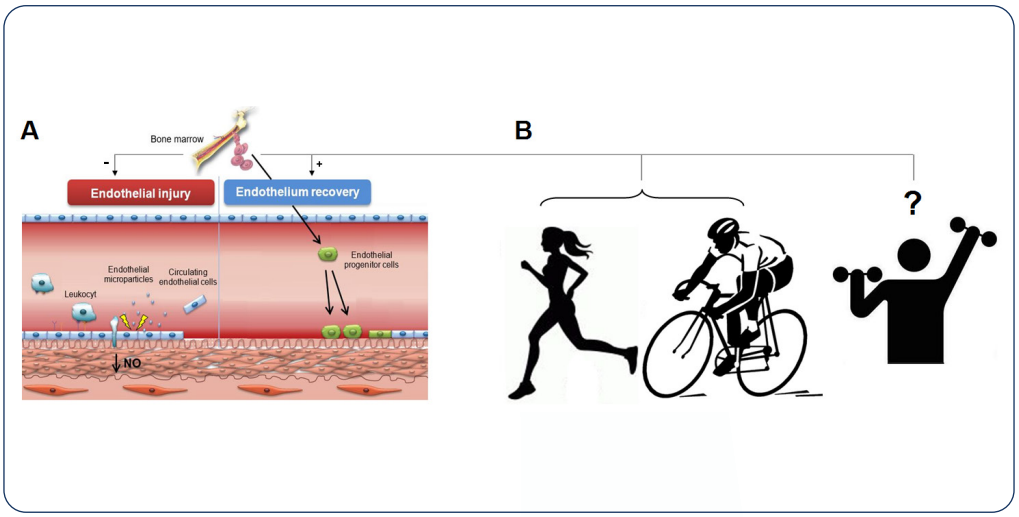
ABC Cardiol
Arquivos Brasileiros de Cardiologia

Volume 116 | Number 5
May 2021

Brazilian Society of Cardiology
ISSN-0066-782X



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Arquivos Brasileiros de Cardiologia
JOURNAL OF BRAZILIAN SOCIETY OF CARDIOLOGY - Published since 1943

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Arquivos Brasileiros de Cardiologia

Volume 116, Nº 5, May 2021

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

Address: Av. Marechal Câmara, 160 - 3º andar - Sala 330
20020-907 • Centro • Rio de Janeiro, RJ • Brasil
Phone.: (21) 3478-2700
E-mail: arquivos@cardiol.br
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Comparison of the Outcomes between Coronary No-Reflow and Slow-Flow Phenomenon in Non-STEMI Patients

Mustafa Ahmet Huyut[1]

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

Abstract

Background: **Coronary slow-flow phenomenon (CSFP) and coronary no-reflow phenomenon (CNP) are associated with increased risk of major cardiovascular adverse events (MACE).**

Objectives: **This study aimed to evaluate and compare the one-year clinical follow-up outcomes among patients with CNP and CSFP who underwent percutaneous coronary interventions (PCI) in non-ST elevation myocardial infarction (NSTEMI).**

Methods: **This study included a total of 858 patients who were diagnosed with NSTEMI and underwent PCI within 24 h of symptom onset. The patients were divided into two groups, the CSFP group (n=221) and the CNP group (n=25), regarding the angiographic characteristics of thrombolysis in myocardial infarction (TIMI) flow of the infarct-related artery. Patients were followed for one-year. A p-value of <0.05 was considered significant.**

Results: **CNP was observed in 2.91%, and CSFP was observed in 25.75% of the patients. Clinical endpoints analyzed that stroke was significantly higher in the CNP group than in the CSFP group (6 (24%) vs. 6 (2.70%), p<0.001) and MACE was significantly higher in the CNP group than in the CSFP group (11 (44%) vs. 51 (23.10%), p=0.022). Forward conditional logistic regression analysis demonstrated that body mass index (BMI) (OR=1.11, 95%CI: 1.00-1.24, p=0.038) and baseline heart rate (HR) (OR=0.923, 95%CI: 0.88-0.96, p<0.001) were the independent predictors of CNP in NSTEMI.**

Conclusion: **CNP patients have worse clinical outcomes and a higher risk of stroke compared with CSFP patients in NSTEMI. (Arq Bras Cardiol. 2021; 116(5):856-864)**

Keywords: **Myocardial Infarction; No-Reflow Phenomenon; Percutaneous Coronary Interventon; Acute Coronary Syndrome/complications; Risk Factors; Coronary Angiography; Stroke.**

Introduction

Acute coronary syndromes remain a major cause of mortality and morbidity in industrialized countries and are becoming an increasingly important problem in developing countries, despite improvements in its management and prevention.[1] Among the acute coronary syndromes, patients with non-ST elevation myocardial infarction (NSTEMI) have been shown to have worse long-term outcomes.[2] Few studies have, however, reported on the outcomes in NSTEMI, but these reports have not clarified the difference between coronary slow-flow phenomenon (CSFP) and coronary no-reflow phenomenon (CNP) subgroups' characteristics in clinical practice, both in the hospital and over the long term follow-up, from a 'real-world' perspective.[3,4] In the absence of obstructive coronary artery disease, TIMI-II coronary flow and delayed coronary opacification are defined as CSFP.[5] In addition, TIMI 0-I flows without dissection, mechanical obstruction, significant residual stenosis, spasm or coronary artery thrombus are defined as angiographic CNP.[6] The underlying mechanisms in CNP and CSFP are inflammation, atherothrombotic microembolization, neutrophil and platelet activation, which triggers the release of oxygen-free radicals, proteolytic enzymes, and proinflammatory mediators that can trigger tissue and endothelial damage, especially in critically-injured myocytes.[5,6]

Moreover, it is unclear under what circumstances the differences in clinical characteristics and outcomes persist in NSTEMI patients. Also, there is no evidence in the literature about how slow-flow could affect the outcomes in NSTEMI. Additionally, the comparison of outcomes between CSFP and CNP in NSTEMI patients has not been addressed in the literature. We hypothesized that the worst clinical outcomes in NSTEMI are strongly related to the non-TIMI III flow in the coronary arteries and especially in the CNP group subset. In the present study, we aimed to investigate the clinical characteristics and compare the major cardiovascular outcomes between CSFP and CNP in NSTEMI patients who were followed for 12 months.

Mailing Address: Mustafa Ahmet Huyut •
Yeni Yuzyil University, Faculty of Medicine, Department of Cardiology, Merkez Mah. Cukurcesme Caddesi No:51 Gaziosmanpasa Istanbul - Turkey
E-mail: ahuyut@yahoo.com
Manuscript received December 24, 2019, revised manuscript February 19, 2020, accepted April 08, 2020

DOI: https://doi.org/10.36660/abc.20190905

Methods

For this single-center, prospectively conducted study, 858 patients aged between 18 and 90 years were enrolled between June 2016 and June 2018 at Bezmialem University Hospital, who were diagnosed with NSTEMI and submitted to early PCI within 24 hours of symptom onset (Figure1). Patients with TIMI III flow, coronary artery bypass graft (CABG), cardiogenic shock, pulmonary edema, signs of acute left ventricular dysfunction, stent thrombosis, underwent thrombus aspiration in index event, had acute or chronic infective or neoplastic disease, moderate-to-severe chronic kidney disease, and chronic liver disease were excluded from this study (n=602). The final results of the angiographic characteristics of TIMI flow of the treated culprit artery assigned a total of 25 patients with angiographically-proven CNP to the CNP group and 221 patients with angiographically-proven CSFP to the CSFP group. All patients received a total of 300 mg acetylsalicylic acid and a loading dose (600 mg) of clopidogrel and UF heparin (100mg / kg) during the PCI. The follow-up information was obtained from hospital records and after 1, 3, 6, and 12 months during patients' visits by the same investigator. The endpoints of this study were obtained from hospital records and death certificates, or telephone contact with the patients' relatives. Major cardiovascular adverse events (MACE) was defined as all-cause mortality, cardiovascular death, stroke, and myocardial re-infarction. All participants gave written informed consent prior to study participation and the study was approved by the local ethics committee (Number:7/70-04/17). Furthermore, the study was conducted according to the provisions of the Declaration of Helsinki.

Biochemical Assessment

Venous blood samples were taken from the antecubital vein immediately after admission to the hospital before PCI. A 12-lead electrocardiogram was obtained at the time of admission to the emergency department and heart rate (HR) was noted. The estimated glomerular filtration rate (eGFR) of each patient was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation. The BMI was calculated using the formula weight (kg)/ height^2 (m^2).Routine blood chemistry, lipid parameters, and cardiac troponin-I levels were measured using a standard auto-analyzer. Blood counts were measured in a Sysmex K-1000 (Block Scientific, Bohemia, NY, USA) auto-analyzer. Samples were centrifuged at 3000 rpm for 10 min, the supernatant and serum were separated in the samples and then they were frozen at -80° C until further analysis. The serum creatinine level measurement was repeated at 72 hours after contrast medium (CM) administration. Contrast-induced nephropathy was defined as a 0.5 mg/dL absolute increase in serum creatinine level above baseline or ≥25% relative increase in basal serum creatinine level within 72 hours of CM exposure.

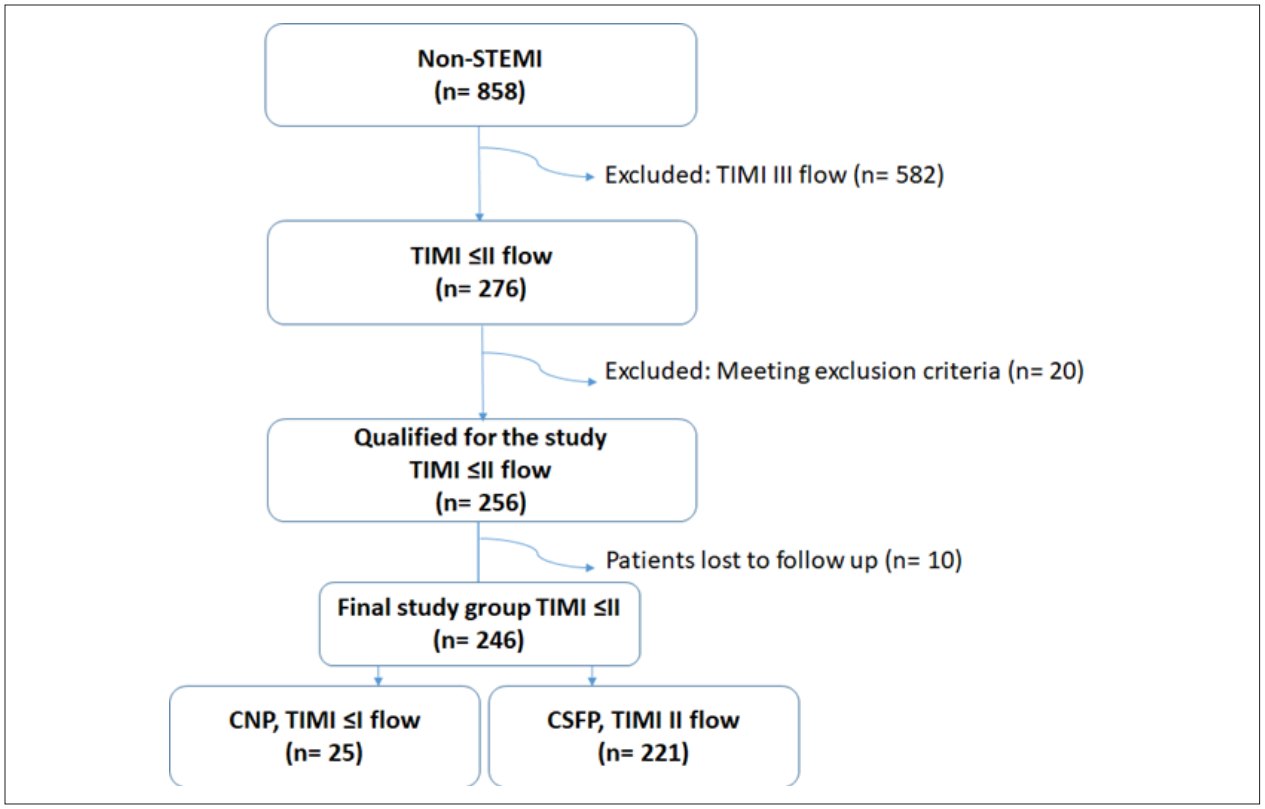

Figure 1 – *Diagram shows the selection of the study groups. Non-STEMI: non-ST elevation myocardial infarction; TIMI: thrombolysis in myocardial infarction; CNP: coronary no-reflow phenomenon; CSFP: coronary slow-flow phenomenon.*

Diagnosis of non-ST-segment Elevation Myocardial Infarction

The diagnosis of NSTEMI was made in the presence of characteristics based on definitions from clinical practice guidelines.[7] The NSTEMI patients had typical chest pain or discomfort occurring at rest or minimal exertion, for at least 10 minutes, and the initial ECG showed normal ECG or ischemic changes, such as ST-depression or T-wave inversion with elevated cardiac troponin-I level with at least 1 value above the 99th percentile of the upper reference limit.

Cardiovascular Risk Factors

After detailed examinations, the medical history of each patient was collected by the same investigator. Risk factors were identified for coronary artery disease (CAD), cardiovascular risk factors including age, gender, diabetes mellitus (DM), hypertension (HT), hyperlipidemia (HPL), and smoking status. Patients receiving prior antihypertensive therapy or blood pressure levels ≥140/90 mmHg, measured at least twice, were considered hypertensive.[8] Patients previously treated with oral antidiabetic and/or insulin therapy or whose fasting blood glucose was as high as ≥125 mg/dL, after being measured at least twice, were considered diabetic.[9] The presence of HPL was considered when a measurement of total cholesterol > 200 mg/dL or low-density lipoprotein cholesterol (LDL-C) >100 mg / dL was obtained, or when the patient used lipid-lowering medication in accordance with the "Adult Treatment Panel III" guideline.[10] Patients who still used tobacco products on admission to the emergency service and those who had stopped smoking in the past month were considered smokers.

Transthoracic Echocardiography

Before discharge, each patient underwent a transthoracic echocardiographic examination using a 3.5-MHz transducer (Vivid 7 GE Medical System, Horten, Norway). Examinations and assessments were carried out according to the recommendations of the American Echocardiography Unit guidelines. Simpson's method was used to calculate left ventricular ejection fraction (LVEF).[11]

Coronary Angiography

Coronary angiography procedures were performed via the femoral approach using a Philips (Optimus 200 DCA and Integris Allura 9, Philips Medical Systems, Eindhoven, Netherlands) angiography system. Coronary angiography and PCI were conducted using nonionic, iso-osmolar contrast media (iodixanol, Visipaque 320mg/100mL, GE Healthcare, Cork, Ireland) according to standard clinical practices. The PCI of the infarct-related artery was performed. Angiographic images were taken at a rate of at least 80 frames and recorded at a rate of 25 frames per second. At least two expert cardiologists evaluated coronary anatomy and TIMI flow grade offline. Coronary artery TIMI flow was determined by the quantitative number of frame counts as described by Gibson et al.[12] TIMI 0-I flows without dissection, mechanical obstruction, significant residual stenosis, spasm or coronary artery thrombus were defined as angiographic CNP. In the absence of obstructive coronary artery disease, TIMI-II coronary flow and delayed coronary opacification are defined as CSFP. CNP patients received treatment with intracoronary (IC) glycoprotein IIb/IIIa inhibitors (Gp-IIb/IIIa inh.) or IC adenosine or IC epinephrine. After the procedure, all patients received intravenous (IV) hydration with isotonic saline (1mL/kg/h) for at least 12 hours.

Statistical Analysis

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

Results

In this study, we included a total of 858 NSTEMI patients and at the end, we concluded the present study with 246 patients (171 males; mean age: 61.69±12.60 years). In NSTEMI patients, CNP was observed in 2.91% (n=25) and CSFP was observed in 25.75% (n=221). Regarding the final study population, the CNP group had 25 (10.16%) patients and the CSFP group had 221 (89.84%) patients. Demographic findings are described in Table1. Moreover, NYHA class, heart rate, hospital length of stay, Mehran score, and eGFR were significantly associated with EuroSCORE-II ($p<0.05$) (Table 2). Clinical follow-up findings were described in Table 3. We did not identify any hemorrhagic stroke during follow-up. Kaplan-Meier estimates for stroke and MACE rates are described in Figure 2A and Figure 2B. Forward conditional logistic regression analysis demonstrated that BMI and HR were the independent predictors of CNP (Table 4).

In the ROC analysis, a BMI > 28.38 kg/m^2 predicted the presence of CNP with 80% of sensitivity and 54% of specificity. The area under the curve was 0.649 (95%CI: 0.548–0.750, $p=0.015$) (Figure 3A). Moreover, HR < 66.5 bpm predicted the presence of CNP with 86% of sensitivity and 60% of specificity. The area under the curve was 0.741 (95%CI: 0.88–0.96, $p<0.001$) (Figure 3B).

Table 1 – Baseline and laboratory characteristics of the patients

Variable, n (%)	CNP, n=25 (10.16)	CSFP, n=221 (89.84)	p-value
Age, y	66.28±14.14	61.17±12.34	0.057
Female gender, n (%)	12 (48)	63 (28.50)	0.045
BMI, kg/m²	30.51±3.99	28.34±4.55	0.015
HT, n (%)	19 (76)	129 (58.40)	0.088
DM, n (%)	10 (40)	70 (31.70)	0.400
HL, n (%)	9 (36)	95 (43)	0.503
Smoker, n (%)	15 (60)	132 (59.70)	0.979
Family History, n (%)	8 (32)	73 (33)	0.917
PAD, n (%)	5 (20)	13 (5.90)	0.010
COPD, n (%)	5 (20)	31 (14)	0.423
LVEF, %	50±7.40	52.29±7.19	0.126
Glucose, mg/dl	115 (90.50-174)	106 (96-146)	0.719
Uric acid, mg/dl	5.60 (4.55-7.25)	5.80 (4.20-6.90)	0.303
Creatinine, mg/dl	0.86 (0.77-1.23)	0.87 (0.76-1.05)	0.175
eGFR, mL/min per 1.73 m2	70.90±25.95	82.86±20.80	0.021
Triglycerides, mg/dL	153 (125-195)	147 (110.5-180)	0.353
LDL, mg/dL	135 (114-171)	125 (98-149)	0.051
HTC, %	40.60 (35.80-42)	41 (37.10-43.15)	0.344
Platelets, 10³/uL	220 (185-266)	225 (190-276.50)	0.428
Peak Troponin-I, pg/ml	814 (156-5693.50)	146 (116-2113)	0.037
hs-CRP, mg/dL	0.10 (0.01-0.57)	0.18 (0.04-0.50)	0.836
Heart Rate, bpm	69.60±19.86	78.81±13.46	<0.001
Hospital length of stay, d.	3.40±0.95	3.00±0.88	0.015
Mehran Score	7.56±6.20	5.24±4.91	0.017
CIN development, n (%)	4 (16)	19 (8.60)	0.228
NYHA class	2.48±0.50	2.04±0.40	<0.001
EuroSCORE II, %	3.96±3.95	2.14±2.32	<0.001
Medications, n (%)			
Ace inh	17 (68)	110 (49.80)	0.084
ARB	7 (28)	75 (33.90)	0.551
B-blocker	24 (96)	212 (95.90)	0.986
CCB	9 (36)	52 (23.50)	0.171
Statin	25 (100)	194 (87.80)	0.064
Nitrate	11 (44)	73 (33)	0.273
OAD	10 (40)	68 (30.80)	0.347
Diuretic	13 (52)	71 (32.10)	0.047
IC Gp-IIb/IIIa inh.	25 (100)	8 (3.61)	<0.001
IC adenosine	25 (100)	1 (0.45)	<0.001
IC epinephrine	25 (100)	1 (0.45)	<0.001

Values are mean±SD or numbers and percentages or median and 25th-75th percentiles. The p-value for categorical data from Chi-square. The p-value for independent samples t-test or the Mann-Whitney U test was used to compare continuous variables. CNP: coronary no-reflow phenomenon; CSFP: coronary slow-flow phenomenon; Y: year; BMI: body mass index; HT: hypertension; DM: diabetes mellitus type 2; HL: hyperlipidemia; PAD: peripheral arterial disease; COPD: chronic obstructive pulmonary disease; LVEF: left ventricular ejection fraction; eGFR: estimated glomerular filtration rate; LDL: low-density lipoprotein; HTC: hematocrit; hs-CRP: high-sensitivity C-reactive protein; bpm: beats per minute; d: days; CIN: Contrast-induced nephropathy; NYHA: the New York Heart Association Functional Classification; EuroSCORE: European System for Cardiac Operative Risk Evaluation; ACE inh: angiotensin-converting enzyme inhibitors; ARB: angiotensin receptor blockers; B-blocker: beta-blocker; CCB. calcium channel blockers; OAD: oral antihyperglycemic drugs; IC: intracoronary; Gp-IIb/IIIa inh: glycoprotein-IIb/IIIa inhibitors.

Table 2 – Baseline characteristics significantly associated with EuroSCORE II

Variable	r	p-value
NYHA class	0.590	<0.001
Heart Rate	0.192	0.003
Hospital length of stay	0.468	<0.001
Mehran Score	0.763	<0.001
eGFR	-0.671	<0.001

EuroSCORE II: European System for Cardiac Operative Risk Evaluation II; r: Spearman's rank correlation coefficient, NYHA: the New York Heart Association Functional Classification; eGFR: estimated glomerular filtration rate.

Table 3 – One-year clinical follow-up findings

Variable, n (%)	CNP, n=25 (10.16)	CSFP, n=221 (89.84)	p-value
All-Cause Mortality	4 (16)	29 (13.10)	0.689
Cardiovascular Death	4 (16)	23 (10.40)	0.396
Stroke	6 (24)	6 (2.70)	<0.001
Myocardial re-infarction	3 (12)	25 (11.30)	0.918
MACE	11 (44)	51 (23.10)	0.022

Values are numbers and percentages. CNP: coronary no-reflow phenomenon; CSFP: coronary slow-flow phenomenon; MACE: Major Adverse cardiovascular events.

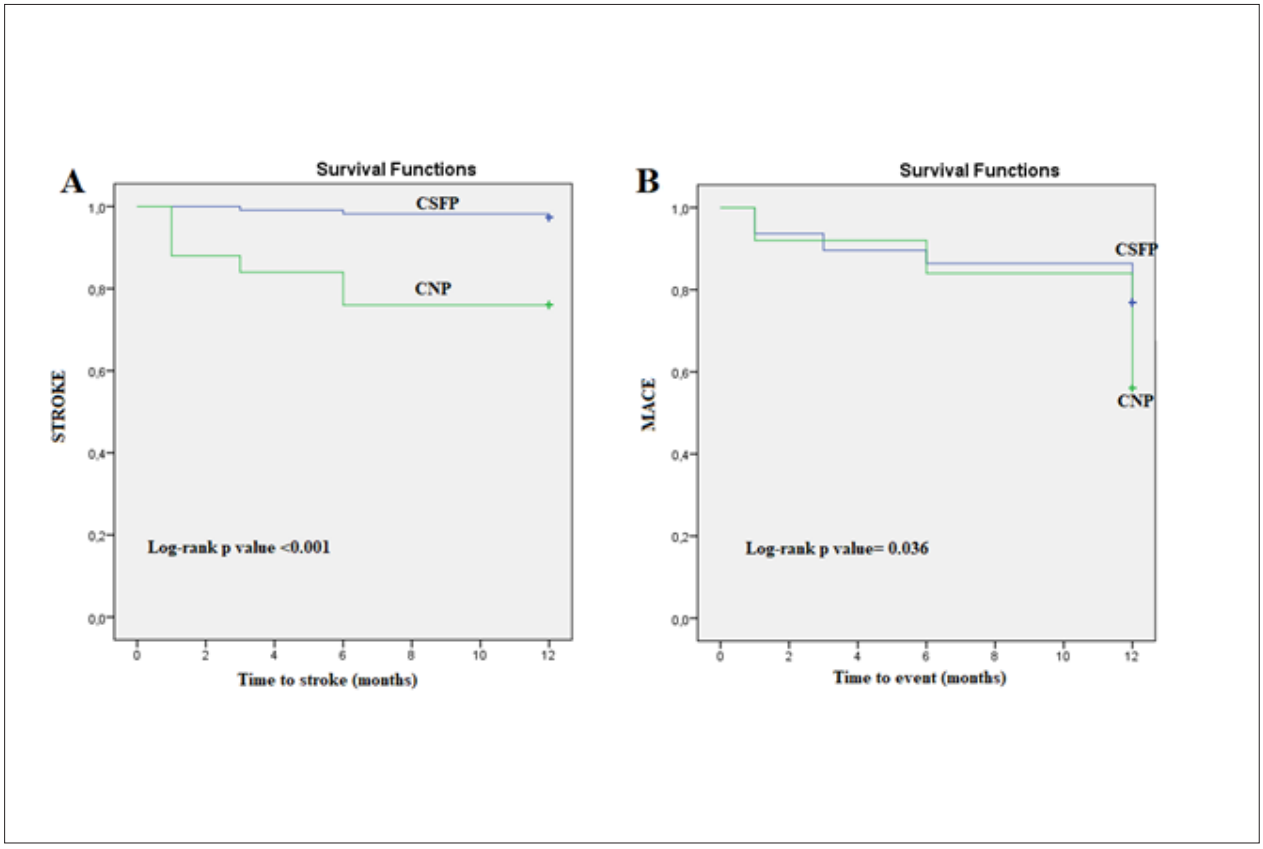

Figure 2 – *(A) Kaplan-Meier estimates for Stroke. (B) Kaplan-Meier estimates for MACE. MACE: major adverse cardiac events; CNP: coronary no-reflow phenomenon; CSFP: coronary slow-flow phenomenon.*

Table 4 – Independent predictors of CNP

Variable	OR	95% CI	p-value
BMI	1.11	1.00-1.24	0.038
HR	0.923	0.88-0.96	<0.001

OR: Odds ratio; CI: Confidence interval; BMI: body mass index; HR: heart rate.

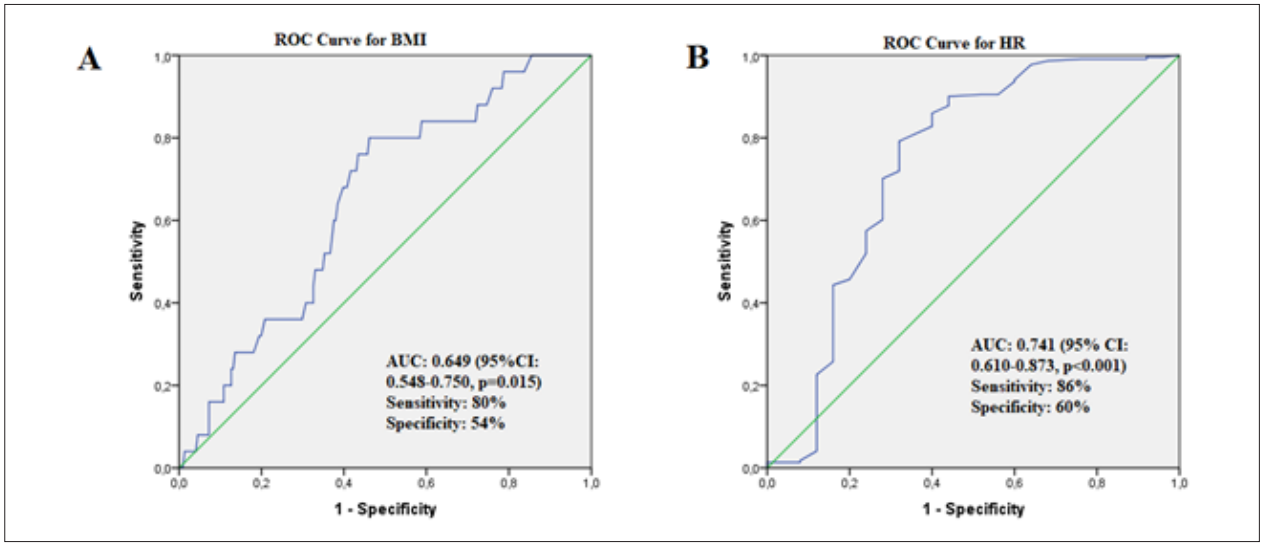

Figure 3 – *(A) ROC curve for the specificity and sensitivity of BMI. (B) ROC curve for the specificity and sensitivity of HR. BMI: body mass index; HR: heart rate; ROC: receiver operating characteristic curve; AUC: area under the curve; CI: confidence interval.*

Discussion

The key finding of this research was that the two determinants of CNP in NSTEMI patients were increased BMI levels and lower HR. Additionally, in patients with NSTEMI, CNP was significantly associated with poor outcomes. We showed that BMI values > 28.38 kg/m^2 suggest the presence of CNP in NSTEMI. Moreover, HR < 66.5 bpm suggests the presence of CNP in NSTEMI. To the best of our knowledge, this is the first report in the literature demonstrating the relationship between BMI and lower HR in CNP patients with NSTEMI. In our study, the results of the one-year clinical follow-up showed that the incidence of stroke and MACE was significantly higher in the CNP group. In this study, we showed that CNP worsened NSTEMI patients' outcomes.

CSFP and CNP are not frequent findings, with an incidence of approximately 1% in patients undergoing coronary angiography; however, according to the published data, the estimated frequency of CNP and CSFP range from 1% to 60% in acute coronary syndrome.[13,14] In this study, CNP was observed in 2.91% and CSFP was observed in 25.75% of the study population. CSFP and CNP are associated with poor short-term and long-term clinical outcomes.[15] In particular, CNP is a significant predictor of poor cardiac outcomes in NSTEMI.[13,16] Consistent with the published data, we found the worst outcomes in the CNP group. In our study, the one-year clinical follow-up findings demonstrated that MACE and stroke outcomes were significantly higher in the CNP group. In the CNP group, the probability of stroke was 8.88-fold higher than in the CSFP group.

Moreover, in the CNP group, we observed that the probability of MACE was 1.90-fold higher than in the CSFP group. Previous meta-analyses including both retrospective and prospective studies found a positive association between cardiac troponin and adverse events in NSTEMI.[17] In this study, consistent with the literature, we found a significantly higher peak troponin-I level in the CNP group. Meanwhile, stroke was associated with thrombus burden. According to our research, the associated mechanism causing this adverse event is continuing thrombus activation after the index event, and we considered that may be the main reason for the increased risk of stroke. Although all NSTEMI patients were regularly treated with antithrombotic drugs, stoke occurred with a significantly higher incidence in the CNP group. Thus, after discharge, such patients should be carefully monitored. In addition, BMI is the most commonly used method for cardiovascular risk and obesity assessment.[18]

In patients with NSTEMI, Bakirci et al.[19] found that epicardial fat, which is increased in obese patients, is associated with an impaired coronary flow.[19] Recent studies have suggested that CNP is more commonly seen in combination with hyperglycemia, hypercholesterolemia, and mild to moderate renal insufficiency.[20] In the present study, we found significantly lower rates of eGFR and higher Mehran scores in the CNP

group, consistent with the literature. Moreover, in our study, the CNP group patients had significantly higher BMI and we considered this might be associated with an increased risk of stroke. Therefore, the calculation of the BMI may be a useful method for estimating cardiac outcomes in NSTEMI patients with CNP. We also considered that decreasing BMI may protect patients from stroke.

Meanwhile, randomized studies showed that using a manual thrombus aspiration catheter may provide better microvascular perfusion and long-term outcomes when compared to control patients.[21] However, the use of thrombus aspiration may cause stroke due to device complications, which is why in our study we excluded the patients (n=6) submitted to thrombus aspiration catheter during the index procedure, so it would not influence the stroke endpoint. The routine use of platelet inhibitors (Gp-IIb/IIIa inh., abciximab, tirofiban), nicorandil, nitroprusside, and adenosine have shown beneficial effects on myocardial perfusion in NSTEMI.[22] In addition, Aksu et al. found that intracoronary epinephrine use had a beneficial effect on CNP.[23] Moreover, Skelding et al.[24] have found that increasing blood pressure in the coronary circulation and tachycardia may be other potential beneficial effects of epinephrine.[24] In our study, consistent with the literature, we have found that a lower HR was independently associated with CNP in NSTEMI patients. If microcirculation is slow, CNP occurs, and we suggest that lower HR could be a CNP indicator in NSTEMI patients. Operators must be aware of the patient's HR, and a patient with lower HR should be considered as a CNP candidate, before starting the PCI. In spite of the encouraging results of our study, the lower HR findings should be explained by large and randomized trials.

Limitations

First, although a multivariate model was used to adjust confounding variables, a bias was inevitable, since this was a single-center analysis with a fairly small sample size. Multicenter trials with more patients might show better results and yield more data. Second, only angiographic parameters were used to determine CNP and CSFP; microcirculation was not directly evaluated; on the other hand, neither the echocardiography nor the patients were evaluated with magnetic resonance imaging (MRI) to confirm appropriate microvascular reperfusion. MRI is the best method for the evaluation of microvascular obstruction. Third, in order to assess long-term clinical results, a follow-up period of one year may not be adequate. These factors limit our study.

Conclusion

The two determinants of CNP in NSTEMI patients were increased BMI and lower HR. In our study, the results of the one-year clinical follow-up showed that the incidence of stroke and MACE were significantly higher in the CNP group. This study showed that CNP worsened NSTEMI patients' outcomes.

Author Contributions

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

Potential Conflict of Interest

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

Sources of Funding

There were no external funding sources for this study.

Study Association

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

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In Search of the Perfect Coronary Perfusion

Carlos Eduardo Lucena Montenegro[1]

Universidade de Pernambuco,[1] *Recife, PE – Brasil*

Since medical school, we always heard that "time is muscle" and that the faster we reperfuse a culprit artery in acute coronary syndrome (ACS), the better for the patient. Over time, evidence-based cardiology has taught us that not every patent artery is the same. The fact that we have an artery with a "TIMI 3" flow seemed enough to define the patient's prognosis, but after the concept of microvascular ischemia, we also started to care about small-vessel perfusion.[1,2]

Based on this concern, came the concept of 'no reflow', which means that even after the recanalization of a culprit artery, the tissue flow related to that myocardial territory might not be reestablished.[3] Going back in time, the phenomenon of slow flow[4] has been described since 1972, defined as delayed coronary opacification in the absence of epicardial obstructive coronary disease, while maintaining myocardial perfusion. Slow flow seems to be more common in patients with metabolic syndrome, in the male gender and smokers.[5] Both the phenomenon of no reflow and slow flow are associated with significant cardiovascular outcomes, the first being related to ventricular dysfunction and cardiac remodeling[3,6] and the latter, to cases of ventricular arrhythmias or sudden death,[7,8] in addition to refractory angina.[9]

In the study by Dr. Huyut, published in this issue of the Brazilian Archives of Cardiology,[10] we have a new approach on this topic, with the author trying to make a comparison between the 2 phenomena and their clinical implications, in the context of an ACS without ST-segment elevation. Both from the point of view of the "clash" between these two clinical entities, and because they are being approached after an acute coronary event, we are facing a rare dissertation, perhaps even unprecedented in the literature. In this study, a body mass index >28.3 kg/m^2 and a heart rate below 66.5 bpm were predictors of no reflow, and patients with this phenomenon had a higher incidence of stroke and major adverse cardiovascular events (MACE) at the end of 1 year.[10]

Some limitations should be considered, such as the discrepancy between the analyzed groups (221 patients with slow flow *vs*. 25 with no reflow) and the fact that nuclear magnetic resonance was not used to assess microvascular ischemia, which would be the gold standard for that purpose. However, these limitations should not overshadow the analysis of this work, which, on the other hand, provides us with a significant time of follow-up (1 year) and with important clinical outcomes.[10]

We are talking about a topic that still raises many doubts. For instance, how to prevent no reflow in these patients? Drugs such as glycoprotein IIb/IIIa inhibitors may be recommended in patients with elevated door-to-balloon time in a context of ACS with ST-segment elevation, but does this apply to ACS without ST-segment elevation? Embolism prevention devices in patients with lesions involving venous grafts have also been recommended,[11] but it is still very complicated to assess which patients can benefit from any slow flow or no reflow prevention strategy, especially in an acute context. And is there a preventive approach that is really effective for these phenomena, with clinically relevant outcomes? These questions remain unanswered.

In a recent edition of the Brazilian Archives of Cardiology, the same author published about the relationship between a biochemical marker (kidney injury molecule-1 - KIM-1) and found out that its serum levels and, there you are, a lower heart rate, were associated with no reflow in patients with ACS with ST-segment elevation.[12] But we are talking about a marker not yet available in clinical practice. What do we have in clinical practice to identify patients who will develop no reflow/slow flow? The heart rate just does not seem to be enough.

Another study also published in ABC in 2020, showed that patients with slow coronary flow (not related to ACS) may have the presence of delayed enhancement on cardiac magnetic resonance imaging and that in these patients, NT-proBNP seems to be higher than in the group control,[13] which, in agreement with the work presented here, shows that this phenomenon has nothing harmless.

We are still treading uncharted territory regarding patients who develop or have some type of microvascular dysfunction, whether spontaneous or induced by percutaneous procedure, but Dr. Huyut's work sheds some light on this dark path, while encouraging us to continue in our search of the perfect coronary perfusion.

Keywords

Metabolic Syndrome; Acute Coronary Syndrome; Myocardial Infarction; Myocardial Perfusion; Coronary Thrombosis; Heart Rate; Stroke; Kidney Injury Prognosis.

Mailing Address: Carlos Eduardo Lucena Montenegro •
Universidade de Pernambuco - Miocardiopatias/ Transplante cardíaco - Rua dos Palmares, S/N. Postal Code 50100-010, Recife, PE – Brazil
E-mail: ce_montenegro@yahoo.com.br

DOI: https://doi.org/10.36660/abc.20210228

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Original Article

Revascularization Strategies in Patients with Acute Myocardial Infarction and Cardiogenic Shock: Results from the Portuguese Registry on Acute Coronary Syndromes

Sofia Alegria,[1] Ana Marques,[1] Ana Catarina Gomes,[1] Ana Rita F. Pereira,[1] Daniel Sebaiti,[1] Gonçalo Morgado,[1] Rita Calé,[1] Cristina Martins,[1] Adriana Belo,[2] Inês Rangel,[1] Hélder Pereira[1]

Hospital Garcia de Orta EPE,[1] Almada - Portugal

Centro Nacional Coleção de Dados em Cardiologia,[2] Coimbra - Portugal

On behalf of researchers from the National Registry of Acute Coronary Syndromes

Abstract

Background: **In patients with acute myocardial infarction (MI), cardiogenic shock (CS), and multivessel disease (MVD) questions remain unanswered when it comes to intervention on non-culprit arteries.**

Objective: **This article aims to 1) characterize patients with MI, CS and MVD included in the Portuguese Registry on Acute Coronary Syndromes (ProACS); 2) compare different revascularization strategies in the sample; 3) identify predictors of in-hospital mortality among these patients.**

Methods: **Observational retrospective study of patients with MI, CS and MVD included in the ProACS between 2010 and 2018. Two revascularization strategies were compared: complete during the index procedure (group 1); and complete or incomplete during the index hospitalization (groups 2-3). The primary endpoint was a composite of in-hospital death or MI. Statistical significance was defined by a p-value <0.05.**

Results: **We identified 127 patients with MI, CS, and MVD (18.1% in group 1, and 81.9% in groups 2-3), with a mean age of 7012 years, and 92.9% of the sample being diagnosed with ST-segment elevation MI (STEMI). The primary endpoint occurred in 47.8% of the patients in group 1 and 37.5% in group 2-3 (p = 0.359). The rates of in-hospital death, recurrent MI, stroke, and major bleeding were also similar. The predictors of in-hospital death in this sample were the presence of left ventricle systolic dysfunction on admission (OR 16.8), right bundle branch block (OR 7.6), and anemia (OR 5.2) (p ≤ 0.02 for both).**

Conclusions: **Among patients with MI, CS, and MVD included in the ProACS, there was no significant difference between complete and incomplete revascularization during the index hospitalization regarding the occurrence of in-hospital death or MI. (Arq Bras Cardiol. 2021; 116(5):867-876)**

Keywords: **Myocardial Infarction; Shock, Cardiogenic; Myocardial Revascularization; Acute Coronary Syndrome; Ventricular Dysfunction ,Left; Mortality; Biomarkers; Intracranial Hemorrhage.**

Introduction

In patients with acute myocardial infarction (MI) and cardiogenic shock (CS), revascularization of the culprit artery is associated with improved prognosis.[1] Even so, a significant number of these patients evolve with multivessel disease (MVD),[2] which raises doubts regarding the indication and timing of the revascularization of non-culprit arteries.

The 2017 European Society of Cardiology (ESC) guidelines for the management of ST-segment elevation MI (STEMI) recommend immediate revascularization of non-culprit arteries in patients with CS (class IIa recommendation, level of evidence C).[3]

However, the results of the CULPRIT-SHOCK clinical trial, published in the same year, challenged this recommendation.[4] This trial included 706 patients with acute MI, CS and MVD randomly assigned to one of two initial revascularization strategies: percutaneous coronary intervention (PCI) of the culprit lesion only, with the option of staged revascularization of remaining lesions, or immediate multivessel PCI. The results showed that the primary endpoint—a composite of death or severe renal failure leading to renal-replacement therapy within 30 days after randomization—was significantly lower among patients submitted to PCI of the culprit lesion only.[4]

Considering these results, the most recent 2018 ESC guidelines on myocardial revascularization attributes a class III recommendation to routine revascularization of non-culprit lesions during primary PCI in patients with STEMI and CS.[5]

Mailing Address: Sofia Alegria •
Avenida Torrado da Silva 2805-267, Almada - Portugal
Email: asofia.alegria@gmail.com
Manuscript received October 25, 2019, revised manuscript March 11, 2020, accepted April 15, 2020

DOI: https://doi.org/10.36660/abc.20190739

In this regard, the aims of the current study were: 1) to characterize the sample of patients with acute MI, CS and MVD included in the Portuguese Registry on Acute Coronary Syndromes (ProACS); 2) to compare outcomes associated with different revascularization strategies; and 3) to identify predictors of in-hospital mortality.

