageal exams with an experienced operator. Anesthesiologists experienced in complex cardiovascular interventions should be part of the local team. The institution should also have a structured cardiac surgery service. It is not considered necessary to keep a cardiac surgery team on stand-by during the procedure; it should, nonetheless, be possible to activate this team rapidly, if necessary.

6.2.2.11.2. Basic Knowledge

- Basic knowledge about management of patients with atrial fibrillation, including mastery of tools for assessing risk of stroke and bleeding.
- Detailed understanding of cardiac anatomy, surrounding structures, and the anatomical variability of the LAA, with the ability to interpret invasive pressure curves, fluoroscopy, echocardiography, and cardiac angiotomography images related to the procedure and its possible complications.
- Interpretation and familiarity with different imaging exams related to the LAA: TTE, TEE, CT, MR, and angiography.
- Knowledge of current guidelines for LAAO.
- Therapeutic options and outcomes.
- Indications for intervention.

6.2.2.11.3. Interventional Cardiologists' Abilities

- Interpretation of LAA images.
- Selective transseptal puncture.
- Safe access to the LAA.
- Sheaths, wires, and catheters utilized.
- Proper technical knowledge of the different devices available, their characteristics, sizes, forms of release, and contraindications.
- Recognition and rapid management of complications (vascular occlusions, dissections, thromboembolism, hemodynamic collapse, cardiac perforations, cardiac tamponade, device embolism, arrhythmias/atrioventricular blocks, coronary occlusion etc.).
- Immediate and long-term post-procedural care.

6.2.2.11.4. Acquisition of Competence and Training Models

Once these prerequisites have been met, the acquisition of competence for an operator to become independent in this intervention should follow a structured, consistent model. Training should involve practical activities that include simulation of cases of transseptal puncture and implantation of LAA occluder prostheses, with manipulation of the material utilized during the procedure. During the first effective implants, the operator should be assisted by a medical instructor (proctor) with proven experience in the intervention.

The duration of the learning curve for LAAO varies significantly, in accordance with the operator's degree of familiarity with congenital and/or structural heart disease procedures and the frequency with which the procedure is performed. There is no consensus in the literature with respect to the minimum number of cases required in order to complete this learning curve;[39,40] nevertheless, within the Brazilian context, considering the complexity of the intervention, the practical experience of the authors of these guidelines has made it possible to estimate that a beginner operator reaches the level of proficiency and safety necessary for LAAO once he or she has performed approximately ten cases. Although all of the prostheses available in the Brazilian market follow different requirements and implantation techniques, there is a "group effect" in learning the general technique, which allows for partial sharing of the learning curves between prosteses.[39,41]

6.2.2.12. Transcatheter Aortic Valve Replacement

AoS currently shows a growing prevalence due to increased life expectancy and consequent population aging. Currently, the most common cause of AoS is aortic calcification, which mainly affects elderly patients, being observed at a prevalence of 4.6% in individuals over 75 years old.[42-44] TAVR has become an option for surgical valve replacement in select cases following careful assessment of life expectancy, degree of frailty, and aortic valve anatomy.[43,45-52]

Interventional cardiologists who perform this procedure should have extensive knowledge of the results, limitations, and complications of medical therapy, aortic valve replacement, stimulation with a pacemaker, and TAVR itself.[45-52] It is recommended that TAVR involve a multidisciplinary program that includes the contributions of a clinical cardiologist, an echocardiographist, a radiologist, and a cardiac surgeon. The following are, furthermore, recommended for the operator in accordance with the joint resolution established between the SBHCI and the Brazilian Society of Cardiovascular Surgery (Sociedade Brasileira de Cirurgia Cardiovascular – SBCCV) in January 2017:

- A certificate in the area of hemodynamics and interventional cardiology.
- Participation in theoretical didactic sessions, with a minimum course load of 24 hours, in courses administrated or recognized by the SBHCI and the SBCCV.
- Participation in training sessions with simulators, with a minimum course load of 2 hours.
- Participation, as an observer, in at least two TAVR procedures in training centers accredited by Brazilian medical societies or care centers that regularly contribute to the Brazilian Registry of Transcatheter Aortic Valve Bioprosthesis Implantation, as certified by the coordinator of the Center.
- Participation in discussions of clinical cases related to TAVR procedures, with a minimum course load of four hours, in training centers accredited by the medical societies, as certified by the coordinator of the Center.
- In transfemoral procedures, perform a minimum of five procedures over the past two years, as a first operator, under the supervision of a qualified specialist (proctor).
- Proficiency and autonomy attested by a supervisor specialist accredited by the SBCCV and the SBHCI (at the supervisor's discretion, training may be extended to a higher number of supervised cases).
- Contribution to the Brazilian Registry of Catheter Valve Therapy during at least the first 25 procedures, performed without supervision.

Candidates for TAVR Qualification Certificates must submit the proof of training documents to the Certification Committee of the SBHCI and the SBCCV, in order to verify that they have met the previously described requirements.

Candidates who undergo training in TAVR abroad may be certified, provided that they have met the requirements established here and that they present documentation which proves that they have completed training, with the signature of the technical manager of the institution.

6.2.2.12.1. Basic Knowledge

- Natural history and etiology of aortic valve stenosis.
- Hemodynamics of left ventricular outlet obstructions.
- Interpretation and familiarity with different imaging exams: TTE, TEE, CT, MR, and angiography.
- Knowledge of current guidelines for aortic valve stenosis.
- Therapeutic options.
- Indications for intervention.

6.2.2.12.2. Interventional Cardiologists' Abilities

- Hemodynamic interpretation of pressure curves.
- Choice of vascular access.
- Introducers, wires, and catheters utilized.
- Angiographic projections for performing the procedure.
- Pre-procedure assessment of CT and other exams for procedure planning.
- Right ventricular pacemaker during intervention (rapid pacing).
- Crossing of the aortic valve orifice with diverse guidewires for positioning inside the left ventricle.
- Performance of balloon aortic valvuloplasty.
- Recognition and rapid management of complications (vascular complications, coronary occlusion, stroke, cardiac tamponade, hemodynamic collapse, iatrogenic IVC, cardiac perforations, arrhythmias/atrioventricular blocks, etc.).
- Immediate and long-term post-procedural care.

6.2.2.13. Transcatheter Mitral Valve Repair

Mitral valve insufficiency, one of the most common acquired valve diseases, frequently affects elderly patients, who present many comorbidities and, at times, are not able to be treated conventionally by mitral valve surgery due to the high operative risk of death and complications.[42,43] TMVR is a viable option for treating moderate or severe mitral insufficiency, in symptomatic patients, patients with high surgical risks, or inoperable patients, with degenerative or functional etiology, as an alternative to conventional surgical treatment or isolated clinical treatment.[53-59]

Interventional cardiologists who perform this procedure must have specific training in cardiovascular catheterization, required during professional qualification, as well as experience in diagnostic procedures for valve diseases, which are essential to their safety and success.[53-59] Mastery of the transseptal puncture technique is also necessary, as is knowledge of its anatomical relation with the pulmonary artery, the coronary sinus, the aorta, and other cardiac structures, because, in some cases, accidents may occur during puncture of the interatrial septum. Specific knowledge is also necessary regarding the general characteristics of implantable medical devices utilized by this technique and their appropriate indications, as well as understanding of anticoagulation control and appropriate management of possible complications, such as cardiac tamponade, cardiac or vascular perforation, clip embolization, thrombus formation, infectious endocarditis, cardiac arrhythmias, and other complications.

It is recommended that TMVR involve a multidisciplinary program that includes the contributions of a clinical cardiologist, an echocardiographist, a radiologist, and a cardiac surgeon. Qualification of physicians for mitral clip therapy requires thorough knowledge of normal cardiac anatomy, anatomy of right and left chambers, and, above all, an understanding of anatomical anomalies, their functional repercussions, and the corresponding relative values of therapeutic options. The duration of the learning curve varies significantly in accordance with the operator's degree of familiarity with procedures for congenital and/or structural heart diseases, as well as the frequency with which the procedure is performed. Although there is no consensus in the literature with respect to the minimum number of cases required in order to complete this learning curve, within the Brazilian context, considering the complexity of the intervention, it is possible to estimate that a beginner operator will reach the level of proficiency and safety necessary for TMVR once he or she has performed approximately ten cases.

6.2.2.13.1. Basic Knowledge

- Natural history and etiology of mitral valve insufficiency.
- Hemodynamics of mitral insufficiency.
- Interpretation and familiarity with different imaging exams: TTE, TEE, CT, MR, and angiography.
- Knowledge of current Brazilian guidelines for treating mitral valve insufficiency.
- Therapeutic options.
- Indications for intervention.

6.2.2.13.2 Interventional Cardiologists' Abilities

- Hemodynamic interpretation of pressure curves.
- Access management.
- Ability with the introducers, wires, and catheters utilized.
- Angiographic projections for performing the procedure.
- Pre-procedure assessment of TEE for patient selection.
- Recognition and rapid management of complications (vascular complications, stroke, cardiac tamponade, hemodynamic collapse, cardiac perforations, arrhythmias/atrioventricular blocks, etc.).
- Immediate and long-term post-procedural care.

6.2.2.14 Transcatheter Pulmonary Valve Bioprosthesis Implantation

Right ventricular outflow tract dysfunctions are frequently involved in the late postoperative period of right ventricle to pulmonary artery (RV-PA) connection surgeries in patients with tetralogy of Fallot, pulmonary atresia, truncus arteriosus, or any other congenital heart disease in which pulmonary flow must be anatomically restored. In this context, pulmonary insufficiency and, mainly, its association with pulmonary stenosis (double pulmonary valve lesion) may result in dilatation and progressive right ventricular dysfunction, exercise intolerance, potentially severe arrhythmias, and sudden death. Reestablishing pulmonary valve function at an appropriate moment may reverse this process, thus restoring ventricular function and improving symptoms.[60,61]

Surgical replacement of the pulmonary valve requires extracorporeal circulation, which may further aggravate right ventricular function, when it is already compromised.[61] There are several options and surgical techniques for treating pulmonary insufficiency, including the use of cadaver homografts, valved synthetic conduits, bovine jugular vein grafts, or a bioprosthetic valve implanted directly in the right ventricular outflow tract. With the passing of time, however, all of these conduits or surgically implanted valves present varying degrees of dysfunction characterized by stenosis, accompanied or unaccompanied by insufficiency. It is estimated that after four to five years, 25% of patients who have undergone a homograft implantation will require some type of intervention to increase the longevity of these conduits.[62] The probability of not needing a conduit replacement is approximately 50% over ten years, with even less favorable figures in small children.[62]

In 2011, the American Heart Association (AHA) published a scientific statement on interventions in congenital heart diseases, in which the recommendation for TPVI was classified as IIa (level of evidence B), stating that, "It is reasonable to consider percutaneous pulmonary valve replacement in a patient with an RV-to-pulmonary artery conduit with associated moderate to severe pulmonary regurgitation or stenosis provided the patient meets inclusion/exclusion criteria for the available valve."[63]

The TPVI procedure should be performed in a conventional catheterization laboratory or in a hybrid operating room, and the institution should have a group of professionals qualified to treat congenital and structural heart diseases (heart team), made up of a clinical cardiologist, a cardiologist with a

certificate in the area of hemodynamics and interventional cardiology, a cardiovascular surgeon, and other professionals directly or indirectly related to the procedure. It is highly recommendable that the operators possess vast experience in diagnostic and therapeutic percutaneous procedures for congenital heart diseases, especially stent implantations in pulmonary arteries. Also necessary are mastery of the coronary catheterization technique and knowledge of the anatomical relation of the origins of coronary arteries with the pulmonary artery, given that, in some cases, release of the pulmonary bioprosthesis might lead to coronary occlusion, which would contraindicate the therapy.

In addition to these prerequisites, it is necessary to possess specific knowledge regarding the general characteristics of catheter-implanted valve prostheses, their appropriate indications in accordance with the underlying congenital heart disease, anticoagulation control, and adequate management of possible complications, such as coronary compression, cardiac or vascular perforation, partial or total rupture of the treated conduit, prosthesis embolization, prosthetic thrombus formation, infectious endocarditis, cardiac arrhythmias, etc.

The specialist physician should possess knowledge of the different surgical strategies used for right ventricular outflow reconstruction, which are necessary to treat complex congenital heart diseases, such as tetralogy of Fallot, pulmonary atresia with IVC, double right ventricular outflow with infundibular pulmonary stenosis, transposition of great arteries with IVC and infundibular pulmonary stenosis, corrected transposition of great arteries with pulmonary stenosis, and common truncus arteriosus.

Concerning, moreover, qualification of physicians, specialists responsible for performing TPVI are required to bear a certificate in the area of hemodynamics and interventional cardiology, duly registered with the CRM in the jurisdiction in which they are professionally active, in accordance with current legislation, and they must have participated in at least ten procedures under the supervision of a qualified physician (proctor), in order to have adequate proficiency and safety for the implantation.

6.2.2.14.1 Basic Knowledge

- Natural history of different types of conduits or valves (synthetic, biological, homografts, valved, or non-valved) utilized for the connection between the right ventricle and the pulmonary trunk (RV-PT).
- Knowledge of the anatomy and physiology of different intra- and extracardiac surgical conduits and tunnels.
- Comprehension of the anatomy and hemodynamics of different surgical procedures used for treating complex congenital heart diseases.
- Knowledge of the effects of pressure and volume overloads on the pulmonary ventricle in patients with complex congenital heart diseases and conduits.
- Indications for intervention.

6.2.2.14.2 Interventional Cardiologists' Abilities

- Hemodynamic interpretation of complex congenital heart diseases in the hemodynamics laboratory.
- Choice of access.
- Knowledge and abilities with imaging methods for guiding the procedure: echocardiography, CT, MR, and angiography.
- Knowledge and appropriate choice of different catheters, guides, balloons, sheaths, stents, covered stents, and devices available for this procedure and their techniques.
- Assessment of coronary circulation during balloon compression test in the conduit.
- Knowledge of balloon catheters for dilatation.
- Techniques for stent implantations.
- Adequate and safe implantation of pulmonary valve replacement devices.
- Recognition and rapid management of complications (vascular complications, coronary occlusion, stroke, cardiac tamponade, hemodynamic collapse, iatrogenic IVC, cardiac perforations, arrhythmias/atrioventricular blocks, etc.).
- Immediate and long-term post-procedural care.

6.3. Extracardiac Interventions

Since their appearance, diagnostic and therapeutic endovascular procedures in the extracardiac vascular bed have historically been performed by interventional cardiologists.