Methods

Retrospective observational study of patients admitted with acute MI, presenting with CS (Killip-Kimball class IV) and MVD, included in the ProACS between October 2010 and January 2018.

Three revascularization strategies were compared: complete revascularization during the index procedure (group 1); complete staged revascularization during hospitalization (group 2); and incomplete revascularization during hospitalization (group 3).

The definition of a significant coronary lesion was based on angiographic criteria, that is, a lesion associated with stenosis of at least 50%. Complete revascularization was defined as revascularization of all significant lesions.

Definition of Acute MI

Acute MI was defined according to the definitions of variables in the ProACS.[6] Therefore, STEMI was described as the presence of persistent (lasting more than 30 minutes) ST-segment elevation above 1 mm (0.1 mV) in at least two contiguous leads or de novo left bundle branch block (LBBB), in a clinical setting suggestive of myocardial ischemia, while non-ST-segment elevation MI (NSTEMI) was defined by the absence of persistent ST-segment elevation associated with elevation of biomarkers of myocardial necrosis (troponin or CK-mb) in a clinical setting suggestive of myocardial ischemia.

Endpoints

The primary endpoint was a composite of in-hospital death or reinfarction. The endpoints were defined according to the definitions of variables in the ProACS.[6] Reinfarction was defined by the recurrence of chest pain suggestive of ischemia after resolution of the admission pain episode, lasting more than 20 minutes, with concomitant electrocardiographic changes and new elevation of biomarkers of myocardial necrosis in comparison with the previous level (elevation of CK-mb of at least twice the reference level or at least 50% more than the previous level; or elevation of I or T troponin of at least 20% more than the previous level).

Ischemic stroke was defined by the occurrence of de *novo* focal neurological deficits without evidence of hemorrhage in head computed tomography (CT) scan during hospitalization, as well as hemorrhagic stroke by the occurrence of de *novo* focal neurological deficits with concomitant hemorrhage in head CT scan. The definition of mechanical complication of MI includes left ventricular free-wall rupture (LVFWR), ventricular septal rupture and severe acute mitral regurgitation due to involvement of the papillary muscles.

Major bleeding during hospitalization was defined according to the criteria by the Global Strategies for Opening Occluded Coronary Arteries (GUSTO): intracranial bleeding or bleeding with hemodynamic compromise requiring intervention.[7]

Statistical Analysis

Continuous variables were expressed by mean and standard deviation or median and interquartile range, according to the analysis of normality in the distribution of data, assessed with the Kolmogorov-Smirnov test. These variables were compared using the unpaired t-Student test or the non-parametric Mann-Whitney test. Categorical variables were shown as percentages, and the association between groups was assessed by the Chi-square or the Fisher test, as appropriate. The multivariate logistic regression was used to identify independent predictors of in-hospital mortality, with adjustment for demographical variables, diagnosis, STEMI location, cardiovascular risk factors, previous diagnosis, heart rate, blood pressure, heart rhythm, QRS complex morphology, coronary arteries with significant lesions, left ventricle ejection fraction (LVEF), laboratory data, and previous and in-hospital medication.

Statistical analysis was performed aided by the SPSS software, version 19.0.0.2. A p-value below 0.05 was considered statistically significant.

Results

Patient Characterization

Among the 17.834 patients included in the ProACS between October 2010 and January 2018, 222 patients with acute MI and CS on admission, submitted to PCI, were identified (1.2%) (Figure 1). Of these, 57.2% (n=127) presented with MVD and were included in the analysis (18.1% in group 1, n=23; 3.1% in group 2, n=4; 78.7% in group 3, n=100).

The characterization is detailed in Tables 1-4. Patients' mean age was 70 ± 12 years and 68.5% of them (n=87) were males. About three-quarters of them (72.5%) had a history of arterial hypertension, 33.1% diabetes mellitus, 57.5% dyslipidemia, 23.0% smoking habits, 14.5% acute MI and 8.2% chronic kidney disease; 4.2% had a family history of premature coronary artery disease.

About one-third of patients (36.3%, n=45) was admitted to hospitals without on-site Interventional Cardiology and 28.6% (n=30) resorted to the emergency department by their own means. Most patients presented with STEMI (92.9%), 6.3% with NSTEMI and 0.8% with acute MI with LBBB or ventricular paced rhythm. The culprit artery was the left main artery (LM) in 17.2% of patients, the left anterior descending (LAD) in 25.9%, the left circumflex in 10.3%, and the right coronary artery (RCA) in 35.3%. The intra-aortic balloon pump (IABP) was used in 18.9% of patients (n=24) and none of them received a ventricular assist device (VAD), while 37.0% required invasive mechanical ventilation (n=47).

The primary endpoint occurred in 39.4% of patients (n=50), with in-hospital mortality rate of 37.8% (n=48).

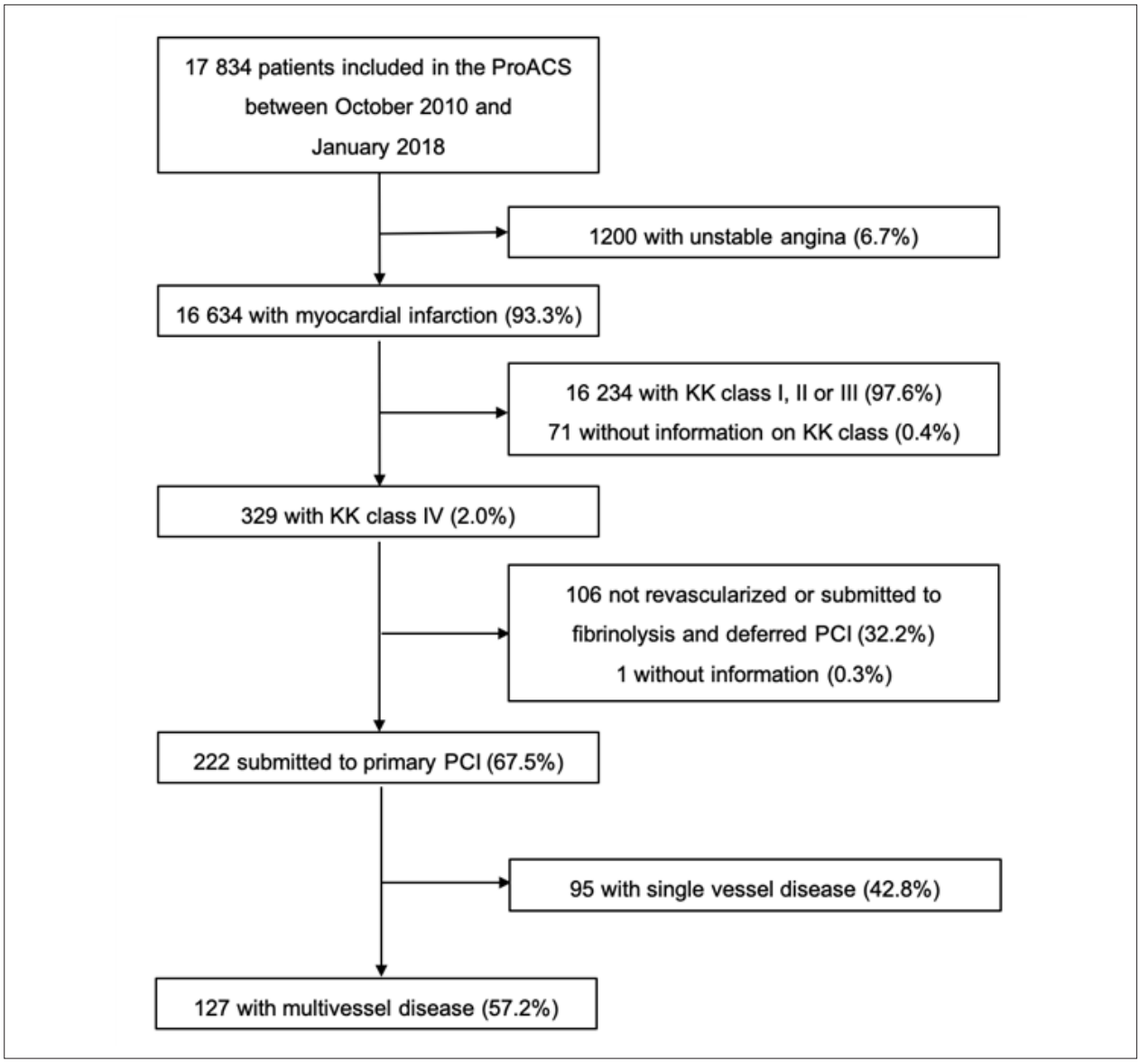

Figure 1 – *Flowchart of patient inclusion in the analysis. KK: Killip-Kimball; PCI: percutaneous coronary intervention; ProACS: Portuguese Registry on Acute Coronary Syndromes.*

Comparison between Revascularization Strategies

Considering the small number of patients in group 2, the comparison between revascularization strategies was performed between group 1 and groups 2-3 as one (complete revascularization in the index procedure versus complete staged or incomplete revascularization during hospitalization), with 18.1% of patients in group 1 (n=23) and 81.9% in groups 2-3 (n=104). Most patients in groups 2-3 were revascularized by PCI, and only three patients (2.9%) were accepted for surgical revascularization of non-culprit arteries.

Patients in group 1 were younger (63±10 vs. 72±12 years, p<0.001) and had a higher prevalence of smoking habit (45.5 vs. 18.0%, p=0.006); on admission, they were more likely to be in sinus rhythm (95.7 vs. 76.0%, p=0.043), have a higher hemoglobin level (14.2±8.0 vs. 13.1±1.9 g/dl, p=0.033) and lower brain natriuretic peptide (BNP) levels (median 88, interquartile range (IQR) 34-535 vs. 455.5, IQR 176.5-1234.5 pg/ml, p=0.040) (Tables 1 and 2). There were no significant differences in peak serum creatinine (Cr) level during hospitalization between the two groups. Anterior MI was more common in group 1 (72.7 vs. 45.8%, p=0.023) and inferior MI in groups 2-3 (13.6 vs. 52.1%, p=0.001) (Table 2). Regarding coronary anatomy, all patients in group 1 had two-vessel disease, so three-vessel disease was more common in groups 2-3 (0.0 vs. 48.9%, p<0.001). The LM artery was frequently identified as culprit artery in group 1 (40.0 vs. 12.5%, p=0.007), while the RCA was more common in groups 2-3 (5.0 vs. 41.7%, p=0.002) (Table 3).

Table 1 – Baseline characteristics

	Sample (n=127)	Group 1 (n=23)	Groups 2-3 (n=104)	p-value*
Age (years) – mean ± SD	70 ± 12	63 ± 10	72 ± 12	< 0.001
Male sex (%)	68.5	78.3	66.3	0.266
BMI (Kg/m2)	26.9 ± 4.2	28.2 ± 4.8	26.5 ± 4.0	0.081
Smoking habits (%)	23.0	45.5	18.0	0.006
Arterial hypertension (%)	72.5	66.7	73.7	0.510
Diabetes *mellitus* (%)	33.1	27.3	34.3	0.504
Dyslipidemia (%)	57.5	66.7	55.4	0.347
Family history of premature coronary artery disease (%)	4.2	10.5	2.6	0.174
Previous acute MI (%)	14.5	13.6	14.7	1.000
Previous PCI (%)	10.3	13.0	9.7	0.704
Previous CABG (%)	1.6	0.0	1.9	1.000
Previous TIA/stroke (%)	15.1	4.3	17.5	0.194
Peripheral artery disease (%)	5.7	4.3	6.0	1.000
Chronic kidney disease (%)	8.2	13.0	7.1	0.397

**Comparison between complete revascularization in the index procedure and complete staged or incomplete revascularization. BMI: body mass index; CABG: coronary artery bypass graft; MI: myocardial infarction; PCI: percutaneous coronary intervention; SD: standard deviation; TIA: transient ischemic attack.*

The primary endpoint occurred in 47.8% (n=11) of patients in group 1 and 37.5% (n=39) in groups 2-3 (p=0.359). The rates of in-hospital mortality, reinfarction, stroke, and GUSTO major bleeding did not differ significantly either between groups, although there was a higher incidence of Mobitz II second-degree or third-degree atrioventricular block in groups 2-3 (8.7 vs. 31.7%, p=0.025) (Table 4 and Figure 2).

Predictors of In-hospital Mortality

In multivariate logistic regression analysis, the independent predictors of in-hospital mortality were: presence of LV systolic dysfunction (ejection fraction below 40%) (OR 16.79; 95%CI 5.03-56.02; p=0.001), RBBB (OR 7.60; 95% CI 2.22-25.97; p=0.001), and hemoglobin below 12 g/dl on admission (OR 5.18; 95% CI 1.82-14.76; p=0.002) (Table 5).

Discussion

MVD is common in patients with acute MI and is related to a worse prognosis, including increased mortality.[8] This study included a sample of patients with MI, CS and MVD on admission, included in the ProACS, and shows that, contrary to previous recommendations, the most common practice in the index procedure was to perform PCI of the culprit lesion only.

Furthermore, we found no significant differences between complete revascularization in the index procedure compared with complete staged revascularization or incomplete revascularization during hospitalization, regarding the composite endpoint of in-hospital death or reinfarction, so this strategy seems safe in these patients.

In the comparison between groups, patients submitted to complete revascularization were found to be younger, more likely to be in sinus rhythm on admission, and presented higher levels of hemoglobin and lower levels of BNP. Being younger, they were less fragile and probably presented with a less severe condition, therefore, they were at lower risk for a complete revascularization, especially regarding the occurrence of contrast nephropathy.

In patients with acute MI and MVD, PCI of the culprit lesion is the standard care, but the management of the remaining lesions have been subject of controversy. The results of the most recent clinical trials, including the Preventive angioplasty in acute myocardial infarction (PRAMI),[9] the Complete versus lesion-only primary PCI trial (CvLPRIT),[10] the Third danish study of optimal acute treatment of patients with STEMI: primary PCI in patients with ST-elevation MI and MVD (DANAMI-3 PRIMULTI)[11] and the Compare-Acute trial (Comparison between FFR guided revascularization versus conventional strategy in acute STEMI patients with MVD),[12] suggest that complete revascularization may be beneficial in these patients, contributing, for instance, for the recovery of LV systolic function and the hemodynamic status.[3] Actually, the argument for complete revascularization is based on the potential to improve myocardial perfusion and the global function, even though performing it in the index procedure raises additional issues, such as inducing further ischemia, volume overload and worsening of kidney function associated with the use of more contrast.[8] It is important to note that in every trial the primary endpoint was lower in the group of complete revascularization, mostly due to a reduction in the

Table 2 – Patients' characteristics on admission/hospitalization

	Sample (n=127)	Group 1 (n=23)	Groups 2-3 (n=104)	p-value *
Transportation by ambulance with physician (%)	32.4	52.9	28.4	0.048
Transportation by ambulance without physician (%)	25.7	11.8	28.4	0.227
Transportation by own means (%)	28.6	17.6	30.7	0.384
Transportation by other means (%)	13.3	17.7	12.5	0.462
Admission to primary PCI center (%)	36.3	30.4	37.6	0.518
Symptom-to-door time (minutes) – median (IQR)	152 (82-270)	130 (90-223)	154 (79-271)	0.387
STEMI (%)	92.9	95.7	92.3	1.000
NSTEMI (%)	6.3	4.3	6.7	1.000
MI with LBBB or ventricular paced rhythm (%)	0.8	0.0	1.0	1.000
Anterior MI (%)	50.8	72.7	45.8	0.023
Inferior MI (%)	44.9	13.6	52.1	0.001
Heart rate (bpm) – mean ± SD	82 ± 33	93 ± 36	80 ± 32	0.162
Systolic BP (mmHg) – mean ± SD	93 ± 27	90 ± 27	94 ± 27	0.446
Atrial fibrillation (%)	10.2	4.3	11.5	0.460
Creatinine on admission (mg/dl) – median (IQR)	1.2 (0.9-1.7)	1.5 (0.8-2.0)	1.2 (1.0-1.7)	0.835
Maximum creatinine (mg/dl) – median (IQR)	1.6 (1.1-2.6)	1.6 (1.2-2.8)	1.6 (1.1-2.6)	0.731
Hemoglobin (g/dl) – mean ± SD	13.3 ± 1.9	14.2 ± 1.8	13.1 ± 1.9	0.033
BNP (pg/mL) – median (IQR)	388 (100-779)	88 (34-535)	456 (177-1235)	0.040
LVEF <40% (%)	61.0	77.8	57.3	0.107

** Comparison between complete revascularization in the index procedure and complete staged or incomplete revascularization. BNP: brain natriuretic peptide; BP: blood pressure; bpm: beats per minute; IQR: interquartile range; LBBB: left bundle branch block; LVEF: left ventricular ejection fraction; MI: myocardial infarction; NSTEMI: non-ST-segment elevation myocardial infarction; PCI: percutaneous coronary intervention; SD: standard deviation; STEMI: ST-segment elevation myocardial infarction.*

need for additional revascularization and non-fatal MI, but without significant reduction in mortality.

There is not sufficient evidence regarding the best timing of revascularization of non-culprit arteries (immediate vs. deferred), since the trials used different strategies: revascularization in the index procedure (PRAMI and Compare-Acute),[9,12] during hospitalization (DANAMI-3 PRIMULTI)[11] or at any time before hospital discharge (immediate or deferred) (CvLPRIT).[10]

In this setting, in 2017 the ESC guidelines on the management of STEMI updated the recommendations on the revascularization strategy in patients with MVD, attributing a class IIa recommendation, level of evidence A, for routine complete revascularization before hospital discharge.[3]

However, patients in CS were not included in these trials, but the Culprit-Shock trial (*Culprit lesion only PCI versus multivessel PCI in cardiogenic shock*)[4] showed that, in patients with acute MI and CS, routine treatment of non-culprit lesions during primary PCI was associated with an increase of the composite endpoint of death or severe renal failure leading to renal replacement therapy. Based on these results, the most recent ESC guidelines on myocardial revascularization, published in 2018, considered that revascularization of non-culprit arteries should not be performed during primary PCI, giving this strategy a class III recommendation.[5]

Considering the most recent evidence, it is important to assess real-world data. In the present study, patients submitted to complete revascularization in the index procedure presented higher rates of in-hospital mortality and of the composite endpoint of in-hospital death or reinfarction, although these differences did not reach statistical significance (43.5 vs. 36.5%, p=0.535; and 47.8 vs. 37.5%, p=0.359, respectively). The rates of reinfarction, stroke or major bleeding were similar between the two groups. In comparison, the Culprit-Shock trial showed superiority of culprit lesion-only PCI (with possibility of complete staged revascularization), translated in reduction of the composite endpoint of death or severe renal failure leading to renal replacement therapy within 30 days (43.3. vs. 51.6%; HR 0.84, 95% CI 0.72-0.98; p=0.03) and 30-day mortality.[4] There is no information on renal replacement therapy in the ProACS, so it was not possible to assess this event, although no differences were found in maximum creatinine level during hospitalization between the two groups.

Table 3 – In-hospital therapy and procedures

	Sample (n=127)	Group 1 (n=23)	Groups 2-3 (n=104)	p-value*
Aspirin (%)	96.1	91.3	97.1	0.222
Clopidogrel (%)	84.1	73.9	86.4	0.202
Ticagrelor (%)	16.8	23.5	15.4	0.476
GP IIb/IIIa inhibitors (%)	37.6	52.2	34.3	0.110
Unfractionated heparin (%)	66.7	65.2	67.0	0.870
Low-molecular-weight heparin (%)	45.7	34.8	48.1	0.247
Bivalirudin (%)	0.8	0.0	1.0	1.000
Beta-blocker (%)	36.5	43.5	35.0	0.334
ACEI (%)	46.5	34.8	49.0	0.215
ARB (%)	0.8	0.0	1.0	1.000
MRA (%)	21.3	30.4	19.2	0.263
Statin (%)	74.0	73.9	74.0	0.990
Femoral arterial access (%)	66.4	60.9	67.6	0.534
2-vessel coronary artery disease (%)	58.7	100.0	51.1	< 0.001
3-vessel coronary artery disease (%)	41.3	0.0	48.9	< 0.001
Culprit artery				
Left main (%)	17.2	40.0	12.5	0.007
Left anterior descending (%)	25.9	40.0	22.9	0.112
Left circumflex (%)	10.3	5.0	11.5	0.688
Right coronary artery (%)	35.3	5.0	41.7	0.002
Thrombectomy devices (%)	39.3	36.4	40.0	0.752
Swan-Ganz catheter (%)	4.7	8.7	3.8	0.297
Intra-aortic balloon pump (%)	18.9	21.7	18.3	0.769
IMV (%)	37.0	43.5	35.6	0.478
NIV (%)	18.9	26.1	17.3	0.379
Temporary pacemaker (%)	21.3	8.7	24.0	0.158

** Comparison between complete revascularization in the index procedure and complete staged or incomplete revascularization. ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blocker; GP IIb/IIIa: glycoprotein IIb/IIIa; IMV: invasive mechanical ventilation; MRA: mineralocorticoid receptor antagonist; NIV: non-invasive ventilation.*

Other questions still need to be clarified, namely regarding the identification of the non-culprit lesions that could benefit from revascularization (by angiography, functional assessment or intracoronary imaging) and the best timing for the performance of the staged procedure. Actually, in the main randomized clinical trials, the decision to perform PCI in non-culprit arteries was guided in different ways, specifically by angiography with a decision to treat lesions with a stenosis above 50% (PRAMI)[9] or 70% (CvLPRIT),[10] or by functional assessment with fractional flow reserve (FFR) (DANAMI-3 PRIMULTI and Compare-Acute).[11,12]

In the present study, the small number of patients with complete staged revascularization during hospitalization limited the comparison between strategies, as we were not able to evaluate the difference between complete revascularization in the index procedure and complete staged revascularization.

The Culprit-Shock trial compared complete revascularization during primary PCI with culprit artery-only revascularization, with possibility of staged revascularization of the remaining arteries. It is important to highlight, however, that staged revascularization during hospitalization was only performed in 18% of patients.[4] Similarly, several meta-analyses including both randomized and non-randomized studies in patients with STEMI with or without CS also showed similar or superior mortality rates with complete revascularization in a single

Table 4 – Adverse events during hospitalization

	Sample (n=127)	Group 1 (n=23)	Groups 2-3 (n=104)	p-value*
Reinfarction (%)	1.6	4.3	1.0	0.331
Mechanical complication (%)	4.7	0.0	5.8	0.591
AV block (%)	27.6	8.7	31.7	0.025
Sustained VT (%)	9.4	8.7	9.6	1.000
Cardiac arrest (%)	24.4	17.4	26.0	0.387
Stroke (%)	0.8	0.0	1.0	1.000
Major bleeding (%)	5.5	4.3	5.8	1.000
In-hospital death (%)	37.8	43.5	36.5	0.535
In-hospital death or reinfarction (%)	39.4	47.8	37.5	0.359

** Comparison between complete revascularization in the index procedure and complete staged or incomplete revascularization. AV: atrioventricular; VT: ventricular tachycardia.*

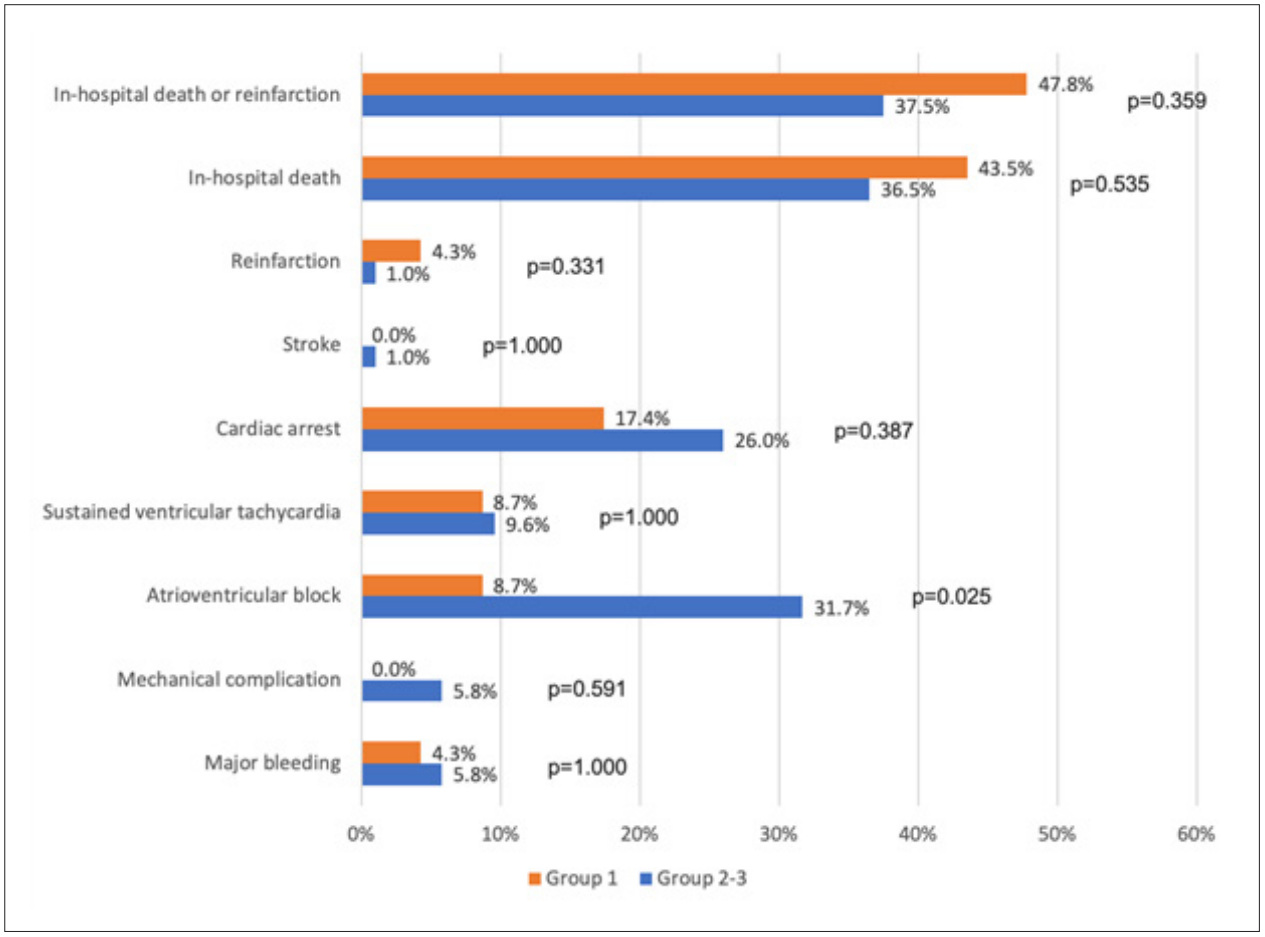

Figure 2 – *Comparison of adverse events between the two revascularization strategies.*

Table 5 – Independent predictors of in-hospital mortality in the overall sample on admission

Predictor	Beta	OR	95% CI	p-value
LVEF < 40%	2.821	16.79	5.03-56.02	0.001
RBBB	2.028	7.60	2.22-25.97	0.001
Hemoglobin < 12 g/dl	1.645	5.18	1.82-14.76	0.002

CI: confidence interval; LVEF: left ventricular ejection fraction; OR: odds ratio; RBBB: right bundle branch block.

procedure when compared to revascularization of the culprit artery only, but a reduction in short and long-term mortality with complete staged revascularization in comparison with the other strategies.[13-15]

The predictors of in-hospital mortality in this sample—apart from LV systolic dysfunction, which has already been extensively described[5,16,17]—were the presence of RBBB and anemia on admission, similarly to other published studies. The prevalence of RBBB in the setting of acute coronary syndrome is about 6 to 10% and it has been associated with increased in-hospital mortality, mostly in patients with STEMI and *de novo* RBBB. This association is probably justified by the irrigation of the right branch of the His bundle by branches of the LAD artery.[18-20] Given this, the most recent ESC guidelines on STEMI suggest that primary PCI should be considered in the presence of RBBB and persistent ischemia.[4] Considering that previous studies on anemia have shown its association with a worse prognosis in patients with acute MI, especially when CS is present, with a higher rate of major bleeding and short and long-term mortality.[21,22]

This is another issue that should make us reflect is the high percentage of patients (about one-third) that resorts to the hospital by their own means. This may have an impact in the time to revascularization and represent worse prognosis. These data reinforce the notion that it is critical to optimize the coronary care network (in Portugal, named as "coronary green pathway"), acting mostly in the time frame from symptoms to first medical contact in order to achieve a reduction in overall mortality, especially in these critical patients with such a high mortality rate. It is worth highlighting that, despite advances in revascularization therapy that have been associated with improved survival rate among these patients, there are still regional disparities and in-hospital mortality remains high (37.8%), which is in line with published data (27-51%).[23]

Limitations

The main limitations of this study are related to its design as an observational study, including selection bias in the strategies used and unquantified confounding factors that may correlate with outcomes. This may be particularly relevant for patients included in the incomplete revascularization group, since one cannot exclude that some of them died before a staged intervention, instead of the revascularization strategy being selected based on clinical criteria. Another important issue is the absence of a uniform criteria for the decision regarding revascularization of non-culprit arteries, namely a stenosis percentage in angiography or the need for intracoronary functional or imaging assessment, yet this reflects real life practice. Finally, this study compared a strategy of complete revascularization in the index procedure with staged complete or incomplete revascularization, but the number of patients in the group of complete staged revascularization was insufficient for an assessment of the best timing for revascularization of non-culprit arteries.

Conclusions

In this sample of patients with acute MI, CS on admission, and MVD included in the ProACS, there was no significant difference between complete revascularization in the index procedure and staged complete or incomplete revascularization during hospitalization when it comes to the composite endpoint of in-hospital death or reinfarction.

Ethics Approval and Consent to Participate

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

Author Contributions

Conception and design of the research: Alegria S, Calé R, Rangel I; Acquisition of data: Alegria S, Marques A, Gomes AC, Pereira ARF, Sebaiti D, Morgado G, Calé R, Martins C, Rangel I; Analysis and interpretation of the data: Alegria S; Statistical analysis: Belo A; Writing of the manuscript: Alegria S; Critical revision of the manuscript for intellectual contente: Alegria S, Martins C, Rangel I, Pereira H.

Potential Conflict of Interest

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

Sources of Funding

There were no external funding sources for this study.

Study Association

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

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Analysis of Revascularization Strategies in Patients with Acute Myocardial Infarction and Cardiogenic Shock - Results from the Portuguese Registry on Acute Coronary Syndromes

Gabriel Porto Soares[1,2,3]

Universidade Federal do Rio de Janeiro,[1] *Rio de Janeiro, RJ – Brazil*
Universidade de Vassouras,[2] *Vassouras, RJ – Brazil*
Centro Universitário de Valença,[3] *Valença, RJ – Brazil*

Short Editorial related to the article: Revascularization Strategies in Patients with Acute Myocardial Infarction and Cardiogenic Shock: Results from the Portuguese Registry on Acute Coronary Syndromes

The Portuguese Registry on Acute Coronary Syndromes was drafted in 2002 by the Portuguese Cardiology Society due to the need for a broader knowledge concerning the national approach to Acute Coronary Syndromes (ACS) and created the National Cardiology Data Collection Center (NCDCC) to centralize all of the information and support its analysis, culminating in the creation of its first records: The National Registry of Acute Coronary Syndromes (NRACS) was created simultaneously with the National Register of Interventional Cardiology. The NRACS is a prospective and continuous observational registry. All Portuguese hospital cardiology services and departments were invited to participate voluntarily in this study. The inclusion of patients began on January 1, 2002, and has been maintained to the present day without interruption. Briefly, each center received a request to consecutively include all patients hospitalized with a diagnosis of ACS (including acute ST-elevation myocardial infarction (STEMI), without unstable ST-elevation or angina), based on clinical evaluation, on the electrocardiogram, and on the biomarkers of myocardial necrosis. The collected data include demographic data, baseline characteristics, laboratory evolution, clinical evolution, executed therapy, data on percutaneous intervention, as well as data on hospital discharge and follow-up for six months (in the first stage of the registry) or for one year (in the second stage of the registry). Initially, the data were collected on paper and then transferred to an electronic data base, but since 2004, they are being submitted directly in electronic form. Upon consulting the NRACS e-mail address in February 2021, 62,029 records were found.[1,2]

One question arises in the ACS revascularization approach, which evolves with cardiogenic shock: Treat only the culprit blood vessel or treat all of the significant coronary lesions? The study of revascularization strategies in patients with acute myocardial infarction in cardiogenic shock stemming from the results of the Portuguese Registry of Acute Coronary Syndromes sheds light on the issue and aids professionals in decision-making.[3] Currently, the recommendations from the Brazilian Society of Hemodynamics and Interventional Cardiology are as follows: "The invasive strategy seeking to achieve the myocardial revascularization of the culprit blood vessel and, potentially, of the non-culprit blood vessels with significant coronary disease, is recommended in the cases of acute STEMI (IAMCSST) evolving with heart failure and cardiogenic shock, regardless of the time elapsed since its onset."[4]

One Brazilian multicenter study demonstrated that the complete revascularization strategy was associated with a significant reduction in the primary (cardiovascular death, re-infarction, and recurring angina) and secondary (stroke, non-fatal cardiorespiratory failure, greater bleeding, or the need for reintervention) outcomes in the one-year follow-up when compared to the incomplete revascularization strategy.[5]

The study based on the Portuguese NRACS involves patients with knowingly poor prognostic markers, as they are anatomically multiarterial[6] and hemodynamically in cardiogenic shock,[7] which justified the high mortality in the study. The results showed no difference between complete revascularization in the procedure index as compared to a group consisting of differed complete or incomplete revascularization in relation to the primary outcome of intra-hospital death or re-infarction.[3] It is important to note that the follow-up time was shorter when compared to similar studies[8-10] to evaluate the revascularization strategy in ACS, bearing in mind only the hospitalization during the main event. The results of similar studies demonstrate that complete revascularization is superior, but it did not involve only patients in cardiogenic shock.[5,8-10]

One major advantage illustrated in this study3 is the availability of a continuous, long-standing, national Registry, with a broad coverage and multiple variables that make it possible to conduct different studies; the temporary follow-up of events, recommendations, or interventions; and the tendency in the numbers and outcomes of ACS throughout Portugal. Brazil lacks a similar registry. It is not impossible to create, but, as a continental country with two different health systems, it is, to say the least, quite difficult.

Keywords

Myocardial Infarction; Myocardial Revascularization; Shock,Cardiogenic; Acute Coronary Syndrome.

Mailing Address: Gabriel Porto Soares •
Universidade Federal do Rio de Janeiro Instituto do Coração Edson Abdala Saad – Av. Brigadeiro Trompowski, s/n. Postal Code 21941-913, Rio de Janeiro, RJ – Brazil
E-mail: gp.soares@yahoo.com.br

DOI: https://doi.org/10.36660/abc.20210127

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Original Article

The Direct Effect of Body Mass Index on Cardiovascular Outcomes among Participants Without Central Obesity by Targeted Maximum Likelihood Estimation

Hossein Mozafar Saadati,[1] Siamak Sabour,[1] Mohammad Ali Mansournia,[2] Yadollah Mehrabi,[1] Seyed Saeed Hashemi Nazari[3]

Department of Epidemiology, School of Public Health and safety, Shahid Beheshti University of Medical Sciences,[1] Tehran - Iran
Department of Epidemiology and Biostatistics, School of Public Health, Tehran University of Medical Sciences,[2] Tehran - Iran
Prevention of Cardiovascular Disease Research Center, School of Public Health and Safety, Shahid Beheshti University of Medical Sciences,[3] Tehran - Iran

Abstract

Background: **Body mass index (BMI) is the most commonly used index to categorize a person as obese or non-obese, which is subject to important limitations.**

Objective: **To evaluate the direct effect of BMI on cardiovascular outcomes among participants without central obesity.**

Methods: **This analysis included 14,983 males and females aged 45-75 years from the Atherosclerosis Risk in Communities Study (ARIC). BMI was measured as general obesity, and waist circumference (WC), waist-to-hip ratio (WHR) and hip circumference as central obesity. Targeted maximum likelihood estimation (TMLE) was used to estimate the total effects (TEs) and the controlled direct effects (CDEs). The proportion of TE that would be eliminated if all participants were non-obese regarding central obesity was computed using the proportion eliminated (PE) index. P <0.05 was considered statistically significant. Analyses were performed in the TMLE R package.**

Results: **The risk of cardiovascular outcomes attributed to BMI was significantly reversed by eliminating WHR obesity (p<0.001). The proportion eliminated of BMI effects was more tangible for non-obese participants regarding WC (PE=127%; 95%CI (126,128)) and WHR (PE=97%; 95%CI (96,98)) for coronary heart disease (CHD), and WHR (PE=92%; 95%CI (91,94)) for stroke, respectively. With respect to sex, the proportion eliminated of BMI effects was more tangible for non-obese participants regarding WHR (PE=428%; 95%CI (408,439)) for CHD in males, and WC (PE=99%; 95%CI (89,111)) for stroke in females, respectively.**

Conclusion: **These results indicate different potential effects of eliminating central obesity on the association between BMI and cardiovascular outcomes for males and females. (Arq Bras Cardiol. 2021; 116(5):879-886)**

Keywords: **Body mass index; central obesity; cardiovascular; controlled direct effect; proportion eliminated.**

Introduction

Obesity, as a predictor of cardiovascular disease, has several definitions and criteria. Body mass index (BMI) is the most commonly used index to categorize a person as obese or non-obese.[1] However, this index is subject to important limitations,[1,2] as it gives no information regarding fat distribution, and also cannot discriminate between different body masses (muscles, bones and fat). These limitations may lead to a misclassification of obesity levels.[3,4] On the other hand, central obesity indices, such as waist circumference (WC) and waist-to-hip ratio (WHR), as simple and alternative measures of obesity, directly measure the central fat mass that gives important information on health outcomes.[5] In a cohort study, it was found that WC may not always be aligned with BMI and it was proposed that a combination of BMI and WC could provide a better estimate of obesity-related diseases.[6] In addition, BMI is a general obesity index and provides contradictory evidence among adults and people aged 65 years and older. This phenomenon is known as "the obesity paradox".[7,8]

In order to reveal a causal relationship, we need to maximally control the potential confounders and causal assumptions. In this regard, two causal methods—inverse probability weighting (IPW) and G-formula—have been introduced. They are based on exposure and outcome models, respectively. Regarding this issue, if the fitted model

Mailing Address: Seyed Saeed Hashemi Nazari •
Associate Professor, Prevention of Cardiovascular Disease Research Center, School of Public Health and Safety, Shahid Beheshti University of Medical Sciences, Tehran - Iran
E-mail: saeedh_1999@yahoo.com
Manuscript received March 23, 2020, revised manuscript August 03, 2020, accepted September 09, 2020

DOI: https://doi.org/10.36660/abc.20200231

is misspecified, the results would then be biased. Double-robust methods have the advantage of simultaneously using both exposure and outcome models, and, if only one of them is misspecified, the result is still valid.[9,10] Considering the limitations of BMI and the constraints of observational studies, we used the targeted maximum likelihood estimation (TMLE) as a double-robust estimator to reduce the bias of the target parameters if either exposure or outcome mechanisms are estimated consistently,[10] aiming to estimate the total effects (TEs) and the controlled direct effects (CDEs) of BMI. Therefore, this study aimed to determine the TEs and CDEs of BMI on cardiovascular outcomes to demonstrate how important the total effect of BMI on cardiovascular outcomes is and how much of this effect would be eliminated if all participants were non-obese with regard to central obesity (CDE).

Method

Participants

The Atherosclerosis Risk in Communities (ARIC) study is a prospective cohort study which began in 1987 in four counties in the USA (Washington County, Maryland; Jackson, Mississippi; Forsyth County, North Carolina; and the suburbs of Minneapolis, Minnesota). Investigators recruited 15,792 participants aged 45-64 years. More details are described elsewhere.[11] We analyzed all data of visit one (1987-1989) and outcome occurrence until 2014. For the present study, participants with missing information or history of any previous cardiovascular disease were excluded. The institutional review boards in each site approved the ARIC study protocol and an informed consent form was obtained from all participants in each study visit.

Measurements

Exposure: Obesity with Body Mass Index Definition

In this study, the main exposure of interest is obesity with BMI definition. BMI was calculated as weight in kilograms divided by the square of height in meters. General obesity was defined as BMI $\geq$30 kg/m^2.

Mediators: Central Obesity Indices Defined by Waist Circumference, Waist-To-Hip Ratio and Hip Circumference

For evaluating the controlled direct effect of BMI mediated by central obesity (central fat mass), we considered three definitions for central obesity, including WC, WHR and hip circumference. WC was categorized at the cut-off point of $\geq$102 cm in men and at the cut-off point of $\geq$88 cm in women. The WHR cut-off value was set at $\geq$0.9 in men and $\geq$0.85 in women, according to the World Health Organization (WHO).[12] Since there is no universal agreement regarding the hip circumference cut-off value, it was evaluated based on the best threshold value in a receiver operating characteristic (ROC) curve.

Coronary Heart Disease, Heart Failure, Stroke and All-Cause Mortality as Outcomes

The outcomes of this study included coronary heart disease (CHD) and heart failure (HF) events registered by 31 December 2014. According to the ARIC study criteria, CHD outcomes are defined as definite or probable myocardial infarction or fatal CHD. The HF outcomes are defined based on ICD-9 and ICD-10 criteria. Incident HF was defined as hospitalization that included code for HF beginning with "428" (i.e., 428.0 to 428.9) in any position, or a death certificate ICD-9 code beginning with "428" or ICD-10 code "I50" (HF or I50.0 to I50.9) in any position. Stroke events were identified by annual follow-up, hospital ICD-9 codes 430 to 436 (listed as a discharge diagnostic code at any position), or in death certificates. Cause-specific mortality was classified based on death certificates: cardiovascular mortality (ICD-9 codes 390–459, ICD-10 codes I00–I99), cancer mortality (ICD-9 codes 140–239, ICD-10 codes C00–D49), and all other causes of death.