Interventional cardiologists notably possess extensive scientific knowledge about systemic atherosclerotic diseases and the use of anticoagulants and antiplatelet agents, and they also have mastery of the technical procedures for performing angioplasty with stent implantation, using embolic protection filters, and others.[2,3,8,64]

With the expansion and rapid advancement of techniques for peripheral intervention over the past decade, it has become necessary for the SBHCI to accompany the formation and maintenance of training and expertise of its affiliated professionals closely.

6.3.1. Norms for Establishing Hemodynamics and interventional Cardiology Training Centers that Include Extracardiac Interventions

The basic rules are the same as those previously described in this Position Paper. Centers must, additionally, routinely perform extracardiac vascular procedures, in a manner that trainees are able to acquire the theoretical and practical knowledge required for good medical practice. In the literature, there is not a defined number of procedures that establish a service's competence in this area.

6.3.1.1. Medical Teams

Medical teams must be made up of preceptors and a coordinator, with the same prerequisites previously defined. There should, additionally, be professionals with experience and recognized expertise in extracardiac interventions. The number of vascular procedures necessary for maintaining competence has not been established, and it is controversial

in the literature. One motive which justifies this difficulty is that we are dealing with procedures which are less prevalent in all services. It is however, recommended, as an analogy of the proposed volume for maintaining trainee competence, that preceptors perform at least 50 therapeutic endovascular interventions annually.

6.3.1.2. Trainees

The prerequisites and basic obligations of trainees have been previously described. For specific acquisition of competence in extracardiac interventions, trainees must act as first operators in:

- 100 diagnostic exams (including aortographies; angiographies of carotid, vertebral, subclavian, upper-member, lower-member, abdominal, and renal arteries; venous angiographies; cavographies, and pulmonary artery catheterizations).
- 50 endovascular interventions in different peripheral beds (miscellany).
- 12 carotid angioplasties.

6.3.1.3. The Theoretical-Practical Program

- The minimum specific training period is 12 consecutive months, with 30 days of vacation per year, scientific improvement, and participation in congresses and reunions related to the specialization.
- The year of extracardiac training may simultaneously correspond to the second year of specialization at the training center, in the event that the center routinely performs this type of intervention.
- In the event that the training does not routinely perform the extracardiac vascular procedures necessary for the acquisition of abilities on the part of the trainee, specific training may take place by means of improvement courses, sanctioned by the SBHCI, concomitant to or after the second year of specialization.

The minimum syllabus for trainees in hemodynamics and interventional cardiology has already been described. In relation to specific aspects of training for the peripheral bed, the following are also necessary:

- Mastery of alternative vascular accesses, such as anterograde puncture of the common femoral artery, brachial puncture, radial puncture, fistula puncture, superficial femoral puncture, popliteal puncture, distal vessel puncture in the lower limbs, whether ultrasound-guided or not.
- Comprehensive knowledge of peripheral vascular anatomy.
- Accompanying theoretical discussions of extracardiac cases for one year with preceptors in the specialization or with SBHCI endovascular course coordinators.
- For training in the improvement course, the minimum theoretical course load is 200 hours/year.

6.3.2. Individualized Knowledge for Each Type of Intervention

6.3.2.1. Interventions in Lower Limbs

6.3.2.1.1. Basic Knowledge

- Knowledge of the natural history of atherosclerosis and its manifestations in lower members, differentiating the needs of claudicating patients from those who have critical ischemia, whether acute or chronic.
- Clinical treatment of ischemia of the lower limbs.
- Differentiation of conduct for inflow and outflow diseases.
- Diagnostic exams required for image interpretation.
- Indications for invasive intervention.
- How to proceed with follow-up.

6.3.2.1.2 Interventional Cardiologists' Abilities

- Definition and execution of the best vascular access: anterograde or retrograde.
- Selection of introducers, sheaths, guides, and catheters.
- Selection of appropriate balloons; whether or not prostheses are necessary and their characteristics, balloon- or self-expandable, coated or uncoated.
- Mastery of management of complications by means of rescue of distal occlusions or embolisms with or without the use of local thrombolysis or perforations with embolotherapy techniques.

6.3.2.2. Aortic Interventions (Aneurysms)

6.3.2.2.1. Basic Knowledge

- Natural history of the disease.
- Differentiation of conduct based on the affected segment of the aorta.
- Diagnostic exams required for image interpretation.
- Indications for invasive intervention and technical knowledge for prevention and treatment of leaks.
- Planning, indication, and management by a multidisciplinary team (heart team).
- How to conduct follow-up.

6.3.2.2.2 Interventional Cardiologists' Abilities

- Definition of the best vascular access and mastery of totally percutaneous techniques and hemostatic devices.
- Selection of introducers, sheaths, guides, and catheters.
- Selection of endoprostheses and their characteristics.
- Mastery of management of complications by means of rescue of occlusions or perforations with techniques for covered prostheses.

6.3.2.3. Interventions in Renal Arteries

6.3.2.3.1. Basic Knowledge

- Natural history of the disease.
- Differentiation of conduct based on the clinic and anatomy.
- Diagnostic exams required for image interpretation.
- Indications for invasive intervention.
- How to conduct follow-up.

6.3.2.3.2. Interventional Cardiologists' Abilities

- Definition of best vascular access.
- Selection of introducers, sheaths, guides, and catheters.
- Selection of balloons and stents.
- Mastery of management of complications by means of rescue of occlusions or perforations with embolotherapy techniques.

6.3.2.4. Interventions in Carotid Arteries and Vessels of the Base

6.3.2.4.1. Basic Knowledge

- Natural history of the disease.
- Differentiation of conduct based on the clinic and extra- and intracranial vascular anatomy.
- Diagnostic exams required for image interpretation.
- Indications for invasive intervention.
- How to conduct follow-up.

6.3.2.4.2. Interventional Cardiologists' Abilities

- Definition of best vascular access.
- Selection of introducers, sheaths, guides, and catheters.
- Selective, atraumatic catheterization of the vessels of the base.
- Selection of the form of cerebral protection, filters, or proximal protection, balloons, and stents.
- Mastery of management of local complications by means of rescue of intracranial occlusions by local thrombolysis and retriever devices.

6.3.2.5. Embolotherapy

6.3.2.5.1. Basic Knowledge

- Identification of which conditions of vascular complications require endovascular intervention for occlusion of the target vessel.
- Diagnostic exams required for image interpretation.
- Indications for invasive intervention.
- How to conduct follow-up.

6.3.2.5.2. Interventional Cardiologists' Abilities

- Definition of best vascular access.
- Selection of introducers, sheaths, guides, and catheters.
- Selective, atraumatic catheterization of target vessels.
- Correct selection of embolization agent for every necessity.
- Mastery of the use of microcatheters, microguides, coils, particles, plugs, Onyx, and biological glue.

6.3.2.6. Venous Diseases

6.3.2.6.1. Basic Knowledge

- Venous diseases treatable by endovascular treatment, such as thromboses, central occlusions, stenoses, May-Thurner syndrome, and nutcracker syndrome, among others.
- Diagnostic exams required for image interpretation.
- Indications for invasive intervention.
- How to conduct follow-up.

6.3.2.6.2. Interventional Cardiologists' Abilities

- Selection of introducers, sheaths, guides, and catheters based on the condition to be handled.
- Selection of balloons and stents.
- Knowledge of techniques for chemical and mechanical thrombolysis; indications and management of vena cava filters.

Regarding procedures whose indications and degrees of evidence have fluctuated over the past years, such as pulmonary branch angioplasty and renal denervation, it is necessary for trainees and interventional cardiologists who are already qualified to stay continuously updated.

Finally, interventional cardiologists are encouraged to have knowledge and training for the use of mechanical thrombectomy in the case of an acute ischemic stroke, which may result from both percutaneous procedures performed and separate events, whose limited therapeutic window makes transfer to another center difficult.

7. Final Considerations

The great advance recently observed in interventional cardiology is limited not only to percutaneous treatment of the coronary artery disease, but also to the treatment of congenital heart diseases, the extracardiac vascular bed and, above all, structural heart diseases. Establishment and maintenance of training centers are fundamental in order to guarantee that new interventionists acquire the abilities necessary to carry out interventional treatment of diseases that are included in this vast and complex area of cardiology practice, with excellence. In this manner, the SBHCI must assume the coordination of actions and norms that provide for the certification of training centers and new interventionists. The SBHCI must also act as a facilitator of continued medical education in the area of interventional cardiology, with the objective of providing society with professionals whose abilities and responsibilities adequately meet the population's expectations. This entire process should be periodically revised, and any eventual adaptations should be published in the form of guidelines or recommendations.

Annex 1

RADIATION PROTECTION

Technological advances over the past decades have made it possible for interventional cardiology to expand visibly, promoting diagnosis and therapy of numerous diseases in a less invasive manner and with minimal risks for patients. This area of practice has gone from having a diagnostic perspective to intensely acting to treat cardiovascular conditions, encompassing complex coronary interventions, extracardiac vascular diseases, and congenital and structural heart diseases. In addition, the type and complexity of interventions, as well as the clinical severity of patients have significantly increased.[65] What is thus observed is an increasing radiation dose used for interventional procedures over the past years.

Biological Risk of Exposure to Ionizing Radiation in Interventional Cardiology

Exposure to ionizing radiation in a routine and continuous manner may lead to harmful biological effects on the human body, by direct or indirect action on the cells, causing physiological and/or functional effects on the organs. Studies have shown that exposed professionals have increased risks of cataracts,[66,67] brain tumors, skin lesions, and hereditary genetic alterations.[68] Radiation protection measures, both for individuals and for institutional requirements, are thus essential for everyone who works with these agents.

Institutional Requirements

It is necessary for the institution where the hemodynamics and interventional cardiology laboratory functions to have the following:

a. A medical technician responsible for ensuring all service licensing norms, in compliance with federal and state health legislation.
b. A physician specialist in radiodiagnostics, as required by current legislation.
c. Personal protective equipment (PPE) in sufficient quantity for the whole team, such as a 0.5 mm lead-equivalent apron, lead glasses with side shields, and thyroid shields.
d. Barrier measures, such as lower ("skirt") and upper ("shield") screens are also requisites for protection.
e. Upkeep of PPE and its respective integrity tests, also on an annual basis (carried out and registered).
f. Individual dosimeter.

Technical Responsibility

The managing technician has the following responsibilities:

a. Be duly qualified and capacitated to exercise this function and ensure the service's proper functioning.
b. Establish a radiation protection program that includes service routines, technique standardization, and specific radiation protection measures.
c. Ensure that annual training and qualification of medical, care, and technical teams take place, including radiation protection measures, correct use of PPE, correct use of individual dosimeter, and correct equipment use.
d. Nominate subordinate people to assist in the construction and execution of activities that involve the radiation protection program, such as other physicians, physician specialists in radiodiagnostics, radiology technicians, and work safety technicians, i.e., encourage a culture of protection.
e. Guarantee preventative maintenance and dosimetry of equipment and a specific quality program for cinefluoroscopic equipment, including performance tests that evaluate precepts of image quality and radiological safety, with the frequency recommended by current legislation.

Individual Protection Measures

Individual protection measures include the following:

a. All individuals who work with radiation must use the aforementioned PPE (apron, lead glasses with side shield, and thyroid shield).
b. The operators, in addition to PPE, must use protective barriers (upper and lower screens) during all procedures.
c. No employee should exceed individual dose limits stipulated by current legislation:[69]
   - The average annual effective dose must not exceed 20 mSv during any period of five consecutive years, and it must not exceed 50 mSv during any year.
   - The equivalent annual dose must not exceed 500 mSv for any extremity and 150 mSv for the lens of the eye.

Quality Control

Quality control measures include:

a. The service should monitor all procedure doses and maintain the records of patient doses for consultation.

b. The radiation protection program should establish dose limits for investigation, in the event of patient overexposure, and patients who exceed the program's established dose must be followed up, with the entire investigation duly registered and attached to his or her medical record. Medical and care teams must also have their doses monitored and registered monthly with the use of a dosimeter, and cases where monthly and/or annual doses are exceeded must also be investigated.

c. It is recommended that procedure doses be described in their procedure reports.

d. It is recommended that the service implement monthly indicators that refer to radiation exposure and that these be widely disseminated among the members of medical and care teams.

Annex 2

FREE AND INFORMED CONSENT AND AUTHORIZATION FORM FOR PERFORMANCE OF THE EXAM/PROCEDURE OF CORONARY CINEANGIOGRAPHY WITH LEFT VENTRICULOGRAPHY, FFR, OR IFR AND ASSESSMENT OF MYOCARDIAL BRIDGING

By the present Consent and Authorization Form, I, ..., nationality ....., a legal adult and able, marital status ....., profession ....., identity document ....., issued by ....., CPF ....., resident of ...., city ....., state ....., date of birth ...../...../....., parents' names ....., hereby declare that I have received from the Hemodynamics Service, here represented by the physician fully identified below, explanations and warnings concerning the exam/procedure solicited by my clinical physician and that the discussion regarding the nature and extent of the actions necessary for its execution is registered below.

I further declare that it has been explained to me that the exam/procedure cineangiography with left ventriculography, intracoronary ultrasound (ICUS), fractional flow reserve (FFR), or instantaneous free-wave ratio (iFR) and assessment of myocardial bridging will be performed in the hemodynamics laboratory of this hospital institution (corporate name ...., CNPJ/MF no. .....headquarters.....) and that it consists of punctures in the patient's skin in order to introduce special catheters, using iodized contrast, with the administration of local anesthesia, sedation, or general anesthesia, at the attending physician's discretion.

The following text has been read and explained to me in more accessible language by the signing physician: the aim of this exam/procedure is to facilitate diagnosis of obstructions or blocks in arteries that irrigate or supply the cardiac muscle, known as coronary arteries. The exam/procedure consists of the insertion of a fine catheter through an arterial puncture, generally in the inguinal region or the radial artery. Exceptionally, it may be done by dissection/puncture of the brachial artery. Using this fine catheter, iodized contrast, and X-rays, it will be possible to understand the anatomy of the coronary arteries and, consequently, the extent of blocks which limit the free flow of blood to supply the heart, if they are present. In the event of doubts regarding the significance of the coronary artery blocks found, ICUS may be performed through a microcatheter specifically dedicated to this purpose, which will be introduced into the obstructed coronary artery. Diagnostic clarification regarding the severity of the coronary obstruction or block may be further carried out by means of the introduction of a very fine guidewire inside the coronary artery; this is known as FFR or iFR.

I declare that, in the manner explained to me by the physician, I am perfectly able to understand what the exam/procedure which I am to undergo will comprise.

I declare that I am aware that the intended purpose of performing the forenamed exam/procedure may not be achieved, even though the physician and his/her team adopt the best techniques and employ all of the scientific means and resources available.

I am also aware that the exam/procedure involves risks, and I have received all the pertinent information regarding possible complications due to known and unknown causes, including death, stroke, myocardial infarction, cardiac arrhythmia, acute pulmonary edema, anaphylactic shock, varying types and degrees of infection, allergies and/or reactions to contrast, bleedings, hematomas, renal insufficiency, vascular and hemodynamic complications, perforation of cardiac chambers or vessels, and loss of limbs and/or their function, in addition to the risks inherent in anesthesia and the use of diverse instruments and equipment itself. It has also been explained to me that these adverse reactions and infrequent, occurring in less than 2% of cases, but they may be aggravated when associated with other patient personal factors, which include underlying diseases, previous heart surgery, prior history of allergies, uncontrolled arterial hypertension, tobacco use, alcoholism, diabetes, obesity, renal insufficiency, cerebrovascular disease, prolonged hospitalization, liver failure, heart disease, atherosclerotic disease, cancer, severe malnutrition, and advanced age, which are the most common.

It has also been explained to me that the catheters and prostheses used are subjected to previous tests, but that they may present defects or even fracture, causing adverse reactions and varying types and degrees of injury, including the possibility of requiring surgery to remove them.

It has been reiterated to me that no guarantees or assurances are given with respect to the results expected from the proposed exam/procedure. I am aware that, in executing the proposed exam/procedure, the hemodynamicist and his/her team will be present, and it will be possible to solicit the presence of other specialists, as well as observers from the manufacturer of the equipment and material used. My signature at the end of this consent form authorizes the participation of these professionals and grants them full access to records and medical information related to my case. I have also been informed that, should it be necessary, bed restraint may be performed, as prescribed by the physician, and that I will be under the surveillance of the nursing staff.

Statement

I further declare that I have had the opportunity to read this document carefully and also to listen attentively to the physician's reading of all the information presented herein, and I was able to clarify all of my doubts regarding the risks involved and the possible consequences of not performing the suggested treatment, as well as the possible existence of alternative procedures, and my doubts have been satisfactorily addressed and answered. I am aware that there is a possibility of alteration of the original procedure over the course of the aforementioned exam/procedure and/or new procedure or surgery for the sake of continuity of treatment in a different region from the one originally designated, which, if applicable, will be evaluated, decided upon, and performed, by the medical professional in charge, with which I now agree and hereby authorize.

All my questions having been answered and having understood the procedure in and of itself, as well as its real repercussions, I sign this CONSENT FORM, in the presence of Dr. ....., who, in this act, represents the Hemodynamic Medical Service, together with 2 (two) witnesses, expressly and voluntarily declaring my authorization for the exam/procedure of coronary cineangiography with left ventriculography, FFR, or iFR and assessment of myocardial bridging, consenting, furthermore, to the performance of the proposed exam/procedure as well as its preparatory acts; the physicians are hereby authorized to performed additional procedures and therapeutic interventions that may become necessary due to unforeseen conditions which may occur during the course of the exam/procedure, remaining always at the discretion and judgment of the attending physician.

For the purpose of promoting scientific development, by signing the present Consent Form, I further agree and authorize the performance of photography, video recording, or televised transmission of the proposed exam/procedure, being assured that my identity will not be revealed. I also authorize the examination of any organ or tissue eventually removed, which may be treated by the medical team and/or the hospital for medical, scientific, and educational purposes.

Finally, I consent to the eventual possibility of a blood transfusion, should this procedure be directly linked to the treatment mentioned in this consent and authorization form or resulting from it.

If, during or immediately after the performance of the exam/procedure which I am to undergo, I am not in full possession of my physical and/or mental abilities, I authorize my legal representative ....., nationality ....., marital status ....., profession ....., identity document ....., issued by ....., CPF ....., resident of ....., city ....., state ....., date of birth ...../...../....., parents' names....., relationship to patient ....., to make decisions in my name.

In this manner, I offer my full and free consent, and I authorize the performance of the exam/procedure of coronary cineangiography with left ventriculography, FFR, or iFR and assessment of myocardial bridging, explained herein, to be administered by the signing physician and his/her related medical team.

In conclusion, I certify, that I have signed two copies of the present Form, one of which has been given to me.

Center Location: .....

Date: ...../...../.....

Patient's Name: ..... Signature: .....

Representative: ..... Signature: .....

Physician's Name: ..... CRM no.: .....

Signature: .....

Witnesses:

Name: ..... Name: .....

Annex 3

FREE AND INFORMED CONSENT AND AUTHORIZATION FORM FOR PERFORMANCE OF THE PROCEDURE OF CORONARY ANGIOPLASTY WITH OR WITHOUT STENT IMPLANTATIONS

By the present Consent and Authorization Form, I, ..., nationality ....., a legal adult and able, marital status ....., profession ....., identity document ....., issued by ....., CPF ....., resident of ...., city ....., state ....., date of birth ...../...../....., parents' names ....., hereby declare that I have received from the Hemodynamics Service, here represented by the physician fully identified below, explanations and warnings concerning the procedure solicited by my clinical physician and that the discussion regarding the nature and extent of the actions necessary for its execution is registered below.

I further declare that it has been explained to me that the procedure of coronary angioplasty with or without stent implantations will be performed in the hemodynamics laboratory of this hospital institution (corporate name ...., CNPJ/MF no. .....headquarters.....)

and that it consists of punctures in the patient's skin in order to introduce special catheters, using iodized contrast, with the administration of local anesthesia, sedation, or general anesthesia, at the attending physician's discretion.

The following text has been read and explained to me in more accessible language by the signing physician: the objective of this procedure is to treat obstructions or blocks in the arteries that irrigate or supply the heart, known as coronary arteries. The procedure consists of the insertion of a fine catheter through a puncture in the radial artery or the inguinal region, at the physician's discretion. By means of this fine catheter, iodized contrast, and X-rays, the obstructed or blocked coronary artery(ies) will be approached with one or more very fine guidewires, and a balloon catheter and a very small metallic mesh called a "stent" may be utilized to unblock the artery. Depending on the type of block, other devices may be used to treat the coronary artery(ies), such as the Rotablator, which consists of a very small burr used to unblock extremely calcified (hard) arteries, and a balloon catheter that cuts the plaque or the coronary artery block may also be used. In addition to treatment with the diverse materials mentioned, medications that help decrease the occurrence of clots, such as glycoprotein IIb/IIIa antagonists or other antiplatelet agents, may be used. Moderate or angiographically indeterminate coronary artery blocks may be assessed by means of a very fine guidewire dedicated to assessing these types of blocks. To facilitate the success of this treatment, intravascular ultrasound study, by means of a microcatheter dedicated to this purpose, may be introduced into the coronary artery to guide stent placement. In the event of a medical emergency, a balloon catheter with a diameter similar to that of the aorta may be used and positioned in the descending thoracic portion to facilitate the filling of coronary arteries.

I declare that, in the manner explained to me by the physician, I am perfectly able to understand what the procedure which I am to undergo will comprise.

I declare that I am aware that the intended purpose of performing the forenamed procedure may not be achieved, even though the physician and his/her team adopt the best techniques and employ all of the scientific means and resources available.

I am also aware that the procedure involves risks, and I have received all the pertinent information regarding possible complications due to known and unknown causes, including death, stroke, myocardial infarction, cardiac arrhythmia, acute pulmonary edema, anaphylactic shock, varying types and degrees of infection, allergies and/or reactions to contrast, bleedings, hematomas, renal insufficiency, vascular and hemodynamic complications, perforation of cardiac chambers or vessels, and loss of limbs and/or their function, in addition to the risks inherent in anesthesia and the use of diverse instruments and equipment itself. It has also been explained to me that these adverse reactions and infrequent, occurring in less than 2% of cases, but they may be aggravated when associated with other patient personal factors, which include underlying diseases, previous heart surgery, prior history of allergies, uncontrolled arterial hypertension, tobacco use, alcoholism, diabetes, obesity, renal insufficiency, cerebrovascular disease, prolonged hospitalization, liver failure, heart disease, atherosclerotic disease, cancer, severe malnutrition, and advanced age, which are the most common.

It has also been explained to me that the catheters and prostheses used are subjected to previous tests, but that they may present defects or even fracture, causing adverse reactions and varying types and degrees of injury, including the possibility of requiring surgery to remove them.

It has been reiterated to me that no guarantees or assurances are given with respect to the results expected from the proposed procedure. I am aware that, in executing the proposed procedure, the hemodynamicist and his/her team will be present, and it will be possible to solicit the presence of other specialists, as well as observers from the manufacturer of the equipment and material used. My signature at the end of this consent form authorizes the participation of these professionals and grants them

Statement

full access to records and medical information related to my case. I have also been informed that, should it be necessary, bed restraint may be performed, as prescribed by the physician, and that I will be under the surveillance of the nursing staff.

I further declare that I have had the opportunity to read this document carefully and also to listen attentively to the physician's reading of all the information presented herein, and I was able to clarify all of my doubts regarding the risks involved and the possible consequences of not performing the suggested treatment, as well as the possible existence of alternative procedures, and my doubts have been satisfactorily addressed and answered. I am aware that there is a possibility of alteration of the original procedure over the course of the aforementioned procedure and/or new procedure or surgery for the sake of continuity of treatment in a different region from the one originally designated, which, if applicable, will be evaluated, decided upon, and performed, by the medical professional in charge, with which I now agree and hereby authorize.

All my questions having been answered and having understood the procedure in and of itself, as well as its real repercussions, I sign this CONSENT FORM, in the presence of Dr. ....., who, in this act, represents the Hemodynamic Medical Service, together with 2 (two) witnesses, expressly and voluntarily declaring my authorization for the procedure of coronary angioplasty with or without stent implantations, consenting, furthermore, to the performance of the proposed procedure as well as its preparatory acts; the physicians are hereby authorized to performed additional procedures and therapeutic interventions that may become necessary due to unforeseen conditions which may occur during the course of the procedure, remaining always at the discretion and judgment of the attending physician. Finally, I consent to the eventual possibility of a blood transfusion, should this procedure be directly linked to the treatment mentioned in this consent and authorization form or resulting from it.

If, during or immediately after the performance of the procedure which I am to undergo, I am not in full possession of my physical and/or mental abilities, I authorize my legal representative ...., nationality ....., marital status ....., profession ....., identity document ....., issued by ....., CPF ....., resident of ...., city ....., state ....., date of birth ...../...../....., parents' names....., relationship to patient ....., to make decisions in my name.

In this manner, I offer my full and free consent, and I authorize the performance of the procedure of coronary angioplasty with or without stent implantations, explained herein, to be administered by the signing physician and his/her related medical team.

In conclusion, I certify, that I have signed two copies of the present Form, one of which has been given to me.

Center Location: .....

Date: ...../...../.....

Patient's Name: ..... Signature: .....

Representative: ..... Signature: .....

Physician's Name: ..... CRM no.: .....

Signature: .....

Witnesses:

Name: ..... Name: .....

Annex 4

FREE AND INFORMED CONSENT AND AUTHORIZATION FORM FOR PERFORMANCE OF THE PROCEDURE OF BALLOON MITRAL VALVULOPLASTY

By the present Consent and Authorization Form, I, ..., nationality ....., a legal adult and able, marital status ....., profession ....., identity document ....., issued by ....., CPF ....., resident of ...., city ....., state ....., date of birth ...../...../....., parents' names ....., hereby declare that I have received from the Hemodynamics Service, here represented by the physician fully identified below, explanations and warnings concerning the procedure solicited by my clinical physician and that the discussion regarding the nature and extent of the actions necessary for its execution is registered below.

I further declare that it has been explained to me that the procedure balloon mitral valvuloplasty will be performed in the hemodynamics laboratory of this hospital institution (corporate name ...., CNPJ/MF no. .....headquarters.....) and that it consists of punctures in the patient's skin in order to introduce special catheters, using iodized contrast, with the administration of local anesthesia, sedation, or general anesthesia, at the attending physician's discretion.

The following text has been read and explained to me in more accessible language by the signing physician: the aim of this procedure is to treat narrowing or severe stenosis of the mitral valve by means of a balloon catheter dedicated to this purpose. The procedure consists of puncture in a deep vein and an artery in the inguinal region. Through the femoral vein, from the right atrium, a puncture will be made in the interatrial septum using a special needle. This puncture may be guided by fluoroscopy (X-rays) with or without transesophageal echocardiography. Subsequently, with the aid of a special guidewire, a dedicated balloon catheter will be positioned in the inside of the left atrium. Following predefined maneuvers, the balloon catheter will be positioned in the mitral valve and inflated. Following angiographic control and pressure measurements, simultaneously performed in the left atrium and the left ventricle, the latter by means of a catheter positioned through arterial access, the procedure will be concluded with the removal of the instruments.

I declare that, in the manner explained to me by the physician, I am perfectly able to understand what the procedure which I am to undergo will comprise.

I declare that I am aware that the intended purpose of performing the forenamed procedure may not be achieved, even though the physician and his/her team adopt the best techniques and employ all of the scientific means and resources available.

I am also aware that the procedure involves risks, and I have received all the pertinent information regarding possible complications due to known and unknown causes, including death, stroke, myocardial infarction, cardiac arrhythmia, acute pulmonary edema, anaphylactic shock, varying types and degrees of infection, allergies and/or reactions to contrast, bleedings, hematomas, renal insufficiency, vascular and hemodynamic complications, perforation of cardiac chambers or vessels, and loss of limbs and/or their function, in addition to the risks inherent in anesthesia and the use of diverse instruments and equipment itself. It has also been explained to me that these adverse reactions and infrequent, occurring in less than 2% of cases, but they may be aggravated when associated with other patient personal factors, which include underlying diseases, previous heart surgery, prior history of allergies, uncontrolled arterial hypertension, tobacco use, alcoholism, diabetes, obesity, renal insufficiency, cerebrovascular disease, prolonged hospitalization, liver failure, heart disease, atherosclerotic disease, cancer, severe malnutrition, and advanced age, which are the most common.

It has also been explained to me that the catheters and prostheses used are subjected to previous tests, but that they may present defects or even fracture, causing adverse reactions and varying types and degrees of injury, including the possibility of requiring surgery to remove them.