Covariates and Confounders

Covariate data were derived as confounders in exposure-outcome, exposure-mediator and mediator-outcome association. Age, gender (male and female), race (black and white), education level (basic, intermediate, advanced), center (Washington County, Forsyth County, the city of Jackson, selected northwestern suburbs of Minneapolis), cigarette smoking status (defined as current, former and never smoker), drinking status (defined as current, former and never drinking alcoholic beverages), and total physical activity score (in three dimensions: at work, during leisure time and sports) were based on self-reported questionnaires. Other covariates included total calorie intake (kcal), hypertension (systolic blood pressure $\geq$140 or diastolic blood pressure $\geq$90 mmHg, or use of any medication for high blood pressure), diabetes mellitus (blood glucose $\geq$200 and fasting blood glucose $\geq$126 mg/dl, or taking any medication for diabetes), plasma lipids (mg/dl) and history of stroke at the baseline. The plasma lipids included cholesterol, high-density lipoprotein cholesterol, and triglycerides. The biologic covariates were excluded from TE analyses and were included as potential confounders of the mediator-outcome association in CDE analyses.

Statistical Analysis

Descriptive statistics were used to describe the participants (mean $\pm$ standard deviation (SD) for continuous variables, and number and percentage for categorical variables). An independent t-test analysis was used to examine the statistical differences in continuous covariates between two levels of exposure of interest (BMI). In addition, the $\chi 2$ test was used to examine the associations of categorical variables with exposure. The normality of data was evaluated by the normal curve (skewness and standard deviation of skewness) and the Kolmogorov-Smirnov test. To calculate the controlled direct effect of BMI on the outcomes (CHD, HF, stroke and all-cause mortality) mediated through central obesity, the TMLE model was used. TMLE, as a double-robust estimator, uses both outcome and exposure models. The implementation of

TMLE has the following steps: in the first step, we generated estimators for outcome model on exposure and all listed confounders. Then, we generated estimators for treatment model (both exposure and missing outcome) on all listed confounders. In the third step, we calculated the clever covariate, H, based on treatment model (both exposure and missing outcome) for both exposed "H = 1/PS" (PS as propensity score, the probability of exposure) and unexposed "H = -1/(1 - PS)" groups.[10,13]

The missing mechanism is defined as the occurrence of a competing event (total mortality of all other causes, stroke, CHD and HF, for each interested outcome) or loss to follow-up before occurrence of the outcome of interest, where "missing = 1" indicates the outcome is observed, and "missing = 0" indicates the outcome is missing. We used a dichotomous definition of exposure (BMI); values above the defined cut-off point were classified as "obese" and those below the cut-off as "non-obese". For the mediator variable, the three central obesity indices were used. In this way, we fixed the mediator values to zero (non-obese according to central obesity), according to the counterfactual causal model, and evaluated the controlled direct effect. TE, in the causal inference approach, is often defined as the difference between the outcome of interest of an individual or a group if exposed to a specific exposure, and the outcome of the same individual or group if unexposed. The CDE is often defined as the difference between the outcome of interest of an individual or a group if exposed to a specific exposure, and the outcome of the same individual or group if unexposed while fixing the value of the mediators. In our study, CDE of BMI was defined as the effect of BMI after controlling for WC, WHR and hip circumference indices.[14,15]

To control the confounders and possible interactions, we used a super learner machine-learning algorithm, which models different combinations of confounders and interactors in different models, and the final estimates are the weighted average of different model estimates.

We fitted the algorithms (generalized linear model, stepwise GLM, and interaction GLM) for each of the exposure and outcome models, inserting all listed covariates as predictors and BMI as binary exposure.

We then calculated the additive treatment effect (ATE) as risk difference for TEs and CDEs, and the corresponding confidence intervals. Influence-curve-based variance estimation was used to estimate the confidence intervals. Internal validation was performed in the super learner model as cross-validation. The proportion eliminated was calculated according to the following formula:[16]

$$PE\ (m) = \frac{TE - CDE\ (m)}{TE}$$

Where PE is proportion eliminated, TE is total effect, CDE is controlled direct effect and m is fixing the mediator level to zero (non-obese). Confidence intervals (95%) for PE were assessed using the bootstrap method. The value of $P < 0.05$ was considered statistically significant. The analysis was performed in the TMLE R package version 3.5.3.

Results

Participants' Characteristics

Out of the 14,983 participants at the baseline, we included 12,085, 12,085, 12,725 and 12,936 participants in this analysis after excluding all subjects with a history of any cardiovascular disorder and missing data at the baseline for CHD, HF, stroke and all-cause mortality, respectively. For all-cause mortality, we included all participants with a history of any cardiovascular disorder. During a median 27 years of follow-up, 1,616 (13.37%), 2,229 (18.44%), 1,078 (8.47%) and 5,364 (41.47%) participants experienced CHD, HF, stroke and all-cause mortality, respectively. Within this timeframe, 3,416 (22.8%) and 1,035 (6.91%) participants experienced administrative loss to follow-up and competing risk, respectively. Regarding the participants with obesity based on BMI, during a median 27 years of follow-up, 500 (16.43%), 848 (27.86%), 357 (10.67%) and 1,676 (49.08%) participants experienced CHD, HF, stroke and all-cause mortality, respectively. Baseline characteristics (mean and standard deviation for continuous variables, and number and percentage for categorical variables for participants with and without obesity based on body mass index) are provided in Table 1 and supplementary Tables 1-4. Obese participants by BMI definition were more likely to be females, black-skinned, to have lower educational level, lower annual family income, and were less likely to have health insurance compared to non-obese individuals. Regarding the mediator variables, obese participants were more likely to be obese based on WC, hip circumference and WHR indices, respectively.

Total Effects and Controlled Direct Effects

The TEs and CDEs of BMI, for all outcomes of interest as additive treatment effect (risk difference) with 95% confidence intervals, estimated by TMLE for all participants and sex groups, are demonstrated in Tables 2 and 3 and supplementary Figure 1. Regarding TEs, the results show a strong and significant association between BMI and all outcomes. The stronger results are estimated for HF, all-cause mortality, CHD and stroke, respectively. Regarding CDEs, large CDEs for HF and all-cause mortality, after controlling for all three central obesity indices separately (ATE between = 4.27 and 7.95), suggest that even if central obesities were eliminated, a large effect would remain for BMI. On the other hand, small controlled direct effects for CHD and stroke, after controlling for all three central obesity indices separately, especially for WC in CHD and hip circumference in stroke (ATE between = -2.81 and 3.06), suggest that if central obesities were eliminated, a large effect would be eliminated for BMI.

Regarding sex, the results show strong and significant association between BMI and all outcomes for both males and females. Large controlled direct effect for HF in males and females, except for WHR index in males for central obesity indices (ATE between = 4.94 and 15.06), suggests that even if central obesities were eliminated, a large effect would remain for BMI. On the other hand, small controlled direct effect for stroke in males and females, except for the hip circumference in females (ATE between = -6.27 and 1.14) and for CHD in

Table 1 – Baseline characteristics of participants in the ARIC Study by BMI, 1987-2014

Characteristics		Body mass index		p-value*
		Obese	Non-obese	
Categorical confounders		No. %		
Sex	female	2,484 (60.85)	5,686 (52.16)	<0.001
	male	1,598 (39.15)	5,215 (47.84)	
Race	white	2,514 (61.59)	8,613 (79.01)	<0.001
	black	1,568 (38.41)	2,288 (20.99)	
Education	Basic	1,237 (30.39)	2,300 (21.12)	<0.001
	Intermediate	1,633 (40.11)	4,494 (41.27)	
	Advanced	1,201 (29.50)	4,094 (37.60)	
Family Income (per year)	Less than $16,000	1,208 (31.71)	2,011 (19.48)	<0.001
	$16,000 –$50,000	1,948 (51.13)	5,437 (52.66)	
	More than $50,000	654 (17.17)	2,876 (27.86)	
Drinking	Current drinker	1,805 (44.61)	6,591 (60.64)	<0.001
	Former drinker	912 (22.54)	1,931 (17.77)	
	Never been a drinker	1,329 (32.85)	2,347 (21.59)	
Smoking	Current smoker	793 (19.44)	3,158 (28.99)	<0.001
	Former smoker	1,369 (33.56)	3,487 (32.01)	
	Never been a smoker	1,917 (47.00)	4,248 (39.00)	
Health insurance	No	562 (13.82)	901 (8.27)	<0.001
	Yes	3,506 (86.18)	9,991(91.73)	
Family history of CVD	No	1,719 (42.70)	4,556 (42.42)	0.76
	Yes	2,307 (57.30)	6,183 (57.58)	
Hypertension	No	2,229 (54.97)	8,258 (76.16)	<0.001
	Yes	1,826 (45.03)	2,585 (23.84)	
Antihypertensive medicine	No	2,208 (54.12)	8,156 (74.85)	<0.001
	Yes	1,872 (45.88)	2,740 (25.15)	
Diabetes mellitus	No	3,234 (80.31)	10,114 (93.38)	<0.001
	Yes	793 (19.69)	717 (6.62)	
Continual confounders		Mean (SD)		
Age, years		54.09 (5.70)	54.30 (5.78)	0.04
Physical activity (work)		2.18 (0.99)	2.17 (0.93)	0.67
Physical activity (sport)		2.27 (0.72)	2.49 (0.81)	<0.001
Physical activity (leisure time)		2.26 (0.57)	2.39 (0.57)	<0.001
Total energy intake (Kcal)		1632.4 (702.3)	1637.2 (703.1)	0.72
Saturated fatty acid (%Kcal)		12.23 (2.93)	11.93 (3.02)	<0.001
Total cholesterol mg/dl		5.62 (1.12)	5.54 (1.07)	<0.001
Triglycerides mg/dl		1.76 (1.28)	1.40 (0.89)	<0.001
HDL cholesterol mg/dl		1.20 (0.36)	1.37 (0.46)	<0.001
Mediators		No. %		
Waist circumference	Non-obese	108 (2.65)	6,893 (63.23)	<0.001
	Obese	3,974 (97.35)	4,008 (36.77)	
Waist-to-hip ratio	Non-obese	275 (6.74)	2,927 (26.85)	<0.001
	Obese	3,807 (93.26)	7,974 (73.15)	
Hip circumference	Non-obese	989 (24.23)	10,246 (93.99)	<0.001
	Obese	3,093 (75.77)	655 (6.01)	

P-value was based on the χ2 test and independent t-test for categorical and continues variables, respectively; ARIC: Atherosclerosis Risk in Communities Study; Mean and standard deviation of continuous variables in each group of body mass index; Number and percentage of categorical variables in each group of body mass index.

Table 2 – Estimated controlled direct effect of body mass index on CHD, HF, Stroke and all-cause mortality, by Central Obesity (non-obese), participants in the ARIC Study, 1987–2014 (complete case)

Outcomes	Mediator (Central Obesity index, non-obese)	Controlled direct effect	Proportion eliminated	Total effect (ATE) (95%CI)
		ATE (95% CI)	PE % (95% CI)	
CHD	WC	-2.81 (-5.01, -0.61)	127 (109, 135)	10.47 (7.76, 13.18)
	WHR	0.62 (-2.58, 3.82)	94 (79, 99)	
	Hip	3.06 (-1.20, 7.33)	71 (63, 75)	
HF	WC	6.41 (4.09, 8.72)	60 (55,75)	15.92 (13.45, 18.39)
	WHR	7.95 (4.54, 11.37)	50 (36,52)	
	Hip	7.23 (3.33,11.13)	54 (57,64)	
Stroke	WC	2.11 (-0.06, 4.29)	76 (74,101)	8.32 (6.01, 10.63)
	WHR	0.69 (-2.34, 3.73)	92 (81,106)	
	Hip	0.05 (-3.82,3.92)	99 (93,108)	
Mortality (all-cause)	WC	4.88 (2.56, 7.20)	56 (49,73)	11.05 (9.21, 12.88)
	WHR	4.27 (0.36, 8.17)	61 (52,69)	
	Hip	5.19 (2.01,8.36)	53 (50,59)	

ATE: additive treatment effect; PE: proportion eliminated; CHD: coronary heart disease; HF: heart failure; WC: waist circumference; WHR: waist-to-hip ratio; Hip: hip circumference.

Table 3 – Estimated controlled direct effect of BMI on CHD, HF, stroke and all-cause mortality, by Central Obesity (non-obese), in males and females in the ARIC Study, 1987–2014 (complete case)

Sex	Outcomes	Mediator (Central Obesity index)	Controlled direct effect	Proportion eliminated	Total effect (ATE) (95%CI)
			ATE (95% CI)	PE % (95% CI)	
Males	CHD	WC	-4.32 (-7.69, -0.96)	144 (124,161)	9.83 (5.74, 13.92)
		WHR	-32.28 (-36.07, -28.48)	428 (408,439)	
		Hip	2.86 (-2.54, 8.26)	71 (62,81)	
	HF	WC	4.94 (1.31, 8.56)	69 (57,79)	15.76 (12.04,19.49)
		WHR	-11.20 (-14.98, -7.42)	171 (158,186)	
		Hip	15.06 (10.32, 19.79)	4 (0.07,11)	
	Stroke	WC	1.14 (-1.63, 3.91)	86 (75,107)	8.10 (3.84, 12.37)
		WHR	-6.57 (-10.63, -2.50)	181 (174,201)	
		Hip	1.13 (-4.42, 6.69)	86 (76,95)	
	Mortality (all-cause)	WC	5.57 (1.38, 9.77)	49 (37,68)	10.89 (8.12, 13.65)
		WHR	-23.53 (-27.02, -20.04)	316 (301,329)	
		Hip	6.00 (1.54, 10.46)	45 (36,57)	
Females	CHD	WC	5.02 (3.11, 6.93)	57 (43,69)	11.78 (8.70, 14.86)
		WHR	1.13 (-2.67, 4.92)	90 (79,103)	
		Hip	4.68 (-0.25, 9.62)	60 (52,67)	
	HF	WC	11.57 (9.18, 13.96)	30 (15,39)	16.66 (13.79,19.53)
		WHR	9.36 (4.01, 14.70)	44 (31,52)	
		Hip	8.28 (3.66, 12.89)	50 (37,61)	
	Stroke	WC	0.06 (-1.92, 2.05)	99 (89,111)	7.70 (4.73, 10.68)
		WHR	0.23 (-4.09, 4.55)	97 (87,113)	
		Hip	4.04 (0.90, 7.19)	47 (34,63)	
	Mortality (all-cause)	WC	5.24 (2.91, 7.57)	53 (41,66)	11.24 (8.76,13.73)
		WHR	5.22 (-0.72, 11.16)	53 (42,64)	
		Hip	1.67 (-3.43, 6.77)	85 (77,98)	

ATE: additive treatment effect; PE: proportion eliminated; CHD: coronary heart disease; HF: heart failure; WC: waist circumference; WHR: waist-to-hip ratio; Hip: hip circumference.

males (ATE between = -32.28 to 2.86) for central obesity indices, suggests that if central obesities were eliminated, a large effect would be eliminated for BMI, and in some cases the effect of BMI would be reversed (protective).

Proportion Eliminated

The PE index for TEs of BMI, for all outcomes of interest with 95% confidence intervals for all participants and sex groups, is listed in Tables 2 and 3. The total association of BMI with CHD could be completely eliminated by eliminating the role of WC, in 127%. This effect could be reduced by 94% and 71% by eliminating the role of WHR and hip circumference, respectively. Regarding stroke, the effect of BMI could be eliminated by eliminating the role of hip circumference, in 99%. With respect to HF and all-cause mortality, the role of central obesity indices in eliminating the effect of BMI was somewhat similar and between 50% and 61%. With respect to sex, the total association of BMI with CHD, HF, stroke and all-cause mortality in males could be completely eliminated by eliminating the role of WHR, in 428%, 171%, 181% and 316%, respectively. On the other hand, in females, the total association of BMI with CHD, HF, stroke and all-cause mortality could not be completely eliminated by eliminating the role of any central obesity indices (between 30% for WC index for HF and 99% for WC index for stroke).

Discussion

In this large, community-based cohort study, the TEs and CDEs of BMI related to the risk of CHD, HF, stroke and all-cause mortality in participants without central obesity were evaluated using the TMLE method. It is worth mentioning that we considered two common limitations of BMI and conventional estimators, including limited capacity of BMI to distinguish between fat mass and fat-free mass, which result in misclassification, and model misspecification, which is a common source of bias in conventional estimators.

In brief, compared to TEs of BMI, the CDEs of BMI among participants without central obesity for all outcomes of interest were attenuated and close to null. Remarkably, these results are more highlighted for CHD and stroke. This finding highlights the capability of central obesity indices to predict the risk of cardiovascular disease and all-cause mortality. In addition, with regard to the three central obesity indices for all participants, the proportion eliminated of BMI effects did not have consistent results for all outcomes. The proportion eliminated of BMI effects was more tangible for WHR index in males, while results were not consistent for females. In general, for most of the outcomes, the results showed that, with reduction or elimination of central obesity based on WHR index, the effect of BMI was completely or mostly removed.

Furthermore, these findings highlighted the limitations of BMI in predicting cardiovascular risk as a whole or based on sex. This disagreement of BMI in relation to cardiovascular outcomes was considered as “the obesity paradox”. Several explanations for the obesity paradox related to the association of BMI with cardiovascular disease have been reported. One of the most important explanations refers to the misclassification of obesity levels based on BMI definition[4]. Considering that BMI is unable to discriminate between fat mass, muscle mass and body surface area, the effect of BMI refers to a combination of these three types of mass.[17] Therefore, a higher BMI is an indicator not only of greater amount of central and visceral fat, but also of higher muscle or peripheral mass (fat or bone).

In recent decades, many studies have evaluated the association of different fat distributions and cardiovascular disease, demonstrating that the distribution of body fat, especially excess central fat, independent from total body fat, is an important risk factor for these outcomes.[18-22] In this regard, previous studies have shown that excessive fat in males is commonly stored in visceral parts, while in females it is stored in peripheral subcutaneous parts.[23,24] The results of the present study confirm the previous findings and underline the importance of fat distribution for males and females separately.

Regarding the statistical method in use, previous methodological and original studies confirm the superiority of the TMLE method over other approaches regularly used in observational studies to measure causality. In this regard, the inverse probability weighting (IPW) method result in unstable estimates in the presence of extreme weights and violations of positivity assumption. On the other hand, compared to the TMLE method, the G-formula method is only performed based on the outcome model and, if misspecified, it brings biased estimations. TMLE is a double-robust estimator that remains consistent if either exposure or outcome mechanisms are estimated consistently.[9,10,25]

Previous papers confirm the usefulness of the controlled direct effect, especially in policy assessment.[26,27] However, the use of this concept needs assumptions other than TEs.[16,26] In controlled direct analysis, one must consider the assumption for the association between mediator and outcome as well as the association between exposure and outcome.[28] In addition, the interaction between exposure and mediators is an important issue in this analysis.[16,28] Regarding this issue, we cannot use the difference between TE and CDE to estimate the direct and indirect effects.

In summary, based on previous methodological studies, regarding the limitation of the controlled direct effect and the need for stronger assumptions, this cannot be used as a valid estimation of mediation; but if we have a non-zero controlled mediated effect, it can be suggestive of the presence of mediator effect.[28]

Before interpreting the results and concluding anything, the strengths and limitations of this study should be addressed. The strengths of this study include the application of a double-robust method that consistently estimates the parameter under a semiparametric model when one of two (exposure and outcome) models is correctly specified, regardless of which. In addition, we consider the missing mechanism to minimize the impact of a competing risk and loss to follow-up for better estimation of true effects. However, due to the problem of small sample size of the outcome of interest and sparse-data bias, we could not evaluate these estimations in age groups. In addition, this study is limited by the fact that we did not consider the variation of time-varying confounders.

Conclusion

In this study, the controlled direct effect of BMI decreased to almost null in participants without central obesity. These results highlight the importance of considering the distribution of fat masses when estimating the association between obesity and an outcome of interest, for males and females separately.

Acknowledgments

This study is related to project No. IR.SBMU.PHNS.REC.1396.152 from Shahid Beheshti University of Medical Sciences, Tehran, Iran. The institutional review boards from each site approved the ARIC Study protocol and an informed consent form was obtained from participants in all study's visits. The authors would like to thank the staff and participants of the ARIC Study for their important contributions. In order to access the data, we signed an RMDA (NHLBI Research Materials Distribution Agreement), which is available upon request.

Author contributions

Conception and design of the research, Analysis and interpretation of the data and Statistical analysis: Saadati HM, Sabour S, Mansournia MA, Mehrabi Y, Nazari SSH; Data acquisition and Writing of the manuscript: Saadati HM, Nazari SSH; Critical revision of the manuscript for intellectual content: Sabour S, Mansournia MA, Mehrabi Y, Nazari SSH.

Potential Conflict of Interest

The authors report no conflict of interest concerning the materials and methods used in this study or the findings specified in this paper.

Sources of Funding

There was no external funding source for this study.

Study Association

This article is part of the thesis of doctoral submitted by Hossein Mozafar Saadati, from Shahid Beheshti University of Medical Sciences.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the vicechancellor in research affair- Shahid Beheshti University of Medical Sciences under the protocol number IR.SBMU.RETECH.REC.1399.763. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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*Supplemental Materials

For additional information, please click here.

Obesity, Body Fat Content and Cardiovascular Outcome: Beyond Body Mass Index

Desiderio Favarato[1]

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

Short Editorial related to the article: The Direct Effect of Body Mass Index on Cardiovascular Outcomes among Participants Without Central Obesity by Targeted Maximum Likelihood Estimation

Obesity pandemic has been associated with an increment of cardiovascular disease (CVD). Diagnosis of CVD is delivered ten years early in obese people.

Although body mass index (BMI) has been widely used as the main index of obesity, it is not an accurate predictor of cardiovascular disease. There are other ways to measure obesity, varying from a simple waist circumference (WC) measurement to more sophisticated methods, like bioelectrical impedance and dual energy X-ray densitometry.

The main cause of BMI inaccuracy to determine body fat distribution is that it may be normal in subjects with central obesity determined by waist circumference or high in increased muscle mass.[1]

This has generated the obesity paradox – overweight and obese patients with cardiovascular disease present better prognosis than those with normal BMI values.[2]

The disagreement between the two measures of obesity, BMI, and WC has been described in Brazilian children and young adults.[3] Santos et al.[3] found that 5.8% of non-obese boys, according to BMI, presented WC over the cut-off value, while 10.6% of obese boys, according to BMI, were not classified as obese if the WC was used as a classification criterion.[3]

In adults, as showed in a Spanish cohort, in the ENRICA Study,[4] the prevalence of central obesity and abnormal WC was more frequent than obesity by BMI (36% vs. 22.9%); and in the elderly, in whom although the frequency of BMI obesity was similar between males and female, central obesity was about twice as high in women.[5]

When the exposure groups are dissimilar, as in observational studies, careful statistical adjustment for confounders is necessary to obtain unbiased estimates of exposure effect. A simple comparison between incidence rates may be misleading, so more sophisticated computational approaches have been implemented.

If two groups are similar, we usually calculate the average group influence, that is, the difference of frequency of outcome when some characteristics are present or not. However, if the two study populations are dissimilar, such as in observational and epidemiological studies, this comparison may give misleading results. Thus, on account of these different or confounding characteristics, more sophisticated computational machine learning approaches have been developed.

The confounding variables may be analyzed as a mediator variable, that is, although some variables share the same cause, they may influence the outcome differently. Thus, fat accumulation leads to central obesity (increased WC) and "general" obesity (higher BMI) with different frequencies. Some people may present central obesity but no elevated BMI. However, the opposite is unusual. This is a situation where complex computational approaches work well in revealing the effect of each one.

One of them is G-computation, which relies on the estimation of the outcome mechanism, the conditional expectation of the outcome given the exposure (grouping variable) and covariates. That is, an exposure variable with other confounding variables is likely to present an outcome. Another method is the propensity score that involves estimation of the exposure mechanism, that is, the conditional probability of being exposed given an observed confounder. The probability of association in a determined variable (exposure) when another (confounder) is present.

The idea underlying propensity score matching is that by giving each individual in the study a propensity score, we can compare individuals in different treatment groups and try to make the individuals as equivalent as possible so that we can control the confounding factors. The different result would be from the treatment only. However, the true propensity score is never really known, so there is always some level of uncertainty in observational studies.

Usually, the propensity score (PS) is used as its inverse value named inverse propensity weight. The weight for active or targeted groups is 1/PS and for control groups, 1/(1-PS).

Another method that involves both G-computation and propensity score is TMLE (Targeted Maximum Likelihood Estimation), which estimates both the conditional expectation of an outcome given the exposure and covariate variables (G-computation), and the conditional expectation of exposure being determined by a confounding variable.

In this issue, Saadati et al.[6] use TMLE to evaluate the total effects (TE) and the controlled direct effect of BMI obesity influence on cardiovascular events.

Again, a mismatch between central obesity measures to BMI obesity was found.

The final result is that central obesity measures are better predictors of cardiovascular disease from fat accumulation than high BMI, and are responsible for almost all cardiovascular disease risks.

Keywords

Obesity; Adipose Tissue; Body Mass Index; Cardiovascular Diseases; Risk Factors; Abdominal Circumference.

Mailing Address: Desiderio Favarato •
Av. Dr. Eneas Carvalho de Aguiar, 40 Incor, bloco II, 2º andar, sala 2. Postal Code 05403-000, São Paulo, SP – Brazil
E-mail: desiderio.favarato@gmail.com

DOI: https://doi.org/10.36660/abc.20210074

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Original Article

The Six-Minute Step Test as a Predictor of Functional Capacity according to Peak VO_2 in Cardiac Patients

Luiz Eduardo Fonteles Ritt,[1,2] Eduardo Sahade Darzé,[1,2] Gustavo Freitas Feitosa,[1] Jessica Santana Porto,[1] Gabriela Bastos,[1] Renata Braga Linhares de Albuquerque,[2] Cristiane Miura Feitosa,[1] Thaissa Costa Claro,[1] Eloisa Ferreira Prado,[1] Queila Borges de Oliveira,[1] Ricardo Stein[3,4]

Hospital Cárdio Pulmonar,[1] Salvador, BA - Brazil
Escola Bahiana de Medicina e Saúde Pública,[2] Salvador, BA - Brazil
Hospital de Clínicas de Porto Alegre,[3] Porto Alegre, RS - Brazil
Universidade Federal do Rio Grande do Sul,[4] Porto Alegre, RS - Brazil

Abstract

Background: **Six-minute step test (6MST) is a simple way to evaluate functional capacity, although it has not been well studied in patients with coronary artery disease (CAD) or heart failure (HF).**

Objective: **Analyze the association between the 6MST and peak oxygen uptake (VO_{2peak}) and develop an equation for estimating VO_{2peak} based on the 6MST, as well as to determine a cutoff point for the 6MST that predicts a VO_{2peak} ≥20 $mL.Kg^{-1}.min^{-1}$**

Methods: **In 171 patients who underwent the 6MST and a cardiopulmonary exercise test, correlation, regression, and ROC analysis were used and a $p < 0.05$ was admitted as significant.**

Results: **mean age was 60±14 years and 74% were male. Mean left ventricle ejection fraction was 57±16%, 74% had CAD and 28% had HF. Mean VO_{2peak} was 19±6 $mL.Kg^{-1}.min^{-1}$ and mean 6MST performance was 87±45 steps. Association between 6MST and VO_{2peak} was r 0.69 ($p < 0.001$). The model VO_{2peak} =19.6 + (0.075 x 6MST) – (0.10 x age) for men and VO_{2peak} =19.6 + (0.075 x 6MST) – (0.10 x age) – 2 for women could predict VO_{2peak} based on 6MST results (adjusted R 0.72; adjusted R^2 0.53). The most accurate cutoff point for 6MST to predict a VO_{2peak} ≥20 $mL.Kg^{-1}.min^{-1}$ was >105 steps (AUC 0.85; 95% CI 0.79 -0.90; $p < 0.001$).**

Conclusion: **An equation for predicting VO_{2peak} based on 6MST results was derived, and a significant association was found between 6MST and VO_{2peak}. The cutoff point for 6MST, which predicts a VO_{2peak} ≥20 $mL.Kg^{-1}.min^{-1}$, was >105 steps. (Arq Bras Cardiol. 2021; 116(5):889-895)**

Keywords: **Heart Failure; Oxygen Consumption; Respiratoty Capacity; Tidal Volume; Exercise Test.**

Introduction

In cardiovascular disease, functional capacity is directly related to prognosis.[1] Functional performance, as determined by peak oxygen consumption (VO_{2peak}) and measured with a cardiopulmonary exercise test (CPET), is the gold standard and is used to determine prognosis in heart failure (HF) and heart transplant selection, as well as to gauge therapeutic response.[2-4] Patients with a VO_{2peak} below 15 $mL.Kg^{-1}.min^{-1}$ have a worse prognosis profile, and those with a VO_{2peak} above 20 $mL.Kg^{-1}.min^{-1}$ have a better prognosis profile, independent of HF etiology and ventricular function.[5,6] Although widely used and validated, the CPET is not available in most centers, since the equipment is expensive and a specialized physician is required to administer the test and interpret its results.

Mailing Address: Luiz Eduardo Fonteles Ritt •
Centro de Estudos Clínicos - Hospital Cárdio Pulmonar - Avenida Anita Garibaldi, 2199. Postal Code 40170-130, Ondina, Salvador, BA – Brazil
E-mail: luizritt@hotmail.com, lefr@cardiol.br
Manuscript received September 11, 2019, revised manuscript March 16, 2020, accepted April 08, 2020

DOI: https://doi.org/10.36660/abc.20190624

One alternative to CPET is the six-minute walk test (6MWT), which is well validated and has a good correlation with CPET in cardiomyopathy patients.[7] However, the 6MWT requires a long corridor (at least 30 meters), which could limit its use in normal practice.

The six-minute step test (6MST) is a simple test in which the patient climbs and descends a 2-step ladder for 6 minutes in free cadence, and the number of steps the patient takes is counted. It requires neither sophisticated equipment nor large spaces. Although studied in patients with chronic lung disease and in normal subjects,[8-11] there are no data on 6MST performance in cardiac patients.

The objectives of this study were to: (1) analyze the association between 6MST and VO_{2peak}, (2) develop an equation for estimating VO_{2peak} based on 6MST results, and (3) determine a cutoff point for lower risk category in the 6MST (VO_{2peak} ≥ 20 $mL.Kg^{-1}.min^{-1}$).

Methods

In this cross-sectional study, we evaluated patients referred for cardiac rehabilitation between May 2014 and

September 2017 who, as per clinical protocol, underwent symptom-limited CPET and 6MST as their baseline evaluation in the cardiac rehabilitation program of the Hospital Cárdio Pulmonar, Salvador, Brazil.

The inclusion criteria were patients older than 18 years who had been diagnosed with coronary artery disease (CAD) or heart failure (HF), characterized by previous acute myocardial infarction, coronary angioplasty/stent placed post-operatively to cardiac or vascular surgery, or patients with implantable devices such as pacemakers or cardiac defibrillators. These individuals were referred to the cardiac rehabilitation program and underwent an initial evaluation with a cardiologist and a physical therapist. CAD and/or HF diagnosis was established by medical history (acute myocardial infarction, stable CAD, myocardial revascularization or angioplasty, or symptoms of dyspnea or angina), electrocardiographic abnormalities (pathological Q waves) and echocardiographic abnormalities (ventricular dysfunction and segmental abnormalities).

The exclusion criteria were inability to perform the CPET or the 6MST. Patients with symptoms of angina or ischemia at an stage lower than the anaerobic threshold were also excluded as they were not submitted to the 6MST.

Clinical and demographic data were retrieved from the initial cardiologist evaluation on the day of the CPET, including the most recent (within the last 3 months) echocardiogram. The CPET and 6MST were applied separately, 2 to 7 days apart.

The 6MST was performed on a 20 cm high step covered with non-slip rubber. Patients were instructed to go up and down the step as fast as possible for 6 minutes without using their arms to support themselves; rest breaks were permitted.

A symptom-limited CPET was performed on a treadmill with a gas analyzer (Cortex, Leipzig, Germany) with breath-by-breath measurements. An individualized ramp protocol based on the functional class of each patient was used, having a targeted exercise phase duration between 8 and 12 minutes. The collected ventilatory data were tabulated and analyzed at 10-second intervals.

Ethical aspects: the study protocol was approved by the Celso Figueiroa Research Ethics Committee of the Hospital Santa Izabel (case 1.711.505). The study was conducted in accordance with national and international legislation for human research, including the Helsinki guidelines and resolution 466/12 of the Brazilian National Health Council. Informed consent was exempted since the study utilized only medical record data.

Statistical Analysis

SPSS version 25.0 was used for all analyses. Continuous variables were presented as mean ± standard deviation (SD) for parametric distribution. The Shapiro-Wilk test and visual inspection of histograms were used to determine normality. Categorical variables were presented as proportion or percentage. The Pearson correlation was applied to determine associations between continuous variables and Bland-Altman plots to analyze their agreement. Univariate and multivariate linear regression analyses (after adequate assumptions were analyzed) were performed to determine the model's prediction of VO_{2peak} based on the 6MST, which was controlled for age, ejection fraction, sex, presence of CAD or HF, and weight. ROC curve analysis was applied to determine the best cutoff points for predicting a $VO_{2peak} \geq 20$ mL.Kg^{-1}.min^{-1}. A p-value <0.05 was considered significant for all analyses.

Results

The total sample consisted of 171 patients. Table 1 shows their general demographic and clinical characteristics. Most patients were in NYHA class I or II (54% and 24%, respectively) with a mean VO_{2peak} of 19±6 mL.kg^{-1}.min^{-1}.

Figure 1 shows the association between 6MST and VO_{2peak}; the r correlation index was 0.69 (95% CI 0.60 – 0.78; p < 0.001) and the R^2 was 0.47. Figure 2 shows the Bland-Altman plot analysis, and in only 5 patients the agreement was away from the upper or the lower reference limit.

In the multivariate analysis, age, sex and 6MST result were independent predictors of VO_{2peak} (Table 2). The equations for estimating VO_{2peak} based on 6MST were: VO_{2peak}=19.6 + (0.075 x 6MST) – (0.10 x age) for men, and VO_{2peak}=19.6 + (0.075 x 6MST) – (0.10 x age) – 2 for women. The final model's adjusted r was 0.72 and the adjusted R^2 was 0.53.

Figure 3 shows the ROC curve for the 6MST as a predictor of $VO_{2peak} \geq 20$ mL.kg^{-1}.min^{-1}. The most accurate cutoff point for 6MST prediction of $VO_{2peak} \geq 20$ mL.kg^{-1}.min^{-1} was >105 steps (AUC 0.85, 95% CI 0.79-0.90, p <0.001).

Table 1 – General demographic and clinical characteristics of the population

Variable	Result
Male % (n)	74% (121)
Age (years)	60±14
CAD % (n)	74% (121)
Heart failure %(n)	28% (47)
Cardiac valvular disease %(n)	13% (22)
Diabetes %(n)	25% (44)
Hypertension %(n)	62% (102)
NYHA I, II, III%	53%/24%/10%
ACE inhibitor-ARB %(n)	65% (110)
Beta-blocker %(n)	77% (130)
Statins %(n)	75% (128)
Ejection fraction (%)	57±16
VO_{2peak} (mL.kg^{-1}.min^{-1})	19±6
VO_2 at anaerobic threshold (mL.kg^{-1}.min^{-1})	12.6±3
RER	1.12±0.8
VE/VCO_2 slope	36±10
6MST (steps)	85±47

CAD: coronary artery disease; NYHA: New York Heart Association; ACE: angiotensin receptor enzyme; ARB: angiotensin receptor blocker; RER: respiratory exchange ratio.

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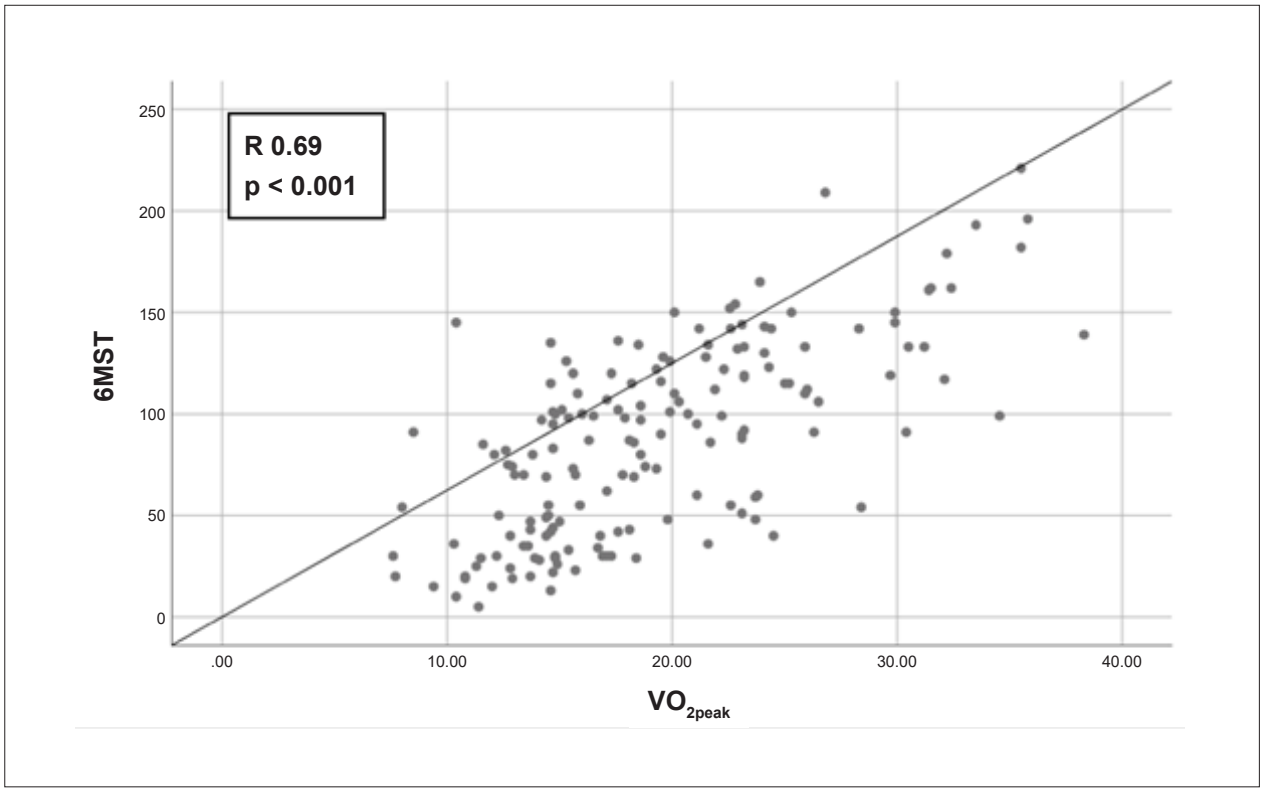

Figure 1 – *Association between 6MST and VO_{2peak}.*

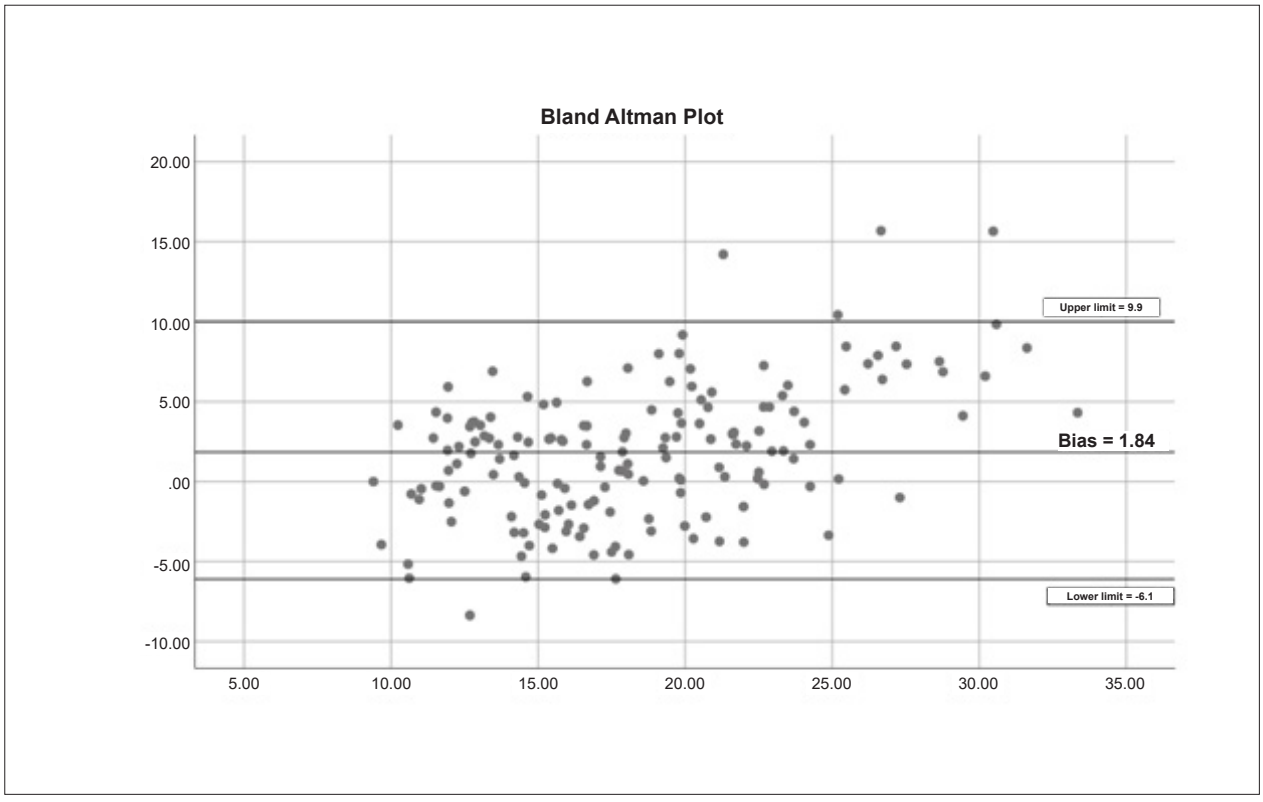

Figure 2 – *Bland-Altman plot for predicted versus determined VO_{2peak}.*

Table 2 – Final multiple linear regression model for predicting VO_{2peak} based on the 6MST

Variable	Beta	Beta 95% CI	p
6MST	0.075	(0.06) – (0.09)	<0.001
Age (years)	-0.10	(-0.16) – (- 0.5)	<0.001
Female	- 2.0	(- 3.6) – (- 0.33)	0.02
Constant	19.6	(15.2) – (24.1)	<0.001

Adjusted for age, ejection fraction, coronary artery disease, heart failure, and weight. 6MST: six-minute step test; OR: odds ratio; CI: confidence interval.