It has been reiterated to me that no guarantees or assurances are given with respect to the results expected from the proposed procedure. I am aware that, in executing the proposed procedure, the hemodynamicist and his/her team will be present, and it will be possible to solicit the presence of other specialists, as well as observers from the manufacturer of the equipment and material used. My signature at the end of this consent form authorizes the participation of these professionals and grants them full access to records and medical information related to my case. I have also been informed that, should it be necessary, bed restraint may be performed, as prescribed by the physician, and that I will be under the surveillance of the nursing staff.

I further declare that I have had the opportunity to read this document carefully and also to listen attentively to the physician's reading of all the information presented herein, and I was able to clarify all of my doubts regarding the risks involved and the possible consequences of not performing the suggested treatment, as well as the possible existence of alternative procedures, and my doubts have been satisfactorily addressed and answered. I am aware that there is a possibility of alteration of the original

procedure over the course of the aforementioned procedure and/or new procedure or surgery for the sake of continuity of treatment in a different region from the one originally designated, which, if applicable, will be evaluated, decided upon, and performed, by the medical professional in charge, with which I now agree and hereby authorize.

All my questions having been answered and having understood the procedure in and of itself, as well as its real repercussions, I sign this CONSENT FORM, in the presence of Dr. ....., who, in this act, represents the Hemodynamic Medical Service, together with 2 (two) witnesses, expressly and voluntarily declaring my authorization for the procedure of balloon mitral valvuloplasty, consenting, furthermore, to the performance of the proposed procedure as well as its preparatory acts; the physicians are hereby authorized to performed additional procedures and therapeutic interventions that may become necessary due to unforeseen conditions which may occur during the course of the procedure, remaining always at the discretion and judgment of the attending physician. Finally, I consent to the eventual possibility of a blood transfusion, should this procedure be directly linked to the treatment mentioned in this consent and authorization form or resulting from it.

If, during or immediately after the performance of the procedure which I am to undergo, I am not in full possession of my physical and/or mental abilities, I authorize my legal representative ....., nationality ....., marital status ....., profession ....., identity document ....., issued by ....., CPF ....., resident of ....., city ....., state ....., date of birth ...../...../....., parents' names....., relationship to patient ....., to make decisions in my name.

In this manner, I offer my full and free consent, and I authorize the performance of the procedure of balloon mitral valvuloplasty, explained herein, to be administered by the signing physician and his/her related medical team.

In conclusion, I certify, that I have signed two copies of the present Form, one of which has been given to me.

Center Location: .....

Date: ...../...../.....

Patient's Name: ..... Signature: .....

Representative: ..... Signature: .....

Physician's Name: ..... CRM no.: .....

Signature: .....

Witnesses:

Name: ..... Name: .....

Annex 5

FREE AND INFORMED CONSENT AND AUTHORIZATION FORM FOR PERFORMANCE OF THE PROCEDURE OF TRANSCATHETER MITRAL VALVE REPAIR

By the present Consent and Authorization Form, I, ..., nationality ....., a legal adult and able, marital status ....., profession ....., identity document ....., issued by ....., CPF ....., resident of ...., city ....., state ....., date of birth ...../...../....., parents' names ....., hereby declare that I have received from the Hemodynamics Service, here represented by the physician fully identified below, explanations and warnings concerning the procedure solicited by my clinical physician and that the discussion regarding the nature and extent of the actions necessary for its execution is registered below.

I further declare that it has been explained to me that the procedure transcatheter mitral valve repair will be performed in the hemodynamics laboratory of this hospital institution (corporate name ...., CNPJ/MF no. .....headquarters.....) and that it consists of punctures in the patient's skin in order to introduce special catheters, using iodized contrast, with the administration of local anesthesia, sedation, or general anesthesia, at the attending physician's discretion.

The following text has been read and explained to me in more accessible language by the signing physician: the aim of this procedure is to repair insufficiency or regurgitation of the native mitral valve by means of the placement of a small clip (clamp) in the diseased valve by means of a specific catheter introduced in the inguinal region. This procedure has been recommended by a multidisciplinary team of specialists for patients who have contraindications to cardiac valve repair surgery. Device placement is carried out by means of the insertion of a catheter in the inguinal region to the right atrium of the heart. A puncture will be made in the interatrial septum (the septum that separates the right and left atria), in order to make it possible to position the device containing the clip. The entire procedure is guided by X-ray and mainly by transesophageal echocardiography, which will aid the medical team in the correct positioning and safe release of the mitral valve clip. Once the device has been successfully released, the catheter will be removed and maneuvers will be performed to contain eventual bleedings in the puncture site, and the procedure will be concluded.

I declare that, in the manner explained to me by the physician, I am perfectly able to understand what the procedure which I am to undergo will comprise.

I declare that I am aware that the intended purpose of performing the forenamed procedure may not be achieved, even though the physician and his/her team adopt the best techniques and employ all of the scientific means and resources available.

I am also aware that the procedure involves risks, and I have received all the pertinent information regarding possible complications due to known and unknown causes, including death, stroke, myocardial infarction, cardiac arrhythmia, acute pulmonary edema, anaphylactic shock, varying types and degrees of infection, allergies and/or reactions to contrast, bleedings, hematomas, renal insufficiency, vascular and hemodynamic complications, perforation of cardiac chambers or vessels, and loss of limbs and/or their function, in addition to the risks inherent in anesthesia and the use of diverse instruments and equipment itself. It has also been explained to me that these adverse reactions and infrequent, occurring in less than 2% of cases, but they may be aggravated when associated with other patient personal factors, which include underlying diseases, previous heart surgery, prior history of allergies, uncontrolled arterial hypertension, tobacco use, alcoholism, diabetes, obesity, renal insufficiency, cerebrovascular disease, prolonged hospitalization, liver failure, heart disease, atherosclerotic disease, cancer, severe malnutrition, and advanced age, which are the most common.

It has also been explained to me that the catheters and prostheses used are subjected to previous tests, but that they may present defects or even fracture, causing adverse reactions and varying types and degrees of injury, including the possibility of requiring surgery to remove them.

It has been reiterated to me that no guarantees or assurances are given with respect to the results expected from the proposed procedure. I am aware that, in executing the proposed procedure, the hemodynamicist and his/her team will be present, and it will be possible to solicit the presence of other specialists, as well as observers from the manufacturer of the equipment and material used. My signature at the end of this consent form authorizes the participation of these professionals and grants them full access to records and medical information related to my case. I have also been informed that, should it be necessary, bed restraint may be performed, as prescribed by the physician, and that I will be under the surveillance of the nursing staff.

I further declare that I have had the opportunity to read this document carefully and also to listen attentively to the physician's reading of all the information presented herein, and I was able to clarify all of my doubts regarding the risks involved and the possible consequences of not performing the suggested treatment, as well as the possible existence of alternative procedures,

and my doubts have been satisfactorily addressed and answered. I am aware that there is a possibility of alteration of the original procedure over the course of the aforementioned procedure and/or new procedure or surgery for the sake of continuity of treatment in a different region from the one originally designated, which, if applicable, will be evaluated, decided upon, and performed, by the medical professional in charge, with which I now agree and hereby authorize.

All my questions having been answered and having understood the procedure in and of itself, as well as its real repercussions, I sign this CONSENT FORM, in the presence of Dr. ....., who, in this act, represents the Hemodynamic Medical Service, together with 2 (two) witnesses, expressly and voluntarily declaring my authorization for the procedure of transcatheter mitral valve repair, consenting, furthermore, to the performance of the proposed procedure as well as its preparatory acts; the physicians are hereby authorized to performed additional procedures and therapeutic interventions that may become necessary due to unforeseen conditions which may occur during the course of the procedure, remaining always at the discretion and judgment of the attending physician. Finally, I consent to the eventual possibility of a blood transfusion, should this procedure be directly linked to the treatment mentioned in this consent and authorization form or resulting from it.

If, during or immediately after the performance of the procedure which I am to undergo, I am not in full possession of my physical and/or mental abilities, I authorize my legal representative ....., nationality ....., marital status ....., profession ....., identity document ....., issued by ....., CPF ....., resident of ....., city ....., state ....., date of birth ...../...../....., parents' names....., relationship to patient ....., to make decisions in my name.

In this manner, I offer my full and free consent, and I authorize the performance of the procedure of transcatheter mitral valve repair, explained herein, to be administered by the signing physician and his/her related medical team.

In conclusion, I certify, that I have signed two copies of the present Form, one of which has been given to me.

Center Location: .....

Date: ...../...../.....

Patient's Name: ..... Signature: .....

Representative: ..... Signature: .....

Physician's Name: ..... CRM no.: .....

Signature: .....

Witnesses:

Name: ..... Name: .....

Annex 6

FREE AND INFORMED CONSENT AND AUTHORIZATION FORM FOR PERFORMANCE OF THE PROCEDURE OF PERCUTANEOUS LEFT ATRIAL APPENDAGE CLOSURE

By the present Consent and Authorization Form, I, ..., nationality ....., a legal adult and able, marital status ....., profession ....., identity document ....., issued by ....., CPF ....., resident of ...., city ....., state ....., date of birth ...../...../....., parents' names ....., hereby declare that I have received from the Hemodynamics Service, here represented by the physician fully identified below, explanations and warnings concerning the exam/procedure solicited by my clinical physician and that the discussion regarding the nature and extent of the actions necessary for its execution is registered below.

I further declare that it has been explained to me that the exam/procedure percutaneous left atrial appendage closure will be performed in the hemodynamics laboratory of this hospital institution (corporate name ...., CNPJ/MF no. .....headquarters.....) and that it consists of punctures in the patient's skin in order to introduce special catheters, using iodized contrast, with the administration of local anesthesia, sedation, or general anesthesia, at the attending physician's discretion.

The following text has been read and explained to me in more accessible language by the signing physician: the aim of this procedure is to close the left atrial appendage (LAA) by means of implantation or release of a device that will block the LAA off from the rest of the heart in order to decrease the chance of clots forming and provoking a stroke. This is done by means of a puncture in the vein in the inguinal region, through which a catheter will be inserted to the heart. Subsequently, a puncture will be made in the interatrial septum (the septum that separates the right and left atria) in order to allow for positioning of the device in the LAA. The entire procedure is guided by X-ray and mainly by transesophageal echocardiography, which will aid the medical team in the correct positioning and safe release of the device in the LAA. Once the device has been successfully released, the catheter will be removed and the procedure will be concluded.

I declare that, in the manner explained to me by the physician, I am perfectly able to understand what the procedure which I am to undergo will comprise.

I declare that I am aware that the intended purpose of performing the forenamed procedure may not be achieved, even though the physician and his/her team adopt the best techniques and employ all of the scientific means and resources available.

I am also aware that the procedure involves risks, and I have received all the pertinent information regarding possible complications due to known and unknown causes, including death, stroke, myocardial infarction, cardiac arrhythmia, acute pulmonary edema, anaphylactic shock, varying types and degrees of infection, allergies and/or reactions to contrast, bleedings, hematomas, renal insufficiency, vascular and hemodynamic complications, perforation of cardiac chambers or vessels, and loss of limbs and/or their function, in addition to the risks inherent in anesthesia and the use of diverse instruments and equipment itself. It has also been explained to me that these adverse reactions and infrequent, occurring in less than 2% of cases, but they may be aggravated when associated with other patient personal factors, which include underlying diseases, previous heart surgery, prior history of allergies, uncontrolled arterial hypertension, tobacco use, alcoholism, diabetes, obesity, renal insufficiency, cerebrovascular disease, prolonged hospitalization, liver failure, heart disease, atherosclerotic disease, cancer, severe malnutrition, and advanced age, which are the most common.

It has also been explained to me that the catheters and prostheses used are subjected to previous tests, but that they may present defects or even fracture, causing adverse reactions and varying types and degrees of injury, including the possibility of requiring surgery to remove them.

It has been reiterated to me that no guarantees or assurances are given with respect to the results expected from the proposed procedure. I am aware that, in executing the proposed procedure, the hemodynamicist and his/her team will be present, and it will be possible to solicit the presence of other specialists, as well as observers from the manufacturer of the equipment and material used. My signature at the end of this consent form authorizes the participation of these professionals and grants them full access to records and medical information related to my case. I have also been informed that, should it be necessary, bed restraint may be performed, as prescribed by the physician, and that I will be under the surveillance of the nursing staff.

I further declare that I have had the opportunity to read this document carefully and also to listen attentively to the physician's reading of all the information presented herein, and I was able to clarify all of my doubts regarding the risks involved and the possible consequences of not performing the suggested treatment, as well as the possible existence of alternative procedures, and my doubts have been satisfactorily addressed and answered. I am aware that there is a possibility of alteration of the original procedure over the course of the aforementioned exam/procedure and/or new procedure or surgery for the sake of continuity

of treatment in a different region from the one originally designated, which, if applicable, will be evaluated, decided upon, and performed, by the medical professional in charge, with which I now agree and hereby authorize.

All my questions having been answered and having understood the procedure in and of itself, as well as its real repercussions, I sign this CONSENT FORM, in the presence of Dr. ....., who, in this act, represents the Hemodynamic Medical Service, together with 2 (two) witnesses, expressly and voluntarily declaring my authorization for the exam/procedure of percutaneous left atrial appendage closure, consenting, furthermore, to the performance of the proposed procedure as well as its preparatory acts; the physicians are hereby authorized to performed additional procedures and therapeutic interventions that may become necessary due to unforeseen conditions which may occur during the course of the procedure, remaining always at the discretion and judgment of the attending physician. Finally, I consent to the eventual possibility of a blood transfusion, should this procedure be directly linked to the treatment mentioned in this consent and authorization form or resulting from it.

If, during or immediately after the performance of the procedure which I am to undergo, I am not in full possession of my physical and/or mental abilities, I authorize my legal representative ....., nationality ....., marital status ....., profession ....., identity document ....., issued by ....., CPF ....., resident of ....., city ....., state ....., date of birth ...../...../....., parents' names....., relationship to patient ....., to make decisions in my name.

In this manner, I offer my full and free consent, and I authorize the performance of the procedure of percutaneous left atrial appendage closure, explained herein, to be administered by the signing physician and his/her related medical team.

In conclusion, I certify, that I have signed two copies of the present Form, one of which has been given to me.

Center Location: .....

Date: ...../...../.....

Patient's Name: ..... Signature: .....

Representative: ..... Signature: .....

Physician's Name: ..... CRM no.: .....

Signature: .....

Witnesses:

Name: ..... Name: .....

Annex 7

FREE AND INFORMED CONSENT AND AUTHORIZATION FORM FOR PERFORMANCE OF THE PROCEDURE OF TRANSCATHETER AORTIC VALVE REPLACEMENT (TAVR)

By the present Consent and Authorization Form, I, ..., nationality ....., a legal adult and able, marital status ....., profession ....., identity document ....., issued by ....., CPF ....., resident of ...., city ....., state ....., date of birth ...../...../....., parents' names ....., hereby declare that I have received from the Hemodynamics Service, here represented by the physician(s), who are completely identified below, as well as the team known as the "Heart Team," composed of a clinical cardiology, cardiovascular surgeon, and interventional cardiologist, all the information, explanations, and warnings concerning the exam/procedure solicited by my clinical physician and that the discussion regarding the nature and extent of the actions necessary for its execution is registered below.

I further declare that it has been explained to me that the procedure transcatheter aortic valve implantation (TAVI) will be performed in the hemodynamics laboratory of this hospital institution (corporate name ...., CNPJ/MF no. .....headquarters.....) and that it consists of punctures in the patient's skin in order to introduce special catheters, using iodized contrast, with the administration of local anesthesia, sedation, or general anesthesia, at the attending physician's discretion.

The following text has been read and explained to me in more accessible language by one of the signing physicians: the aim of this procedure is to treat narrowing or severe stenosis of the aortic valve by means of transcatheter implantation of a biological prosthesis. The valve is positioned using a delivery system. This delivery system helps position the process through the narrow aortic valve. With the heart beating, the prosthesis is released in the site, pushing the leaflets of the diseased valve against the aorta. The new prosthesis will, thus, function in the place of the valve that was diseased, without requiring the latter's removal. The delivery system is removed and some tests are performed before closing the small incision in the inguinal region. In addition to angiography, the procedure is guided by echocardiography. Depending on each case, dilation may be performed with a special balloon catheter before or after release of the prosthesis. A temporary pacemaker lead will be placed in the right ventricle and it may remain in the patient after the procedure if indicated by the physician.

I declare that, in the manner explained to me by the physician, I am perfectly able to understand what the procedure which I am to undergo will comprise.

I declare that I am aware that the intended purpose of performing the forenamed procedure may not be achieved, even though the physician and his/her team adopt the best techniques and employ all of the scientific means and resources available.

I am also aware that the procedure involves risks, and I have received all the pertinent information regarding possible complications due to known and unknown causes, including death, stroke, myocardial infarction, cardiac arrhythmia, acute pulmonary edema, anaphylactic shock, varying types and degrees of infection, allergies and/or reactions to contrast, bleedings, hematomas, renal insufficiency, vascular and hemodynamic complications, perforation of cardiac chambers or vessels, and loss of limbs and/or their function, in addition to the risks inherent in anesthesia and the use of diverse instruments and equipment itself. It has also been explained to me that these adverse reactions and infrequent, occurring in less than 5% of cases, but they may be aggravated when associated with other patient personal factors, which include underlying diseases, previous heart surgery, prior history of allergies, uncontrolled arterial hypertension, tobacco use, alcoholism, diabetes, obesity, renal insufficiency, cerebrovascular disease, prolonged hospitalization, liver failure, heart disease, atherosclerotic disease, cancer, severe malnutrition, and advanced age, which are the most common.

It has also been explained to me that the catheters and prostheses used are subjected to previous tests, but that they may present defects or even fracture, causing adverse reactions and varying types and degrees of injury, including the possibility of requiring surgery to remove them. These risks, however, are less than 1%.

It has been reiterated to me that no guarantees or assurances are given with respect to the results expected from the proposed procedure. I am aware that, in executing the proposed procedure, the hemodynamicist and his/her team will be present, and it will be possible to solicit the presence of other specialists, as well as observers from the manufacturer of the equipment and material used. My signature at the end of this consent form authorizes the participation of these professionals and grants them full access to records and medical information related to my case. I have also been informed that, should it be necessary, bed restraint may be performed, as prescribed by the physician, and that I will be under the surveillance of the nursing staff.

I further declare that I have had the opportunity to read this document carefully and also to listen attentively to the physician's reading of all the information presented herein, and I was able to clarify all of my doubts regarding the risks involved and the possible consequences of not performing the suggested treatment, as well as the possible existence of alternative procedures,

Statement

and my doubts have been satisfactorily addressed and answered. I am aware that there is a possibility of alteration of the original procedure over the course of the aforementioned procedure and/or new procedure or surgery for the sake of continuity of treatment in a different region from the one originally designated, which, if applicable, will be evaluated, decided upon, and performed, by the medical professional in charge, with which I now agree and hereby authorize.

All my questions having been answered and having understood the procedure in and of itself, as well as its real repercussions, I sign this CONSENT FORM, in the presence of Dr(s).

..... and ....., Who, in this act, represents the Hemodynamic Medical Service, together with 2 (two) witnesses, expressly and voluntarily declaring my authorization for the procedure of transcatheter aortic valve implantation (TAVI), consenting, furthermore, to the performance of the proposed procedure as well as its preparatory acts; the physicians are hereby authorized to performed additional procedures and therapeutic interventions that may become necessary due to unforeseen conditions which may occur during the course of the procedure, remaining always at the discretion and judgment of the attending physician. Finally, I consent to the eventual possibility of a blood transfusion, should this procedure be directly linked to the treatment mentioned in this consent and authorization form or resulting from it.

If, during or immediately after the performance of the procedure which I am to undergo, I am not in full possession of my physical and/or mental abilities, I authorize my legal representative ...., nationality ....., marital status ....., profession ....., identity document ....., issued by ....., CPF ....., resident of ...., city ....., state ....., date of birth ...../...../....., parents' names....., relationship to patient ....., to make decisions in my name.

In this manner, I offer my full and free consent, and I authorize the performance of the procedure of transcatheter aortic valve implantation (TAVI), explained herein, to be administered by the signing physician and his/her related medical team.

In conclusion, I certify, that I have signed two copies of the present Form, one of which has been given to me.

Center Location: .....

Date: ...../...../.....

Patient's Name: ..... Signature: .....

Representative: ..... Signature: .....

Physician's Name: ..... CRM no.: .....

Signature: .....

Dr.(a) ..... CRM no.: .....

Signature: .....

Witnesses:

Name: ..... Name: .....

Annex 8

FREE AND INFORMED CONSENT AND AUTHORIZATION FORM FOR PERFORMANCE OF THE PROCEDURE OF ALCOHOL SEPTAL ABLATION

By the present Consent and Authorization Form, I, ..., nationality ....., a legal adult and able, marital status ....., profession ....., identity document ....., issued by ....., CPF ....., resident of ...., city ....., state ....., date of birth ...../...../....., parents' names ....., hereby declare that I have received from the Hemodynamics Service, here represented by the physician fully identified below, explanations and warnings concerning the procedure solicited by my clinical physician and that the discussion regarding the nature and extent of the actions necessary for its execution is registered below.

I further declare that it has been explained to me that the procedure alcohol septal ablation will be performed in the hemodynamics laboratory of this hospital institution (corporate name ...., CNPJ/MF no. .....headquarters.....) and that it consists of punctures in the patient's skin in order to introduce special catheters, using iodized contrast, with the administration of local anesthesia, sedation, or general anesthesia, at the attending physician's discretion.

The following text has been read and explained to me in more accessible language by the signing physician: the aim of this procedure is to reduce significant muscular thickening in the interventricular septum (which separates the left and right ventricles) by means of alcoholization of the septal artery accessed by puncture of an artery in the inguinal region. Subsequently, a catheter is selectively placed in the left coronary artery. Through this catheter a very small guidewire is positioned in the first septal branch of the anterior descending coronary artery. This guidewire will allow for the correct positioning of a catheter specifically dedicated to this purpose, which has a small balloon on its end. This balloon will be inflated, closing the septal branch in its proximal portion and, then, one to two milliliters of absolute alcohol or other liquid substances or mechanical microdevices will be administered through the balloon catheter to the distal end of the septal branch. The alcohol or other agents will provoke direct damage to the thickened muscle of the interventricular septum, which, during the course of weeks or even months, will reduce in volume. From that moment onward, the mitral valve will function better and the pressure in the left ventricle will be reduced, which will result in improvements to symptoms of cardiac insufficiency.

I declare that, in the manner explained to me by the physician, I am perfectly able to understand what the procedure which I am to undergo will comprise.

I am also aware that it may take weeks or months for the interventricular septum to become reduced and for me to observe the complete benefit of this procedure. A temporary pacemaker lead may be placed in the right ventricle through the venous access in the inguinal region. Echocardiogram may be performed during the procedure in accordance with the medical team's indications.

I declare that I am aware that the intended purpose of performing the forenamed procedure may not be achieved, even though the physician and his/her team adopt the best techniques and employ all of the scientific means and resources available.

I am also aware that the procedure involves risks, and I have received all the pertinent information regarding possible complications due to known and unknown causes, including death, stroke, myocardial infarction, cardiac arrhythmia, acute pulmonary edema, anaphylactic shock, varying types and degrees of infection, allergies and/or reactions to contrast, bleedings, hematomas, renal insufficiency, vascular and hemodynamic complications, perforation of cardiac chambers or vessels, and loss of limbs and/or their function, in addition to the risks inherent in anesthesia and the use of diverse instruments and equipment itself. It has also been explained to me that these adverse reactions and infrequent, occurring in approximately 2% to 8% of cases, but they may be aggravated when associated with other patient personal factors, which include underlying diseases, previous heart surgery, prior history of allergies, uncontrolled arterial hypertension, tobacco use, alcoholism, diabetes, obesity, renal insufficiency, cerebrovascular disease, prolonged hospitalization, liver failure, heart disease, atherosclerotic disease, cancer, severe malnutrition, and advanced age, which are the most common.

It has also been explained to me that the catheters and prostheses used are subjected to previous tests, but that they may present defects or even fracture, causing adverse reactions and varying types and degrees of injury, including the possibility of requiring surgery to remove them.

It has been reiterated to me that no guarantees or assurances are given with respect to the results expected from the proposed procedure. I am aware that, in executing the proposed procedure, the hemodynamicist and his/her team will be present, and it will be possible to solicit the presence of other specialists, as well as observers from the manufacturer of the equipment and material used. My signature at the end of this consent form authorizes the participation of these professionals and grants them

Statement

full access to records and medical information related to my case. I have also been informed that, should it be necessary, bed restraint may be performed, as prescribed by the physician, and that I will be under the surveillance of the nursing staff.

I further declare that I have had the opportunity to read this document carefully and also to listen attentively to the physician's reading of all the information presented herein, and I was able to clarify all of my doubts regarding the risks involved and the possible consequences of not performing the suggested treatment, as well as the possible existence of alternative procedures, and my doubts have been satisfactorily addressed and answered. I am aware that there is a possibility of alteration of the original procedure over the course of the aforementioned procedure and/or new procedure or surgery for the sake of continuity of treatment in a different region from the one originally designated, which, if applicable, will be evaluated, decided upon, and performed, by the medical professional in charge, with which I now agree and hereby authorize.

All my questions having been answered and having understood the procedure in and of itself, as well as its real repercussions, I sign this CONSENT FORM, in the presence of Dr. ....., who, in this act, represents the Hemodynamic Medical Service, together with 2 (two) witnesses, expressly and voluntarily declaring my authorization for the procedure of alcohol septal ablation, consenting, furthermore, to the performance of the proposed procedure as well as its preparatory acts; the physicians are hereby authorized to performed additional procedures and therapeutic interventions that may become necessary due to unforeseen conditions which may occur during the course of the procedure, remaining always at the discretion and judgment of the attending physician. Finally, I consent to the eventual possibility of a blood transfusion, should this procedure be directly linked to the treatment mentioned in this consent and authorization form or resulting from it.

If, during or immediately after the performance of the procedure which I am to undergo, I am not in full possession of my physical and/or mental abilities, I authorize my legal representative ...., nationality ....., marital status ....., profession ....., identity document ....., issued by ....., CPF ....., resident of ...., city ....., state ....., date of birth ...../...../....., parents' names....., relationship to patient ....., to make decisions in my name.

In this manner, I offer my full and free consent, and I authorize the performance of the procedure of alcohol septal ablation, explained herein, to be administered by the signing physician and his/her related medical team.

In conclusion, I certify, that I have signed two copies of the present Form, one of which has been given to me.

Center Location: .....

Date: ...../...../.....

Patient's Name: ..... Signature: .....

Representative: ..... Signature: .....

Physician's Name: ..... CRM no.: .....

Signature: .....

Witnesses:

Name: ..... Name: .....

Annex 9

FREE AND INFORMED CONSENT AND AUTHORIZATION FORM FOR PERFORMANCE OF THE PROCEDURE OF PATENT FORAMEN OVALE OCCLUSION OR CLOSURE

By the present Consent and Authorization Form, I, ..., nationality ....., a legal adult and able, marital status ....., profession ....., identity document ....., issued by ....., CPF ....., resident of ....., city ....., state ....., date of birth ...../...../....., parents' names ....., hereby declare that I have received from the Hemodynamics Service, here represented by the physician fully identified below, explanations and warnings concerning the procedure solicited by my clinical physician and that the discussion regarding the nature and extent of the actions necessary for its execution is registered below.

I further declare that it has been explained to me that the procedure patent foramen ovale occlusion or closure will be performed in the hemodynamics laboratory of this hospital institution (corporate name ....., CNPJ/MF no. .....headquarters.....)

and that it consists of punctures in the patient's skin in order to introduce special catheters, prostheses and/or devices, using iodized contrast, with the administration of local anesthesia, sedation, or general anesthesia, at the attending physician's discretion.

The following text has been read and explained to me in more accessible language by the signing physician: the aim of this procedure is to repair abnormal communication, resulting from the persistence of a small opening or orifice, known as patent foramen ovale (PFO), located between the right and left atria. The procedure is performed by means of a specific catheter, introduced in the inguinal region or groin, and it has been recommended by a multidisciplinary team of specialists for patients who have clinical and anatomical characteristics favorable to this approach. The placement of a device similar to an "umbrella," known as a prosthesis for PFO closure, occurs by means of the insertion of a catheter in a vein in the inguinal region to the left atrium of the heart, through the PFO. The entire procedure is guided by X-ray and mainly by transesophageal echocardiography, which will aid the medical team in the correct positioning and safe release of the prosthesis in the PFO. Once the device has been successfully released, the catheter will be removed and maneuvers will be performed to contain eventual bleedings in the puncture site, and the procedure will subsequently be concluded.