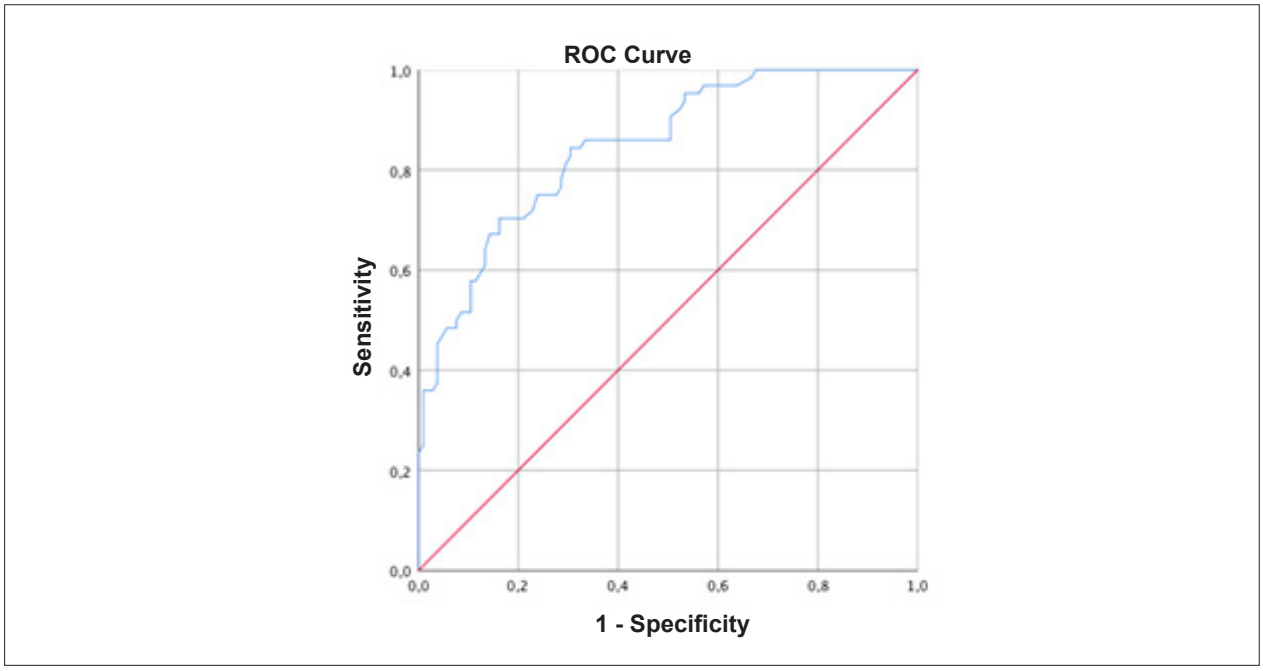

Figure 3 – *ROC curve for 6MST to predict a $VO_{2peak} \geq 20$ mL.Kg^{-1}.min^{-1} AUC 0.85 (95% CI 0.79 – 0.90) p < 0.001.*

Discussion

Functional capacity is one of the most important clinical parameters for measuring functional capacity.[1] Functional impairment is related to worse prognosis, independently of the diagnosis or clinical scenario.[1,7] Cardiorespiratory fitness (CRF) can be estimated by several methods, although the CPET is the only method that allows direct determination based on VO_{2peak}. Since the CPET requires specific equipment and well-trained medical staff, an accurate indirect measurement of functional capacity is highly desirable. Simpler alternative forms of CRF evaluation are important to be validated as they may be more broadly applied.

In a population of CAD and HF patients, we demonstrated that the 6MST had a good correlation with VO_{2peak} as measured by CPET. We were also able to derive an equation to predict VO_{2peak} based on 6MST results, as well as to determine a cutoff point for the number of steps necessary to identify lower-risk patients (minimum VO_{2peak} of 20 mL.Kg^{-1}.min^{-1}).

Step Test in Cardiology

Step tests are not a new tool in cardiology. Back in the 1930s, Master et al.[8] used a 1-step stair test in a 2-minute protocol to observe exercise ECGs. This was the precursor of actual exercise stress tests using ergometers. The Master step test was widely used as a provocative test for coronary ischemia, but was not routinely used for predicting CRF/functional capacity and prognosis. The main purpose of the 6MST as a submaximal test is to determine CRF and not to diagnose coronary ischemia. As well as the 6MWT, the 6MST is safe and can be performed at submaximal effort, although with a slightly higher energy expenditure.

Functional Capacity as a Vital Sign

Functional capacity can be considered a vital sign and should be assessed in each clinical visit.[9,10] It can be predicted with a regular exercise test or submaximal functional tests such as the 6MWT, but the CPET is the only way to directly assess and determine functional capacity. Based on classic studies of cardiac patients, a VO_{2peak} above 20 mL.kg^{-1}.min^{-1}

is a marker of good prognosis regardless of other parameters, whereas those with a VO_{2peak} below 12 mL.kg^{-1}.min^{-1} and HF may even be considered candidates for heart transplant.[5,6]

As an alternative to CPET, the 6MWT has been validated and is used for prognostic evaluation in different diseases.[11] It is easy to replicate and can be related to outcome, but the requirement of a large space prevents its use in office settings. Therefore, a test that can estimate functional capacity in the office without the need for sophisticated equipment is of value.

It is important to point out that the 6MST was previously compared to the 6MWT in a population free of cardiac or pulmonary diseases and showed good correlation.[12]

The 6-minute Step Test is a Simple Way to Predict Functional Capacity

The 6MST is a simple test that does not require much space. It can be applied in a medical office or by other health professionals. It has been previously used in patients with chronic pulmonary disease, but it has not yet been validated in cardiac patients.

In patients with chronic obstructive pulmonary disease, a cutoff point of <78 steps was associated with worse prognosis.[13] In a healthy population with a mean age of 39 years, the mean step count was 149 ± 34.[14]

According to our data, the 6MST has acceptable accuracy for predicting VO_{2peak} in a sample of CAD/HF patients, and clinicians may want to use these results in their clinical practice.

We found that the cutoff point of >105 steps is related to achieving a VO_{2peak} above 20 mL.kg^{-1}.min^{-1}. This cutoff may be useful, for example, when CPET is not available. Furthermore, if a patient can climb more than 105 steps, a CPET may not be necessary, since a VO_{2peak} above 20 mL.kg^{-1}.min^{-1} is estimated.

Functional capacity estimates based on daily life activities are inaccurate and have not been directly validated through CPET data,[15] although this strategy is still used when prompt estimates are necessary, even for serial evaluation. Thus, the 6MST can be easily and quickly applied, but with more confidence regarding the determination of functional capacity.

Limitations

This study has some limitations. A larger sample size and prospective validation of these results in other populations should be considered. Our population consisted of CAD and/or HF patients who were analyzed together, and one may want to analyze these phenotypes separately. To mitigate the influence of the clinical diagnosis on the performance of the test, we controlled the multivariate analysis for the diagnosis of HF or CAD and found that the diagnosis did not influence the result. Also, we controlled the analysis for ejection fraction. As CAD is the most prevalent cause of HF and functional capacity is an independent prognostic factor for both, having a test and a single cutoff point that can be applied to a broader spectrum of heart disease may be of value as the 6MST may be better applied to triage and follow-up. The Bland-Altman plot analysis showed that in only 5 patients the agreement was considered away from the upper or lower reference limits. Of these, 4 patients had VO_{2peak} above 20 mL.kg^{-1}.min^{-1} and the predicted value from the 6MST was also greater than 20 mL.kg^{-1}.min^{-1}. Thus, these 4 patients would not be misclassified as having a lower risk than expected. In 1 patient, the VO_{2peak} predicted by the 6MST was higher than the measured one. By analyzing this case, we note that the CPET respiratory exchange ratio was just 0.94 compatible with a submaximal effort, which was due to poor adaptation to the treadmill and mask. This same patient climbed up and down 91 steps in 6 minutes. One may understand that the 6MST is more suitable as a triage tool than as a substitute for the CPET. Therefore, although they are correlated, in cases in which functional capacity needs to be exactly determined, the CPET is still needed. At the present moment, we have no 6MWT performance data for these individuals, although a correlation between the tests in these patients could be of value. Studies correlating the performance of the 6MST in terms of clinical outcomes should provide more information about the best cutoff points. Finally, although CPET VO_{2peak} is the gold standard for functional evaluation, it is possible that the 6MST could provide some prognostic implications according to the results.

Conclusion

An equation capable of predicting VO_{2peak} based on 6MST results was derived, and a significant association was found between 6MST and VO_{2peak}. The cutoff point for the 6MST, which predicts a $VO_{2peak} \geq 20$ mL.Kg^{-1}.min^{-1}, was >105 steps.

Acknowledgements

Partial financial support was provided by the FIPE-HCPA (Research Support Fund of the Hospital de Clínicas de Porto Alegre).

Author Contributions

Conception and design of the research: Ritt LE, Porto JS, Bastos G, Feitosa CM, Claro TC, Prado EF, Oliveira QB, Stein R; Acquisition of data: Ritt LE, Feitosa GF, Porto JS, Bastos G, Albuquerque RBL, Feitosa CM, Claro TC, Prado EF, Oliveira QB, Stein R; Analysis and interpretation of the data: Ritt LE, Darzé ES, Feitosa GF, Porto JS, Bastos G, Prado EF, Stein R; Statistical analysis: Ritt LE, Darzé ES, Porto JS, Bastos G, Albuquerque RBL, Oliveira QB, Stein R; Obtaining financing: Ritt LE, Stein R; Writing of the manuscript: Ritt LE, Darzé ES, Feitosa GF, Porto JS, Bastos G, Albuquerque RBL, Oliveira QB, Stein R; Critical revision of the manuscript for intellectual content: Ritt LE, Darzé ES, Feitosa GF, Porto JS, Bastos G, Feitosa CM, Claro TC, Prado EF, Stein R.

Potential Conflict of Interest

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

Sources of Funding

There were no external funding sources for this study.

Study Association

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

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The Six-Minute Step Test as an Alternative for Functional Capacity Assessment in Patients with Cardiovascular Diseases

Raphael Mendes Ritti-Dias and Breno Quintella Farah[2,3]

Programa de Pós-Graduação em Ciências da Reabilitação - Universidade Nove de Julho,[1] *São Paulo, SP - Brazil*
Departamento de Educação Física da Universidade Federal Rural de Pernambuco,[2] *Recife, PE - Brazil*
Programa de Pós-Graduação em Educação Física da Universidade Federal de Pernambuco,[3] *Recife, PE - Brazil*

Short Editorial related to the article: The Six-Minute Step Test as a Predictor of Functional Capacity according to Peak VO_2 in Cardiac Patients

Functional capacity is an important morbimortality marker in patients with cardiopulmonary diseases.[1,2] Although the direct measurement of peak oxygen consumption (VO_{2peak}), using cardiopulmonary tests (the gold standard), is the most adequate method for assessing functional capacity, its use in clinical practice is still restricted due to its high cost.[1,2]

The 6-minute step test (6MST), in addition to being fast, has as its main advantage the need for minimum space for its performance. These factors, added to the fact that it does not require audible signals, become very attractive for its use in clinics and hospitals. Step tests have been used for a long time to assess functional capacity, especially in healthy individuals or those with lung diseases.[3] In patients with pulmonary diseases, a positive correlation (r = 0.76) was observed between the 6MST and the 6-minute walk test[4] (6MWT), a test that requires more space to be carried out.[5] Interestingly, correlation data between the 6MST and the direct measurement of functional capacity are scarce, especially in patients with cardiovascular diseases.

The study by Ritt et al.[6] seeks to fill this gap by submitting 171 patients with heart failure and coronary artery disease to the 6MST and to the cardiopulmonary test on a treadmill. The results showed a significant correlation between VO_2peak obtained in the treadmill test and the performance at the 6MST (r = 0.69). Moreover, a prediction equation for VO_{2peak} estimation was developed for men [VO_{2peak} = 19.6 + (0.075*6MST) - (0.10*age)] and for women [VO_{2peak} = 19.6 + (0.075*6 6MST) - (0.10*age) - 2], based on the step test results. Finally, the authors identified 105 climbs as the cutoff point for VO_{2peak} > 20 mL/kg*min, which in cardiac patients is considered a good indicator of cardiovascular prognosis.

Despite the interesting results, it is important to highlight aspects that still deserve to be elucidated in future studies. Important psychometric indicators of the 6MST are still lacking, such as reproducibility, sensitivity to change. The identification of cutoff points is highly relevant and applicable in clinical practice. However, to identify individuals with low functional aptitude, it is necessary that new points be established, considering age, gender, height, among other factors. Cutoff points based on a single and heterogeneous sample are possibly identifying those who are older and female. However, it may be that compared to peers of the same age and gender, they have functional capacity within the expected range. These aspects have already been widely discussed regarding the 6-minute walk test and could be considered for the 6MST.[7-9]

In summary, the work by Ritt et al.[6] shows interesting initial evidence of the use of the 6MST to assess the functional aptitude in patients with coronary artery disease and heart failure. As this is a test with great potential for use in clinical practice, future studies on the 6MST as a prognostic marker, on its psychometric characteristics, as well as reference values according to gender and age, will be welcome.

Keywords

Hypertension; Blood Pressure; Heredity/genetic; Exercise; Sports; Football; Endothelium; Athletes.

Mailing Address: Breno Quintella Farah •
Breno Quintella Farah
Universidade Federal Rural de Pernambuco - Rua Dom Manuel de Medeiros, s/n Dois Irmãos. Postal Code 52171-900, Recife, PE - Brazil
E-mail: brenofarah@hotmail.com

DOI: https://doi.org/10.36660/abc.20210252

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Walking Training Improves Ambulatory Blood Pressure Variability in Claudication

Marcel da Rocha Chehuen,[1] Gabriel Grizzo Cucato,[2] Celso Ricardo Fernandes de Carvalho,[3] Antonio Eduardo Zerati,[3] Anthony Leicht,[4] Nelson Wolosker,[5] Raphael Mendes Ritti-Dias,[6] Claudia Lucia de Moraes Forjaz[1]

Universidade de São Paulo - Escola de Educação Física e Esporte,[1] São Paulo, SP - Brazil
Northumbria University, Newcastle Upon Tyne,[2] United Kingdom
Hospital das Clinicas (HCFMUSP), Faculdade de Medicina, Universidade de Sao Paulo,[3] São Paulo, SP - Brazil
James Cook University,[4] Queensland - Australia
Hospital Israelita Albert Einstein,[5] São Paulo, SP - Brazil
Universidade Nove de Julho - Programa de Pós-Graduação em Ciências da Reabilitação,[6] São Paulo, SP - Brazil

Abstract

Background: Walking training (WT) improves walking capacity and reduces clinic blood pressure (BP) in patients with peripheral artery disease (PAD), but its effects on ambulatory BP remains unknown.

Objectives: To investigate the effect of 12 weeks of WT on ambulatory BP and its variability in patients with PAD.

Methods: Thirty-five male patients with PAD and claudication symptoms were randomly allocated into two groups: control (n = 16, 30 min of stretching) and WT (n = 19, 15 bouts of 2 min of walking at the heart rate of leg pain threshold interspersed by 2 min of upright rest). Before and after 12 weeks, 24-hour ambulatory BP was assessed. Ambulatory BP variability indices assessed at both time points included the 24-hour standard deviation (SD_{24}), the awake and asleep weighted standard deviation (SD_{dn}), and the 24-hour average real variability (ARV_{24}). Data were analyzed by mixed two-way ANOVAs, considering $P<0.05$ as significant.

Results: After 12 weeks, neither group had significant changes in 24-hour, awake and sleep BPs. The WT decreased systolic and mean BP variabilities (Systolic BP – 13.3±2.8 vs 11.8±2.3, 12.1±2.84 vs 10.7±2.5 and 9.4±2.3 vs 8.8±2.2 mmHg); Mean BP – 11.0±1.7 vs 10.4±1.9, 10.1±1.6 vs 9.1±1.7 and 8.0.±1.7 vs 7.2±1.5 mmHg) for SD_{24}, SD_{dn} and ARV_{24}, respectively). Neither group had significant changes in diastolic BP variabilities after 12 weeks.

Conclusion: The WT does not change ambulatory BP levels but decreases ambulatory BP variability in patients with PAD. This improvement may have a favorable impact on the cardiovascular risk of patients with symptomatic PAD. (Arq Bras Cardiol. 2021; 116(5):898-905)

Keywords: Intermittent Claudication; Walking; Blood Pressure; Blood Pressure Monitoring Ambulatory; Muscle Weakness; Endurance Training.

Introduction

Intermittent claudication, the most prevalent symptom of peripheral artery disease (PAD), impairs walking capacity, impacting on patient's physical activity levels[1] and quality of life.[2] In addition, this functional limitation is associated with increased rates of fatal and non-fatal cardiovascular events in this population.[3]

Among cardiovascular diseases, arterial hypertension is a common comorbidity that affects more than 80% of the patients with PAD,[4] who present higher clinic and specially higher ambulatory BP levels compared with healthy individuals.[5] Interestingly, we recently demonstrated that walking capacity was negatively associated with ambulatory BP in PAD,[6] indicating a poorer BP control in patients with greater functional impairment. Thus, therapeutic strategies that increase functional capacity, such as walking training, may improve cardiovascular outcomes and reduce cardiovascular risk in this group.

We have recently demonstrated that supervised walking training (WT) improves walking capacity in addition to reducing clinic BP in patients with symptomatic PAD,[7] however its effects on ambulatory BP remains unknown. This is a very important issue, since ambulatory BP is considered a stronger predictor of all-cause and cardiovascular mortality than clinic BP.[8] Additionally, a previous study reported no effect of resistance training on ambulatory BP levels, but an improvement in ambulatory BP variability,[9] a new and strong marker for target-organ damage, cardiovascular events, and mortality.[10] Given that

Mailing Address: Cláudia Lúcia de Moraes Forjaz •
Universidade de São Paulo - Escola de Educação Física e Esporte, Av. Prof. Mello Moraes, 65 - Cidade Universitária - CEP: 05508-030 - São Paulo - SP
E-mail: cforjaz@usp.br
Manuscript received November 21, 2019, revised manuscript February 03, 2020, accepted March 16, 2020

DOI: https://doi.org/10.36660/abc.20190822

aerobic training such as walking promotes considerable reduction on ambulatory BP levels compared to resistance training in normotensive and hypertensive populations,[11] one may suppose that this mode of exercise can also improve ambulatory BP and its variability in patients with PAD, which needs to be checked. Thus, the aim of this study was to investigate the effects of WT on ambulatory BP and its variability in patients with symptomatic PAD.

Methods

Study Population

This is a complementary data from a previous study.[7] Patients were recruited from the Clinic Hospital's Vascular Unit, University of Sao Paulo, Brazil. Male patients previously diagnosed with PAD and with symptoms of intermittent claudication were invited. Inclusion criteria were: (a) age ≥ 50 years; (b) ankle-brachial index (ABI) ≤ 0.90;[11,12] c) Fontaine stage II of PAD;[13] (d) body mass index ≤ 35 kg/m^2; (e) resting systolic BP ≤ 160 mmHg and diastolic BP ≤ 105 mmHg; (f) not taking β-blockers or non-dihydropyridine calcium channel blockers; (g) absence of cardiovascular autonomic neuropathy for diabetic patients;[14] (h) ability to walk for at least 2 minutes at 3.2 km/h on a treadmill; (i) ability to undertake an incremental treadmill test limited by symptoms of intermittent claudication; (j) absence of myocardial ischemia or complex arrhythmias during a maximal treadmill test; (k) decrease of at least 15% in ABI after a maximal treadmill test; and (l) not engaged in any exercise program. In addition, patients were not included if they met at least one of the following criteria: 1) revascularization surgery or angioplasty less than one year earlier; 2) use of peripheral vasodilators, 3) lower limb amputation, and 4) orthopedic problems that contraindicate walking exercise. Subjects were excluded if they had their medications changed during the study. The study's protocol was registered at the Brazilian Clinical Trials (RBR-7M3D8W) and approved by the Human Research Ethics Committee of the School of Physical Education and Sport of the University of Sao Paulo (process: 39-2008/55) and the Clinic Hospital (process:1179/09), being conducted in accordance with the Declaration of Helsinki. A written informed consent was obtained from all patients prior to participation.

Participant screening

Diagnosis of PAD was made based on clinical history and ABI measurement at rest and after a treadmill maximal test.[15] Arm systolic BP was measured using the auscultatory method, and ankle systolic BP of each leg was assessed with a Doppler ultrasound (Martec, DV 6000, Ribeirão Preto, Brazil). For each patient, the lowest ABI was recorded. Body mass and height were measured (Welmy, 110, São Paulo, Brazil), and body mass index was calculated. Resting brachial BP was measured in two visits, and the mean value was calculated and used for analysis. In each visit, after five minutes of seated rest, three auscultatory measurements were taken in each arm, and the highest mean value was recorded. Medication use and exercise habits were assessed via interview. In diabetic patients, the presence of cardiovascular autonomic neuropathy, was assessed according to the recommendations of the American Diabetes Association.[14] Drug treatment was kept constant for all patients throughout the study.

Design

The experimental protocol is shown in Figure 1. The study had an initial pre-screening including a maximal treadmill test following Gardner's protocol for assessing pain threshold.[16] Then, subjects who met all the study criteria underwent 24-hour ambulatory BP monitoring at baseline and after 12-weeks of intervention. Patients were randomized using a specific online program (www.randomizer.org) into two groups: walking training (WTG) and control (CG).

For all the assessments, recommendations included no vigorous exercise in the previous 48 hours, a light meal 2 hours before, no ingestion of food with stimulant properties such as caffeine, no alcoholic beverages or smoking in the previous 12 hours. Clinic assessments were conducted in the morning in a temperature-controlled laboratory (20-22°C).

Measurements

Primary outcome: ambulatory blood pressure

Ambulatory BP monitoring was performed with a noninvasive oscillometric device (SpaceLabs Medical Inc, 90207, Washington, USA) placed on the non-dominant arm and programmed to perform measurements every 15 minutes for 24 hours. The accuracy of the device was confirmed by a mercury sphygmomanometer prior to use.

For the analysis, ambulatory systolic, diastolic and mean BP levels were calculated by the average of all BP measurements taken during the 24 hours as well as during the awake and asleep periods reported by the patient. In addition, ambulatory BP variability was calculated for systolic, diastolic and mean BP using three different indices:[17] the 24-hour standard deviation (SD_{24}); the awake and asleep weighted standard deviation (SD_{dn}), and the 24-hour average real variability (ARV_{24}). These indices were calculated as previously reported. Briefly, SD_{24} was calculated by the standard deviation (SD) over 24 hours weighted for the time interval between measures. SD_{dn} was calculated by the mean of awake and asleep SD corrected for the number of hours of each of these periods [i.e SD_{dn} = [(awake SD x awake hours) + (asleep SD x asleep hours)]/(wake + asleep hours)]. ARV_{24} was calculated by the average of absolute differences between consecutive measurements accounting for the order of measurement using following formula:

$$ARM = \frac{1}{\Sigma_w} \sum_{k=1}^{n-1} w \times |BP_{k+1} - BP_k|$$

where k ranges from 1 to N−1, BP is the blood pressure

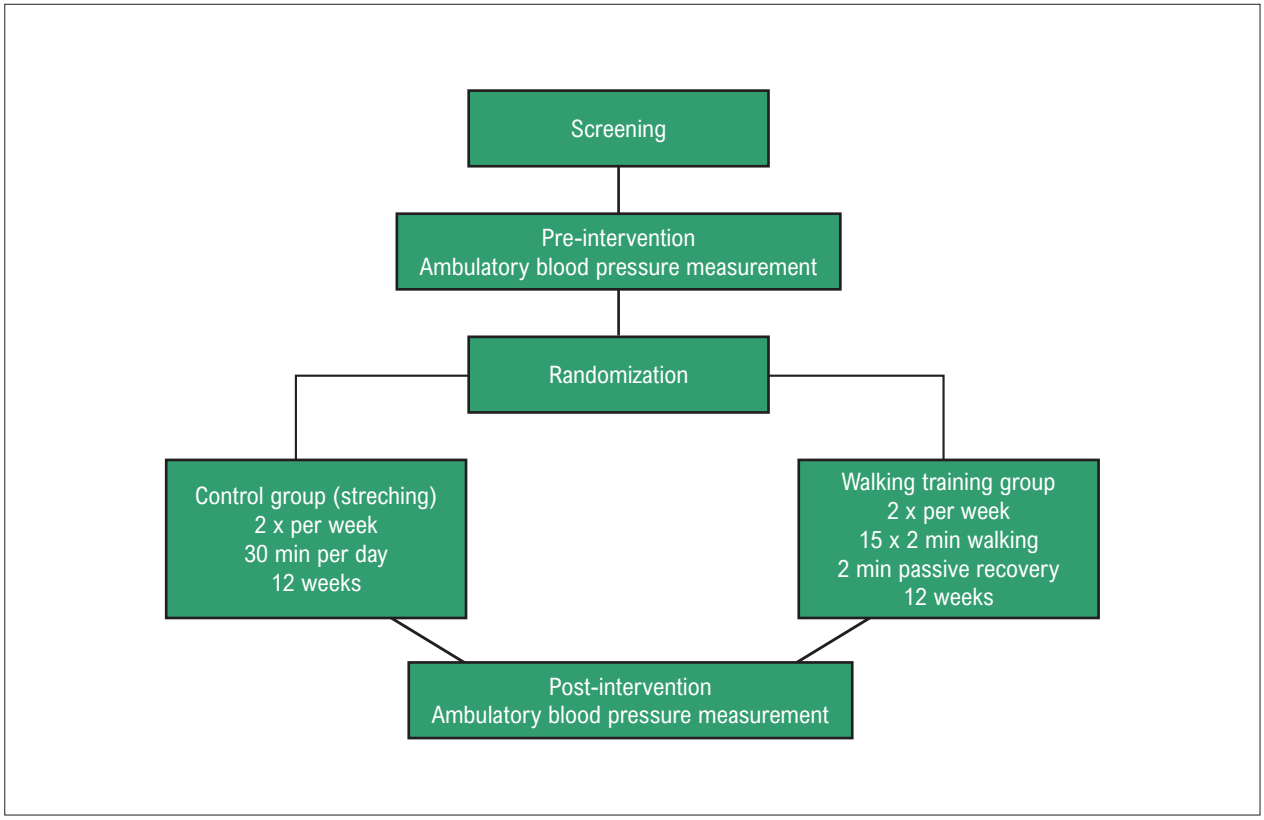

Figure 1 – *Experimental design of the study.*

and w is the time interval between BPk and BPk+1. N is the number of blood pressure readings.

Interventions

Details of the interventions have been previously reported.[7] Briefly, interventions were conducted twice a week for 12 weeks and supervised by one of the researchers. CG patients performed stretching exercises for 30 minutes. WTG patients performed 15 bouts of 2-minute walking on a treadmill intersected by 2 minutes of resting. During each walking bouts, speed was kept at 3.2 km/h and intensity was adjusted by setting the treadmill grade to maintain heart rate within 4 bpm of the heart rate obtained at the pain threshold assessed during maximal treadmill test[18] (e.g., if the patient reported the pain threshold during maximal treadmill test at 100 bpm, the heart rate during each training session was kept between 96 to 104 bpm).

Statistical analysis

As previously described,[7] the sample size was estimated considering a power of 90%, alpha error of 5%, and standard deviation of 3 mmHg for systolic BP. The minimal sample size necessary to detect a difference of 4 mmHg was 7 subjects in each group.

Normality of data distribution and homogeneity of variance were evaluated using the Shapiro-Wilk and Levene tests, respectively. Skewed distributions were normalized using logarithmic transformations. At baseline, group differences were identified via chi-square test (comorbidities and drug therapy prevalence) or unpaired Student's t-test (continuous variables). The effects of the interventions were assessed using a mixed two-way ANOVA (Statsoft, Statistic for Windows 4.3, Oklahoma, USA), the groups being the between factor, and the study phase (baseline and 12 weeks) being the within factor. Newman-Keuls post-hoc tests were used when necessary. $P<0.05$ was considered significant, and data were presented as mean ± SD.

Results

Patients flowchart is shown in Figure 2. Eighty-four patients were screened, but 35 were excluded for not meeting the eligibility criteria (n=7) or declining participation (n=28, not available to perform training sessions). The remaining 49 patients were randomly allocated in the CG (n=24) and the WTG (n=25). Fourteen patients withdrew due to circumstances unrelated to the the study. Thus, the final sample was composed of 35 patients (CG, n=16; WTG, n=19).

These groups had similar initial characteristics regarding age, obesity level, clinic BP levels, disease limitations, comorbidities, and medication use (Table 1).

Ambulatory BP levels were similar between WTG and CG at baseline, and neither group presented any significant change in 24-hour, awake and asleep BPs after the 12 weeks of intervention (Table 2).

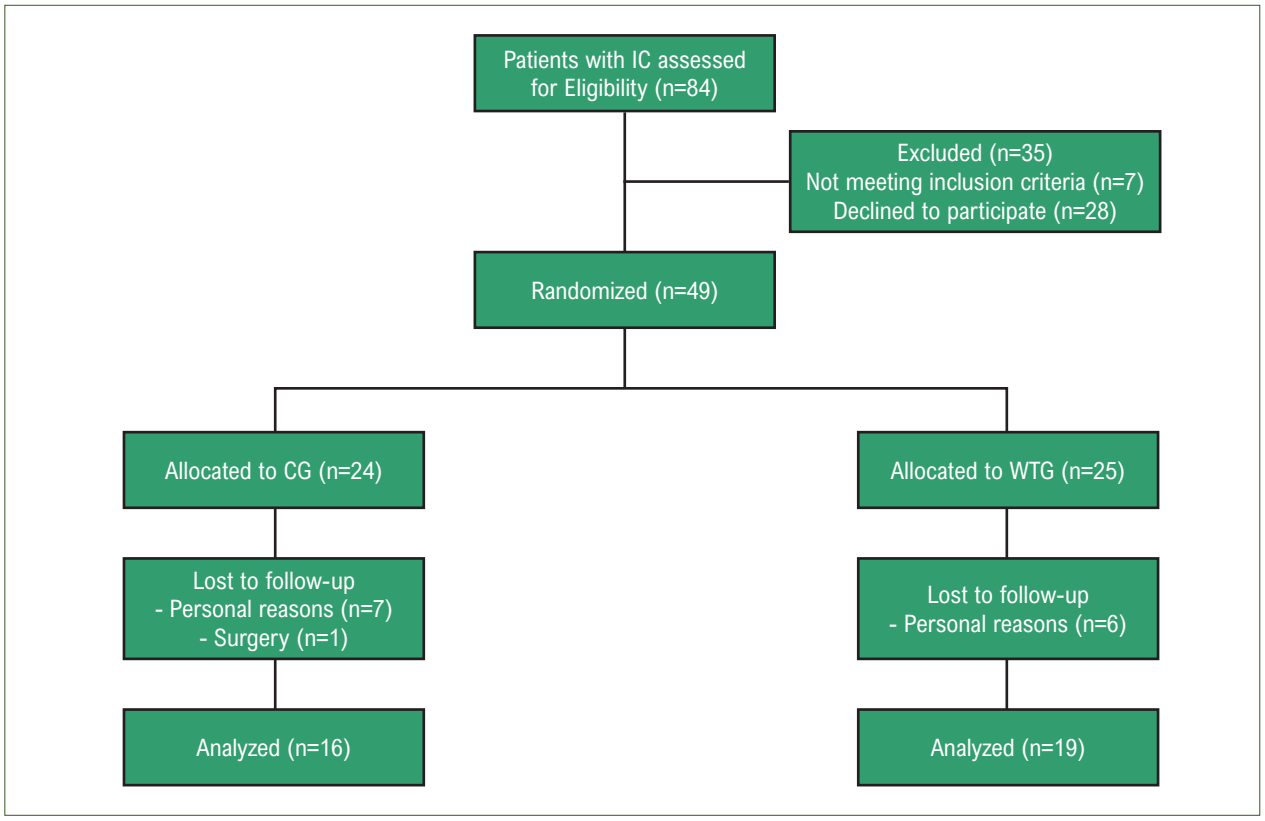

Figure 2 – *Participants flowchart. IC: Intermittent claudication, CG: Control group, WTG: Walking training group*

BP variability indices assessed at baseline were similar between WTG and CG. There was a significant interaction between group and study phase for systolic and mean BP variability indices (all $p<0,05$), showing a reduction in SD_{24}, SD_{dn}, and AVR_{24} of systolic and mean BP in the WTG (Table 3, Figure 3). Neither group had any significant change in the indices of diastolic BP variability.

Discussion

The main finding of this study was that 12 weeks of WT decreased systolic and mean BP variability indices without changing ambulatory BP levels.

In the present study, 12 weeks of WT did not alter ambulatory BP in patients with PAD, which contrasts with studies with normotensive subjects and hypertensive patients[19] that have consistently reported decreases around 3 mmHg for systolic and diastolic ambulatory BP after aerobic training. However, 12 weeks of resistance training have also not changed ambulatory BP in patients with PAD.[9] Thus, it has been hypothesized that the frequent episodes of ischemia during daily activities in patients with PAD produce claudication pain, oxidative stress and metabolic accumulation, increasing sympathetic nerve activity and, consequently, blunting any possible hypotensive effect of exercise training on ambulatory BP levels.[20] Another potential explanation, however, can be the too short duration of the training program, since a previous study[21] conducted with elderly hypertensive patients showed no change in ambulatory BP levels after 6 months of training, but a significant reduction after 12 months.

Despite the absence of change in ambulatory BP levels, reductions in ambulatory systolic and mean BP variabilities were observed for all variability indices: SD_{24}, SD_{dn} and ARV_{24}. These results are in accordance with a previous study with resistance training in symptomatic PAD patients.[9] In addition, this result is coherent with the concept that changes in autonomic control precede alterations in BP levels, since BP variability mainly reflects autonomic control of BP.[22,23] Additionally, these results are also in accordance with our previous clinic findings of improvements in cardiac autonomic modulation and baroreflex sensitivity, all markers of autonomic control, after WT in patients with PAD.[7] The absence of changes in diastolic ambulatory BP variability is also coherent with the absence of effects of walking training on calf vascular resistance, as previously described.[7]

Even without any changes in ambulatory BP levels, the decrease in ambulatory BP variability obtained with WT may have relevant clinical implications. BP variability has been associated with the presence and progression of subclinical organ damage as well as the incidence of hard endpoints such as cardiovascular events[10], leading to a worse cardiovascular prognosis.[8] Thus, the decrease induced by WT may have favorable impact on the cardiovascular risk of patients with PAD, reinforcing the recommendation of WT for these patients.

Table 1 – Characteristics of the patients allocated in the control (CG) and the walking (WTG) training groups.

	CG (n = 16)	WTG (n = 19)	p value
Age (years)	62 ± 7	63 ± 7	0.64
Body mass index (kg/m^2)	25.7 ± 3.9	26.1 ± 3.1	0.76
Ankle brachial index	0.60 ± 0.12	0.62 ± 0.14	0.61
Claudication onset distance (m)	319 ± 152	277 ± 164	0.45
Total walking distance (m)	759 ± 305	624 ± 255	0.16
Clinic systolic BP (mmHg)	136 ± 19	133 ± 14	0.60
Clinic diastolic BP (mmHg)	79 ± 10	77 ± 9	0.53
Comorbidities			
Obesity (%)	12.5	10.5	0.55
Hypertension (%)	81.3	84.2	0.89
Diabetes Mellitus (%)	25.0	21.1	0.61
Dyslipidemia (%)	100.0	89.5	0.17
Current Smokers (%)	37.5	26.3	0.38
Heart Disease/Stroke (%)	18.8	21.1	0.80
Drug therapy			
Aspirin (%)	93.8	100.0	0.28
Statin (%)	62.5	78.9	0.83
Angiotensin-converting enzyme inhibitor (%)	43.8	68.4	0.20
Diuretics (%)	25.0	47.4	0.17
Calcium channel blocker (%)	18.8	21.1	0.86
Oral hypoglycemic (%)	18.8	15.8	0.69
Number of antihypertensive			
Monotherapy	50.0		

Data are shown as mean ± SD or percentage (%). BP: Blood pressure. Continuous variable – unpaired Student's t-test. Categorical variable – chi-square test.

Table 2 – Ambulatory blood pressure levels measured at baseline and after the 12-week intervention period for the walking training (WTG) and the control (CG) groups

	CG (n = 16)		WTG (n = 19)		P group	P study phase	P interaction
	Baseline	12 weeks	Baseline	12 weeks			
24h							
Systolic BP (mmHg)	130 ± 14	132 ± 15	128 ± 14	126 ± 11	0.51	0.74	0.21
Diastolic BP (mmHg)	78 ± 7	80 ± 7	78 ± 12	76 ± 10	0.44	0.42	0.16
Mean BP (mmHg)	96 ± 9	98 ± 8	94 ± 9	93 ± 9	0.32	0.60	0.14
Awake							
Systolic BP (mmHg)	135 ± 14	137 ± 16	130 ± 14	129 ± 12	0.16	0.74	0.44
Diastolic BP (mmHg)	83 ± 7	84 ± 7	80 ± 12	79 ± 11	0.16	0.41	0.35
Mean BP (mmHg)	101 ± 9	103 ± 9	96 ± 10	95 ± 10	0.08	0.60	0.25
Asleep							
Systolic BP (mmHg)	119 ± 16	121 ± 16	124 ± 16	122 ± 12	0.50	0.85	0.51
Diastolic BP (mmHg)	69 ± 9	71 ± 8	73 ± 9	71 ± 11	0.61	0.80	0.32
Mean BP (mmHg)	87 ± 11	89 ± 11	89 ± 9	89 ± 9	0.63	0.82	0.33

Data are shown as mean ± standard deviation. BP: Blood pressure. Mixed two-way ANOVA, with the group being the between main factor and the study phase being the within main factor.