I declare that, in the manner explained to me by the physician, I am perfectly able to understand what the procedure which I am to undergo will comprise.

I declare that I am aware that the intended purpose of performing the forenamed procedure may not be achieved, even though the physician and his/her team adopt the best techniques and employ all of the scientific means and resources available.

I am also aware that the procedure involves risks, and I have received all the pertinent information regarding possible complications due to known and unknown causes, including death, stroke, myocardial infarction, cardiac arrhythmia, acute pulmonary edema, anaphylactic shock, varying types and degrees of infection, allergies and/or reactions to contrast, bleedings, hematomas, renal insufficiency, vascular and hemodynamic complications, perforation of cardiac chambers or vessels, and loss of limbs and/or their function, in addition to the risks inherent in anesthesia and the use of diverse instruments and equipment itself. It has also been explained to me that these adverse reactions and infrequent, occurring in less than 2% of cases, but they may be aggravated when associated with other patient personal factors, which include underlying diseases, previous heart surgery, prior history of allergies, uncontrolled arterial hypertension, tobacco use, alcoholism, diabetes, obesity, renal insufficiency, cerebrovascular disease, prolonged hospitalization, liver failure, heart disease, atherosclerotic disease, cancer, severe malnutrition, and advanced age, which are the most common.

It has also been explained to me that the catheters and prostheses used are subjected to previous tests, but that they may present defects or even fracture, causing adverse reactions and varying types and degrees of injury, including the possibility of requiring surgery to remove them.

It has been reiterated to me that no guarantees or assurances are given with respect to the results expected from the proposed procedure. I am aware that, in executing the proposed procedure, the hemodynamicist and his/her team will be present, and it will be possible to solicit the presence of other specialists, as well as observers from the manufacturer of the equipment and material used. My signature at the end of this consent form authorizes the participation of these professionals and grants them full access to records and medical information related to my case. I have also been informed that, should it be necessary, bed restraint may be performed, as prescribed by the physician, and that I will be under the surveillance of the nursing staff.

I further declare that I have had the opportunity to read this document carefully and also to listen attentively to the physician's reading of all the information presented herein, and I was able to clarify all of my doubts regarding the risks involved and the

Statement

possible consequences of not performing the suggested treatment, as well as the possible existence of alternative procedures, and my doubts have been satisfactorily addressed and answered. I am aware that there is a possibility of alteration of the original procedure over the course of the aforementioned procedure and/or new procedure or surgery for the sake of continuity of treatment in a different region from the one originally designated, which, if applicable, will be evaluated, decided upon, and performed, by the medical professional in charge, with which I now agree and hereby authorize.

All my questions having been answered and having understood the procedure in and of itself, as well as its real repercussions, I sign this CONSENT FORM, in the presence of Dr. ....., who, in this act, represents the Hemodynamic Medical Service, together with 2 (two) witnesses, expressly and voluntarily declaring my authorization for the procedure of patent foramen ovale occlusion or closure, consenting, furthermore, to the performance of the proposed procedure as well as its preparatory acts; the physicians are hereby authorized to performed additional procedures and therapeutic interventions that may become necessary due to unforeseen conditions which may occur during the course of the procedure, remaining always at the discretion and judgment of the attending physician. Finally, I consent to the eventual possibility of a blood transfusion, should this procedure be directly linked to the treatment mentioned in this consent and authorization form or resulting from it.

If, during or immediately after the performance of the procedure which I am to undergo, I am not in full possession of my physical and/or mental abilities, I authorize my legal representative ....., nationality ....., marital status ....., profession ....., identity document ....., issued by ....., CPF ....., resident of ....., city ....., state ....., date of birth ...../...../....., parents' names....., relationship to patient ....., to make decisions in my name.

In this manner, I offer my full and free consent, and I authorize the performance of the procedure of patent foramen ovale occlusion or closure, explained herein, to be administered by the signing physician and his/her related medical team.

In conclusion, I certify, that I have signed two copies of the present Form, one of which has been given to me.

Center Location: .....

Date: ...../...../.....

Patient's Name: ..... Signature: .....

Annex 10

FREE AND INFORMED CONSENT AND AUTHORIZATION FORM FOR PERFORMANCE OF THE PROCEDURE OF INTERATRIAL COMMUNICATION CLOSURE OR OCCLUSION

By the present Consent and Authorization Form, I, ..., nationality ....., a legal adult and able, marital status ....., profession ....., identity document ....., issued by ....., CPF ....., resident of ...., city ....., state ....., date of birth ...../...../....., parents' names ....., hereby declare that I have received from the Hemodynamics Service, here represented by the physician fully identified below, explanations and warnings concerning the procedure solicited by my clinical physician and that the discussion regarding the nature and extent of the actions necessary for its execution is registered below.

I further declare that it has been explained to me that the procedure interatrial communication closure or occlusion will be performed in the hemodynamics laboratory of this hospital institution (corporate name ...., CNPJ/MF no. .....headquarters.....)

and that it consists of a puncture in the skin of the patient in order to introduce special catheters, using iodized contrast, with the administration of local anesthesia, sedation, or general anesthesia, at the attending physician's discretion.

The following text has been read and explained to me in more accessible language by the signing physician: the aim of this procedure is to repair abnormal communication of a small opening (orifice) located in the septum that separates two cavities of the heart (right and left atria), known as interatrial communication (IAC). The procedure consists of the introduction of a specific catheter in the inguinal region or groin. This procedure has been recommended by a multidisciplinary team of specialists for patients who have clinical and anatomical characteristics favorable to this approach. The placement of a device similar to an "umbrella" or a spring, known as a prosthesis for IAC closure, occurs by means of the insertion of a catheter in a vein in the inguinal region to the left atrium of the heart, through the IAC. The entire procedure is guided by X-ray and mainly by transesophageal echocardiography, which will aid the medical team in the correct positioning and safe release of the prosthesis in the IAC. Once the device has been successfully released, the catheter will be removed and maneuvers will be performed to contain eventual bleedings in the puncture site, and the procedure will subsequently be concluded.

I declare that, in the manner explained to me by the physician, I am perfectly able to understand what the procedure which I am to undergo will comprise.

I declare that I am aware that the intended purpose of performing the forenamed procedure may not be achieved, even though the physician and his/her team adopt the best techniques and employ all of the scientific means and resources available.

I am also aware that the procedure involves risks, and I have received all the pertinent information regarding possible complications due to known and unknown causes, including death, stroke, myocardial infarction, cardiac arrhythmia, acute pulmonary edema, anaphylactic shock, varying types and degrees of infection, allergies and/or reactions to contrast, bleedings, hematomas, renal insufficiency, vascular and hemodynamic complications, perforation of cardiac chambers or vessels, and loss of limbs and/or their function, in addition to the risks inherent in anesthesia and the use of diverse instruments and equipment itself. It has also been explained to me that these adverse reactions and infrequent, occurring in less than 2% of cases, but they may be aggravated when associated with other patient personal factors, which include underlying diseases, previous heart surgery, prior history of allergies, uncontrolled arterial hypertension, tobacco use, alcoholism, diabetes, obesity, renal insufficiency, cerebrovascular disease, prolonged hospitalization, liver failure, heart disease, atherosclerotic disease, cancer, severe malnutrition, and advanced age, which are the most common.

It has also been explained to me that the catheters and prostheses used are subjected to previous tests, but that they may present defects or even fracture, causing adverse reactions and varying types and degrees of injury, including the possibility of requiring surgery to remove them.

It has been reiterated to me that no guarantees or assurances are given with respect to the results expected from the proposed procedure. I am aware that, in executing the proposed procedure, the hemodynamicist and his/her team will be present, and it will be possible to solicit the presence of other specialists, as well as observers from the manufacturer of the equipment and material used. My signature at the end of this consent form authorizes the participation of these professionals and grants them full access to records and medical information related to my case. I have also been informed that, should it be necessary, bed restraint may be performed, as prescribed by the physician, and that I will be under the surveillance of the nursing staff.

I further declare that I have had the opportunity to read this document carefully and also to listen attentively to the physician's reading of all the information presented herein, and I was able to clarify all of my doubts regarding the risks involved and the

possible consequences of not performing the suggested treatment, as well as the possible existence of alternative procedures, and my doubts have been satisfactorily addressed and answered. I am aware that there is a possibility of alteration of the original procedure over the course of the aforementioned procedure and/or new procedure or surgery for the sake of continuity of treatment in a different region from the one originally designated, which, if applicable, will be evaluated, decided upon, and performed, by the medical professional in charge, with which I now agree and hereby authorize.

All my questions having been answered and having understood the procedure in and of itself, as well as its real repercussions, I sign this CONSENT FORM, in the presence of Dr. ....., who, in this act, represents the Hemodynamic Medical Service, together with 2 (two) witnesses, expressly and voluntarily declaring my authorization for the procedure of interatrial communication closure or occlusion, consenting, furthermore, to the performance of the proposed procedure as well as its preparatory acts; the physicians are hereby authorized to performed additional procedures and therapeutic interventions that may become necessary due to unforeseen conditions which may occur during the course of the procedure, remaining always at the discretion and judgment of the attending physician. Finally, I consent to the eventual possibility of a blood transfusion, should this procedure be directly linked to the treatment mentioned in this consent and authorization form or resulting from it.

If, during or immediately after the performance of the procedure which I am to undergo, I am not in full possession of my physical and/or mental abilities, I authorize my legal representative ....., nationality ....., marital status ....., profession ....., identity document ....., issued by ....., CPF ....., resident of ....., city ....., state ....., date of birth ...../...../....., parents' names....., relationship to patient ....., to make decisions in my name.

In this manner, I offer my full and free consent, and I authorize the performance of the procedure of interatrial communication closure or occlusion, explained herein, to be administered by the signing physician and his/her related medical team.

In conclusion, I certify, that I have signed two copies of the present Form, one of which has been given to me.

Center Location: .....

Date: ...../...../.....

Patient's Name: ..... Signature: .....

Representative: ..... Signature: .....

Physician's Name: ..... CRM no.: .....

Signature: .....

Witnesses:

Name: ..... Name: .....

Annex 11

FREE AND INFORMED CONSENT AND AUTHORIZATION FORM FOR PERFORMANCE OF THE PROCEDURE OF TRANSCATHETER INTERVENTRICULAR COMMUNICATION CLOSURE OR OCCLUSION

By the present Consent and Authorization Form, I, ..., nationality ....., a legal adult and able, marital status ....., profession ....., identity document ....., issued by ....., CPF ....., resident of ...., city ....., state ....., date of birth ...../...../....., parents' names ....., hereby declare that I have received from the Hemodynamics Service, here represented by the physician fully identified below, explanations and warnings concerning the procedure solicited by my clinical physician and that the discussion regarding the nature and extent of the actions necessary for its execution is registered below.

I further declare that it has been explained to me that the procedure transcatheter interventricular communication closure or occlusion will be performed in the hemodynamics laboratory of this hospital institution (corporate name ...., CNPJ/MF no. .....headquarters.....) and that it consists of a puncture in the skin of the patient in order to introduce special catheters, using iodized contrast, with the administration of local anesthesia, sedation, or general anesthesia, at the attending physician's discretion.

The following text has been read and explained to me in more accessible language by the signing physician: the aim of this procedure is to repair abnormal communication resulting from a small opening (orifice) located in the septum that separates two cavities of the heart, the right and left ventricles, known as interventricular communication (IVC). The procedure consists of the introduction of a specific catheter in the inguinal region or groin. This procedure has been recommended by a multidisciplinary team of specialists for patients who have clinical and anatomical characteristics favorable to this approach. The placement of a device similar to an "umbrella" or a spring, known as a prosthesis for IVC closure, occurs by means of the insertion of a catheter in a artery in the inguinal region to the left ventricle of the heart. The entire procedure is guided by X-ray and mainly by transesophageal echocardiography, which will aid the medical team in the correct positioning and safe release of the prosthesis in the IVC. Once the device has been successfully released, the catheter will be removed and maneuvers will be performed to contain eventual bleedings in the puncture site, and the procedure will be concluded.

I declare that, in the manner explained to me by the physician, I am perfectly able to understand what the procedure which I am to undergo will comprise.

I declare that I am aware that the intended purpose of performing the forenamed procedure may not be achieved, even though the physician and his/her team adopt the best techniques and employ all of the scientific means and resources available.

I am also aware that the procedure involves risks, and I have received all the pertinent information regarding possible complications due to known and unknown causes, including death, stroke, myocardial infarction, cardiac arrhythmia, acute pulmonary edema, anaphylactic shock, varying types and degrees of infection, allergies and/or reactions to contrast, bleedings, hematomas, renal insufficiency, vascular and hemodynamic complications, perforation of cardiac chambers or vessels, and loss of limbs and/or their function, in addition to the risks inherent in anesthesia and the use of diverse instruments and equipment itself. It has also been explained to me that these adverse reactions and infrequent, occurring in less than 2% of cases, but they may be aggravated when associated with other patient personal factors, which include underlying diseases, previous heart surgery, prior history of allergies, uncontrolled arterial hypertension, tobacco use, alcoholism, diabetes, obesity, renal insufficiency, cerebrovascular disease, prolonged hospitalization, liver failure, heart disease, atherosclerotic disease, cancer, severe malnutrition, and advanced age, which are the most common.

It has also been explained to me that the catheters and prostheses used are subjected to previous tests, but that they may present defects or even fracture, causing adverse reactions and varying types and degrees of injury, including the possibility of requiring surgery to remove them.

It has been reiterated to me that no guarantees or assurances are given with respect to the results expected from the proposed procedure. I am aware that, in executing the proposed procedure, the hemodynamicist and his/her team will be present, and it will be possible to solicit the presence of other specialists, as well as observers from the manufacturer of the equipment and material used. My signature at the end of this consent form authorizes the participation of these professionals and grants them full access to records and medical information related to my case. I have also been informed that, should it be necessary, bed restraint may be performed, as prescribed by the physician, and that I will be under the surveillance of the nursing staff.

I further declare that I have had the opportunity to read this document carefully and also to listen attentively to the physician's reading of all the information presented herein, and I was able to clarify all of my doubts regarding the risks involved and the

possible consequences of not performing the suggested treatment, as well as the possible existence of alternative procedures, and my doubts have been satisfactorily addressed and answered. I am aware that there is a possibility of alteration of the original procedure over the course of the aforementioned procedure and/or new procedure or surgery for the sake of continuity of treatment in a different region from the one originally designated, which, if applicable, will be evaluated, decided upon, and performed, by the medical professional in charge, with which I now agree and hereby authorize.