Table 3 – Ambulatory blood pressure variability indices assessed at baseline and after the 12-week intervention period for the walking training (WTG) and the control (CG) groups

	CG (n = 16)		WTG (n = 19)		P value group	P value study phase	P value interaction
	Baseline	12 weeks	Baseline	12 weeks			
SD_{24}							
Systolic BP (mmHg)	14.6 ± 3.0	15.5 ± 3.9	13.3 ± 2.8	11.8 ± 2.3*#	0.01	0.65	0.04
Diastolic BP (mmHg)	10.9 ± 1.8	11.2 ± 1.7	9.7 ± 2.3	10.0 ± 2.5	0.06	0.49	0.68
Mean BP (mmHg)	12.0 ± 2.6	13.0 ± 3.0	11.0 ± 1.7	10.4 ± 1.9#	0.01	0.71	0.04
SD_{dn}							
Systolic BP (mmHg)	12.2 ± 2.4	12.7 ± 3.0	12.1 ± 2.4	10.7 ± 2.5*#	0.18	0.27	0.03
Diastolic BP (mmHg)	8.7 ± 1.3	9.0 ± 1.6	9.0 ± 1.8	8.9 ± 2.2	0.98	0.95	0.48
Mean BP (mmHg)	10.0 ± 2.1	10.7 ± 2.2	10.1 ± 1.6	9.1 ± 1.7*#	0.23	0.82	0.01
ARV_{24}							
Systolic BP (mmHg)	9.4 ± 2.1	10.7 ± 2.4*	9.4 ± 2.3	8.8 ± 2.2#	0.18	0.28	0.02
Diastolic BP (mmHg)	6.9 ± 1.8	7.3 ± 1.8	7.3 ± 2.3	7.2 ± 1.6	0.75	0.67	0.54
Mean BP (mmHg)	8.1 ± 1.9	8.6 ± 1.7	8.0 ± 1.7	7.2 ± 1.5*#	0.15	0.88	0.01

*Values are shown as mean ± standard deviation. SD24 = 24-hour weighted standard deviation; SD_{dn}: awake and asleep weighted standard deviation; ARV: average real variability. Mixed two-way ANOVA, with the group being the between main factor and the study phase being the within main factor. *Different from baseline (P<0.05); # Different from CG (P<0.05)*

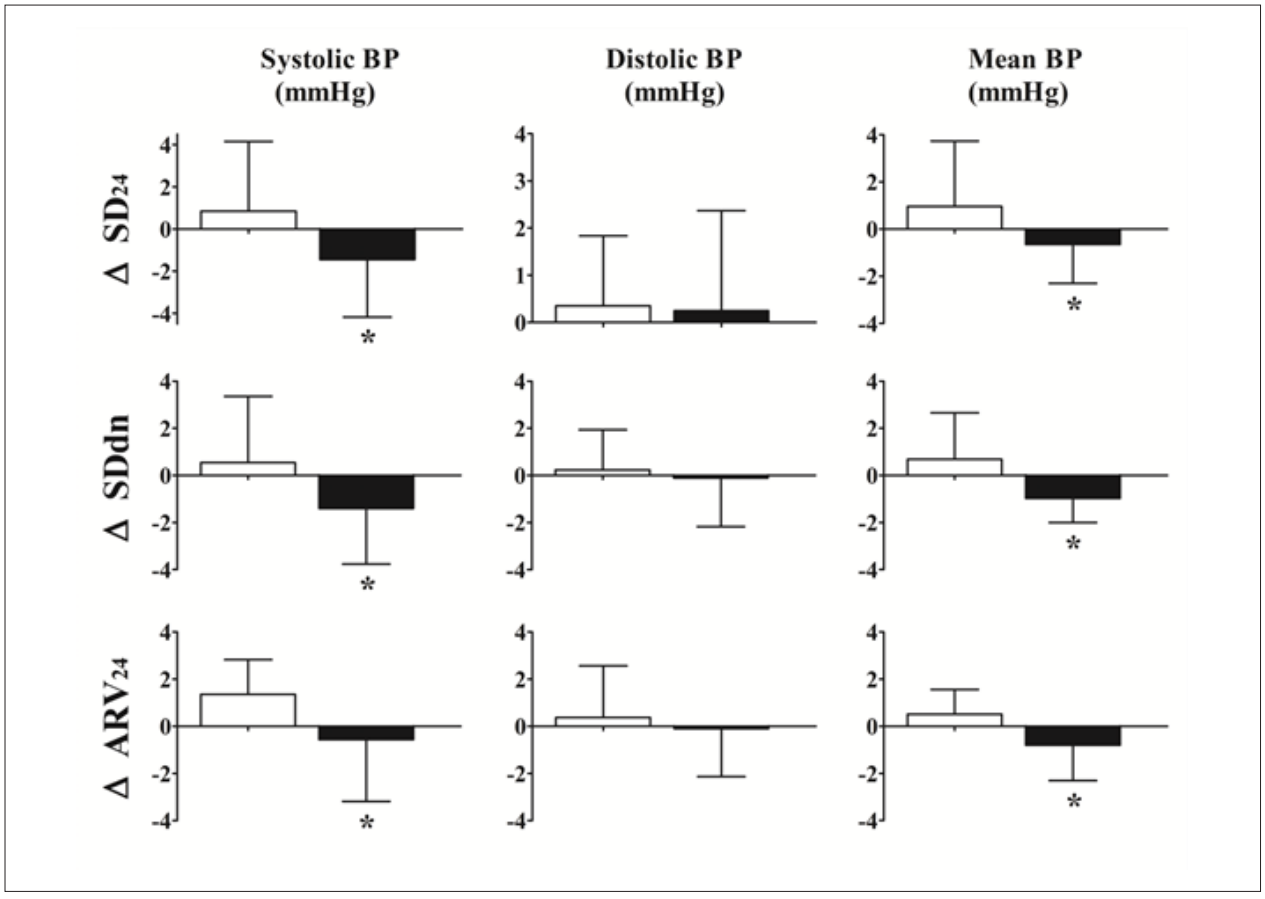

Figure 3 - *Absolute change (Δ) of ambulatory blood pressure variability for the control group (white bars) and walking training group (black bars). BP: blood pressure; SD_{24}: standard deviation over 24 hours weighted for the time interval between consecutive readings; SD_{dn}: the average of the daytime and nighttime SDs weighted for the duration of the daytime and nighttime interval; ARV_{24}: the average real variability weighted for the time interval between consecutive readings in 24-hour ambulatory BP recordings. *p<0.05 vs control group.*

This study has some limitations that should be acknowledged. It was conducted only with men, and training-induced adaptations may differ between genders.[24,25] Thus, future studies should investigate the impact of WT on ambulatory BP and its variability also in women, especially the elderly, who may experience greater cardiovascular risk than men.[24] The current study also only examined patients with claudication symptoms, and further studies should examine the effects of WT in other groups of patients, such as those who are asymptomatic (stage 1) and may also present a decrease in ambulatory BP levels after WT. Finally, the training program lasted 12 weeks, a length that improves functional capacity and clinic cardiovascular parameters in these patients,[7] but a longer training period may be necessary to decrease ambulatory BP levels.

Conclusion

In conclusion, 12 weeks of WT decreases ambulatory BP variability in men with symptomatic PAD.

Author Contributions

Conception and design of the research: Chehuen M, Cucato GG, Zerati AE, Leicht A, Ritti-Dias RM, Forjaz CLM; Acquisition of data: Chehuen M, Cucato GG; Analysis and interpretation of the data: Chehuen M, Cucato GG, Forjaz CLM; Statistical analysis and Obtaining financing: Forjaz CLM; Writing of the manuscript: Chehuen M, Cucato GG, Carvalho C, Wolosker N Ritti-Dias RM; Critical revision of the manuscript for intellectual contente: Chehuen M, Cucato GG, Carvalho C, Zerati AE, Leicht A, Wolosker N, Ritti-Dias RM, Forjaz CLM.

Potential Conflict of Interest

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

Sources of Funding

This study was partially funded by CNPQ (442507/2014-3; 304436/2018-6), FAPESP (2015/13800-0) and CAPES (0001).

Study Association

This article is part of the thesis submitted by Marcel Chehuen, from Universidade de São Paulo.

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Walking Training Improve Ambulatorial Blood Pressure Variability in Claudicants

Leandro Franzoni,[1] Gabriel Pereira de Reis Zubaran,[2] Stephanie Bastos da Motta[3]

Universidade Federal do Rio Grande do Sul - Programa de Pós-Graduação em Ciências da Saúde: Cardiologia e Ciências Cardiovasculares,[1] Porto Alegre, RS - Brazil

Hospital de Clínicas de Porto Alegre - Grupo de Pesquisa em Cardiologia do Exercício,[2] Porto Alegre, RS - Brazil

Hospital de Clínicas de Porto Alegre - Grupo de Vascular e Exercício - VascuEx,[3] Porto Alegre, RS - Brazil

Short Editorial related to the article: Walking Training Improves Ambulatory Blood Pressure Variability in Claudication

Peripheral arterial disease (PAD) has been shown to be increasingly prevalent worldwide.[1] Clinical diagnosis is based on evaluation of the ankle brachial index (ABI), where the ankle systolic blood pressure (BP) is divided by the systolic BP of the arm.[2] Value <0.9 indicate the presence of PAD. Reduction in systolic BP of the ankle is due to atherosclerosis in the lower limbs. Individuals with PAD have significant hemodynamic abnormalities, such as an increase in BP levels.[3] In addition, high BP variability is correlated with the development of PAD in diabetic individuals.[4]

It is important to reduce BP levels in PAD individuals. Physical training is a useful tool that can assist the treatment of clinical symptoms.[5,6] It was what Chehuen et al.[7] did; they investigated the effect of walking training (WT) on ambulatory BP variability in PAD individuals. It is an elegant randomized clinical trial in which individuals with PAD and claudication symptoms were divided into two groups: control (n=16) and WT (n=19). 24-hour ambulatory BP was assessed before and after 12 weeks. As an outcome, they evaluated the mean systolic BP and ambulatory diastolic BP, as well as variables representing systolic, diastolic and average BP variability (24-hour standard deviation – SD24, awake and asleep weighted standard deviation – SDdn, and 24-hour average real variability – ARV24).

As a main result, the WT group was able to reduce systolic and mean BP variabilities compared to the control group. A simple but extremely relevant study, showing that WT is effective to improve the variability of ambulatory BP in PAD individuals. Following are some interesting points of the manuscript. The control group performed 30 minutes of stretching twice a week. This is a key detail for a current randomized controlled trial. It is necessary that a similar time of intervention be made available with the same weekly frequency for both groups. WT included 15 minutes of walking on the treadmill followed by a 2-minute interval (30 minutes of active exercise and 30 minutes of rest). The intensity was controlled by heart rate referring to the claudication threshold (gold standard for prescription of PAD), with a standard speed of 3.2 km/h and grade adjustment when necessary.[8]

The study design also shows the high methodological quality with the correct allocation of the participants.[9] Conducting randomized clinical trials in Brazil is difficult, due to the high cost and shortage of labor. It is difficult to perform blinding in studies with physical exercise, since walking is quite different from stretching. However, for comparison purposes, a control group is mandatory.[10] The authors opted for stretching, but it could be lectures on postural education, physical activity and lifestyle, for example. Most importantly, all outcome assessors were blinded to the intervention type, ensuring allocation confidentiality.[11]

The study has many merits. However, it is important to note that some points related to small limitations should be highlighted. One is that the WT is performed on a treadmill, which reduces the external validity at the population level, since many people do not have a treadmill and walk outdoors. There could be one more group that would walk on the streets to compare the effects with the treadmill, for example. In addition, it is highly recommended that individuals with PAD undergo strength training to improve their muscle strength levels and even their lipid profile. Therefore, they could have made a comparison between different training modalities in these individuals within the context of BP. All of these comments can be used as an incentive for further studies.

Finally, PAD is an underdiagnosed disease, where, for many years, people have had symptoms without a closed diagnosis. Improving BP variability levels can have a favorable impact on the reduction of cardiovascular risk, and improve disease prognosis. Therefore, creating incentive and engagement strategies in physical exercise programs are extremely necessary for this population.

Keywords

Peripheral Arterial Disease; Prevalence; Ankle Brachial Index; Arterial Pressure; Atherosclerosis; Diabetes Melllitus; Intermittent Clauduication; Walking.

Mailing Address: Leandro Franzoni •
Universidade Federal do Rio Grande do Sul (UFRGS) - Rua Itaboraí, 683. Postal Code 90040-060, Porto Alegre, RS – Brazil
E-mail: franzoni_77@hotmail.com

DOI: https://doi.org/10.36660/abc.20210140

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Percutaneous Removal of Cardiac Leads in a Single Center in South America

Bruna Costa Lemos Silva Di Nubila,[1,2] *Gustavo de Castro Lacerda,*[1] *Helena Cramer Veiga Rey,*[1] *Rodrigo Minati Barbosa*[1]

Instituto Nacional de Cardiologia,[1] *Rio de Janeiro, RJ - Brazil*

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

Abstract

Background: **In the last decade, the number of cardiac electronic devices has risen considerably and consequently the occasional need for their removal. Concurrently, the transvenous lead removal became a safe procedure that could prevent open-heart surgery.**

Objective: **The primary objective of this study was to describe the successful performance and the complication rates of pacemaker removals in a Brazilian public hospital. Our secondary aim was to describe the variables associated to successes and complications.**

Methods: **A retrospective case series was conducted in patients submitted to pacemaker removal in a Brazilian public hospital from January 2013 to June 2018. Removal, explant, extraction, success and complication rates were defined by the 2017 Heart Rhythm Society Guideline. Categorical variables were compared using x^2 or Fisher's tests, while continuous variables were compared by unpaired tests. A p-value of 0.05 was considered statistically significant.**

Results: **Cardiac device removals were performed in 61 patients, of which 51 were submitted to lead extractions and 10 to lead explants. In total, 128 leads were removed. Our clinical success rate was 100% in the explant group and 90.2% in the extraction one (p=0.58). Major complications were observed in 6.6% patients. Procedure failure was associated to older right ventricle (p=0.05) and atrial leads (p=0,04). Procedure duration (p=0.003) and need for blood transfusion (p<0,001) were associated to more complications.**

Conclusion: **Complications and clinical success were observed in 11.5% and 91.8% of the population, respectively. Removal of older atrial and ventricular leads were associated with lower success rates. Longer procedures and blood transfusions were associated with complications. (Arq Bras Cardiol. 2021; 116(5):908-916)**

Keywords: **Artificial Pacemaker; Cardiac Resynchronization Therapy; Implantable Electrodes.**

Introduction

In the past decade, the prevalence of cardiac implantable electronic devices (CIEDs) have increased due to broader indications and population aging.[1-5] The number of leads per patient has also increased, with more indications of cardiac resynchronization/defibrillator therapy, upgrades and a higher proportion of dual vs. single-chamber devices.[3-6]

Despite the evolution of CIEDs, situations which require complete device and lead removal, such as infections and vascular complications, are still observed.[5,7-9] Since 1980, new techniques and tools have been developed to allow safe percutaneous removal of these devices.[5,10-19]

Mailing Address: Bruna Costa Lemos Silva Di Nubila •
Instituto Nacional de Cardiologia – Mestrado - Rua das Laranjeiras, 374. Postal Code 22240-006, Rio de Janeiro, RJ – Brazil
E-mail: brunaclemos@icloud.com
Manuscript received January 18, 2019, revised manuscript February 29, 2020, accepted April 08, 2020

DOI: https://doi.org/10.36660/abc.20190726

In Brazil, the number of hospital admissions for CIEDs implant has increased over the last decades and currently there are 11,000 hospitalizations per year.[20] Consequently, hospital admissions to remove these CIEDs increased from 79 hospitalizations in 2008 to 151 in 2016.[20] Worldwide, the annual rate of CIED extraction has increased, ranging from 10,000 to 15,000 leads per year.[21,22]

Data from Brazilian and the South American experience in percutaneous leads extraction are lacking in the literature. Thus, the primary goal of our study was to describe the success and complication rates in CIED removals at a Brazilian public hospital. Additionally, we described the variables associated with procedure success and complications.

Metodology

Study Design

We performed a retrospective study in patients submitted to CIED removal at a Brazilian quaternary hospital.

Inclusion criteria

All patients with the recommendation of CIED removal from January 2012 to June 2018 were included.

Procedure technique

All procedures were performed by the same cardiac surgeon. Simple retraction was attempted first and, if not successful, the Evolution or the Evolution RL mechanical sheaths by Cook Medical® (Cook medical Inc., Bloomington, [USA]) was used.

Reimplantation was performed as a one-step approach on the contralateral side in patients without systemic infection or positive blood cultures. In patients with elevated infection markers or positive blood cultures, a second-step approach was performed. In the latter case, antibiotic therapy was carried out for a minimum of 2 weeks after the first negative blood culture.

Definitions

Lead removal was defined as lead removal by any technique.[23] Lead explant was defined as the lead removal procedure where all leads were removed without tools or with stylets only and all removed leads had < 1 year since the implant.[23] Extraction was defined as the lead removal procedure where at least one lead required the assistance of equipment not typically employed during the implant or at least one lead had been implanted for > 1 year.[23]

Clinical success was defined as the lead extraction procedure with the removal of all target lead material from the vascular space or the retention of a small portion of the lead (<4 cm) that does not negatively impact the procedure outcome.[23] Those in this group who had a complete removal of all target leads and lead material from the vascular space were named as complete procedural success.[23] Failure was defined as the lead extraction procedure in which complete procedural or clinical success could not be achieved, or as the developmentof any permanent disability or procedure-related death.[23] Major complications were the ones that posed an imminent risk of death or resulted in death, while minor ones were undesired adverse events that required medical intervention, including minor intervention, but did not significantly affect patient's functions.[23]

Pocket infection was defined as the presence of erythema, warmth, fluctuation, edema, pain or purulent drainage from the device pocket.[24] Isolated pocket erosion was defined as device and/or lead(s) eroding through the skin, with exposure of the generator or leads, with or without local signs of infection.[23] Pocket site infection with bacteremia was defined as local infection signs and positive blood cultures.[22] Endocarditis was defined as the presence of vegetation in the echocardiogram and/or when Duke criteria were met.[24]

Statistical analysis

The normal distribution was verified with the Kolmogorov-Smirnov test. Continuous variables with normal distribution were expressed as mean and standard deviation and compared by unpaired Student's T-test. The ones with non-normal distribution were expressed as median and interquartile ranges and compared by the Mann–Whitney test. Categorical variables were presented as frequencies and percentages and were compared using x^2 or Fisher's exact tests. A p-value of 0.05 was considered statistically significant. All statistical analyses were performed using the R program, version 3.3.0 and 3.4.1.

Ethical approval

The study was approved by the local Research Ethics Committee (67765317.6.0000.5272).

Results

The study flow chart is provided in Figure 1. Table 1 displays patient demographics. While the explant and extraction groups had 11 (97.67%) and 44 (89.80%) dual chamber devices, only 1 (8.33%) and 5 (10.2%) single-chamber devices were seen in each group, respectively. The majority of the leads had an active fixation, whereas only one lead (5%) in the

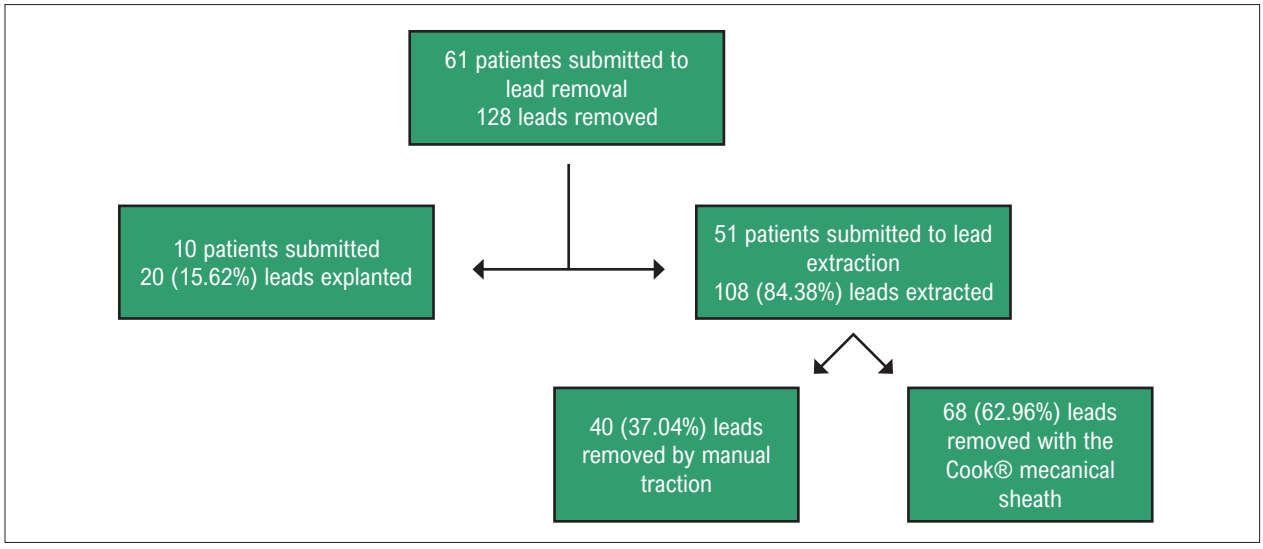

Figure 1 – *Patient selection.*

Table 1 – Patient Demographics

	Explant (n=10)	Extraction (n=51)	p-value
Male gender n(%)	8(80)	33(64.7)	0.47
Age (years)	56.7 ± 25.64	60.63 ± 19.61	0.58
BMI (Kg/m²)	21.43 ± 2.99	25.57 ± 4.15	0.02
Blood tests			
INR	1.15 [1.11 - 1.28]	1.1 [1.03 - 1.24]	0.18
Hemoglobin (g/dl)	12.5 [9.98 -13.68]	12.5 [11.45 -13.4]	0.44
Echocardiographic features			
EF (%)	56.66 [47.42 - 66.45]	56.30 [31.2 - 64.3]	0.6
Presence of tricuspid regurgitation n(%)			0.12
mild	5 (71.4)	13 (56.5)	
moderate	0 (0.0)	7 (30.4)	
severe	0 (0.0)	2 (8.7)	
Comorbidities			
Hypertension n(%)	7 (70.0)	30 (58.8)	1.0
Diabetes Mellitus n(%)	1 (10.0)	16 (31.4)	0.26
Chronic atrial fibrillation n(%)	2 (20.0)	11 (21.6)	1.0
Cerebrovascular disease n(%)	0 (0.0)	2 (3.9)	1.0
Coronary artery disease n(%)	3 (30.0)	14 (27.5)	1.0
Chronic kidney disease n(%)	2 (20.0)	7 (13.7)	0.63
Anticoagulation n(%)	2 (20.0)	11 (21.6)	1.0
Previous cardiac surgery n(%)	4 (40.0)	15 (29.4)	0.71
Lead use (months)			
Atrial leads	3.73 [0.93 - 6.07]	83.6 [46.8 - 115.3]	<0,001
Right ventricular leads	3.73 [0.93 - 6.07]	87.9 [46.8 - 115.3]	<0,001
Left ventricle leads	–	49.7[29.4 - 83.6]	–

Continuous variables were shown as mean ± standard deviation and median ± interquartile ranges. Categorical variables were presented as frequencies and percentages. P-values in the table are related to the Student's or Mann-Whitney test for continuous variables and x^2 and Fisher Tests for categorical variables. BMI: body mass index; INR: International Normalized Ratio; EF: ejection fraction.

explant and 7 (6.5%) in the extraction groups had passive fixation. Another flow chart with the lead types in each group is shown in Figure 2.

The primary implant indication was complete heart block in 27 patients (44.3%), sick-sinus disease in 5 (8.2 %), 2:1 second-degree heart block in 5 (8.2%), sustained ventricular tachycardia with severe ventricular disfunction in 4 (6.6%), non-sustained ventricular tachycardia with severe ventricular disfunction in 2 (3.3%), primary prevention in hypertrophic cardiomyopathy in 2 (3.3%), second-degree heart block in 1 (1.6%), primary prevention in arrhythmogenic right ventricular cardiomyopathy in 1 (1.6%), sudden cardiac arrest in 1 (1.6%), other reasons in 5 (8.2%) and unknow in 8 (13.1%) cases. Forty (65.6%) patients had the cardiac device implanted in our hospital, while 21 (34.42%) had the device implanted in another institution.

A total of 128 leads were removed from these 61 patients. Chronologically, patient procedures were distributed as follow: 6 in 2013, 9 in 2014, 18 in 2015, 12 in 2016, 6 in 2017 and 11 in the first six months of 2018. Procedure characteristics are displayed in Table 2. Before the removal, all patients from the explant group were submitted to a new pacemaker implant, whilst in the extraction group 54.9% (28/51) were submitted to a battery replacement, 41.2% (21/51) to a new implant and in 2% (2/51) the previous procedure was unknown.

Table 2 showed that infection was the most common reason for the device to be removed. More leads were removed in the extraction group. Among the failed procedures, 2 died because of right atrium and superior vena cava tears, which were considered major complications. The three other patients in this group had the removal indicated for pocket infection, lead extrusion and the need to upgrade the right ventricle (RV) lead. One patient with a completely successful procedure died 5 days later due to endocarditis and septic shock. Among those with clinical success, 10 (83.33%) and 38 (88.37%) in the explant and extraction group attained complete success rate, respectively. The overall clinical success rate was 91.8% and the overall complete success rate was 78.7%. Most patients were submitted to a new device implant.

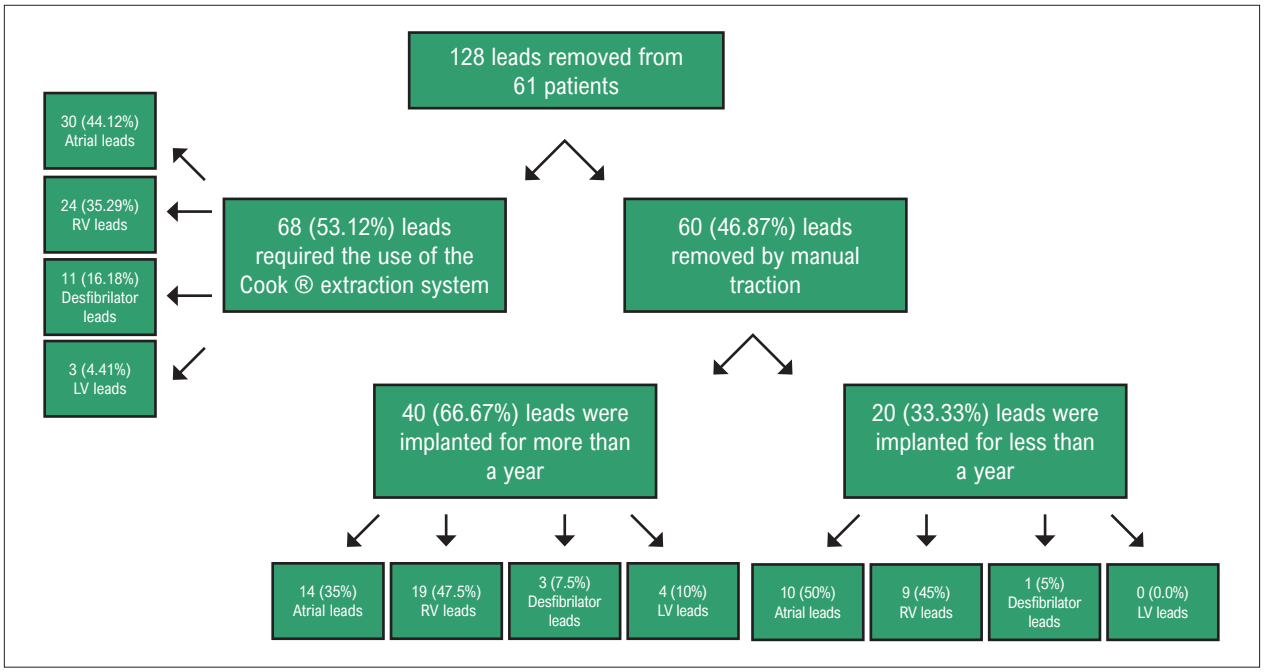

Figure 2 – *Leads type. RV: right ventricle; LV: left ventricle.*

Complications and blood transfusions were only observed in the extraction group. Major complication rate was 6.6% within a 11.5% overall rate of complications. All major complications were during the procedure, comprising 2 deaths; one RV perforation and one cardiac arrest following RV lead removal with full recover after cardiopulmonary resuscitation. All minor complications were due to pocket hematoma, which required a surgical approach. These three patients were taking anticoagulants, of which 2 were on Warfarin and 1 on Dabigatran. All anticoagulants were stopped with an adequate half-life and the INR was normalized prior to the procedure.

Of the 21 patients with positive blood cultures before lead removal, Gram-positive bacteria were more common in 15 patients (93.8%) in the extraction group and 4 (80%) in the explant one. *S. aureus* was the most common bacteria in both groups with 8 cases (50%) in the extraction group and 4 (80%) in the explant one. The second most common microorganism was *S. epidermitis,* followed by Coagulase-negative staphylococci.

Table 3 shows that the only variable associated with procedure failure was older right atrium (p=0.04) and RV (p=0.05) leads. Procedure failure was associated to an older right ventricle lead (p=0.018). Table 4 shows that the need for blood transfusion (p<0.001) and procedure duration (p=0.003) were associated with more complications.

Discussion

The overall age in both groups shows an older population with a high percentage of comorbidities, which we believe contributed to the high infection rate in the device-related procedures. Cardiovascular comorbidities were commonly seen, since our hospital is a quaternary center specialized in cardiology and a considerable percentage of patients have been submitted to a previous cardiac procedure, either valve surgery or coronary artery bypass grafting. Although Sohail et al. described older leads and comorbidities as associated with more complications, this could not be confirmed in this study.[24]

Kusumoto et al. and Sohail et al., found that women have a higher risk of death than men.[23,24] However, in our study, both deaths were observed in male patients. We also found that the extraction group had more defibrillator leads than the explant group. Sohail et al. also stated that these leads show lower success rates with manual traction and that extraction sheaths are commonly needed in the procedure.[24]

In this study, all patients with three or more leads were submitted to an extraction, confirming that a higher number of leads per patient is associated to a higher risk of requiring the use of extraction sheaths. Sohail et al. stated that higher number of leads per patients is associated to more adherence, which could justify this finding.[24] This is also true in cases of failure in removing older atrium and RV leads.

The rates of major complications (6.6%) and deaths (3.3%) were slightly higher when compared to the low-volume centers (less than 30 extractions per year) in the ELECTRA study (4.1% and 2.5%), which is the largest worldwide register of CIED removals.[25] We believe that our smaller population might have contributed to this difference. Minor complication rates (4.9%) were similar to the rates in this registry (5.0%).[25]

As expected, blood transfusion was more frequent among patients with complications, since it was used as treatment in some cases. Longer procedures were associated with more complications. This reinforced the finding in the ELECTRA study, which showed that the low-volume centers had longer procedures and more complications when compared to the high-volume centers.[25]

Table 2 – Procedure description

	Explant (n=10)	Extraction (n=51)	p-value
Reason for device removal			
Dysfunctional lead n(%)	0 (0.0)	8 (15.7)	0.33
Device-related endocarditis n(%)	3 (30)	14 (27.5)	1.0
Isolated pocket erosion n(%)	0 (0.0)	12 (23.5)	0.19
Pocket infection n(%)	1 (10)	10 (19.6)	0.67
Upgrade n(%)	0 (0.0)	1 (2)	1.0
Pocket infection with bacteremia n(%)	4 (40)	5 (9.8)	0.09
Number of leads removed per patient			0.75
1 n(%)	2 (20)	8 (15.7)	
2 n(%)	8 (80)	34 (66.7)	
3 n(%)	0 (0.0)	7 (13.7)	
4 n(%)	0 (0.0)	1 (2.0)	
5 n(%)	0 (0.0)	0 (0.0)	
6 or more n(%)	0 (0.0)	1 (2.0)	
Outcome			0.58
Clinical success n(%)	10 (100)	46 (90.2)	
Failure n(%)	0 (0.0)	5 (9.8)	
Death n(%)	0 (0.0)	2 (3.9)	
Complications n(%)	0 (0.0)	7 (13.7)	1.0
Time of complication			1.0
Intra-procedural n(%)	0 (0.0)	4/7 (57.1)	
Post-procedural n(%)	0 (0.0)	3/7 (42.9)	
Type of complication			1.0
Major n(%)	0 (0.0)	4/7 (57.1)	
Minor n(%)	0 (0.0)	3/7 (42.9)	
Blood transfusion n(%)	0 (0.0)	5 (9.8)	0.58
Implant of a new device on removal date n(%)	2 (22.2)	20 (55.6)	0.14
Implant of a new device after the removal n(%)	9 (90.0)	36 (70.6)	0.27
Days of hospitalization before the procedure n(%)	8 [5.5 - 22.0]	9.0 [4.0 - 17.5]	0.88
Days of hospitalization after the procedure n(%)	23 [6.0 - 63.0]	10.0 [4.0 - 23.5]	0.16

Continuous variables were shown as mean ± standard deviation and median ± interquartile ranges. Categorical variables were presented as frequencies and percentages. P-values in the table are related to the Student's or Mann-Whitney test for continuous variables and x^2 and Fisher Tests for categorical variables.

Our clinical success rate (91.8%) was slightly lower than that described in the low-volume centers in the ELECTRA study (94.3%), probably because of the smaller number of enrolled patients.[25] Recently, Bongiorni et al. showed their experience in a high-volume center in Europe, with 98.4% of complete procedural success (2015).[26] This rate was dramatically higher than in our study (78.7%), but our figure is similar to that described by Eckhard A et al. (81% - 1996).[27] They also had a similar failure rate when compared to ours (7% vs 8%).[27] In the ELECTRA study, manual traction was more common in low-volume centers, which is compatible with our percentage of manual traction.[25]

The number of hospitalization days after the procedure in the explant group was more than double when compared to the extraction group (10 vs. 23 days), due to the fact that more than half of the patients in the former group (70% vs. 37.3%) had device-related endocarditis or pocket infection with bacteremia. The fact that all explant procedures were preceded by a pacemaker implant suggests that bacteremia during the implant was the most common reason for this finding. Hence, positive blood culture results were more frequently observed in the explant group, which was responsible for the longer hospital stay after the procedure to complete the antibiotic therapy.

Kutarski et al. and Bongiorni et al. stated that cardiac tears are more common than vascular tears in centers that use mechanical sheaths.[26,28] This was also seen in this study, since the cardiac tear was present in twice the number of patients

Table 3 – Variables associated with procedure success

	Failure (n=5)	Clinical success (n=56)	p-value
Male gender n(%)	3 (60)	38 (67.9)	1.0
Age (years)	56.4 ±13.7	60.3 ± 21.08	0.687
Ejection fraction ≤ 30% n(%)	2 (40)	8 (14.3)	0.444
Comorbidities			
Coronary artery disease n(%)	0 (0.0)	17 (30.4)	0.352
Mellitus diabetes n(%)	1 (20)	16 (28.6)	1.0
Chronic kidney disease n(%)	0 (0.0)	9 (16.1)	0.754
Previous thoracic surgery n(%)	2 (40)	17 (30.4)	1.0
Previous lead removal n(%)	0 (0.0)	4 (7.1)	0.513
Reason for device removal			
Dysfunctional lead n(%)	0 (0.0)	8 (14.3)	0.83
Device-related endocarditis n(%)	2 (40)	15 (26.8)	0.912
Isolated pocket erosion n(%)	0 (0.0)	12 (21.4)	0.57
Pocket infection n(%)	2 (40)	9 (16.1)	0.468
Upgrade n(%)	1 (20)	0 (0.0)	0.124
Pocket infection with bacteremia n(%)	0 (0.0)	9 (16.1)	0.579
Number of leads removed per patient			0.606
1 n(%)	2 (40)	8 (14.3)	
2 n(%)	3 (60)	38 (69.6)	
3 n(%)	0 (0.0)	7 (12.5)	
4 n(%)	0 (0.0)	1 (1.8)	
6 or more n(%)	0 (0.0)	1 (1.8)	
Type of procedure			0.687
Explant n(%)	0 (0.0)	10 (17.9)	
Extraction n(%)	5 (100)	46 (82.1)	
Type of lead removed			
Atrial n(%)	5 (100)	51 (91.1)	1.0
Right ventricle n(%)	4 (80)	46 (82.1)	1.0
Defibrillator lead n(%)	1 (20)	11 (19.6)	1.0
Left ventricle lead n(%)	1 (20)	9 (16.1)	1.0
Atrial lead age (years)	9.5 [7.9 - 15.2]	5.1 [1.4 - 8.2]	0.04
Right ventricle lead age (years)	9.5 [7.9 - 15.2]	5.1 [1.4 - 8.9]	0.05
Positive Blood culture n(%)	2 (40)	19 (33.9)	0.887
Presence of *S. aureus* in blood culture n(%)	1 (20)	11 (19.6)	1.0
Days in hospital before removal	13.0 [6.0 - 19.0]	8.5 [4.0 - 17.5]	0.343

Continuous variables were shown as mean ± standard deviation and median ± interquartile ranges. Categorical variables were presented as frequencies and percentages. P-values in the table are related to the Student's or Mann-Whitney test for continuous variables and x^2 and Fisher Tests for categorical variables.

with vascular tear. The patient who died due to a vascular tear did not have a prior documented vascular occlusion, which is described as a prognostic factor for this complication by Zucchelli et al. [29] This same author states that the St Jude Medical Riata® defibrillator (St. Jude Medical, Inc., St. Paul, MN, USA) leads and three or more leads were associated with cardiac tears.[29] However, our two patients who had these complications had two leads, in the atrium and non-defibrillator RV leads.

Our study has some limitations which should be considered. This was a retrospective analysis; therefore, clinical events may have been underreported. This study has shown an initial experience with mechanical sheaths in our hospital and this learning curve could have contributed to a lower success and a higher major complication rates. The number of extraction

Table 4 – Variables associated with procedure complications

	Presence of complications (n=7)	Absence of complications (n=54)	p-value
Male gender n(%)	4(57.1)	37(68.5)	0.67
Age (years)	50.14 ± 14.99	61.26 ± 20.9	0.18
Hemoglobin (g/dl)	11.5 [10.35 - 12.70]	12.7 [11.3 - 13.4]	0.34
INR	1.22 [1.17 - 1.29]	1.10 [1.04 - 1.24]	0.17
Ejection fraction ≤ 30% n(%)	2 (28.6)	8 (14.8)	0.78
Presence of tricuspid regurgitationn(%)	4 (57.1)	26 (52.0)	1.0
Comorbidities			-
Coronary artery disease n(%)	0 (0.0)	17 (31.5)	0.18
Mellitus diabetes n(%)	0 (0.0)	17 (31.5)	0.18
Chronic kidney disease n(%)	0 (0.0)	9 (16.7)	0.58
Anticoagulation n(%)	4 (57.1)	9 (16.7)	0.07
Previous cardiac surgery n(%)	4 (57.1)	15 (27.8)	0.19
Previous lead removal n(%)	0 (0.0)	4 (7.4)	0.74
Reason for device removal			-
Dysfunctional lead n(%)	0 (0.0)	8 (14.8)	0.58
Device-related endocarditis n(%)	2 (28.6)	15 (27.8)	1.0
Isolated pocket erosion n(%)	2 (28.6)	10 (18.5)	0.62
Pocket infection n(%)	3 (42.9)	8 (14.8)	0.1
Upgrade n(%)	0 (0.0)	1 (1.9)	1.0
Pocket infection with bacteremia n(%)	0 (0.0)	9 (16.7)	0.58
Number of leads removed per patient		-	1.0
1 n(%)	1 (14.3)	10 (18.5)	
2 n(%)	5 (71.4)	36 (66.7)	
3 n(%)	1 (14.3)	6 (11.1)	
4 n(%)	0 (0.0)	1 (1.9)	
6 or more n(%)	0 (0.0)	1 (1.9)	
Type of procedure		-	0.59
Explant n(%)	0 (0.0)	10 (18.5)	
Extraction n(%)	7 (100)	44 (81.5)	
Type of lead removed			-
Atrial n(%)	6 (85.7)	50 (92.6)	0.47
Right ventricle n(%)	6 (85.7)	44 (81.5)	1.0
Defibrillator lead n(%)	1 (14.3)	11 (20.4)	1.0
Left ventricle lead n(%)	2 (28.6)	8 (14.8)	0.32
Atrial leads age (years)	7.7 [5.1 - 18.1]	5.1 [1.3 - 8.3]	0.16
Right ventricle lead age (years)	8.1 [5.5 - 15.4]	5.2 [1.4 - 8.7]	0.11
Left ventricle lead age (years)	3.9 [3.8 - 4.0]	5.2 [2.3 - 7.6]	0.77
Blood transfusion n(%)	5 (71.4)	0 (0.0%)	<0.001
Presence of *S. aureus* in blood culture n(%)	1 (14.3)	11 (20.4)	1.0
Positive blood culture n(%)	1 (14.3)	20 (37)	0.37
Procedure duration in minutes (minutes)	180 [146.25 - 202.5]	72.5 [47.75 - 105.0]	0.003
Days in hospital before removal	13 [6.5 - 29.5]	8 [4.0 - 15.5]	0.24

Continuous variables were shown as mean ± standard deviation and median ± interquartile ranges. Categorical variables were presented as frequencies and percentages. P-values in the table are related to the Student's or Mann-Whitney test for continuous variables and x^2 and Fisher Tests for categorical variables. INR: International Normalized Ratio.

procedures during the designated period did not reach the ones reported in the European and American studies, of which some have shown more than 1,000 patients. However, in South America, this is a significant number since fewer studies using mechanical sheaths have been published in which the sample had fewer than 40 patients.

Conclusion

Our overall complication and clinical success rates were 11.5% and 91.8%, respectively. Older atrial and ventricular leads were associated to lower success rates. Although longer procedures and blood transfusions were more frequently seen in the complication group, these were not the reasons for complications.

Our results reaffirm that even in public Brazilian hospitals with limited resources and consequently, with lower extraction volumes per year, success can be achieved in the majority of the cases of transvenous lead extractions. Moreover, the success and complication rates were similar to the ones in low-volume centers in Europe.

Author Contributions

Conception and design of the research and Analysis and interpretation of the data: Di Nubila BCLS, Lacerda GC, Barbosa RM; Acquisition of data: Di Nubila BCLS; Statistical analysis and Writing of the manuscript: Di Nubila BCLS, Lacerda GC; Critical revision of the manuscript for intellectual contente: Di Nubila BCLS, Lacerda GC, Rey HCV, Barbosa RM.

Potential Conflict of Interest

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

Sources of Funding

There were no external funding sources for this study.

Study Association

This article is part of the thesis of master submitted by Bruna Costa Lemos Silva Di Nubila, from Instituto Nacional de Cardiologia.

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Removal of Transvenous Pacing Leads in Artificial Cardiac Stimulation Systems

Silas dos Santos Galvão Filho[1]

Centro Avançado de Ritmologia e Eletrofisiologia (CARE) - Hospital da Beneficência Portuguesa de São Paulo,[1] *São Paulo, SP – Brazil*

Short Editorial related to the article: Percutaneous Removal of Cardiac Leads in a Single Center in South America

The pacing leads are the most fragile part of the artificial cardiac stimulation systems, being responsible for the majority of complications. The removal of transvenous pacing leads has always been a challenge, and for a long time the percutaneous removal was reserved for the most recently implanted leads and thoracotomy was the best option for the older cases.

Since the 1990s, several tools for removing leads have been developed, such as: special stainless steel guide wires with locks (locking stylet), counter-traction sheaths without or with mechanical release mechanisms or laser-powered ones and long deflectable sheaths with snare guides for femoral extraction. These instruments allowed the percutaneous extraction of older leads with high success and low complication rates, as demonstrated in the European Electra Study,[1] which involved 3,510 patients with 96.7% of clinical success and 1.7% of major complications. With the increase in indications and greater complexity of artificial cardiac stimulation (ACS)[2] systems, which sometimes required up to 4 leads, in addition to the longer survival of the patients, which implies in several generator exchanges, the need for lead removal, sometimes mandatory, has considerably increased.

Despite these enormous advances, percutaneous removal remains a complex procedure that involves risks. Therefore, in order to carry out these procedures, some aspects must be considered:

1- Indication: In some situations of ACS, as in the presence of infections, the indication of lead removal is mandatory, while in others the complete removal may be debatable. However, in all cases, the risks and benefits of both the indication and the choice of removal method should be carefully evaluated.

2- Group expertise: The operators' experience regarding the use of the several percutaneous lead removal tools is essential to achieve good results. Some international guidelines recommend the performance of 40 lead extractions in at least 30 interventions, to consider the physician qualified to perform these procedures.[3,4] The Electra Study[1] involved 73 centers in 19 European countries and showed that higher volume centers, defined as the ones that perform more than 30 removal procedures per year, have significantly better results regarding both success and complication rates.

3- Availability of materials: The percutaneous removal of lead cables with more than one year of implantation presupposes the use of at least one extraction system, either through the upper subclavian-cava route (counter-traction sheaths with release mechanisms with mechanical rotation or laser-powered ones), or via the femoral vena cava (long deflectable sheaths with snare guides).[5] Ideally, the operator group should have experience with both access routes, since femoral extraction can be complementary that by the subclavian route, and in some cases of abandoned leads, it is the only option for percutaneous extraction. It is also important to have venous occlusion-balloon catheters (Bridge balloon) available, for cases of severe lesions in the venous system.

4- Operating Center conditions: The percutaneous extraction procedure must be performed under general anesthesia, with surgical (cardiovascular) support and a place in the ICU, where the patient must remain at least during the immediate postoperative (IPO) period. The center should also have transthoracic or intracardiac echocardiography available.

The article "Percutaneous Removal of Cardiac Leads in a Single Center in South America"[6] is one of the few publications in the national literature showing the initial experience of a public hospital service in Brazil, with the removal of 128 leads in 61 patients, showing good results (91% of clinical success and 78.7% of total success) and low complication rates (6.6% of major complications, 3.3% of deaths). Recently Costa et al.[7] published in this journal a robust prospective registry of lead removal in one of the largest cardiological centers in Brazil, involving 634 leads in 365 patients, using all the modalities and extraction tools and showing much better results (96.7% of clinical success and 90.1% of total success) but with higher mortality (8.2% of in-hospital deaths, of which only 1.5% are directly related to the extraction procedure). I believe that these two national articles can stimulate the percutaneous removal of lead cables in Brazil, an important procedure in artificial cardiac pacing and still underutilized in our country.

The removal of transvenous lead cables is by far the most complex and the one involving the greatest risk among artificial cardiac pacing procedures. Using the tools that are currently available, percutaneous removal is the best option in the vast majority of cases, being a safe and very effective procedure. However, the experience of the operator group is fundamental to obtain good results and, in this sense, regarding the first procedures using these extraction systems, it is very important to have the support of physicians qualified for training under the proctoring regime, until the operator group has gained experience.

Keywords

Pacing Leads in Artificial Cardiac Stimulation; Percutaneous Removal; Infection of Cardiac Stimulation Systems; Extraction Tools; Cardiac Resynchronization Devices.

Mailing Address: Silas dos Santos Galvão Filho •
Rua Martiniano de Carvalho, 864/702. Postal Code 01321-000, São Paulo, SP – Brazil
E-mail: sdsantos@uol.com.br

DOI: https://doi.org/10.36660/abc.20210204

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Original Article

Clinical Heart Failure Stratification Through Native T1 Mapping: Experience of a Referral Service

Thiago dos Santos Silva Marques,[1] André Maurício de Souza Fernandes,[2] Roberto Nery Dantas Júnior,[1] Robert W. Biederman,[3] Ana Paula Marques de Oliveira Melo,[4] Roque Aras[5]

Instituto do Coração do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo,[1] São Paulo, SP - Brazil
Universidade Federal da Bahia - Faculdade de Medicina de Bahia,[2] Salvador, BA - Brazil
Allegheny General Hospital,[3] Pittsburgh, Pennsylvania - USA
Hospital Heliópolis,[4] São Paulo, SP - Brazil
Hospital Universitário Professor Edgard Santos,[5] Salvador, BA - Brazil

Abstract

Background: **Diffuse cardiac fibrosis is an important factor in the prognostic assessment of patients with ventricular dysfunction. Cardiovascular magnetic resonance imaging (CMR) native T1 mapping is highly sensitive and considered an independent predictor of all-cause mortality and heart failure (HF) development in patients with cardiomyopathy.**

Objectives: **To evaluate the feasibility of native T1 mapping assessment in patients with HF in a cardiology referral hospital and its association with structural parameters and functional profile.**

Methods: **Cross-sectional study with adult patients with HF NYHA functional classes I and II, ischemic and non-ischemic, followed in a referral hospital, who underwent CMR. Native T1 values were analyzed for structural parameters, comorbidities, etiology, and categorization of HF by left ventricular ejection fraction (LVEF). Analyses were performed with a significance level of 5%.**

Results: **Enrollment of 134 patients. Elevated native T1 values were found in patients with greater dilation (1004.9 vs 1042.7ms, p = 0.001), ventricular volumes (1021.3 vs 1050.3ms, p <0.01) and ventricular dysfunction (1010.1 vs 1053.4ms, p <0.001), also present when the non-ischemic group was analyzed separately. Patients classified as HF with reduced ejection fraction had higher T1 values than those with HF and preserved ejection fraction (HFPEF) (992.7 vs 1054.1ms, p <0.001). Of those with HFPEF, 55.2% had higher T1.**

Conclusions: **CMR T1 mapping is feasible for clinical HF evaluation. There was a direct association between higher native T1 values and lower ejection fraction, and with larger LV diameters and volumes, regardless of the etiology of HF. (Arq Bras Cardiol. 2021; 116(5):919-925)**

Keywords: **Heart Failure; Cardiomyopathy, Dilated; Ventricular Dysfunction, Left; Fibrosis; Diagnosis Imaging; Chagas Cardiomyopathy; Magnetic Resonance Spectroscopy/methods.**

Introduction

Cardiac fibrosis has become an important factor in the prognostic evaluation of patients with ventricular dysfunction, considered as one of the consequences of left ventricular (LV) pathological remodeling,[1] which plays an important role in myocardial response to injury. Fibrotic tissue leads to progression of heart failure (HF) and worse prognosis.[2] Noninvasive imaging methods for quantitative assessment at an early stage of the presence and extent of myocardial fibrosis are necessary to better stratify the risk of HF and to monitor the effects of treatment.[3]

Cardiovascular magnetic resonance imaging (CMR), considered an effective tool for evaluating myocardial morphology and function, as well as tissue changes,[4-7] has emerged as a first-line, noninvasive modality for investigation of etiology and prognosis in patients with myocardial dysfunction.[8,9] Native T1 mapping is a fast, non-contrast method that aims to detect diffuse myocardial changes in a variety of cardiac conditions. It has a wide sensitivity for pathological changes, including detection of myocardial edema, infarction, ischemia, cardiomyopathies and diffuse fibrosis.[10-14] Therefore, native T1 mapping provides an alternative imaging method for assessing the cardiac area at risk.[15]

A multicenter observational study showed that native T1 was a better predictor of worse outcomes in dilated cardiomyopathy (DCM) than the classic clinical parameters,

Mailing Address: Thiago dos Santos Silva Marques •
Rua Leonor Calmon, 74, Ed. Principe de Lyon, Apt 1202. Postal Code 40296-210, Cidade Jardim, Salvador, BA - Brazil
E-mail: thiago.ssm@hotmail.com
Manuscript received May 12, 2019, revised manuscript March 08, 2020, accepted April 15, 2020

DOI: https://doi.org/10.36660/abc.20190782

showing that native T1 was the strongest independent predictor of all-cause mortality and development of HF.[16,17]

The severity of diffuse disease, assessed by the T1 map, maybe a pathophysiologically relevant parameter, since it is directly related to the progression of the disease and to the functional capacity of the remaining myocardium. The continuous nature of T1 values corresponds accurately to the rate of clinical events: the higher the native T1, the greater the risk of adverse events. These findings allow us to refine the current approach to risk stratification in patients with cardiomyopathies, especially DCM.[17]

Our study aims to evaluate the feasibility of native T1 mapping assessment in patients with HF in a cardiology referral hospital and its association with structural parameters and the functional profile of these patients.

Methods

Study Population

Patients were included in the period between 2012 and 2016. They were followed up at the HF outpatient clinic at Hospital Ana Nery, Salvador, Bahia, who were consecutively referred for CMR as part of the clinical care and diagnosis.

Patients aged ≥ 18 years with a diagnosis of HF, according to Framingham and/or Boston criteria, according to the Brazilian Guideline for Chronic and Acute Heart Failure, with functional classes I and II by the New York Heart Association (NYHA), with at least type II diastolic HF defined by transthoracic echocardiogram were consecutively selected. Multiple HF etiologies were divided into ischemic or non-ischemic groups, based on the documentation of myocardial infarction (MI), ischemia by some diagnostic method or presence of ischemic (transmural or subendocardial, following a coronary territory) late gadolinium enhancement (LGE) in CMR. In relation to Chagas cardiomyopathy, the diagnosis was considered in the presence of positive serology and after exclusion of ischemia.

All patients underwent routine examinations at the HF outpatient clinic, such as chest radiography, walking test and electrocardiogram, associated with the evaluation of a multidisciplinary team. All patients were followed up at the unit's Heart Failure service and used optimized drug therapy, associated or not with cardiac rehabilitation by the multidisciplinary team, according to the clinical criteria of the attending physician.

The work was approved by the institution's Ethics and Research Committee, as a subproject of the main work entitled "Characteristics of patients submitted to cardiovascular magnetic resonance at a referral hospital".

CMR Exam Acquisition Protocol and Image Evaluation

All CMR examinations were performed on a 1.5T Avanto full body scanner (Siemens Medical Solutions, Germany) using an 8-channel heart coil. Acquired images were performed to obtain 2D cine balanced SSFP stacks in two, three and four chambers, in addition to the short axis. The cine images were acquired during expiratory apnea (20 frames per cardiac cycle with cuts of 8mm thickness, FOV 300, matrix 208 Åx 80, BW 925 KHz / pixel). For analysis of the left ventricular function, the short axis was composed of a minimum of 8 and a maximum of 12 cuts, 8 mm thick and 2 mm wide.

Native T1 mapping images were performed without contrast injection in the mid-section of the LV through the Modified Look-Locker Inversion recovery (MOLLI) sequence, with electrocardiographic gating, 250 to 360 mm FOV; 192 × 122 to 192 × 183 matrix size. Slice thickness of 6-8 mm; 2.2 / 1.1ms ≈ TR / TE, flip angle 35°; Factor GRAPPA = 2; 17 heartbeats (collecting 3 + 3 + 5 samples). Due to the protocol used in the study, the calculation of extracellular volume (ECV) and post-contrast T1 mapping were not performed, since the use of contrast was optional and indicated only when necessary according to clinical evaluation.

The normal native myocardial T1 value for our sample was previously obtained through a pilot study with patients without comorbidities and structurally normal hearts, of the same institution / scanner, as recommended by Society for Cardiovascular Magnetic Resonance (SCMR).[18] According to this evaluation, the average normal value considered for native myocardial T1 was 983.46 ± 34.38 ms.

All the exams were analyzed through the software cvi42 (Circle Cardiovascular Imaging Inc., Calgary, Canada) by a cardiovascular imaging specialist with more than 5 years of experience. After all the contours were drawn in the endocardial and epicardial borders of the LV short axis, in end systole and diastole, all functional variables were quantified, such as left ventricular ejection fraction (LVEF), left ventricular end-diastolic diameter (LVEDD), left ventricular end-diastolic (LVEDV) and end-systolic (LVESV) volumes and myocardial mass, all indexed to the body surface, according to recommended CMR reference values.[19] To calculate the native T1 map, the edges of the tracings were made narrowly in order to avoid maximum contamination with the ventricular cavity or with epicardial fat, and in order to avoid areas with visibly identifiable late myocardial enhancement (Figure 1). The exams were analyzed by a single experienced professional.

Native T1 values obtained were analyzed in relation to clinical comorbidities, structural parameters, etiology and HF categorization. HF was categorized into: 1) HFrEF (heart failure with reduced EF), EF<40%; 2) HFmrEF (heart failure with mid-range EF), EF 40-49% and; 3) HFpEF (heart failure with preserved EF), EF ≥ 50%.[20,21]

Statistical Analysis

The collected data was described through averages and standard deviation for normal distribution variables; and median and interquartile range for the others. Categorical variables were described in absolute numbers and percentages. Variable normality was tested using the Kolmogorov-Smirnov. Statistical tests were performed according to the type of variable and distribution normality: unpaired Student's t-test, Mann Whitney test and chi-square test. P values less than 0.05 were considered statistically significant. Statistical analysis was performed using SSPS software (version 22.0).

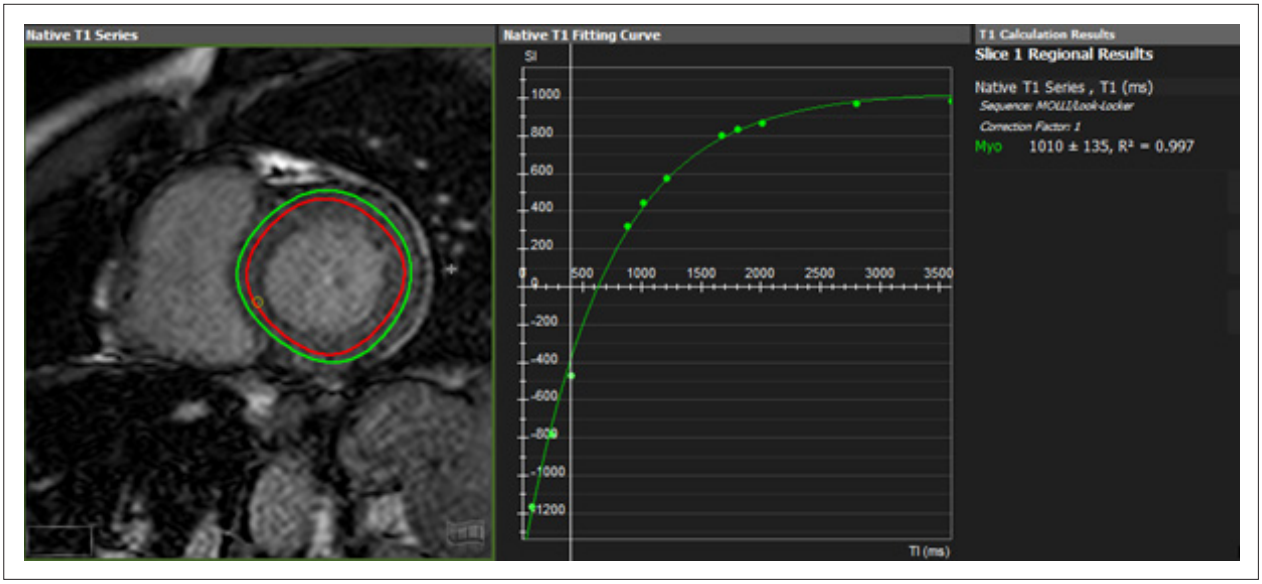

Figure 1 – *Native T1 mapping calculation. Source: Marques, 2019.*

Results

We included 134 patients from January 2014 to December 2016. There was a predominance of male patients, reduced LVEF, and increased cavity diameters/volumes (Table 1). Non-ischemic patients were the majority, in a total of 95 individuals (70.9%). There was late enhancement in 56 patients out of 95 with non-ischemic cardiomyopathy (59%), with a predominance of mesocardial and multifocal enhancement. Among patients with ischemic cardiomyopathy, 34 patients (87%) had delayed enhancement, most of them transmural.

Elevated native myocardial T1 values, when analyzed in relation to the left ventricle, were found in patients with greater dilation ($p = 0.007$), larger ventricular volumes ($p < 0.01$) and ventricular dysfunction ($p < 0.001$) (Table 2). In an additional dichotomized evaluation, considering these same functional variables, the associations of the native myocardial T1 value were maintained, as shown in Table 3. When the subgroup analysis of non-ischemic patients was performed, the same associations found remained present (Tables 3 and 4). There was adequate intraobserver agreement in detecting elevated T1 values (Kappa 0.82; $p = 0.001$).

When analyzing native myocardial T1 in relation to the HF profile, classified according to LVEF, a higher T1 value was observed in patients with LVEF <35% ($p < 0.001$) (Table 5). There was a significant difference between the groups, with higher T1, when comparing HFrEF with HFmrEF ($p = 0.004$); and with HFpEF ($p < 0.001$); as compared to HFmrEF with HFpEF ($p = 0.02$). Of the patients with HFpEF, 55.2% already had elevated T1. When analyzed in relation to diameters and cavity volumes, higher values were observed in patients with HFrEF and HFmrEF when compared with HFpEF ($p < 0.01$).

Considering HF etiology, regardless of etiology, there was a high percentage of patients with elevated native T1 (89.7% in ischemic and 81.1% in non-ischemic), with a higher T1 value in ischemic patients compared to non-ischemic ($p = 0.004$). Specifically analyzing the non-ischemic group, 13 patients were diagnosed with Chagas cardiomyopathy, all presenting elevated native T1 (1077.1 ± 61.1ms) associated with reduced LVEF (27.6 ± 16.8%), high LVEDD (7.1 ± 1.5cm), LVESD (6.1 ± 1.7cm), indexed LVEDV (146.7 ± 52.3 ml/m^2) and indexed LVESV (112.7 ± 54.1 ml/m^2).

Among the comorbidities evaluated, there was a statistical association of higher T1 values, above the normal range, in smokers ($p = 0.032$). (Table 6)

Discussion

The present study demonstrates CMR native T1 mapping feasibility in clinical practice with an association with myocardial dysfunction, expressed by lower LVEF and larger ventricular volumes and diameters, regardless of the etiology of the cardiomyopathy.

CMR allows the detection of diffuse myocardial fibrosis through T1 mapping, with high agreement with myocardial biopsy.[6] A recently published study of 637 non-ischemic DCM patients demonstrated that the presence of fibrosis by native T1 mapping is related to the combined outcome of all-cause mortality and HF ($p < 0.001$), and in the multivariate analysis, it is considered an independent predictor for these outcomes (CI 1.06-1.15, $p < 0.001$).[16] A previous study validated the use of T1 mapping to confirm fibrosis, with an excellent correlation ($R = 0.95$, $p < 0.001$) between CMR examination and histology, and when analyzed in comparison with LGE, the latter was less accurate in the evaluation of diffuse interstitial fibrosis.[6] Thus, native T1 mapping is an imaging method that allows the detection of fibrosis with greater precocity than the LGE, which is related to a worse prognosis.[22]

Table 1 – Population's clinical and functional characteristics

General features	n (134)
Age (years) (SD)	50.2 (14.0)
Male gender (%)	94 (70.1%)
Non-ischemic etiology	95 (70,9%)
Left atrium (cm) (SD)	3,9 (0,8)
Interventricular septum (cm) (SD)	0,8 (0,2)
Posterior wall (cm) (SD)	0,7 (0,2)
RVEF (%) (SD)	39,6 (15,9)
LVEF (%) (SD)	34.4 (17.9)
LVEDD (cm) (SD)	6.4 (1.2)
LVESD (cm) (SD)	5.1 (1.6)
LVEDV (ml) (SD)	215.1 (96.2)
LVEDV index (ml/m^2) (SD)	116.7 (51.9)
LVESV (ml) (SD)	150.9 (93.7)
LVESV index (ml/m^2) (SD)	82.5 (52.3)
MM (g) (IR)	88.5 (73,7; 114,0)
MM index (g) (IR)	49.0 (40,0; 62,5)
Hypertension	53 (39.6%)
Diabetes	21 (15.7%)
Coronary artery disease	33 (24.6%)
Chronic renal failure	13 (9.7%)
Smoking	20 (14.9%)
Chagas Disease	13 (9.7%)
Dyslipidemia	7 (5.2%)

RVEF: right ventricular ejection fraction; LVEF: left ventricular ejection fraction; LVEDD: Left ventricular end-diastolic diameter; LVESD: left ventricular end-systolic diameter; MM: myocardial mass; LVEDV: left ventricular end-diastolic volume; LVESV: left ventricular end-systolic volume; SD: standard deviation; IR: interquartile range. Source: Marques, 2019

Among the etiologies in Brazil, there is a distinct characteristic regarding the prevalence and importance of Chagas disease.[23,24] In the present study, there was a prevalence of 9.7% of Chagas cardiomyopathy, which represents 13.7% of non-ischemic patients. All these patients had elevated native T1 values, with a higher observed native T1 associated with lower LVEF, higher LVEDD and LVEDV when compared to the other non-ischemic T1-elevated patients, but without statistical significance. Fewer previous studies have shown a statistically significant association ($p < 0.001$) between the presence of fibrosis with worse outcomes in these patients, mainly related to arrhythmic events.[23,24] In a previous study, the risk of ventricular tachycardia (VT) was higher in the presence of transmural fibrosis by LGE, being a predictor of clinical VT (RR 4.1, $p = 0.04$).[23]

There are some limitations worth noting, mainly related to the cross-sectional model of the study. The sample size was limited, which precludes proper validation of the results. Some additional pathologies may lead to T1 changes, including diffuse myocardial fibrosis from other causes, edema, inflammation, and infiltrative diseases. As no post-contrast T1 mapping study was performed, the calculation and evaluation of the ECV was not possible, which does not reduce the importance of the findings, since native T1 has been shown in the literature to be comparable to ECV in quantification of histologically demonstrated collagen.[25] Although it was performed and analyzed according to previous recommendations, as T1 mapping is a relatively new method, it still requires methodological standardization.[26]

Conclusions

Native myocardial T1 mapping is feasible for clinical HF assessment, with significant correlation to worse functional profiles. There was a direct association between a higher native T1 value and worse clinical and functional parameters, including a lower ejection fraction, larger LV diameters and volumes, regardless of the etiology of cardiomyopathy. Importantly, in patients with Chagas heart disease, a pathology prevalent in Brazil, the same association was observed.

Table 2 – Evaluation of native T1 values with functional parameters

	Normal T1 (ms)	Abnormal T1 (ms)	p
LVEF (%) (SD)	50.27 (16.3)	31.26 (16.5)	<0.001*
LVEDD (cm) (SD)	5.74 (1.2)	6.55 (1.2)	0.007*
LVESD (cm) (SD)	3.95 (1.42)	5.32 (1.5)	<0.001*
LVEDV (ml) (SD)	155.0 (83.5)	200.0 (107.5)	0.001*
LVEDV index (ml/m^2) (SD)	85.5 (47.0)	109.0 (49.8)	0.001*
LVESV (ml) (SD)	79.0 (72.3)	147.5 (102.8)	0.001*
LVESV index (ml/m^2) (SD)	40.5 (36.0)	82.5 (57.5)	0.001*
MM (g) (IR)	81.0 (66.0; 99.2)	89.5 (77,0; 119.5)	0.05†
MM index (g/m^2) (IR)	41.5 (36.5; 52.5)	50.0 (40.5; 62.7)	0.025†

*LVEF: left ventricular ejection fraction; LVEDD: Left ventricular end-diastolic diameter; LVESD: left ventricular end-systolic diameter; MM: myocardial mass; LVEDV: left ventricular end-diastolic volume; LVESV: left ventricular end-systolic volume; SD: standard deviation; IR: interquartile range. * Student's T test. † Mann-Whitney test. Source: Marques, 2019.*

Table 3 – Evaluation of native myocardial T1 values with functional parameters in the general and non-ischemic population

		General		Non-Ischemic	
		T1 (ms)	p	T1 (ms)	p
LVEF (%) (SD)	>35%	1010.1 (46.6)	<0.001	1008.9 (43.7)	<0.001
	<35%	1053.4 (48.1)		1052.1 (48.1)	
LVEDD (cm) (SD)	Normal	1004.9 (48.1)	0.001	1010.8 (39.9)	0.03
	Dilated	1042.7 (50.4)		1038.3 (53.4)	
LVESD (cm) (SD)	Normal	989.0 (43.7)	<0.001	994.2 (37.7)	0.001
	Dilated	1043.8 (49.0)		1040.3 (51.1)	
LVEDV index (ml/m^2) (SD)	Normal	1021.3 (49.3)	0.001	1015.5 (46.0)	0.001
	Increased	1050.4 (50.8)		1049.2 (52.4)	
LVESV index (ml/m^2) (SD)	Normal	1000.7 (48.3)	<0.001	999.8 (42.5)	<0.001
	Increased	1048.5 (47.3)		1046.2 (49.5)	

*LVEF: left ventricular ejection fraction; LVEDD: left ventricular end-diastolic diameter; LVESD: left ventricular end-systolic diameter; LVEDV: left ventricular end-diastolic volume; LVESV: left ventricular end-systolic volume; SD: standard deviation; * Student's T test.*

Table 4 – Evaluation of native myocardial T1 values with functional parameters in non-ischemic patients

	Normal T1 (ms)	Abnormal T1 (ms)	p
LVEF (%) (SD)	48.9 (16.6)	32.3 (17.9)	0.001*
LVEDD (cm) (SD)	5.9 (1.2)	6.6 (1.4)	0.035*
LVESD (cm) (SD)	4.0 (1.5)	5.4 (1.7)	0.002*
LVEDV (ml) (SD)	173.7 (66.8)	236.5 (112.8)	0.003*
LVEDV index (ml/m^2) (SD)	92.2 (30.6)	122.7 (60.9)	0.001*
LVESV (ml) (SD)	97.7 (63.3)	170.5 (107.9)	<0.001*
LVESV index (ml/m^2) (SD)	50.1 (31.2)	93.0 (60.2)	<0.001*
MM (g) (IR)	84.5 (66.7; 99.2)	91.0 (77.0; 129.0)	0.06†
MM index (g/m^2) (IR)	42.0 (37.7; 52.5)	56.2 (42.0; 95.0)	0.02†

*LVEF: left ventricular ejection fraction; LVEDD: left ventricular end-diastolic diameter; LVESD: left ventricular end-systolic diameter; MM: myocardial mass; LVEDV: left ventricular end-diastolic volume; LVESV: left ventricular end-systolic volume; SD: standard deviation; IR: interquartile range. * Student's T test. † Mann-Whitney test. Source: Marques, 2019*

Table 5 – Association of native T1 values with heart failure classification

	N	Normal T1 (ms)	High T1 (ms)	p
HFrEF	84	5 (6%)	79 (94%)	< 0.001
HFmrEF	21	4 (19%)	17 (81%)	
HFpEF	29	13 (45%)	16 (55%)	

*HFrEF: heart failure with reduced ejection fraction; HFmrEF: heart failure middle range ejection fraction; HFpEF: heart failure with preserved ejection fraction. *chi-square test Source: Marques, 2019*

Table 6 – Native T1 values association with clinical comorbidities

	Normal T1	Abnormal T1	p
Hypertension (%)	9 (17.0%)	44 (83.0%)	0.88
Diabetes (%)	1 (4.8%)	20 (95.2%)	0.11
Coronary artery disease (%)	4 (12.1%)	29 (87.9%)	0.44
Chronic renal failure (%)	0 (0%)	13 (100%)	0.09
Smoking (%)	0 (0%)	20 (100%)	0.03
Chagas Disease (%)	1 (7.1%)	13 (92.9%)	0.09
Dyslipidemia (%)	1 (14.3%)	6 (85.7%)	0.87

chi-square test. Source: Marques, 2019

Acknowledgment

I thank Prof. Dr. Roque Aras, Prof. Dr. André Maurício Fernandes, Dr. Roberto Nery and Dr. Robert Biederman for the support, guidance and review of the project and the final text of the article. I thank Ana Paula Marques for her help in analyzing the data and building the database.

Author Contributions

Conception and design of the research: Marques TSS, Fernandes AMS, Dantas Júnior RN; Acquisition of data, Analysis and interpretation of the data and Statistical analysis: Marques TSS, Melo APMO; Writing of the manuscript: Marques TSS; Critical revision of the manuscript for intellectual content: Fernandes AMS, Dantas Júnior RN, Biederman RW.

Potential Conflict of Interest

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

Sources of Funding

There were no external funding sources for this study.

Study Association

This article is part of the thesis of master submitted by Thiago dos Santos Silva Marques, from Universidade Federal da Bahia.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of the Hospital Ana Nery under the protocol number 171.522. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013.

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T1 Mapping in Heart Failure: Prognostic Implications

Sarah Moharem-Elgamal[1,2]

Liverpool Heart and Chest Hospital,[1] *Liverpool - United Kingdom*
National Heart Institute,[2] *Giza - Egypt*

Short Editorial related to the article: Clinical Heart Failure Stratification Through Native T1 Mapping: Experience of a Referral Service

Myocardial fibrosis leads to impaired diastolic and systolic function and is associated with increased major adverse cardiovascular events. It is a structural correlate that can be found in the different stages of heart failure. The two main types of myocardial fibrosis are interstitial fibrosis and replacement fibrosis. Interstitial fibrosis is a reversible process that occurs early in the disease process as increased collagen synthesis in diffuse microscopic distribution within the myocardium and sometimes by localized perivascular distribution. Replacement fibrosis typically occurs in the later stages of the disease after irreversible myocyte injury or death, in which cell apoptosis triggers fibroblasts and promotes macroscopic deposition of collagen fibrous tissue in the myocardium.

Cardiac magnetic resonance (CMR) has the capability to accurately quantify ventricular volumes and ejection fraction, as well as the non-invasive characterization of the myocardium. These unique features have led to the increased use of CMR in the assessment of patients with heart failure (HF). CMR can detect the presence and extent of replacement fibrosis through late gadolinium enhancement imaging and diffuse interstitial fibrosis through native T1 mapping. Interstitial fibrosis identified by native T1 mapping has been used as a marker of disease activity,[1-3] risk stratification[4] and monitoring of the therapeutic management in heart failure patients.[5]

In this issue of the Brazilian Archives of Cardiology, Marques et al.[6] report the feasibility of native T1 mapping assessment in patients with HF in a cardiology referral hospital and its association with structural parameters and functional profile.[6] They enrolled 134 patients with heart failure of different etiologies from a single center. Most of the study population's etiology comprised non-ischemic patients [n=95 (70.9%)]. Late gadolinium enhancement was observed in 59% (56 patients) with non-ischemic cardiomyopathy and 87% (34 of 39) ischemic cardiomyopathy patients. Increased native myocardial T1 values were associated with larger LV diameters ($p = 0.007$) and ventricular volumes ($p < 0.01$). A significantly higher T1 value was observed in patients with LVEF <35% ($p < 0.001$). Upon comparing the T1 values in relation to systolic dysfunction severity, significantly higher T1 was observed in HFrEF than in HFmrEF ($p = 0.004$); and HFpEF ($p < 0.001$). Elevated T1 was observed in 55.2% of patients with HFpEF ($p < 0.01$).

Furthermore, T1 mapping was elevated regardless of the HF etiology (89.7% in ischemic and 81.1% in non-ischemic cases), with a higher T1 value observed in ischemic vs. non-ischemic patients ($p = 0.004$). Unique to this study, the authors have included Chagas cardiomyopathy. They demonstrated that 13 Chagas cardiomyopathy patients with increased native T1 (1077.1 ± 61.1ms) was associated with reduced LVEF (27.6 ± 16.8%) and increased LV diameters and volumes. In addition to the different etiologies and the severity of heart failure, smoking was the only comorbidity identified with a statistically significant elevated T1 values ($p = 0.032$).

These findings emphasize that the increased native T1 mapping values had a direct association with traditional parameters used to assess disease severity regardless of the underlying etiology. The authors have acknowledged that the limited sample size, other pathologies such as edema, infiltration, and inflammation may affect T1 values, as well as the lack of extracellular volume calculation. Nonetheless, native T1 mapping offers a noninvasive method to characterize diffuse pathology. Their findings support the use of native T1 mapping as a non-invasive biomarker for risk stratification in heart failure.

Keywords

Endomyocardial Fibrosis; Heart Failure; Mortality; Cellular Apoptose Susceptibility Protein; Fibroblasts; Magnetic Resonance Spectroscopy/methods.

Mailing Address: Sarah Moharem-Elgamal •
Cardiology Department- Liverpool Heart and Chest Hospital Thomas Drive Liverpool L14 3PE - United Kingdom
E-mail: sarahmoharem@hotmail.com

DOI: https://doi.org/10.36660/abc.20210205

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Prognostic Value of Isolated Elevated Troponin I Levels in Patients without Acute Coronary Syndrome Admitted to the Emergency Department

Célia Domingues,[1] Maria João Vidigal Ferreira,[1,2] Joana Moura Ferreira,[1] Ana Vera Marinho,[1] Patrícia Marques Alves,[1] Cátia Ferreira,[1] Isabel Fonseca,[1] Lino Gonçalves[1,2]

Centro Hospitalar e Universitário de Coimbra EPE,[1] Coimbra - Portugal

Universidade de Coimbra - Faculdade de Medicina,[2] Coimbra - Portugal

Abstract

Background: **Although non-ischemic troponin elevation is frequently seen in patients admitted to the emergency department (ED), consensus regarding its management is lacking.**

Objectives: **This study aimed to characterize patients admitted to the ED with non-ischemic troponin elevation and to identify potential mortality predictors in this population.**

Methods: **This retrospective observational study included ED patients with a positive troponin test result between June and July of 2015. Patients with a clinical diagnosis of acute coronary syndrome (ACS) were excluded. Data on patient demographics and clinical and laboratory variables were extracted from medical records. Follow-up data were obtained for 16 months or until death occurred. The statistical significance level was 5%.**

Results: **Troponin elevation without ACS was found in 153 ED patients. The median (IQR) patient age was 78 (19) years, 80 (52.3%) were female and 59(38.6%) died during follow-up. The median (IQR) follow-up period was 477(316) days. Survivors were significantly younger 76 (24) vs. 84 (13) years; p=0.004) and featured a higher proportion of isolated troponin elevation (without creatine kinase or myoglobin elevation) in two consecutive evaluations: 48 (53.9%) vs. 8 (17.4%), p<0.001. Survivors also presented a lower rate of antiplatelet treatment and same-day hospitalization. In the multivariate logistic regression with adjustment for significant variables in the univariate analysis, isolated troponin elevation in two consecutive evaluations showed a hazard ratio= 0.43 (95%CI 0.17–0.96, p=0.039); hospitalization, previous antiplatelet treatment and age remained independently associated with mortality.**

Conclusions: **Isolated troponin elevation in two consecutive measurements was a strong predictor of survival in ED patients with troponin elevation but without ACS. (Arq Bras Cardiol. 2021; 116(5):928-937)**

Keywords: **Troponin I; Prognosis; Emergency Department; Myocardial Non-Ischemic Injury.**

Introduction

Clinical myocardial infarction according to the fourth universal definition requires the presence of acute myocardial injury detected by abnormal cardiac biomarkers associated with evidence of acute myocardial ischemia. Cardiac troponin(cTn) above the 99th percentile cutoff point with an increasing or decreasing pattern is the biomarker of myocardial injury,[1] because it cannot be released by non-cardiac tissues and has an excellent accuracy for the diagnosis of acute myocardial infarction.[1-3]

Mailing Address: Célia Domingues •
Centro Hospitalar e Universitário de Coimbra EPE - Praceta Prof Mota Pinto
Coimbra 3000-075 – Portugal
E-mail: celiadomingues@me.com
Manuscript received June 06, 2019, revised manuscript March 10, 2020, accepted April 08, 2020

DOI: DOI: https://doi.org/10.36660/abc.20190356

cTn is a protein distributed within the cytoplasm and sarcomere of a cardiac myocyte, mostly in the sarcoplasmic reticulum. Three subunits make up the troponin complex, an inhibitory component (troponin I), tropomyosin-binding component (troponin T) and calcium-binding component (troponin C).[4]

The T and I subunits (cTnT and cTnI, respectively) are specific to cardiac muscle and, thus, can act as suitable markers of cardiac injury. cTnT shows a double discharge, first the cytoplasmic component and later the binding component.[5] cTnI is cardiac-specific, and was not identified in skeletal muscle. This 100% specificity shows cTnI can be an ideal myocardial necrosis marker (MNM).[6]

Before the advent of troponin, the previous MNM used were muscle/brain isoenzyme of creatine kinase (CK-MB) and myoglobin, which were less sensitive and not specific to myocardial infarction.[7,8] Due to their lack of sensitivity and specificity, they have been progressively excluded from ACS investigations.[2,3]

Although cTn subunits are strongly specific to cardiac myocytes, they can be released under a wide spectrum of non-

cardiac pathological conditions, such sepsis, chronic kidney disease, hypertensive emergencies, gastrointestinal bleeding, stroke and rhabdomyolysis.[6,9] In this setting, the detection of troponin may be the result of 5–8% of the cytosolic component release in response to myocyte cell turnover, cellular release of degradation products, and increased cellular wall permeability.[10]

The widespread use of troponin assays in the emergency department (ED) may pose a difficult diagnostic challenge when the test is abnormal in patient without an ACS.[11]According to the literature, elevated cTn levels in patients without an ACS was associated with a poor prognosis.[10,12-16]

Objective

This study aimed to identify factors predictive of mortality/survival in ED patients without ACS and elevated cTnI using patient characteristics, clinical past history, comorbidities and analytic values (including creatinine, CK-MB, myoglobin and cTnI) measured in ED.

Methods

Study design, setting, and participants

In this retrospective study, we analyzed the laboratory data of consecutive patients that came to the ED of a community teaching hospital during 1-month period from June to July of 2015, and selected patients who presented with cTnI elevation.

All clinical information was collected, including medical and nursing records of the ED and hospitalizations, analyses, and other complementary exams. Follow-up was performed through local and national records to observe the rates of cardiovascular re-hospitalization and death.

The collected data included demographics, cardiovascular risk factors, myocardial biomarker assay and creatinine results, main symptom at the ED, final ED diagnosis, hospitalization, hospitalization mortality, mortality rate at 30 days and 16 months, and cardiovascular re-hospitalization rate.

In this study, the criteria for the diagnosis of acute myocardial infarction were an increase or decrease in Troponin I with at least one abnormal value higher than the upper reference limit of the assay and at least one of the following: 1) symptoms of ischemia; 2) new ST-segment/ T-wave changes or new left bundle-branch block; 3) development of pathological Q waves on electrocardiography; 4) new loss of viable myocardium or regional wall motion abnormalities on imaging test; or 5) identification of an intracoronary thrombus on imaging test.[1]

Emergency and hospitalization registries of all patients with elevated cTnI, were revised by the investigators, and patients were divided into two groups: those diagnosed with an ACS, (Type 1 myocardial infarction(MI) or type 2 with ischemic signs and symptoms (with vasospasm, embolism and non-atherosclerotic coronary dissection) (group A) and those without an ACS with a positive troponin assay due to oxygen supply/demand imbalance or myocardial injury with no signs or symptoms of acute myocardial ischemia(group B). Patients with type 4 or 5 MI were not included in this study, as by definition these are not the regular ED patients, and type 3 MI patients have no cTnI measure.[1]

Non-ACS patients were identified by predefined criteria that included the following: 1) myocarditis/cardiomyopathy: discharge diagnosis or findings suggestive of myocarditis on imaging test or pathology, infiltrative cardiomyopathies such as amyloidosis or sarcoidosis, an ejection fraction ≤30% prior to admission, or prior cardiac transplantation; 2) infections: conditions with systemic impact such as cellulitis, pneumonia, sepsis, and pyelonephritis; 3) acute dysrhythmias unrelated to ACS; 4) chronic or acute kidney disease: stage-5 chronic kidney disease, chronic dialysis, renal transplant recipient, or moderate to severe acute kidney disease; 5) central nervous system pathology: stroke, seizure, or subarachnoid hemorrhage; 6) acute abdominal or gastrointestinal bleeding; 7) pulmonary embolism; 8) unexplained syncope; 9) asthma or chronic obstructive pulmonary disease exacerbation; and 10) others: elevated troponin level of unknown etiology, which does not meet any of the abovementioned criteria.

The primary endpoint for this study was mortality during hospitalization, at 30 days and 16 months, while the secondary endpoint was rehospitalization for cardiovascular disease during follow-up.

Follow-up was completed at 16 months or at death. Follow-up was performed through electronic medical records and the online national death registry. The institutional review board approved the study protocol. The requirement for informed consent was waived, because the patients did not receive any type of different care because of the study.

Myocardial necrosis marker assays

The troponin I level was determined using the same standard cTnI immunoassay (Troponin I Siemens Dimension EXL)[17-19] in all patients. The test was performed in the central hospital laboratory. The lower and upper detection limits established by the manufacturer were 0.017 ng/mL and 4000ng/mL, respectively. Measurements below the detection limit were assigned a value of 0. Troponin I test results were considered positive if the level was higher than the reference limit (>0.059 ng/mL) used in the ED laboratory. The CK-MB and myoglobin assay results were considered normal at <3.6ng/mL and at 9–82 ng/mL, respectively.

Repeated MNM measurements were performed at least 3 hours after the first evaluation.

Using the first and second evaluation of cardiac troponin, the variation was calculated as follows: variation of troponin % = ((second troponin × 100)/first troponin) × 100%.

Statistical methods

All continuous data were tested for normality with the Shapiro-Wilks test; all showed non-normal distribution and are presented as median and interquartile range. The Mann-Whitney test was applied to compare continuous variables. Categorical variables were represented by their frequency and compared using Fisher's exact test or the chi-square-test.

Survival was analyzed using uni- and multivariate Cox proportional hazard models. The results were expressed as hazard ratio (HR) with 95% confidence intervals (95%CI). For the independent survival predictor variables, a survival plot was obtained using the Kaplan-Meier method and the log-rank test. The statistical significance level was set at p-value<0.05. All statistical analyses were performed using SPSS 23.0 for Mac (SPSS, Inc; Chicago, IL, USA).

Results

Baseline characteristics and diagnoses of the study population

During the one-month study period, 10,564 patients were admitted to our institution's ED. Patients who underwent MNM evaluations including troponin I, CK-MB, and myoglobin and their distribution according to troponin status and final diagnosis are described in Figure 1. Patients were assigned to two groups: Group A (n=42 [21.5%]) with ACS (all of them with acute occlusion/subocclusion of coronary arteries: 4 of them with type 2 MI (2 coronary dissection and 2 embolic coronary thrombosis); of 38 with type 1 MI, 14 with acute MI with ST-elevation (STEMI)); while in Group B (n=153 [78.5%]) with Non-ACS, 58 had oxygen supply/demand imbalance, 53 had acute myocardial injury without sign or symptoms of ischemia and 42 had stable elevation of cTnI (cTnI variation on two consecutive analysis ≤ 20%). Among the Non-ACS patients, the first measure of MNM was performed after a median of 6 (IQR 4) hours since symptom onset, and 90 patients had the MNM measure repeated after a median of 5 (IQR 3) hours since the first evaluation.