All my questions having been answered and having understood the procedure in and of itself, as well as its real repercussions, I sign this CONSENT FORM, in the presence of Dr. ....., who, in this act, represents the Hemodynamic Medical Service, together with 2 (two) witnesses, expressly and voluntarily declaring my authorization for the procedure of transcatheter interventricular communication closure or occlusion, consenting, furthermore, to the performance of the proposed procedure as well as its preparatory acts; the physicians are hereby authorized to performed additional procedures and therapeutic interventions that may become necessary due to unforeseen conditions which may occur during the course of the procedure, remaining always at the discretion and judgment of the attending physician. Finally, I consent to the eventual possibility of a blood transfusion, should this procedure be directly linked to the treatment mentioned in this consent and authorization form or resulting from it.

If, during or immediately after the performance of the procedure which I am to undergo, I am not in full possession of my physical and/or mental abilities, I authorize my legal representative ....., nationality ....., marital status ....., profession ....., identity document ....., issued by ....., CPF ....., resident of ....., city ....., state ....., date of birth ...../...../....., parents' names....., relationship to patient ....., to make decisions in my name.

In this manner, I offer my full and free consent, and I authorize the performance of the procedure of transcatheter interventricular communication closure or occlusion, explained herein, to be administered by the signing physician and his/her related medical team.

In conclusion, I certify, that I have signed two copies of the present Form, one of which has been given to me.

Center Location: .....

Date: ...../...../.....

Patient's Name: ..... Signature: .....

Representative: ..... Signature: .....

Physician's Name: ..... CRM no.: .....

Signature: .....

Witnesses:

Name: ..... Name: .....

Annex 12

FREE AND INFORMED CONSENT AND AUTHORIZATION FORM FOR PERFORMANCE OF THE PROCEDURE OF PATENT DUCTUS ARTERIOSUS CLOSURE OR OCCLUSION

By the present Consent and Authorization Form, I, ..., nationality ....., a legal adult and able, marital status ....., profession ....., identity document ....., issued by ....., CPF ....., resident of ...., city ....., state ....., date of birth ...../...../....., parents' names ....., hereby declare that I have received from the Hemodynamics Service, here represented by the physician fully identified below, explanations and warnings concerning the procedure solicited by my clinical physician and that the discussion regarding the nature and extent of the actions necessary for its execution is registered below.

I further declare that it has been explained to me that the procedure patent ductus arteriosus closure or occlusion will be performed in the hemodynamics laboratory of this hospital institution (corporate name ...., CNPJ/MF no. .....headquarters.....) and that it consists of a puncture in the skin of the patient in order to introduce special catheters, using iodized contrast, with the administration of local anesthesia, sedation, or general anesthesia, at the attending physician's discretion.

The following text has been read and explained to me in more accessible language by the signing physician: the aim of this procedure is to repair abnormal communication through a small channel or tube between two important arteries in the heart, the aorta and the pulmonary artery, known as patent ductus arteriosus (PDA). The procedure consists of the introduction of specific guidewires and catheters in the right and/or left inguinal region in order to correct this congenital defect. This procedure has been recommended by a multidisciplinary team of specialists for patients who have clinical and anatomical characteristics favorable to this approach. This communication is closed by means of devices similar to plugs (occluders) or even with coils (springs). The entire procedure is guided by X-ray, which will aid the medical team in the correct positioning and safe release of the prosthesis in the PDA. Once the device has been successfully released, the catheter will be removed and maneuvers will be performed to contain eventual bleedings in the puncture site, and the procedure will subsequently be concluded.

I declare that, in the manner explained to me by the physician, I am perfectly able to understand what the procedure which I am to undergo will comprise.

I declare that I am aware that the intended purpose of performing the forenamed procedure may not be achieved, even though the physician and his/her team adopt the best techniques and employ all of the scientific means and resources available.

I am also aware that the procedure involves risks, and I have received all the pertinent information regarding possible complications due to known and unknown causes, including death, stroke, myocardial infarction, cardiac arrhythmia, acute pulmonary edema, anaphylactic shock, varying types and degrees of infection, allergies and/or reactions to contrast, bleedings, hematomas, renal insufficiency, vascular and hemodynamic complications, perforation of cardiac chambers or vessels, and loss of limbs and/or their function, in addition to the risks inherent in anesthesia and the use of diverse instruments and equipment itself. It has also been explained to me that these adverse reactions and infrequent, occurring in less than 2% of cases, but they may be aggravated when associated with other patient personal factors, which include underlying diseases, previous heart surgery, prior history of allergies, uncontrolled arterial hypertension, tobacco use, alcoholism, diabetes, obesity, renal insufficiency, cerebrovascular disease, prolonged hospitalization, liver failure, heart disease, atherosclerotic disease, cancer, severe malnutrition, and advanced age, which are the most common.

It has also been explained to me that the catheters and prostheses used are subjected to previous tests, but that they may present defects or even fracture, causing adverse reactions and varying types and degrees of injury, including the possibility of requiring surgery to remove them.

It has been reiterated to me that no guarantees or assurances are given with respect to the results expected from the proposed procedure. I am aware that, in executing the proposed procedure, the hemodynamicist and his/her team will be present, and it will be possible to solicit the presence of other specialists, as well as observers from the manufacturer of the equipment and material used. My signature at the end of this consent form authorizes the participation of these professionals and grants them full access to records and medical information related to my case. I have also been informed that, should it be necessary, bed restraint may be performed, as prescribed by the physician, and that I will be under the surveillance of the nursing staff.

I further declare that I have had the opportunity to read this document carefully and also to listen attentively to the physician's reading of all the information presented herein, and I was able to clarify all of my doubts regarding the risks involved and the possible consequences of not performing the suggested treatment, as well as the possible existence of alternative procedures, and my doubts have been satisfactorily addressed and answered. I am aware that there is a possibility of alteration of the original

procedure over the course of the aforementioned procedure and/or new procedure or surgery for the sake of continuity of treatment in a different region from the one originally designated, which, if applicable, will be evaluated, decided upon, and performed, by the medical professional in charge, with which I now agree and hereby authorize.

All my questions having been answered and having understood the procedure in and of itself, as well as its real repercussions, I sign this CONSENT FORM, in the presence of Dr. ....., who, in this act, represents the Hemodynamic Medical Service, together with 2 (two) witnesses, expressly and voluntarily declaring my authorization for the procedure of patent ductus arteriosus closure or occlusion, consenting, furthermore, to the performance of the proposed procedure as well as its preparatory acts; the physicians are hereby authorized to performed additional procedures and therapeutic interventions that may become necessary due to unforeseen conditions which may occur during the course of the procedure, remaining always at the discretion and judgment of the attending physician. Finally, I consent to the eventual possibility of a blood transfusion, should this procedure be directly linked to the treatment mentioned in this consent and authorization form or resulting from it.

If, during or immediately after the performance of the procedure which I am to undergo, I am not in full possession of my physical and/or mental abilities, I authorize my legal representative ....., nationality ....., marital status ....., profession ....., identity document ....., issued by ....., CPF ....., resident of ....., city ....., state ....., date of birth ...../...../....., parents' names....., relationship to patient ....., to make decisions in my name.

In this manner, I offer my full and free consent, and I authorize the performance of the procedure of patent ductus arteriosus closure or occlusion, explained herein, to be administered by the signing physician and his/her related medical team.

In conclusion, I certify, that I have signed two copies of the present Form, one of which has been given to me.

Center Location: .....

Date: ...../...../.....

Patient's Name: ..... Signature: .....

Representative: ..... Signature: .....

Physician's Name: ..... CRM no.: .....

Signature: .....

Witnesses:

Name: ..... Name: .....

Annex 13

FREE AND INFORMED CONSENT AND AUTHORIZATION FORM FOR PERFORMANCE OF THE PROCEDURE OF ANGIOPLASTY WITH CAROTID STENT IMPLANTATION

By the present Consent and Authorization Form, I, ..., nationality ....., a legal adult and able, marital status ....., profession ....., identity document ....., issued by ....., CPF ....., resident of ...., city ....., state ....., date of birth ...../...../....., parents' names ....., hereby declare that I have received from the Hemodynamics Service, here represented by the physician fully identified below, explanations and warnings concerning the procedure solicited by my clinical physician and that the discussion regarding the nature and extent of the actions necessary for its execution is registered below.

I further declare that it has been explained to me that the procedure angioplasty with carotid stent implantation will be performed in the hemodynamics laboratory of this hospital institution (corporate name ...., CNPJ/MF no. .....headquarters.....) and that it consists of a puncture in the skin of the patient in order to introduce special catheters, using iodized contrast, with the administration of local anesthesia, sedation, or general anesthesia, at the attending physician's discretion.

The following text has been read and explained to me in more accessible language by the signing physician: the aim of this procedure is to treat obstructions or blocks in carotid arteries by means of the implantation of a metallic mesh called a stent, via percutaneous access. The procedure is performed by means of a puncture in the femoral artery in the inguinal region, into which a catheter is introduced close to the diseased carotid artery. X-ray emitting equipment and iodized contrast are used to identify the block in the artery. A very small guidewire will cross the obstruction, allowing for positioning of a small device to filter any particle or clot that may come loose from the block being treated. Subsequently, a stent will be positioned and released in the site. Following a few tests, a catheter with a balloon on its end will be inflated inside the stent to improve the final result. Finally, the catheter, the filter, and the guidewire will be removed, and cerebral arteriography will be performed as final angiographic control.

I declare that, in the manner explained to me by the physician, I am perfectly able to understand what the procedure which I am to undergo will comprise.

I declare that I am aware that the intended purpose of performing the forenamed procedure may not be achieved, even though the physician and his/her team adopt the best techniques and employ all of the scientific means and resources available.

I am also aware that the procedure involves risks, and I have received all the pertinent information regarding possible complications due to known and unknown causes, including death, stroke, myocardial infarction, cardiac arrhythmia, acute pulmonary edema, anaphylactic shock, varying types and degrees of infection, allergies and/or reactions to contrast, bleedings, hematomas, renal insufficiency, vascular and hemodynamic complications, perforation of cardiac chambers or vessels, and loss of limbs and/or their function, in addition to the risks inherent in anesthesia and the use of diverse instruments and equipment itself. It has also been explained to me that these adverse reactions and infrequent, occurring in less than 2% of cases, but they may be aggravated when associated with other patient personal factors, which include underlying diseases, previous heart surgery, prior history of allergies, uncontrolled arterial hypertension, tobacco use, alcoholism, diabetes, obesity, renal insufficiency, cerebrovascular disease, prolonged hospitalization, liver failure, heart disease, atherosclerotic disease, cancer, severe malnutrition, and advanced age, which are the most common.

It has also been explained to me that the catheters and prostheses used are subjected to previous tests, but that they may present defects or even fracture, causing adverse reactions and varying types and degrees of injury, including the possibility of requiring surgery to remove them.

It has been reiterated to me that no guarantees or assurances are given with respect to the results expected from the proposed procedure. I am aware that, in executing the proposed procedure, the hemodynamicist and his/her team will be present, and it will be possible to solicit the presence of other specialists, as well as observers from the manufacturer of the equipment and material used. My signature at the end of this consent form authorizes the participation of these professionals and grants them full access to records and medical information related to my case. I have also been informed that, should it be necessary, bed restraint may be performed, as prescribed by the physician, and that I will be under the surveillance of the nursing staff.

I further declare that I have had the opportunity to read this document carefully and also to listen attentively to the physician's reading of all the information presented herein, and I was able to clarify all of my doubts regarding the risks involved and the possible consequences of not performing the suggested treatment, as well as the possible existence of alternative procedures, and my doubts have been satisfactorily addressed and answered. I am aware that there is a possibility of alteration of the original

procedure over the course of the aforementioned procedure and/or new procedure or surgery for the sake of continuity of treatment in a different region from the one originally designated, which, if applicable, will be evaluated, decided upon, and performed, by the medical professional in charge, with which I now agree and hereby authorize.

All my questions having been answered and having understood the procedure in and of itself, as well as its real repercussions, I sign this CONSENT FORM, in the presence of Dr. ....., who, in this act, represents the Hemodynamic Medical Service, together with 2 (two) witnesses, expressly and voluntarily declaring my authorization for the procedure of angioplasty with carotid stent implantation, consenting, furthermore, to the performance of the proposed procedure as well as its preparatory acts; the physicians are hereby authorized to performed additional procedures and therapeutic interventions that may become necessary due to unforeseen conditions which may occur during the course of the procedure, remaining always at the discretion and judgment of the attending physician. Finally, I consent to the eventual possibility of a blood transfusion, should this procedure be directly linked to the treatment mentioned in this consent and authorization form or resulting from it.

If, during or immediately after the performance of the procedure which I am to undergo, I am not in full possession of my physical and/or mental abilities, I authorize my legal representative ....., nationality ....., marital status ....., profession ....., identity document ....., issued by ....., CPF ....., resident of ....., city ....., state ....., date of birth ...../...../....., parents' names....., relationship to patient ....., to make decisions in my name.

In this manner, I offer my full and free consent, and I authorize the performance of the procedure of angioplasty with carotid stent implantation, explained herein, to be administered by the signing physician and his/her related medical team.

In conclusion, I certify, that I have signed two copies of the present Form, one of which has been given to me.

Center Location: .....

Date: ...../...../.....

Patient's Name: ..... Signature: .....

Representative: ..... Signature: .....

Physician's Name: ..... CRM no.: .....

Signature: .....

Witnesses:

Name: ..... Name: .....

Annex 14

FREE AND INFORMED CONSENT AND AUTHORIZATION FORM FOR PERFORMANCE OF THE PROCEDURE OF ANGIOPLASTY WITH RENAL ARTERY STENT IMPLANTATION

By the present Consent and Authorization Form, I, ..., nationality ....., a legal adult and able, marital status ....., profession ....., identity document ....., issued by ....., CPF ....., resident of ...., city ....., state ....., date of birth ...../...../....., parents' names ....., hereby declare that I have received from the Hemodynamics Service, here represented by the physician fully identified below, explanations and warnings concerning the procedure solicited by my clinical physician and that the discussion regarding the nature and extent of the actions necessary for its execution is registered below.

I further declare that it has been explained to me that the procedure angioplasty with renal artery stent implantation will be performed in the hemodynamics laboratory of this hospital institution (corporate name ...., CNPJ/MF no. .....headquarters.....) and that it consists of a puncture in the skin of the patient in order to introduce special catheters, using iodized contrast, with the administration of local anesthesia, sedation, or general anesthesia, at the attending physician's discretion.