On the first MNM evaluation of group B, 81 had CKMB and/or myoglobin elevation (16 showed CKMB and 40 showed myoglobin elevation, whereas 25 showed elevation of both). On the second evaluation, 18 showed elevation of both and 6 showed isolated elevation of CKMB and 31 of myoglobin. At both evaluations, 88 patients showed at least one elevation of CKMB and/or myoglobin.

Patients with a positive troponin test result had a wide spectrum of clinical symptoms at presentation (Figure 2). As expected, patients who ultimately received a diagnosis of ACS (Group A) had a higher proportion of chest pain as the main complaint at hospital presentation.

As shown on Table 1, patients in Groups A and B had a similar median age but had significantly different gender proportions. Concerning cardiovascular risk factors and comorbidity conditions, no significant differences were found in the prevalence of diabetes mellitus and hypertension, but hyperlipidemia and previous coronary artery disease were more common in the ACS patients and previous heart failure and anticoagulant treatment were more prevalent in Non-ACS patients.

The main diagnoses in Group B patients were myocarditis/cardiomyopathy (40[26%]), followed by infection (cellulitis, pneumonia, and pyelonephritis, 24[15.5%]), acute dysrhythmias (25 [16.6%]), chronic or acute kidney disease (17 [11%]), cerebral disease (13 [8.4%]), acute abdominal or gastrointestinal bleeding (11 [7.1%]), pulmonary embolism (6 [3.9%]), unexplained syncope (4[2.6%]), asthma or chronic obstructive pulmonary disease exacerbation (4 [2.6%]), and others (9 [6.5%]).

Outcome data

The median (IQR) follow-up was 477 days (316). No significant intergroup differences were found regarding in-hospital mortality (6 [14.3%] vs. 21 [13.7%], p=0.077), 30-day mortality (6 [14.3%] vs. 27 [17.6%], p=0.4) and cardiovascular rehospitalization at follow-up (11 [29.7%] vs 32 [24.2%], p=0.316). Remarkably, the long-term mortality rate was significantly higher in group B patients (9 [21.4%] vs. 59 [38.6%], p=0.039), although the survival curves of the two groups were not significantly different (log rank, 3.45; p=0.063). The main causes of death in group B were cardiovascular in 12 individuals (none of them with a

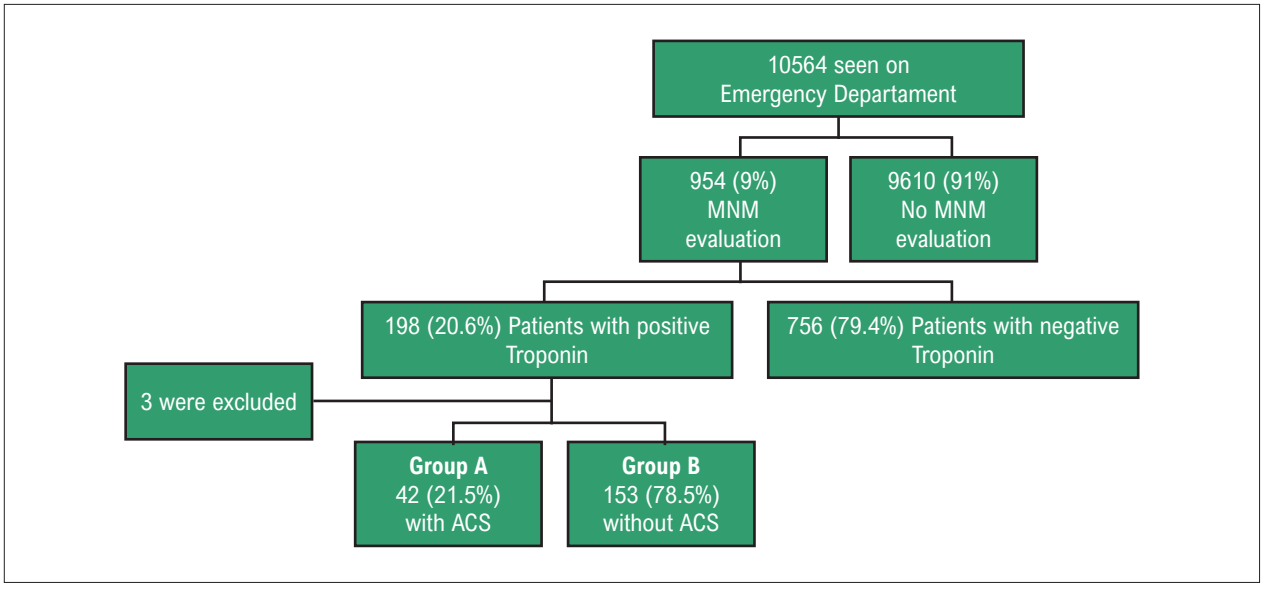

Figure 1 – *Schematic illustration of patients included. MNM, myocardial necrosis markers; ACS, acute coronary syndrome*

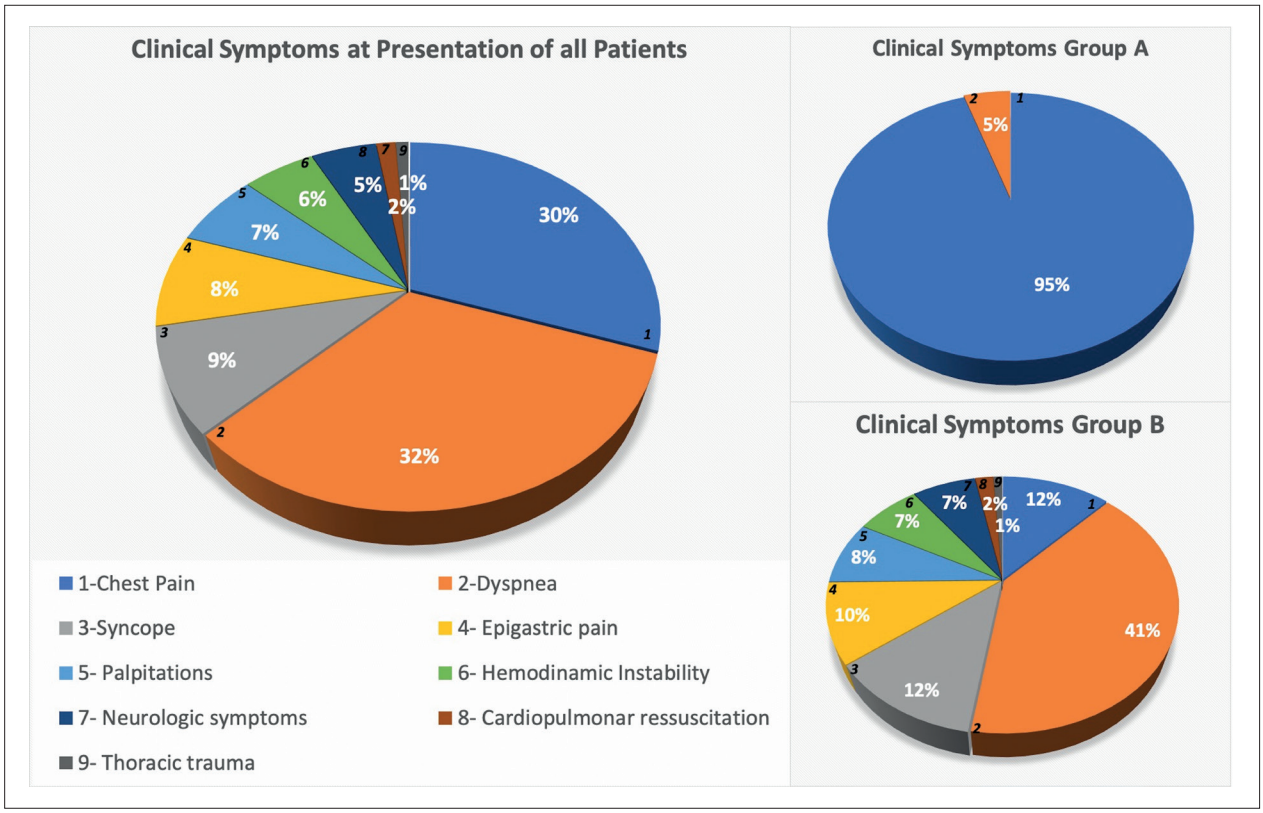

Figure 2 – *Schematic illustration of clinical symptoms at presentation of all patients and different groups A: with ACS and group B: Non ACS.*

diagnosis of acute myocardial infarction), non-cardiovascular in 27, 13 unknown causes and 4 due to mixed of cardiovascular and other comorbidity.

Main results

Predictors of mortality in Group B patients are described in Table 2. We found that older age (p<0.001), previous heart failure (p=0.049), previous antiplatelet medication (p=0.005) and hospitalization after index ED evaluation (p<0.001) were mortality predictors. Death at follow-up was not related to cTnI, CK-MB, or myoglobin levels (first, second, or both evaluations). However, isolated troponin elevation (i.e., without concomitant CK-MB or myoglobin elevation) was a powerful predictor of survival; in fact, isolated troponin elevation at the first measurement was present in 58.7% of survivors vs. 40% of non-survivors (p=0.021); patients with two isolated troponin elevation measurements were more likely to survive (48 [53.9%] of survivors vs. 8[17.4%] of non-survivors [p<0.001]).

Cox regression analysis is shown on Table 3. The univariate analysis showed that in inpatients with isolated troponin in two consecutive MNM measurements, the probability of long-term survival at follow-up increased by four-fold (p<0.001). Cox multivariate analysis corrected for age and gender demonstrated that isolated troponin elevation in two consecutive measurements remained an independent predictor of survival (HR, 0.433; 95%CI, 0.196–0.958; p=0.039). Figure 3 shows the survival curves of Group B patients according to the presence of isolated troponin elevation in two consecutive measurements (log rank, 18.09; p<0.001).

Discussion

Interpretation

In our study, 78% of patients with troponin elevations received a non-ACS diagnosis, which is in agreement with previous studies.[20,21] In some series, myocardial ischemia was not identified in approximately 65% of ED patients with troponin elevation. The spectrum of clinical diagnosis was extremely heterogeneous in our study, encompassing high-risk conditions. Mid-term prognosis was clearly worse for patients with elevated troponin and non-ACS than for patients with normal troponin levels. It was also probably worse than for patients diagnosed with ACS, with these findings having been reported in previous studies.[16,22,23]

In this study, 33.5% of the patients with elevated troponin levels and a non-ACS diagnosis were discharged from the ED without hospitalization. This percentage seems very high, but higher rates have been described by other authors.[21,24,25] In the non-ACS group, the 16-month mortality rate was 38.6%, but 81.4% of these deaths occurred during hospitalization or during the first 30 days, which reinforces the role of MNM as a mortality predictor in this group. Considering the high hospital discharge rate after an ED stay and the high risk of mortality conferred by troponin elevation, it is not surprising that elderly patients with

Table 1 – Baseline characteristics of all patients with troponin elevation at the ED

	Overall N = 195	Group A n = 42 (22%)	Group B n = 153 (78%)	p Value
Age (years), median(IQR)	77(21) years	71(19) years	78(19) years	0.06
Male n (%)	105 (53.8%)	32 (76.2%)	73 (47.7%)	0.001
Diabetes mellitus, n (%)	69 (35.5%)	16 (37.2%)	54 (35%)	0.89
Hypertension, n (%)	155 (79.3%)	35 (84.4%)	119 (78.1%)	0.57
Hyperlipidemia, n (%)	87 (44.4%)	25 (60%)	61 (40.1%)	0.03
Previous CAD, n (%)	37 (19%)	13 (31%)	24 (16%)	0.02
Previous HF, n (%)	43 (21.9%)	9 (21.9%)	71 (46.7%)	0.02
Previous AIS, n (%)	31 (14.8%)	3 (6.3%)	26 (16.8%)	0.26
GFR (ml/[min·1.73 m^2]), median(IQR)	54 (46)	68 (47)	49(47)	0.10
Previous Medications				
Anticoagulants	62 (33.7%)	4 (10%)	47 (31%)	0.007
Antiplatelets	50 (26.7%)	15(37%)	48 (32%)	0.13
Beta-blockers	69 (36.9%)	16 (40%)	53 (36.1%)	0.65
ACE inhibitors/AARA	108 (57.8%)	23 (57.5%)	87 (57.8%)	0.97
MRA	15 (17.6%)	2 (12.5%)	13 (18.8%)	0.55
Statins	83 (44.4%)	24 (60%)	60 (40.1%)	0.02
Standardized troponin at the first evaluation*, n (%)				<0.001
1–2.99	95 (48.9%)	10 (23.1%)	85 (55.8%)	
3–4.99	36 (18.3%)	5 (12.8%)	31 (19.7%)	
5–9.99	19 (9.7%)	4 (10.3%)	15 (9.7%)	
10+	45 (23.1%)	23 (53.8%)	22 (15%)	
Elevated CK-MB, n(%)	54 (53%)	22 (53%)	32 (21%)	<0,001
Elevated myoglobin, n(%)	88 (48%)	23 (56%)	66 (45%)	0,24
Elevated CK-MB + Myoglobin, n(%)	43 (22%)	16 (40%)	25 (16%)	0,003
% troponin elevation between 2 measurements, median (IQR)	7 (73)	183 (666)	2,65(42)	<0.001

Group A- patients with acute coronary syndrome (ACS); Group B- patients without ACS. CAD: coronary artery disease; HF: heart failure; AIS: acute ischemic stroke; GFR: glomerular filtration rate according to the MDRD equation; ACE inhibitor: angiotensin-converting enzyme inhibitor; MRA: mineralocorticoid receptor antagonist.

troponin elevation who receive a diagnosis other than ACS and are not admitted to the hospital are at an unacceptable high risk of death.

We believe that the high mortality rate during hospitalization and follow-up is closely related to older age and greater comorbidities (past heart failure or antiplatelet medication), as reported by others.[21]

The only biomarker recommended to diagnose ACS at this time is cardiac troponin, due to its higher sensitivity and accuracy.[2,3] In fact, up to 80% of patients with ischemic myocardial infarction will have an elevated troponin level within 2–3 hours after ED arrival.[7]

Our study is remarkable for finding that isolated cTnI elevation in two consecutive analyses of MNMs is a survival predictor for patients with cTnI elevation and non-ACS, compared to the elevation in at least two MNMs (cTnI and CK-MB and/or myoglobin). Some particularities of the different properties of MNM molecules could explain this fact. Myoglobin has an early release and quick clearance (released starting 1h after the injury and return to baseline at 24–36h), while CK-MB shows slower release and clearance (release starting 4–9h after the injury and clearance after 48–72h),[26] and troponin shows a release similar to that of CK-MB (4–9h) but delayed clearance (7–10 days).[27] We hypothesize that the persistent elevation of CK-MB and/or myoglobin along with troponin in two consecutive MNM analyses implies a recent or permanent myocardial injury, even in non-ACS patients.

Probably, there was a difference in the release mechanism of different MNM molecules according to the injury type and severity. Some studies in animals and human cells suggested that the discharge of myocardial proteins just like cTn may not imply myocardial necrosis.[28]

Regarding the T and I subunits, cTnI has a molecular weight of 37 kDa and cTnT has a molecular weight of 21 kDa; both presenting mainly in the sarcomeres and 4–6% in the cytoplasm. After the myocardial injury, cytosolic troponin is released first; as

Table 2 – Association between Clinical Variables and Long-Term Survival of Patients with Troponin Elevation and Non-Acute Coronary Syndrome (Group B)

	Survivors (n = 94)	Non-survivors (n = 59)	p-value
Age, median (IQR)	76(24) years	84 (13)	<0.001
Male, n(%)	44 (46.8%)	29 (49.2%)	0.77
CV Risk Factors, n(%)			
Diabetes mellitus	28 (30.8%)	22 (38.6%)	0.33
Hypertension	68 (73.9%)	44 (78.6%)	0.52
Previous CAD	14 (15.2%)	9 (16.4%)	0.85
Previous HF	33 (39.3%)	31 (56.4%)	0.049
GFR, mL/(min·1.73 m^2), median(IQR)	56 (48)	45 (34)	0,05
Heart rate, bpm, median(IQR)	75 (33)	84 (36)	0.10
Previous Medication, n (%)			
Antiplatelets	22 (23.9%)	25 (35.5%)	0.02
Anticoagulants	34 (37%)	12 (21.8%)	0.06
Beta-blockers	35 (38%)	18 (32.7%)	0.52
ACE inhibitors	57 (62%)	28 (50.9%)	0.19
MRA	9 (20.5%)	4 (16%)	0.65
Statins	36 (39.1%)	23 (41.8%)	0.75
ECG, n (%) No significant alterations	51 (64.6%)	16 (50%)	0.38
ST elevation	1 (1.3%)	0 (0%)	
ST-depression or negative T-wave	16 (20.3%)	6 (18.8%)	
Atrial fibrillation	28 (35.0%)	18 (46.2%)	
LBBB	4 (5.1%)	4 (12.5%)	
Pace rhythm	4 (5.1%)	3 (9.4%)	
Myocardial Necrosis Markers, median (IQR)			
Troponin (ng/mL) at the first evaluation	0,13 (0,23)	0,10 (0,18)	0.61
CK-MB (ng/mL) at the first evaluation	1,6 (1,8)	1,9 (2,05)	0.50
Myoglobin (ng/mL) at the first evaluation	70 (120)	99 (175)	0.06
Isolated troponin elevation at the first evaluation, n (%)	54 (58.7%)	22 (40%)	0.028
Troponin (ng/mL) at the second evaluation, median (IQR)	0,12(0,16)	0,14(0,32)	0,28
% troponin I variation on two sequential measurements, median (IQR)	0 (32)	27 (35)	0.002
Isolated troponin elevation at two sequential measurements, n(%)	48 (53.9%)	8 (17.4%)	<0.001
Hospitalization at index event, n(%)	52 (55.3%)	51 (86.4%)	<0.001
Coronary revascularization			0.88
No specific therapy, n(%)	88 (93.6%)	54 (91.5%)	
OMT, n(%)	5 (5.3%)	4 (6.8%)	
PCI + OMT, n(%)	1 (1.1%)	1 (1.1%)	

IQR: interquartile range; CAD: coronary artery disease; HF: heart failure; AIS: acute ischemic stroke; GFR: glomerular filtration rate according to MDRD equation; ACE inhibitor: angiotensin-converting enzyme inhibitor; MRA: mineralocorticoid receptor antagonist; ECG: electrocardiogram; CK: creatine kinase; CK-MB: creatine kinase-MB; OMT: optimized medical therapy; PCI: percutaneous coronary intervention.

Table 3 – Univariate and multivariate (corrected for age and gender) Cox regression analysis of clinical variables and long-term survival of patients with troponin elevation and non-acute coronary syndrome

	Univariate Cox regression		Multivariate Cox Regression	
	HR (95% CI)	p Value	HR (95% CI)	p Value
Age, y	1.040 (1.017–1.063)	**0.001**	1,030 (1,002–1,058)	**0.038**
Gender	0.899 (0.540–1.499)	0.684	0,807 (0,436–1,493)	0.494
CV risk factors				
Diabetes mellitus	1.336 (0.783–2.277)	0.288		
Hypertension	1.245 (0.658–2.358)	0.501		
Previous CAD	1.067 (0.521–2.182)	0.860		
Previous HF	1.649 (0.967–2.812)	0.066		
GFR, mL/(min·1.73 m^2)	0.992 (0.984–1.001)	0.082		
Heart rate, bpm	1.006 (0.997–1.014)	0.193		
Previous Medication				
Antiplatelets	1.867 (1.230–2.835)	**0.006**	1,823 (1,105–3,006)	**0.019**
Beta-blockers	0.806 (0.459–1.416)	0.449		
ACE inhibitors	0.689 (0.406–1.170)	0.170		
MRA	0.764 (0.262–2.226)	0.611		
Statins	1.017 (0.595–1.739)	0.950		
ECG pattern	1.162 (0.999–1.351)	0.067		
Laboratory				
Isolated troponin elevation at the first evaluation	0.533 (0.311–0.916)	**0.021**	1.097 (0.378–3.180)	0.865
Isolated troponin elevation at the second evaluation	0.528 (0.218–1.279)	0.142		
% troponin elevation at two sequential evaluations	1.000 (0.999–1.001)	0.750		
Isolated troponin elevation at two sequential evaluations	0. 239 (0.111–0.512)	**<0.001**	0.433 (0.196–0.958)	**0.039**
Hospitalization at index event	3.782 (1.794–7.973)	**<0.001**	4.708 (1.652–13.423)	**0.004**

95% CI: 95% confidence interval; CAD: coronary artery disease; HF: Heart failure; GFR: glomerular filtration rate according to MDRD equation; CK: creatine kinase; CK-MB: creatine kinase-MB; ACE inhibitor: angiotensin converting enzyme inhibitor; MRA: mineralocorticoid receptor antagonist; ECG: electrocardiogram.

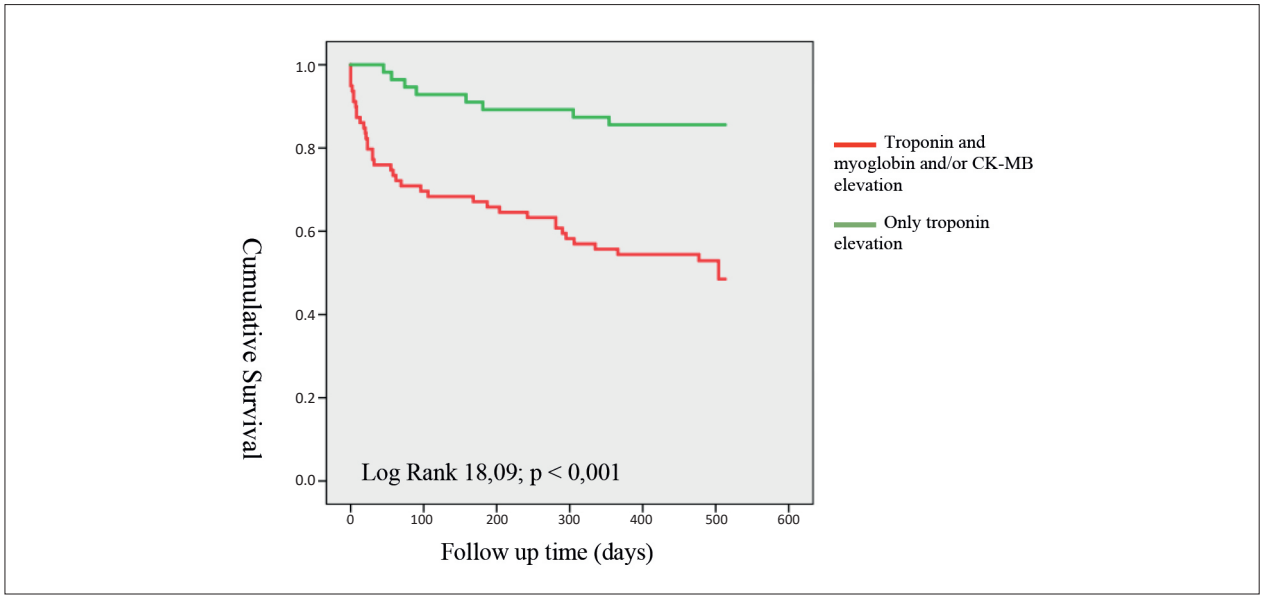

Figure 3 – *Survival Kaplan Meier curve at 16-month follow-up of Non-ACS patients according to the results of two consecutive MNM evaluations.*

further damage occurs, the troponin present in the sarcomere is released into the circulation;[8] previous studies advocated that reversibly injured cardiomyocytes could release troponin.[29-31]

CK-MB is also released when there is tissue necrosis, because of its high molecular weight (86kDa). Myoglobin has a rapid release, probably because of its low molecular weight (17kDa) and cytoplasmic location, and it could be released under myocardial stress without necrosis,[8] just like troponin.

This molecular property of different MNMs could explain the incapacity of a single troponin I measurement to predict mortality in the present study and another one.[32] This finding highlights the valuable role of CK-MB and myoglobin that cannot be accomplished by an isolated troponin measurement. However, current guidelines recommend that cardiac troponin be the only biomarker used for the diagnosis of ACS, owing to its superior sensitivity and accuracy.[2,3] Nevertheless, failing to perform CK-MB and myoglobin measurements may come at a cost, especially for those patients who receive a non-ACS diagnosis. We believe that the exclusion of CK-MB and myoglobin from routine MNM evaluations in many institutions and guidelines should be reconsidered because of its superior adjunctive prognostic value, mainly in non-ACS patients, and the increased number of patients with troponin elevation that will be observed with highly sensitive troponin levels.

Limitations

Our institution follows a non-restrictive protocol for MNM measurement orders at the ED. Therefore, our rate of Non-ACS probably were increased, when compared with more strict protocols.

Our study analyzed patient mortality without considering that patients were managed differently according to the initial diagnosis. This may seem to be an important limitation, but it should be clarified that each clinical process usually has its own specific management, which influences patient prognosis. Therefore, the prognosis of the groups is somehow inherent to the provided management. For instance, patients with ACS are usually admitted for treatment with antiplatelet, anticoagulant agents, statins, revascularization, and other therapies, and this approach has a specific prognosis.

Data were retrospectively collected and it is possible that some medical records were incomplete and the clinical history could have been undervalued.

The troponin assay previously used in our hospital was a contemporary assay called 'sensitive troponin' and it was not highly sensitive, unlike the currently used troponin assay, which is expected to detect positive troponin values in more patients, as described for this troponin assay.[18,19]

Conclusion

High percentage of patients with an elevated troponin level measured in the ED were not diagnosed with ACS. These patients had a high-risk clinical profile, broad heterogeneity regarding the main diagnosis, and an adverse prognosis at 16 months. An isolated troponin I elevation in two consecutive determinations of MNM was a strong predictor of survival in non-ACS patients with troponin elevation.

Acknowledgements

We would like to thank all physicians and nurses involved in patient treatment and their records. We also thank the laboratory department for providing the list of patients with troponin elevation, the initial patient database.

Author contributions

Conception and design of the research: Domingues C, Ferreira MJV, Ferreira JM; Acquisition of data: Domingues C, Marinho AV, Alves PM, Ferreira C; Analysis and interpretation of the data: Domingues C, Ferreira MJV, Marinho AV, Alves PM, Fonseca I, Gonçalves L; Statistical analysis: Domingues C, Ferreira MJV, Ferreira JM, Ferreira C; Writing of the manuscript: Domingues C, Ferreira MJV; Critical revision of the manuscript for intellectual content: Ferreira MJV, Ferreira JM, Marinho AV, Alves PM, Ferreira C, Fonseca I, Gonçalves L.

Potential Conflict of Interest

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

Sources of Funding

There were no external funding sources for this study.

Study Association

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

Ethics approval and consent to participate

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

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Original Article

Effects of Different Types of Exercise Training on Endothelial Function in Prehypertensive and Hypertensive Individuals: A Systematic Review

Gustavo Waclawovsky,[1] Marinei L. Pedralli,[1] Bruna Eibel,[1] Maximiliano I. Schaun,[1] Alexandre M. Lehnen[1]

Laboratório de Pesquisas Clínicas - Instituto de Cardiologia do Rio Grande do Sul / Fundação Universitária de Cardiologia,1 Porto Alegre, RS – Brasil

Abstract

Background: **Sustained high blood pressure can lead to vascular remodeling and endothelial cell injury, which may explain the endothelial dysfunction found in hypertensive individuals. Exercise training can improve vascular health in individuals with cardiovascular risk, but little is known about its effects in prehypertensive and hypertensive individuals.**

Objective: **To review the literature showing evidence of changes in endothelial function in response to different modalities of exercise training in prehypertensive and hypertensive individuals.**

Methods: **We conducted a systematic review of studies in the MEDLINE, Cochrane, LILACS, EMBASE, and SciELO databases following both the PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) and the PICO framework (patient/population, intervention, comparison and outcomes). Randomized clinical trials (RCTs) published up to April 2019 were selected and assessed by four independent reviewers. The methodological quality was assessed using the PEDro (Physiotherapy Evidence Database) scale.**

Results: **Our search yielded 598 abstracts, and 10 studies were eligible for review. All of them had acceptable methodological quality by PEDro scale. Of the 10 studies, 7 involved aerobic training, 1 isometric resistance training, and 2 aerobic training and dynamic resistance training separately. Seven studies used flow-mediated dilation (FMD) to assess the vascular health, and three used plethysmography. Most training protocols involved hypertensive individuals and consisted of low and moderate-intensity exercise.**

Conclusion: **Our systematic review showed that moderate continuous aerobic training is effective to improve vascular health in hypertensive individuals. In prehypertensive individuals, vigorous interval aerobic training seems to be an alternative to determine vascular health benefits. Resistance exercise training, either isometric or dynamic, can be used as a secondary alternative, but still requires further investigation. (Arq Bras Cardiol. 2021; 116(5):938-947)**

Keywords: **Endothelium; Stem Cells; Exercise; Resistance Training; Hypertension; Review.**

Introduction

Systemic hypertension is a multifactorial condition characterized by sustained high blood pressure (BP) levels. An increase of 20 mmHg in systolic blood pressure (SBP) in individuals at the ages of 40–69 years has been associated with a risk 2 times higher of death from ischemic heart disease, due to vascular disease.[1] Cardiovascular events are closely related to vascular dysfunction, in particular due to the impaired endothelial tissue function which plays a central role in the regulation of vascular tone and peripheral vascular resistance.[2] Impaired endothelial function, high levels of circulating endothelial microparticles (EMP)[3] and a lower vascular regenerative capacity, characterized by reduced mobilization of endothelial progenitor cells (EPC),[4,5] is well described in hypertensive individuals and is the main cause of atherosclerosis and consequent fatal and nonfatal cardiovascular events in this population[6] (Figure 1).

Lifestyle changes such as regular physical activity are recommended as a therapeutic approach for restoring endothelial function in individuals with hypertension.[7,8] The exact mechanisms underlying the potential antihypertensive effects and long-term endothelial response to exercise are not fully understood, but a reduction in sympathetic activity,[9] a balance between vasodilators and vasoconstrictors[10] and a reduction in the levels of the vasoconstrictor endothelin-1 (ET-1)[11] have been investigated.

Regular aerobic exercise may prevent the loss of endothelium-dependent vasodilation, even in elderly individuals.[12] This benefit is associated with exercise-induced increases in shear stress on vascular walls. Therefore, regular

Mailing Address: Alexandre M. Lehnen •
Laboratório de Pesquisas Clínicas - Instituto de Cardiologia do Rio Grande do Sul / Fundação Universitária de Cardiologia - Av. Princesa Isabel, 395. Postal Code 90620-001, Santana, Porto Alegre, RS - Brazil
E-mail: amlehnen@gmail.com
Manuscript received November 16, 2019, revised manuscript March 23, 2020, accepted May 06, 2020

DOI: https://doi.org/10.36660/abc.20190807

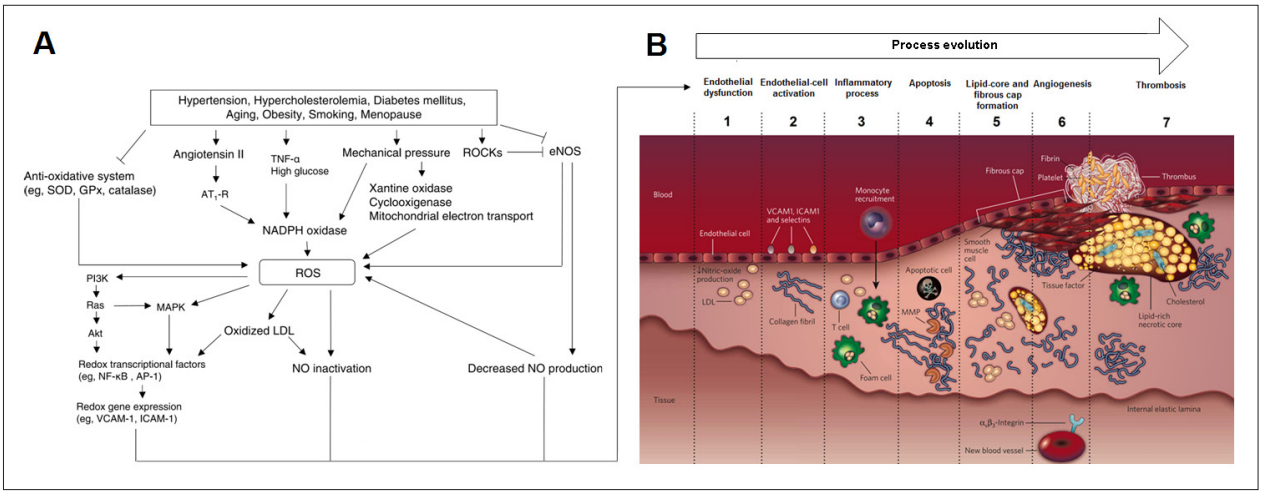

Figure 1 – *General integration of reactive oxygen species with atherosclerosis and balance of endothelial injury versus recovery. Panel A-B: Schematic representation of ROS generation induced by inflammatory and vasoconstrictor responses in disease states and unhealthy lifestyle, and its effects on the process of endothelial dysfunction and atherosclerotic plaque formation. NO: nitric oxide; ROCK: Rho kinase associated; SOD, superoxide dismutase; AT1-R: Receptor AT1; NADPH: reduced nicotinamide adenine dinucleotide phosphate; ROS: reactive oxygen species; eNOS: nitric oxide synthase 3; PI3K: Phosphatidylinositol-4,5-bisphosphate 3-kinase; RAS: renin–angiotensin system; MAPK: mitogen-activated protein kinase; Akt: Protein kinase B; NF-κB: nuclear factor kappa B; AP-1: Activator protein 1; VCAM-1: vascular cell adhesion molecule 1; ICAM-1: Intercellular Adhesion Molecule 1; MMP: matrix metalloproteinases. Adapted from Higashi et al (2009) and Sanz and Fayad (2008).*

exercise increases nitric oxide production, induces increased expression of nitric oxide synthase and dilates all types of blood vessels by stimulating soluble guanylate cyclase and increasing cyclic guanosine monophosphate in smooth muscle cells. It also promotes angiogenesis via the vascular endothelial growth factor and induces increased local antioxidant response, which in turn preserves endothelial nitric oxide bioavailability.[13]

A meta-analysis of individuals with several cardiovascular risk factors and/or established cardiovascular disease has demonstrated that aerobic and resistance exercise training can potentially improve endothelium-dependent dilation response.[14] Other studies have reported the benefits of regular exercise because it promotes the expression of adhesion molecules, modulation of the inflammatory response[15] and EPC mobilization.[16] Yet, this body of evidence comes from studies conducted with highly heterogeneous populations, making it difficult to draw conclusions for the particular population of prehypertensive and hypertensive individuals.

Indeed, our group has published a meta-analysis addressing the effects of exercise training on endothelial function.[17] However, only aerobic exercises were included and the outcome was evaluated by flow-mediated dilation (FMD). Thus, the present systematic review has a broader scope as it discusses potential mechanisms involved in the association between exercise training and endothelial function (Figure 2). Given that, similar to the FMD technique, plethysmography is strongly dependent on endothelial nitric oxide[18-20] and, therefore, both techniques are widely used when endothelial function is the outcome of interest. We chose to include plethysmography and resistance exercises that were not addressed in our previous meta-analysis. Thus, we conducted a systematic review of studies showing evidence of the changes in endothelial function in response to different modalities of exercise training in prehypertensive and hypertensive individuals. Then, we examined the evidence on endothelial markers such as EPC mobilization and EMPs.

Materials and methods

Selection of studies

This systematic review followed the PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyses)[21] and it was conducted until April of 2019 by four independent reviewers (G.W., M.I.S. and M.L.P. and B.E.) on the following databases: MEDLINE (accessed via PubMed), Cochrane Central Register of Controlled Trials (Cochrane); *Latin American and Caribbean* Center on *Health Sciences* Information (LILACS); EMBASE and Scientific Electronic Library Online (SciELO). We set no publication date limits and articles in Portuguese, English or Spanish were eligible for inclusion.

The set of search terms *exercise, systemic hypertension* and *endothelium* was used to searching for studies in the Cochrane, LILACS, EMBASE and SciELO databases. For MEDLINE search, we used three different sets of MeSH descriptors (Figure 3). To increase the precision and the sensitivity of our search of study designs (Randomized Controlled Trial, RCTs) in MEDLINE database, we added the search terms for RCTs (Figure 3).[22] Besides, we used the PICO strategy[21] (patient/population, intervention, comparison and outcomes) for inclusion of studies.

The four reviewers undertook the selection of the studies, and independently reviewed titles and abstracts. When abstracts did not provide sufficient information, they performed a full reading of the articles. Reviewers solved any

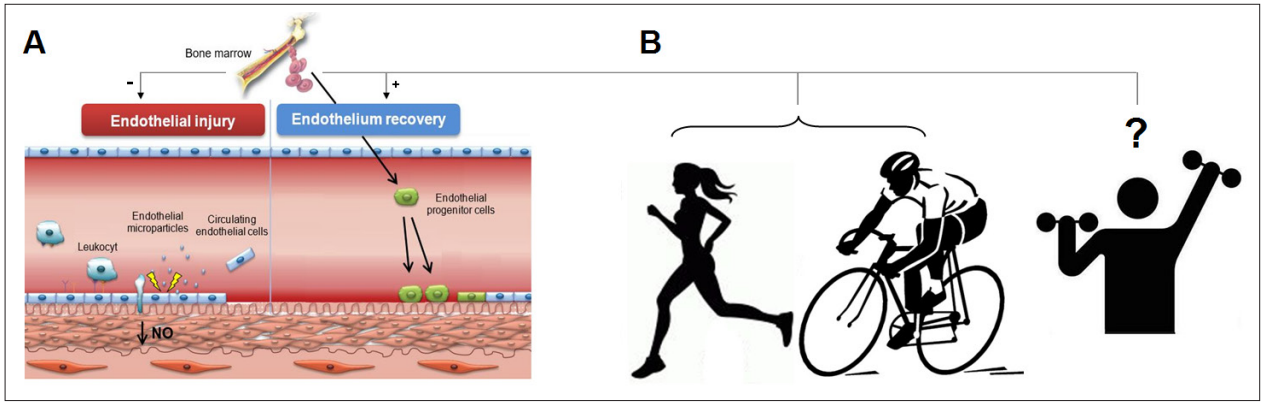

Figure 2 – *Panel A-B: Hypothesis of the adaptative process modulated by physical training to restore the damage/repair balance of the endothelial tissue and the maintenance of its vasomotor function.*

discrepancies by consensus; any disagreements on the inclusion criteria were settled by other reviewer (A.M.L.). Information about the number of articles involving aerobic, resistance and combined training as well as exercise intensities and techniques used to measure endothelial function were set by prehypertension and hypertension groups.

Inclusion and exclusion criteria

The inclusion criteria were: (a) adults aged 18 or more; (b) individuals with prehypertension or systemic hypertension; (c) regular exercise training as part of the intervention protocol; (d) mobilization of EPCs or EMP counts as study outcomes; (e) endothelial assessment by FMD or plethysmography, number of EPCs measured by flow cytometry or cell culture and number of EMPs measured by flow cytometry.

Studies on drug interventions, dietary interventions or a single exercise session were excluded, as well as studies involving animals, children/adolescents, and only normotensive individuals; non-randomized clinical trials; duplicate publications. Studies with individuals with metabolic diseases and cardiovascular diseases other than hypertension were also excluded.

Quality assessment of the studies was based on the Physiotherapy Evidence Database (PEDro) scale[23] (Table 1S, supplemental material).

Statistical analysis

All data were tabulated as categorical variables in Microsoft Excel and a descriptive analysis using SPSS for Windows, version 24 (Chicago, IL), was performed by one of the investigators (G.W.).

Results

This systematic review aimed to evaluate any evidence of changes in endothelial function in response to aerobic, resistance and combined exercise training (pre- vs. post-training) in prehypertensive and hypertensive individuals. We found in our search 598 abstracts (297 in MEDLINE; 43 in Cochrane; 47 in LILACS; 200 in EMBASE; and 11 in SciELO). All titles and abstracts were reviewed and then 46 articles were fully read and reviewed for their eligibility. Ten articles were selected for review (Figure 4).

Among the ten studies, four scored 7 points, other four scored 6 points and only two studies scored 5 points in PEDro scale. However, it is important to highlight that the blinding intervention (exercise training) was not provided because it is not applicable in this kind of intervention. Thus, we considered all the included studies as of acceptable quality according to PEDro scale.

Table 2S (supplemental material) shows detailed information of the studies reviewed. Briefly, of the ten studies selected, seven involved aerobic training, one addressed isometric resistance training, two aerobic training and dynamic resistance training separately, and none involved the combination of aerobic and resistance exercise in the same session (combined training). Of these, only three studies compared the effects of different types of exercise training on endothelial function (continuous *versus* interval training; dynamic resistance *versus* interval training). The sample size ranged from 16 to 155, for a total of 519 prehypertensive and hypertensive individuals.

Of the studies selected, blood samples were analyzed for markers of vascular health in only two of them. EPCs and EMP were not measured in any RCTs with prehypertensive or hypertensive individuals. Endothelial vasomotor function was assessed by FMD (flow-mediated dilation of the brachial artery assessed by ultrasound) in seven studies and plethysmography (total vasodilation of the forearm or calf captured by local strain-gauge flow measurements) in three studies (a detailed description of plethysmography can be seen in Bystrom et al.[24] and Waclawovsky et al.[25]).