The following text has been read and explained to me in more accessible language by the signing physician: the aim of this procedure is to treat obstructions or blocks in the renal artery, clearing the obstruction by inflating a small balloon catheter in the site of the block, followed by implantation of a metallic mesh called a stent, via percutaneous access. The procedure is performed by means of a puncture in the femoral artery in the inguinal region, into which a catheter is introduced close to the diseased renal artery. X-ray emitting equipment and iodized contrast are used to identify the block in the artery. A very small guidewire will cross the obstruction, allowing for positioning of the balloon catheter in the block. Subsequently, a stent will be positioned and released in the site. Finally, renal arteriography will be performed as final angiographic control.

I declare that, in the manner explained to me by the physician, I am perfectly able to understand what the procedure which I am to undergo will comprise.

I declare that I am aware that the intended purpose of performing the forenamed procedure may not be achieved, even though the physician and his/her team adopt the best techniques and employ all of the scientific means and resources available.

I am also aware that the procedure involves risks, and I have received all the pertinent information regarding possible complications due to known and unknown causes, including death, stroke, myocardial infarction, cardiac arrhythmia, acute pulmonary edema, anaphylactic shock, varying types and degrees of infection, allergies and/or reactions to contrast, bleedings, hematomas, renal insufficiency, vascular and hemodynamic complications, perforation of cardiac chambers or vessels, and loss of limbs and/or their function, in addition to the risks inherent in anesthesia and the use of diverse instruments and equipment itself. It has also been explained to me that these adverse reactions and infrequent, occurring in less than 2% of cases, but they may be aggravated when associated with other patient personal factors, which include underlying diseases, previous heart surgery, prior history of allergies, uncontrolled arterial hypertension, tobacco use, alcoholism, diabetes, obesity, renal insufficiency, cerebrovascular disease, prolonged hospitalization, liver failure, heart disease, atherosclerotic disease, cancer, severe malnutrition, and advanced age, which are the most common.

It has also been explained to me that the catheters and prostheses used are subjected to previous tests, but that they may present defects or even fracture, causing adverse reactions and varying types and degrees of injury, including the possibility of requiring surgery to remove them.

It has been reiterated to me that no guarantees or assurances are given with respect to the results expected from the proposed procedure. I am aware that, in executing the proposed procedure, the hemodynamicist and his/her team will be present, and it will be possible to solicit the presence of other specialists, as well as observers from the manufacturer of the equipment and material used. My signature at the end of this consent form authorizes the participation of these professionals and grants them full access to records and medical information related to my case. I have also been informed that, should it be necessary, bed restraint may be performed, as prescribed by the physician, and that I will be under the surveillance of the nursing staff.

I further declare that I have had the opportunity to read this document carefully and also to listen attentively to the physician's reading of all the information presented herein, and I was able to clarify all of my doubts regarding the risks involved and the possible consequences of not performing the suggested treatment, as well as the possible existence of alternative procedures, and my doubts have been satisfactorily addressed and answered. I am aware that there is a possibility of alteration of the original procedure over the course of the aforementioned procedure and/or new procedure or surgery for the sake of continuity of

treatment in a different region from the one originally designated, which, if applicable, will be evaluated, decided upon, and performed, by the medical professional in charge, with which I now agree and hereby authorize.

All my questions having been answered and having understood the procedure in and of itself, as well as its real repercussions, I sign this CONSENT FORM, in the presence of Dr. ....., who, in this act, represents the Hemodynamic Medical Service, together with 2 (two) witnesses, expressly and voluntarily declaring my authorization for the procedure of angioplasty with renal artery stent implantation, consenting, furthermore, to the performance of the proposed procedure as well as its preparatory acts; the physicians are hereby authorized to performed additional procedures and therapeutic interventions that may become necessary due to unforeseen conditions which may occur during the course of the procedure, remaining always at the discretion and judgment of the attending physician. Finally, I consent to the eventual possibility of a blood transfusion, should this procedure be directly linked to the treatment mentioned in this consent and authorization form or resulting from it.

If, during or immediately after the performance of the procedure which I am to undergo, I am not in full possession of my physical and/or mental abilities, I authorize my legal representative ....., nationality ....., marital status ....., profession ....., identity document ....., issued by ....., CPF ....., resident of ....., city ....., state ....., date of birth ...../...../....., parents' names....., relationship to patient ....., to make decisions in my name.

In this manner, I offer my full and free consent, and I authorize the performance of the procedure of angioplasty with renal artery stent implantation, explained herein, to be administered by the signing physician and his/her related medical team.

In conclusion, I certify, that I have signed two copies of the present Form, one of which has been given to me.

Center Location: .....

Date: ...../...../.....

Patient's Name: ..... Signature: .....

Representative: ..... Signature: .....

Physician's Name: ..... CRM no.: .....

Signature: .....

Witnesses:

Name: ..... Name: .....

Annex 15

FREE AND INFORMED CONSENT AND AUTHORIZATION FORM FOR PERFORMANCE OF THE PROCEDURE OF ANGIOPLASTY WITH LOWER LIMB ARTERY STENT IMPLANTATION

By the present Consent and Authorization Form, I, ..., nationality ....., a legal adult and able, marital status ....., profession ....., identity document ....., issued by ....., CPF ....., resident of ...., city ....., state ....., date of birth ...../...../....., parents' names ....., hereby declare that I have received from the Hemodynamics Service, here represented by the physician fully identified below, explanations and warnings concerning the procedure solicited by my clinical physician and that the discussion regarding the nature and extent of the actions necessary for its execution is registered below.

I further declare that it has been explained to me that the procedure angioplasty with lower limb artery stent implantation will be performed in the hemodynamics laboratory of this hospital institution (corporate name ...., CNPJ/MF no. .....headquarters.....) and that it consists of a puncture in the skin of the patient in order to introduce special catheters, using iodized contrast, with the administration of local anesthesia, sedation, or general anesthesia, at the attending physician's discretion.

The following text has been read and explained to me in more accessible language by the signing physician: the aim of this procedure is to treat obstructions or blocks in the arteries of lower limbs, via percutaneous access, clearing the obstruction by inflating a small balloon catheter in the site of the block, followed by implantation of a metallic mesh called a stent, via percutaneous access. The procedure is performed by means of a puncture in the femoral artery in the inguinal region (groin), into which a catheter is introduced. X-ray emitting equipment and iodized contrast are used to identify the block in the artery. A very small guidewire, specific to this procedure, will cross the obstruction and allow for positioning and inflation of the balloon catheter in the block. Subsequently, a stent will be positioned and released in the same site. Once the device has been successfully released, final angiographic control is performed; the catheter is removed, and occlusive dressing is applied.

I declare that, in the manner explained to me by the physician, I am perfectly able to understand what the procedure which I am to undergo will comprise.

I declare that I am aware that the intended purpose of performing the forenamed procedure may not be achieved, even though the physician and his/her team adopt the best techniques and employ all of the scientific means and resources available.

I am also aware that the procedure involves risks, and I have received all the pertinent information regarding possible complications due to known and unknown causes, including death, stroke, myocardial infarction, cardiac arrhythmia, acute pulmonary edema, anaphylactic shock, varying types and degrees of infection, allergies and/or reactions to contrast, bleedings, hematomas, renal insufficiency, vascular and hemodynamic complications, perforation of cardiac chambers or vessels, and loss of limbs and/or their function, in addition to the risks inherent in anesthesia and the use of diverse instruments and equipment itself. It has also been explained to me that these adverse reactions and infrequent, occurring in less than 2% of cases, but they may be aggravated when associated with other patient personal factors, which include underlying diseases, previous heart surgery, prior history of allergies, uncontrolled arterial hypertension, tobacco use, alcoholism, diabetes, obesity, renal insufficiency, cerebrovascular disease, prolonged hospitalization, liver failure, heart disease, atherosclerotic disease, cancer, severe malnutrition, and advanced age, which are the most common.

It has also been explained to me that the catheters and prostheses used are subjected to previous tests, but that they may present defects or even fracture, causing adverse reactions and varying types and degrees of injury, including the possibility of requiring surgery to remove them.

It has been reiterated to me that no guarantees or assurances are given with respect to the results expected from the proposed procedure. I am aware that, in executing the proposed procedure, the hemodynamicist and his/her team will be present, and it will be possible to solicit the presence of other specialists, as well as observers from the manufacturer of the equipment and material used. My signature at the end of this consent form authorizes the participation of these professionals and grants them full access to records and medical information related to my case. I have also been informed that, should it be necessary, bed restraint may be performed, as prescribed by the physician, and that I will be under the surveillance of the nursing staff.

I further declare that I have had the opportunity to read this document carefully and also to listen attentively to the physician's reading of all the information presented herein, and I was able to clarify all of my doubts regarding the risks involved and the possible consequences of not performing the suggested treatment, as well as the possible existence of alternative procedures, and my doubts have been satisfactorily addressed and answered. I am aware that there is a possibility of alteration of the original procedure over the course of the aforementioned procedure and/or new procedure or surgery for the sake of continuity of

Statement

treatment in a different region from the one originally designated, which, if applicable, will be evaluated, decided upon, and performed, by the medical professional in charge, with which I now agree and hereby authorize.

All my questions having been answered and having understood the procedure in and of itself, as well as its real repercussions, I sign this CONSENT FORM, in the presence of Dr. ...., who, in this act, represents the Hemodynamic Medical Service, together with 2 (two) witnesses, expressly and voluntarily declaring my authorization for the procedure of angioplasty with lower limb artery stent implantation, consenting, furthermore, to the performance of the proposed procedure as well as its preparatory acts; the physicians are hereby authorized to performed additional procedures and therapeutic interventions that may become necessary due to unforeseen conditions which may occur during the course of the procedure, remaining always at the discretion and judgment of the attending physician. Finally, I consent to the eventual possibility of a blood transfusion, should this procedure be directly linked to the treatment mentioned in this consent and authorization form or resulting from it.

If, during or immediately after the performance of the procedure which I am to undergo, I am not in full possession of my physical and/or mental abilities, I authorize my legal representative ....., nationality ....., marital status ....., profession ....., identity document ....., issued by ....., CPF ....., resident of ....., city ....., state ....., date of birth ...../...../....., parents' names....., relationship to patient ....., to make decisions in my name.

In this manner, I offer my full and free consent, and I authorize the performance of the procedure of angioplasty with lower limb artery stent implantation, explained herein, to be administered by the signing physician and his/her related medical team.

In conclusion, I certify, that I have signed two copies of the present Form, one of which has been given to me.

Center Location: .....

Date: ...../...../.....

Patient's Name: ..... Signature: .....

Representative: ..... Signature: .....

Physician's Name: ..... CRM no.: .....

Signature: .....

Witnesses:

Name: ..... Name: .....

Annex 16

RECOMMENDATIONS FOR WRITING REPORTS IN HEMODYNAMICS AND INTERVENTIONAL CARDIOLOGY (MINIMUM REQUIREMENTS)[70,71]

Reports in hemodynamics and interventional cardiology are individualized for each physician, hemodynamics service, and procedure performed. The continuous methodological and technological evolution in interventional cardiology leads to minimal uniformity in order to meet current expectations to facilitate comprehension of each procedure by the patient, the hospital, and the source of payment.

The composition of a report in hemodynamics and interventional cardiology includes the following minimal elements:

1. Patient's general information: name, sex, date of birth, day, time, hospital registration, procedure number, source of payment, referring physician.
2. Clinical indication for the procedure.
3. Procedure performed (e.g., left catheterization, coronary cineangiography and left ventriculography; coronary angioplasty with stent implantation; alcohol septal ablation; temporary pacemaker implantation, etc.).
4. Participating physicians: auxiliary physicians and anesthetist.
5. Technique utilized:
   a. Access route.
   b. Material utilized.
   c. Catheter size (French scale).
   d. Number of projections (usual or otherwise).
   e. Technique for vascular hemostasis.
   f. Use of vasoactive drugs or IIb/IIIa platelet antagonists.
6. Procedure findings:
   a. Manometry (invasive pressure of chambers studied).
   b. Oximetry, calculation of cardiac output, flows, and resistances, in indicated cases.
   c. Coronary cineangiography.
   d. Left and right ventriculography and ascending aortography.
   e. Coronary, structural, extracardiac, congenital intervention.
   f. Other results of complementary imaging methods and vascular/coronary physiology performed.
7. Procedure time, radiation dose, type and volume of contrast use in the patient.
8. Complications.
9. Final conclusion on the findings.
10. Comments: note difficulties with projections, different catheter exchanges, angiography of the access site, change of initial access for another.

Annex 17

STRUCTURED FORM | TRAINEE

1. Training Center: .....
2. Person Responsible for the Training Center: .....
3. Date: ...../...../.....

• Does your Training Center possess the infrastructure recommended in the latest Guidelines on Professional Quality of the Brazilian Society of Hemodynamics and Interventional Cardiology (SBHCI)?

_____ Yes _____ No

• During your first year, did you receive training in radiation protection, vascular accesses, complications and management thereof, diagnostic percutaneous procedures, and low complexity coronary interventions?

_____ Yes _____ No

• During your second year, did you receive training in high complexity coronary interventions, adjuvant methods to coronary cineangiography/intervention (FFR, iFR, ICUS, or OCT), and management of structural cardiopathies?

_____ Yes _____ No

• During your entire training period, did you perform, as a first operator under supervision, at least 400 diagnostic cardiac catheterizations and 200 coronary angioplasties?

_____ Yes _____ No

• Did you regularly (at least twice per month) participate in reunions in conjunction with the clinical team and the heart surgery team (heart team)?

_____ Yes _____ No

• Did you have regular courses that covered at least 70% of the Theoretical Program suggesting in the latest Guidelines on Professional Quality of the SBHCI?

_____ Yes _____ No

• Assign a score between 0 and 10 to your Training Center and make suggestions for improvement for the SBHCI to forward to your Training Center coordinator:

Note: .....

Suggestions: .....
.....
.....
.....
.....

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Statement

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In the Original Article " Association of Dietary Patterns with Excess Weight and Body Adiposity in Brazilian Children: The Pase-Brasil Study", in Figure 1, in the chart referring to increased body fat x traditional pattern, consider the sign correct < P75.

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In the Review Article "Artificial Intelligence in Cardiology: Concepts, Tools and Challenges - "The Horse is the One Who Runs, You Must Be the Jockey", in Figure 2, replace the acronym KM with KNN and the acronym DAM with GB.

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