According to the American College of Sports Medicine's exercise intensity classification,[26] low-intensity aerobic training was examined in three studies, moderate exercise in four studies and vigorous exercise in three studies. For isometric resistance training, we selected only one study of low-intensity isometric training. For dynamic resistance training, moderate intensity was examined in two studies, while low and vigorous training in none of them.

Exercise training:*(exercise OR exercises, isometric OR isometric exercises OR warm-up exercise OR exercise, warm-up OR exercises, warm-up OR warm up exercise OR warm-up exercises OR exercise, aerobic OR aerobic exercises OR exercises, aerobic OR aerobic exercise OR endurance, physical OR endurance, physical OR physical endurance OR training, resistance OR strength training OR training, strength OR weight-lifting OR strengthening program OR strengthening program, weight-lifting OR strengthening programs, weight-lifting OR weight lifting strengthening program OR weight-lifting strengthening programs OR weight-lifting exercise program OR exercise program, weight-lifting OR exercise programs, weight-lifting OR weight lifting exercise program OR weight-lifting exercise programs OR weight-bearing strengthening program OR strengthening program, weight-bearing OR strengthening programs, weight-bearing OR weight bearing strengthening program OR weight-bearing strengthening programs OR weight-bearing exercise program OR exercise program, weight-bearing OR exercise programs, weight-bearing OR weight bearing exercise program OR weight-bearing exercise programs OR activities, motor OR activity, motor OR motor activities OR physical activity OR activities, physical OR activity, physical OR physical activities OR locomotor activity OR activities, locomotor OR activity, locomotor OR locomotor activities OR exercise tests OR test, exercise OR tests, exercise OR stress test OR stress tests OR test, stress OR tests, stress OR treadmill test OR test, treadmill OR tests, treadmill OR treadmill tests OR step test OR step tests OR test, step OR tests, step OR arm ergometry test OR arm ergometry tests OR ergometry test, arm OR ergometry tests, arm OR test, arm ergometry OR tests, arm ergometry OR bicycle ergometry test OR bicycle ergometry tests OR ergometry test, bicycle OR ergometry tests, bicycle OR test, bicycle ergometry OR tests, bicycle ergometry) AND*

Systemic hypertension:*(blood pressure, high OR blood pressures, high OR high blood pressure OR high blood pressures OR hypertension OR pre-hypertension OR pre hypertension OR prehypertension) AND*

Endothelium:*(vascular endothelium OR endothelium, vascular OR vascular endothelium OR capillary endothelium OR capillary endothelium OR endothelium, capillary OR endothelium, capillary OR endothelial progenitor cell OR endothelial progenitor OR cell, endothelial OR cells, endothelium endothelial cells OR endothelial progenitor OR vascular endothelial cells OR cell, vascular endothelial OR cells, vascular endothelial OR endothelial cell, vascular OR endothelial cells, vascular OR vascular endothelial cell OR capillary endothelial cells OR capillary endothelial cell or cell, capillary endothelial OR cells, capillary endothelial OR endothelial cell, capillary OR endothelial cells, capillary OR Cell Derived Microparticles OR Cell-Derived Microparticle OR Microparticle, Cell-Derived OR Microparticles, Cell-Derived OR Microparticles, Cell Derived OR Cell Membrane Microparticles OR Cell Membrane Microparticle OR Membrane Microparticle, Cell OR Membrane Microparticles, Cell OR Microparticle, Cell Membrane OR Microparticles, Cell Membrane OR Circulating Cell-Derived Microparticles OR Cell-Derived Microparticle, Circulating OR Cell-Derived Microparticles, Circulating OR Circulating Cell Derived Microparticles OR Circulating Cell-Derived Microparticle OR Microparticle, Circulating Cell-Derived OR Microparticles, Circulating Cell-Derived ORvasorelaxation OR vasodilatation OR vascular endothelium-dependent relaxation OR endothelium-dependent relaxation, vascular OR relaxation, vascular endothelium-dependent OR vascular endothelium dependent relaxation OR hyperemia OR reactive hyperemia OR hyperemia, reactive OR hyperemia, reactive OR reactive hyperemia OR active hyperemia OR hyperemia, active OR arterial hyperemia OR hyperemia, arterial OR venous engorgement OR engorgement, venous OR venous congestion OR congestion, venous OR passive hyperemia OR hyperemia, passive OR flow-mediated dilation).*

Randomized controlled trial:*randomized controlled trial[pt]OR controlled clinical trial[pt] OR randomized controlled trials[mh] OR random allocation[mh] OR double-blind method[mh] OR single-blind method[mh] OR clinical trial[pt] OR clinical trials[mh] OR ("clinical trial"[tw]) OR ((singl*[tw] OR doubl*[tw] OR trebl*[tw] OR tripl*[tw]) AND (mask*[tw] OR blind*[tw])) OR ("latin square"[tw]) OR placebos[mh] OR placebo*[tw] OR random*[tw] OR research design[mh:noexp] OR follow-up studies[mh] OR prospective studies[mh] OR cross-over studies[mh] OR control*[tw] OR prospectiv*[tw] OR volunteer*[tw].*

Figure 3 – *MeSH (Medical Subject Headings for PubMed) descriptors for MEDLINE search.*

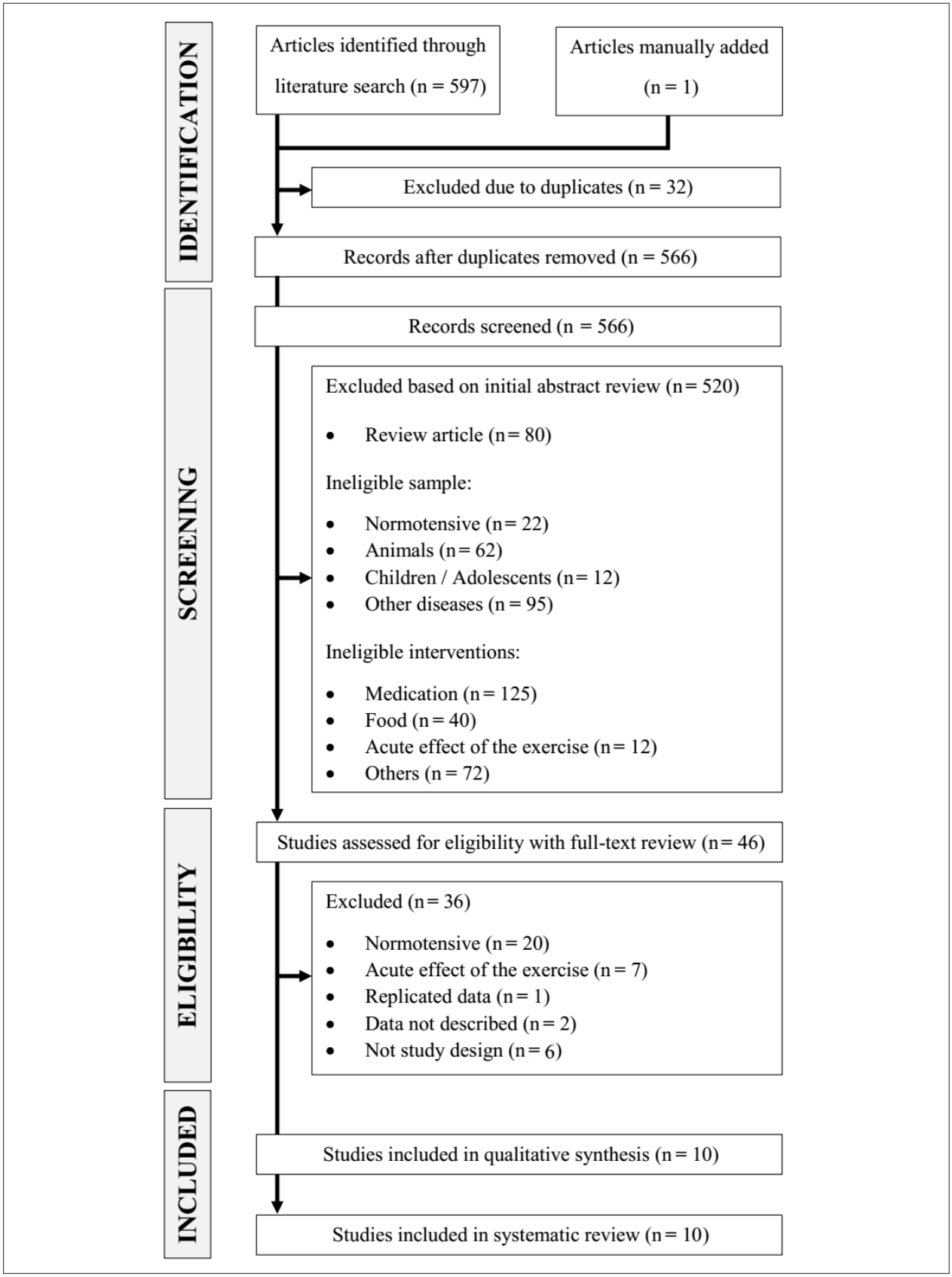

Figure 4 – *Flowchart of the selection of randomized controlled trials included in this systematic review.*

The duration of exercise training was most often 12 weeks (six studies), followed by 8 weeks (three studies), and 24 weeks (one study). The number of training sessions varied: 3 times a week (seven studies); 4 times a week (one studies); and 5 or more times a week (two studies).

Discussion

This systematic review aimed to evaluate any evidence of changes in endothelial function in response to different modalities of exercise training in prehypertensive and hypertensive individuals. The results showed that continuous aerobic training at moderate intensity (50% VO_2max), for 30-40 minutes per session at least 3 times a week appears to be the most appropriate intervention to improve endothelium-dependent vasodilation in hypertensive individuals. In prehypertensive individuals, vigorous aerobic interval training (3 min/walking and 2 min/running; 65% and 85% HRmax), 45 minutes per session 3 times a week seems to be an alternative to determine vascular health benefits. Regarding resistance training, we found an RCT reporting the effects of low-intensity isometric resistance training (30% of maximal effort, 4 times for 2 min, 3 times a week) on endothelial function in hypertensive individuals; and dynamic resistance training at moderate intensity (8 exercises, 60 min/session, 3 times a week, 2x8-12 repetitions until local muscle fatigue) was examined in two studies in prehypertensive individuals. Based on the RCTs involving isometric training assessed, we can speculate that training at low intensity can improve localized endothelial function. As for dynamic resistance training, it could be an alternative to improve endothelial function in prehypertensive individuals when performed at moderate intensity.

Aerobic training

Westhoff et al.[27] developed a low-intensity aerobic exercise training protocol (sessions 2 times a week for 12 weeks) using upper limb cycle ergometer to assess vascular response in patients with hypertension and found no improvement in endothelium-dependent vasodilation of arm vessels. One explanation may be exercise intensity: blood lactate was 2.0 mmol/L, which is a near resting level. The association with exercise intensity is further supported by the fact that individuals with stage I-II hypertension showed improvement of endothelium-dependent vasodilation of arm vessels after aerobic training at near-maximum-intensity exercise.[28] In addition to low-intensity exercise in this study, the use of beta-blockers may have caused systolic volume and cardiac output decrease and reduced shear stress-mediated NO release from endothelial cells, causing therefore less vasodilation.[29]

The intensity of aerobic exercise appears to influence vasomotor response in hypertensive individuals. Aerobic training for an hour on a stationary bike 3 times a week for 6 months at moderate intensity (50% HRreserve) was proven to increase plasma NO levels in hypertensive women.[30] Molmen-Hansen et al.[28] reported that a 3-month aerobic training improved endothelium-dependent vasodilation of arm vessels in hypertensive individuals only at high-intensities (alternating exercise at 60–70% and 90–95% HRmax). It raises the question of which other factors besides increased NO levels may contribute to the improvement of vasomotor function in response to aerobic training in hypertensive individuals.

Hypertension is associated with increased sympathetic activity that is enhanced during exercise. In normotensive individuals, exercise causes an attenuation of sympathetic activity in the active muscles with consequent local vasodilation.[31] This late local vasodilation is parallel to the increasing intensity of muscular work, and this phenomenon involves changes in muscle metabolites and other substances to reduce vascular response to the activation of α-adrenergic receptors involved in the regulation of vascular tone.[32] On the other hand, this mechanism is attenuated in hypertensive individuals,[31] and along with increased arterial stiffness, it leads to reduced blood flow and shear stress during exercise.[33] These factors may act together, precluding improvements in vasomotor capacity in hypertensive individuals following aerobic exercise in moderate or close to moderate intensity, even with preserved NO synthesis.[30]

Interval training appears to benefit vascular health in prehypertensive individuals. As it was demonstrated by Beck et al.,[34] an exercise training program consisting of walking for 3 minutes at moderate intensity alternated with running for 2 minutes at vigorous intensity (alternating exercise at 65–85% HRmax) 3 times a week for 8 weeks may increase endothelial-dependent vasodilation in prehypertensive young.[35]

Contrary to the body of evidence on high-intensity exercise, some studies reported improvements in endothelium-dependent vasodilation of arm vessels in hypertensive elderly patients after 12 weeks of low-intensity aerobic training (blood lactate level ≤2.5 mmol/L).[36,37] However, an important factor affecting the improvement of endothelial function following aerobic training in individuals with hypertension is endothelial dysfunction, i.e., endothelium-dependent vasodilation assessed by FMD lower than 5.5%.[38] Thus, the variation of results from studies involving aerobic exercise at low-and moderate-intensity may also be explained by baseline endothelial dysfunction in participants.

Vascular health in hypertensive individuals in response to aerobic training may be influenced by their lipid profile. In two studies, Higashi et al demonstrated that a 3-month training consisting of unsupervised walking 5–7 times a week at moderate intensity (50% VO_2max) for 30 minutes improved vasodilation of forearm vessels in untreated hypertensive individuals.[39,40] Interestingly, the improvement in vasodilation of forearm vessels was negatively correlated with LDL-cholesterol levels. Thus, since hypertension is commonly associated with low HDL and high LDL levels, failure to modify the lipid profile in this population may contribute to unsatisfactory improvement in endothelial function.

Circulating levels of EMPs in peripheral blood are associated with endothelial integrity. EMPs are small membrane vesicles that are released from endothelial cells in response to cell activation, injury and apoptosis. The major cell surface markers include CD144+, CD31+/CD41-, CD31+/CD42b-, CD31+/Annexin V+ and CD62E.[41] EMPs have been associated with the Framingham risk score,[3] hypertension,[42] among other conditions. While studying Afro-Americans, Feairheller et al.[43] investigated the effects of vigorous aerobic training (up 65%

VO_2max) for 6 months.[43] They reported that FMD increased by 60% and plasma NO levels increased by 77% along with a 50% reduction in EMP counts. However, of the 25 individuals of the sample, 10 were normotensives, 9 prehypertensives and only 7 were hypertensives, making it difficult to extrapolate the data to all three populations. It appears that exercise-induced shear stress can preserve endothelial function through a mechanism that potentiates metabolic functions of vascular cells.

The balance between endothelial injury and repair is the most significant event in the pathogenesis of atherosclerosis. EPCs play an important role in repairing injured endothelial cells and maintaining endothelial integrity. A low number of EPCs expressing the phenotype CD34+/KDR+ is predictive of cardiovascular events and death[44] and low levels of EPCs expressing the CD34+/KDR+/CD45dim phenotype is a strong predictor of atherosclerotic disease progression.[4] It is well established that hypertensive individuals have low numbers of functioning EPCs.[5] In turn, aerobic training increases the levels of EPCs in patients with cardiovascular risk or established cardiovascular disease,[45] balancing out endothelial injury and repair. However, we did not find any studies associating aerobic training and EPCs in prehypertensive and hypertensive individuals. Further investigations are required on this subject.

Resistance training

To date, one RCT has reported the results of isometric resistance training on endothelial function in hypertensive individuals. They assessed endothelium-dependent vasodilation of arm vessels in hypertensive individuals following unilateral and bilateral isometric handgrip training.[46] Interestingly, endothelium-dependent vasodilation improved in the trained arm only (trained arm FMD increased from 2.4 to 6.6%, $p<0.001$; with no change observed in untrained arm).[46] It can thus be assumed that a greater muscle mass subjected to training is required to achieve global endothelial function benefits in this population. It is important to emphasize that most of the included articles performed the FMD technique from Corretti et al.,[47] even those published after 2011, a period in which the technique was already updated. This allows us to question how the current technique, which is more accurate, could alter vascular results found, optimizing them.

Beck et al.[34] examined the effects of dynamic resistance training in prehypertensive individuals. They found that one-hour training, 3 times a week for 2 months consisting of 2x8 to 12 maximum repetitions (moderate intensity) increased endothelium-dependent vasodilatation of arm vessels and reduced ET-1 levels. This same protocol was repeated to assess vascular function in the upper and lower limbs by venous occlusion plethysmography.[35] They found improved vasodilation of forearm and leg vessels as well as improved oxidant-antioxidant balance at the end of the 2-month training. Increased endothelium-dependent vasodilation may be explained by the mechanical occlusion of vessels during exercise that causes continuous ischemia and reperfusion periods in the trained limbs, increases shear stress and leads to local endothelial adaptive changes that chronically increase vasodilatory capacity.[33] Another possible explanation is increased blood flow to the trained muscles. This redistribution of blood flow during exercise increases systolic antegrade and diastolic retrograde blood flow that may induce increased shear stress in the vessels of the untrained limbs.[29] Contrasting with resistance exercise, aerobic exercise continuously increases blood flow, which may lead to increased shear stress[48] and greater exercise-induced vascular adaptations when compared to other modalities. However, improvements in endothelial function in untrained limbs appear to be similar in healthy young individuals and individuals with type 1 diabetes after an exercise session consisting of both aerobic and resistance training with similar duration, intensity and muscle groups trained.[25] This finding raises the possibility that these variables may have impacted the results and could explain inconsistencies among the studies.

We did not find any studies involving isometric or dynamic resistance training that measured EMPs and EPCs in prehypertensive and hypertensive individuals. It requires further investigation.

The study has some limitations that need to be considered. Different aerobic training strategies (brisk walking, cycling and treadmill), participant ages and intervention times assessed in the RCTs make it difficult to infer the effect of each factor on endothelial function. Given the limited body of evidence for resistance training, further investigation is needed so we can delineate the improvement effects on endothelial function in individuals with altered blood pressure, as these are so far speculative.

Conclusion

In the studies included in our systematic review, moderate intensity aerobic training for 30–40 minutes/session and at least 3 times a week is effective to improve endothelial function in hypertensive individuals. In prehypertensive individuals, the vigorous intensity interval aerobic training, 45 minutes/session and 3 times a week seems to be an alternative to determine vascular health benefits. As a perspective, resistance exercise training, either isometric or dynamic, could be used as a secondary strategy to improve endothelial function in individuals with altered blood pressure measurements. With regard to EPCs and EMPs data, no studies involving isometric or dynamic resistance training had measured EMPs and EPCs in prehypertensive and hypertensive individuals.

Author contributions

Conception and design of the research, Writing of the manuscript and Critical revision of the manuscript for intellectual content: Waclawovsky G, Schaun MI, Lehnen AM; Data acquisition: Waclawovsky G, Pedralli ML, Eibel B, Schaun MI; Analysis and interpretation of the data: Waclawovsky G, Pedralli ML, Eibel B, Schaun MI, Lehnen AM.

Potential Conflict of Interest

The authors report no conflict of interest concerning the materials and methods used in this study or the findings specified in this paper.

Sources of Funding

There was no external funding source for this study.

Study Association

This article is part of the thesis of Doctoral submitted by Gustavo Waclawovsky, from Instituto de Cardiologia do Rio Grande do Sul/Fundação Universitária de Cardiologia.

Ethics approval and consent to participate

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

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*Supplemental Materials

For additional information, please click here.

Exercise Training and Endothelial Function in Hypertension: Effects of Aerobic and Resistance Training

Gustavo F. Oliveira,[1,3] Thais C. Marin,[1,3] Cláudia L. M. Forjaz,[2] Leandro C. Brito[1,2,3]

Escola de Artes, Ciências e Humanidades da Universidade de São Paulo,[1] São Paulo, SP - Brazil

Laboratório de Hemodinâmica da Atividade Motora, Escola de Educação Física e Esporte da Universidade de São Paulo,[2] São Paulo, SP - Brazil

Grupo de Pesquisa em Cronobiologia Aplicada & Fisiologia do Exercício, Universidade de São Paulo,[3] São Paulo, SP - Brazil

Short Editorial related to the article: Effects of Different Types of Exercise Training on Endothelial Function in Prehypertensive and Hypertensive Individuals: A Systematic Review

Hypertension is one of the most important risk factors for cardiovascular events, which is strongly related with endothelial dysfunction.[1] Endothelial function assessed by flow-mediated dilation (FMD) is 3.2% lower in hypertensives than in normotensives.[2] The negative balance between damage and regeneration of endothelial cells indicated by a high number of circulating endothelial microparticles (EMP) and reduced levels of endothelial progenitor cells (EPC) is predictor of cardiovascular events in hypertensives.[3] Thus, therapies able to positively influence endothelial function are important to improve prognosis in hypertension.

Regular practice of exercise is recommended not only for the benefit of lowering blood pressure, but also for reducing cardiovascular morbidity and mortality in hypertensives.[4] Important exercise-induced vascular adaptations, mainly resulting in increased endothelium-dependent vasodilation, may partially explain these exercise benefits. A previous meta-analysis showed positive effects of aerobic exercise on the endothelial function of hypertensives.[5] However, the variation of results suggests that different exercise protocols (types and intensity) and subjects' characteristics may influence the response of endothelial function to exercise training. In addition, the underlying mechanisms for endothelial improvement need to be known.

Given that, Waclawovsky et al.[6] helped to clarify some of these points. The authors searched the literature looking for randomized controlled trials (RCT) investigating the effects of different exercise training protocols on endothelial function, EPM and EPC in pre-hypertensives and hypertensives. Different databases (e.g.: MEDLINE, Cochrane, LILACS, EMBASE and SciELO) were searched and the PICOS strategy was applied to reach 10 eligible studies.

Regarding aerobic exercise, 9 studies involved aerobic training groups allowing for dose-response speculations regarding vascular improvement. Thus, the authors suggested that moderate intensity training performed 3 times/week for 30–40 min may be better to improve endothelial function in hypertensives, while vigorous interval training might be an alternative in pre-hypertensives. Actually, a previous study detected that every absolute (2-MET) or relative (10 %) increase in the intensity of aerobic training results in nearly 1% improvement in endothelial function with no influence from volume of training.[7] Theory behind higher intensity promoting greater benefits relies on the greater shear rate produced by faster blood flow leading to higher nitric oxide levels. Noteworthy, a study by Waclawovsky et al.[6] evaluated hypertensives without metabolic syndrome or cardiovascular disease, showing a specific benefit of aerobic training for hypertension regardless of comorbidities. Previous studies involving different populations (e.g.: healthy, hypertensives, diabetics, cardiac patients, etc.) suggest that health and anthropometric characteristics may influence endothelial function improvements induced by aerobic training. Indeed, subgroup analyses in a previous meta-analysis demonstrated that non-obese individuals present greater enhancement in endothelial function with aerobic training than obese ones. Additionally, individuals with lower baseline FMD values present greater improvements after training than those who present higher baseline values.[7]

Concerning resistance exercise, Waclawovsky et al.[6] found only two studies that included dynamic resistance exercise groups and both presented positive endothelial function results. However, a study published after the authors' search (2020) did not find any change in endothelial function with this type of training compared with the control group.[8] Additionally, Waclawovsky et al.'s review[6] found the only one study with isometric resistance training and this training increased FMD but only in trained arms,[9] suggesting a local effect of this type of exercise. Therefore, based on the few number of studies, any conclusion about the effects of resistance training on endothelial function in hypertension or its factors of influence is risky. Nevertheless, a review with more comprehensive populations, including hypertensives, revealed a positive effect of dynamic resistance training on endothelial function.[7]

Regarding the mechanisms for exercise-induced endothelial function improvement, the enhancement of nitric oxide bioavailability by reducing its degradation by free radicals is expected.[10] In addition, the balance between damaging and regeneration of endothelial cells has emerged as a promising tool. The reduction of EMP and an increase of EPC (i.e. repair biomarker) has been reported after exercise training in heterogeneous samples.[11,12] However, Waclawovsky et al.[6]

keywords

Exercise; Endurance Training; Physical Resistance; Hypertension; Endothelium Vascular.

Mailing Address: Leandro C. Brito •
Universidade de São Paulo - Escola de Educação Física e Esporte - Av. Prof. Mello Moraes, 65. Postal Code 05508-030, Cidade Universitária, São Paulo, SP – Brazil
E-mail: leandrobrito@usp.br

DOI: https://doi.org/10.36660/abc.20210111

were not able to find any RCTs investigating the effects of any type of exercise training on these biomarkers in hypertensives. This revealed an important lack in the literature and the need for future studies.

In summary, the findings reported by Waclawovsky et al.[6] contribute to the literature by confirming the positive effect of aerobic training improving endothelial function in hypertensives. It also suggests that the intensity of aerobic exercise may influence this improvement, which should be strengthened with more studies. However, the lack of studies with dynamic and isometric resistance training in hypertensives exposed the need for more RCTs to allow robust conclusions about their benefit on endothelial function. Finally, the literature suggests that balance between damage and regeneration of endothelial tissue seems to be a promising key to understand exercise benefits in endothelial function. Waclawovsky et al.[6] clearly showed the need for studies investigating the exercise effects on endothelial function mechanisms.

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Blood Pressure in Children: Association with Anthropometric Indicators, Body Composition, Cardiorespiratory Fitness and Physical Activity

Gisele Pinheiro,[1] Júlio Mello,[1,2] Adroaldo Gaya,[1] Anelise Reis Gaya[1]
Universidade Federal do Rio Grande do Sul,[1] Porto Alegre, RS – Brazil
Faculdade SOGIPA de Educação Física,[2] Porto Alegre, RS - Brazil

Abstract

Background: **Evidence points to anthropometric and fitness variables as associated factors with children's blood pressure. Analysing these factors in a single context is a relevant possibility of identifying the weight that each factor can present for the development of arterial hypertension.**

Objective: **Identify the possible associations between anthropometric measurements, body composition, moderate-vigorous physical activity (MVPA) and cardiorespiratory fitness (CRF) with blood pressure in children.**

Methods: **Correlational study with a quantitative approach. Sample: 215 schoolchildren aged 6-12 years selected by convenience criteria of a public school in Porto Alegre, Brazil. Blood pressure was measured with a digital sphygmomanometer. For data treatment, the values of systolic and diastolic blood pressure were standardized (Z score) and added. The variables tested as predictors were: MVPA; body fat percentage (BF%); Body Mass Index (BMI); waist-height ratio (WHTR); maturity-offset and CRF. After checking the normality parameters, the crude and adjusted associations (for sex, age and maturity-offset) were tested with linear regression equations. For the analyses, $p < 0.05$ was considered.**

Results: **Three different models indicated the best sets of factors associated with standardized blood pressure. Model 1 ($R^2 = 0.21$) consisted of the variables WHTR ($\beta = 9.702$) and MVPA ($\beta = -0.021$). Model 2 ($R^2 = 0.19$) was composed of the variables BMI ($\beta = 0.156$) and MVPA ($\beta = -0.021$). Model 3 ($R^2 = 0.18$) included the variables BF% ($\beta = 0.063$) and CRF ($\beta = -0.004$).**

Conclusion: **Blood pressure in children is predicted by the body variables BF%, BMI and WHTR, in addition, it is negatively associated with MVPA and CRF. (Arq Bras Cardiol. 2021; 116(5):950-956)**

Keywords: **Child; Blood Pressure; Anthropometry; Exercise; Body Composition; Physical Fitness; Motor Activity.**

Introduction

Blood pressure is an important indicator of cardiovascular and metabolic health. Children with high blood pressure levels are highly likely to become hypertensive adults, then, the early diagnosis and treatment can prevent long-term adverse cardiovascular events.[1] Although arterial hypertension is more frequent in adulthood, epidemiological evidence suggests that its genesis may be in childhood.[2] However, it is noteworthy that recent researches have shown considerable prevalence rates of high blood pressure values.[3]

In order to understand hypertension in childhood and adolescence, it is relevant to consider variables such as: age, height, sex, overweight/obesity, physical activity and fitness levels.[4-6] The study by Freedman et al.[7] suggested that overweight or obese children are more likely to have high blood pressure. Other studies have shown a negative association between the level of physical activity and blood pressure.[3] As well as other studies[8,9] have shown that children and adolescents with low cardiorespiratory fitness levels plus overweight/obesity have a greater chance of presenting cardiovascular diseases risk factors.

In this sense, evidence about all factors evaluated together in the same study adds relevant information on the magnitude of the influence that each one can present for the development of arterial hypertension. In this context, the present study aims to identify the possible associations between anthropometric measurements, body composition, moderate-vigorous physical activity and cardiorespiratory fitness with blood pressure in children

Methods

Study Design

This is a cross-sectional study with correlational method and quantitative approach.[10]

Mailing Address: Gisele Pinheiro •
Universidade Federal do Rio Grande do Sul - Rua Felizardo, 750. Postal Code 90040-060, Jardim Botânico, Porto Alegre, RS – Brazil
E-mail: giselepinheiros@hotmail.com
Manuscript received August 05, 2019, revised manuscript March 05, 2020, accepted May 06, 2020

DOI: https://doi.org/10.36660/abc.20190520

Research Subjects

Target population[11] are students from the first to fifth year of elementary school, aged between 6-12 years enrolled in public schools. The available population[11] was composed of approximately 400 schoolchildren from the first to fifth year of elementary school at a public school at Porto Alegre, Brazil. The available population was selected for convenience, justified for this school meets the supervised internship subject in the Physical Education graduation of the researchers' university and, as such, allows full access of researchers to the school community.

To compose the sample, all children enrolled in the early five years of elementary school were invited. 215 children from 6-12 years old were evaluated. After data collection, to identify the sample size that most balances the probability between type I and II errors and to justify the use of statistical tests in a non-random sample, the G-Power version 3.1 program was used. The calculation was performed for F family tests, more specifically multiple linear regression, the alpha used was 0.05, the effect size was 0.15 (medium), the test power was 0.95 and the number of predictors was eight (considering the model with the greatest possible number of variables in this study: waist-to-height ratio (WHTR), Body Mass Index (BMI), body fat percentage (BF%), moderate-vigorous physical activity, cardiorespiratory fitness, sex, age and maturity-offset). From these criteria, a minimum sample size of 160 subjects was stipulated.

Data collection was carried out between March and April 2017. The school was invited to participate in the study and consented through a consent letter. Afterwards, a meeting was held with the parents detailing the study and then, they received and signed a Free and Informed Consent Form and the students signed an Informed Assent Form, both terms explaining the study. The research was approved by the Human Research Ethics Committee of the Universidade Federal do Rio Grande do Sul, ,Brazil under number 2.571.198.

Data Collection Procedures

Anthropometric variables (height, mass and waist circumference) were assessed following the Guidelines for Measurement and Tests of PROESP-Br.[12] Body mass was assessed with the students barefoot using a portable digital scale (Tech Line) with 100g precision and the value in Kg was recorded using a decimal place. To measure height, a measuring tape with two millimetres precision was used, which was attached to the wall one meter from the ground vertically, extended from the bottom up and noted in centimetres with a decimal point with the aid of a square for reading. Waist circumference was measured using a measuring tape, positioning it at the midpoint between the lower edge of the last rib and the iliac crest, usually close to the umbilical scar. The other anthropometric variables followed the recommendations of Mirwald et al.[13] The seated height was measured with a standard bench for all children and a measuring tape with two millimetres precision fixed to the wall. The zero point of the measuring tape was fixed to the bench.

Height and body mass were used to calculate BMI, while height and waist circumference were used to calculate WHTR.[12] For the maturity-offset calculation, the variables sex, height, body mass, sitting height, leg length (the difference between total height and sitting height) and age were used.[13]

Blood pressure was measured during the school's class period using a digital sphygmomanometer with appropriate OMRON cuffs. All measurements were carried out between the first and the second school period in the morning (≈8-9h), so in general, all children were not fasting. Children were invited to remain seated for five minutes to obtain a value closer to rest. Three measurements were performed on the right arm and the average value was computed. The values of systolic and diastolic blood pressure were standardized (using Z score). The Z score of systolic blood pressure was added to the Z score of diastolic blood pressure, creating a new standardized blood pressure variable.

Body fat percentage was assessed by the imaging exam of Dual Energy X-ray Absorptiometry (DXA) of the GE Healthcare model Lunar Prodigy, performed by a trained researcher. Children were instructed to wear clothes without zippers and buckles; to remove any metal piece; to lying in the supine position and; remain stationary until the device arm passes over the body in the head-to-foot direction. The values, in percentage, were calculated automatically by the equipment software.

ActiGraph accelerometers (wActiSleep-BT Monitor) were used to measure physical activity, which was placed on the students' waist on an elastic belt on the right midline axillary. Children were encouraged to use it for seven consecutive days. For analysis purposes, five days (including one weekend day) were considered, with at least 10 hours/day of usage time. The equipment was maintained throughout the day and removed only for bathing or any water activities. After the last day of use, the device was removed by the evaluation team and subsequently it was verified if data were complete, using the Actilife software (ActiGraph®, version 5.6, USA). The data were collected at a sampling rate of 30Hz, downloaded in periods of one second, and aggregated for periods of 15 seconds. Everson et al.[14] proposal for 15 seconds periods was used for classifying the accelerometers counts (≤25 counts/15 seconds for sedentary time, ≥574 counts/15 seconds for moderate physical activity and ≥1003 counts/15 seconds for vigorous physical activity).

For the measurement of cardiorespiratory fitness, the six-minute running/walking test was performed according to the Guidelines for Measurement and Tests of PROESP-Br.[12] To perform this test, a court with a 56-meter perimeter marked with cones and marked with chalk every two meters was used to record the distance covered by each child at the end of the test. A stopwatch and a whistle were also used to start and end the test. Children were instructed to run (run or walk) the largest number of laps, that is, the longest distance possible. During the test, the evaluators informed the passage of the test time in two, four and five minutes ("attention: one minute left") and at the end of the test (at the whistle) the children should stop in place and remain until the evaluator notes the distance covered.

Statistics Procedures

Initially, the Kolmogorov-Smirnov normality test was performed in all variables. All variables showed a normal distribution. For descriptive analysis, mean values, standard deviations, minimum and maximum were used in continuous variables and values of absolute and relative frequency in categorical variables. The variance difference between sexes was tested in all variables with the Student's T-test for independent samples. Associations were initially tested with Pearson's correlation test. Multicollinearity was previously tested and a high relationship was identified only between moderate-vigorous physical activity and cardiorespiratory fitness. These procedures were performed to meet the assumptions of multiple linear regression. The following analysis proposed to estimate the variance of standardized blood pressure from the other variables studied. Different multiple linear regression models were tested using the Stepwise method and those with the highest values of adjusted R^2 were considered, as long as they maintained the theoretical logic. All associations were adjusted for sex, age and maturity-offset in order to remove the effect of the possible confounder. For all analyses, an alpha of 0.05 was considered a priori. The analyses were performed with the SPSS software for Windows version 20.0.

Results

In the sample 53.5% are boys and 46.5% are girls. Table 1 shows the characteristics of the research subjects in relation to the studied variables. Only the variables: body fat percentage, moderate-vigorous physical activity and cardiorespiratory fitness showed differences between sexes ($p<0.05$). The low performance in the six-minute running/walking test in both sexes is highlighted.

The correlation analysis is shown in table 2. Standardized blood pressure is associated in a negative and positive way with some variables in boys, however with reasonably low correlation (r) indexes. In girls, all values are below 0.3, indicating that in the bivariate analysis, associations are weak.

After checking the correlations, adjusted association analyses were performed. In these analyses, the results demonstrate that considering sex, age and maturity-offset, the variables waist-height ratio, body mass index and body fat percentage indicated a positive association with standardized blood pressure, while moderate-vigorous physical activity and cardiorespiratory fitness indicated a negative relationship.

The predictor variables were tested in several models, however, three different models indicated the sets of factors that best explained the variance of standardized blood pressure (table 3). Although the three models are composed of different variables, they explained between 18 and 21% of the standardized blood pressure variance. Another highlight is that the two measures of nutritional status (body mass index and waist-height ratio) were the indicators that showed the highest magnitudes of association, considering the adjustments already described.

Discussion

The main results of the present study indicated that moderate-vigorous physical activity, cardiorespiratory fitness, anthropometric variables, age, sex and maturity-offset are important predictors of the standardized blood pressure variability in children. In our results, we observed that the systolic blood pressure mean was 103.0 mmHg in boys and 103.8 in girls and diastolic was 60.7 mmHg in boys and 60.6 in girls.

Table 1 – Description of research subjects characteristics (n = 215)

	Boys				Girls				
	n	X ± SD	Mín	Máx	n	X ± SD	Mín	Máx	p-value
Age (years)	115	8.25 ±1.54	6	12	100	8.51 ± 1.44	6	11	0.211
SBP (mmHg)	115	103.04 ± 11.35	83	143	100	103.81 ± 11.75	77	134	0.628
DBP (mmHg)	115	60.78 ± 9.13	41	81	100	60.67 ± 8.59	42	82	0.926
Height (cm)	111	134.27 ± 10.09	111	161	98	134.47 ± 10.84	108	154	0.890
Weight (kg)	111	32.98 ± 9.58	18	61	98	33.82 ± 11.23	15	67	0.558
WC (cm)	111	63.41 ± 9.09	48	86	98	61.75 ± 10	35	90	0.209
BF%	55	31.86 ± 9.09	15.6	51.2	57	35.24 ± 7.55	17.2	49.6	**0.035**
BMI (kg/m²)	111	18 ± 3.47	12.4	29.5	98	18.27 ± 3.98	12.6	29.78	0.600
WHTR	111	0.47 ± 0.05	0.37	0.64	98	0.45 ± 0.05	0.27	0.60	0.800
MVPA (min)	57	70.26 ± 29.57	23.62	147.16	60	55.33 ± 18.75	23.64	110.24	**0.002**
CRF (m)	101	800.43 ± 142.99	438	1158	91	749.25 ± 104.64	504	952	**0.005**

Source: the Authors. n: subjects number; X: average; SD: standard deviation; SBP: systolic blood pressure; DBP: diastolic blood pressure; WC: waist circumference; BF%: body fat percentage; BMI: body mass index; WHTR: waist-height ratio; MVPA: moderate-vigorous physical activity; CRF: cardiorespiratory fitness.

Table 2 – Correlation values between standardized blood pressure and body composition, moderate-vigorous physical activity and cardiorespiratory fitness (n = 215)

	zBP	
	Boys (n:115)	Girls (n:100)
	r	r
WHTR	0.368	0.252
BMI	0.454	0.342
BF%	0.490	0.288
MVPA	-0.349	-0.253
CRF	-0.216	-0.227

zBP: standardized blood pressure; r: correlation coefficient; WHTR: Waist-height ratio; BMI: Body mass index; BF%: Body fat percentage; MVPA: moderate-vigorous physical activity; CRF: cardiorespiratory fitness.

In the study by Gaya et al.[15] with 416 Portuguese boys between 8-15 years old, the systolic blood pressure mean was 117.2 mmHg and diastolic blood pressure was 61.1 mmHg. In the study by Monteiro et al. (2015)[16] with 51 Brazilian schoolchildren, the systolic blood pressure mean was 111.6 mmHg in boys and 107.6 in girls and diastolic was 66.8 mmHg in boys and 66.5 in girls aged between 13 and 16 years. A possible explanation for the systolic blood pressure values to be higher in the aforementioned studies compared to the findings may be due to the subjects' chronological age being higher. This directly influences blood pressure levels, as older children tend to be higher, which naturally raises blood pressure levels.[2]

Regarding cardiorespiratory fitness, we noticed that the average number of meters covered in the six-minute test is low for boys and girls. In the study by Mello et al.[17], although with children and adolescents between 10-17 years old, the prevalence of low cardiorespiratory fitness was 74.1% among

Table 3 – Multiple linear regression to estimate the standardized blood pressure variability from 3 models (n = 215)

zBP			
	Model 1 (adjusted R^2: 0.210)		
	β	p-value	CI 95%
WHTR	7.170	0.022	1.033 – 13.308
MVPA	-0.021	0.004	-0.035 – -0.007
Sex	-0.998	0.136	-2.315 – 0.320
Age	-0.302	0.212	-0.778 – 0.174
Maturity-offset	0.456	0.079	-0.054 – 0.965
	Model 2 (adjusted R^2: 0.192)		
BMI	0,113	0,090	-0,018 – 0,245
MVPA	-0,023	0,002	-0,037 – -0,008
Sex	-0,697	0,408	-2,360 – 0,967
Age	-0,254	0,364	-0,808 – 0,299
Maturity-offset	0,260	0,471	-0,453 – 0,973
	Model 3 (adjusted R^2: 0.183)		
BF%	0.054	0.043	0.002 – 0.107
CRF	-0.003	0.037	-0.006 – 0.001
Sex	-0.737	0.307	-2.163 – 0.689
Age	0.090	0.765	-0.508 – 0.688
Maturity-offset	0.238	0.466	-0.408 – 0.884

zBP: standardized blood pressure; adjusted R^2: adjusted coefficient of determination to model variables; β: adjusted association for sex, age and maturity-offset; p-value: significance level; WHTR: Waist-height ratio; MVPA: moderate-vigorous physical activity; BMI: body mass index; BF%: body fat percentage; CRF: cardiorespiratory fitness.

young people, being higher in girls. Even using the PROESP-Br criteria, the same as in this study, the results found by Mello et al.[17] were more worrying. However, in the studies by Coledam et al.[18] and Minatto et al.[19] the authors observed results similar to the present study, showing that around 50% of children have low levels of cardiorespiratory fitness.

Regarding moderate-vigorous physical activity, in the present study, we observed an average of 70.2 min/week in boys and 55.3 min/week in girls. Matsudo et al.[20] observed in Brazilian children aged 9-11 years an average of moderate-vigorous physical activity of 59.5 min/day, with children accumulating more moderate-vigorous physical activity on weekdays than on weekends. In addition, 55.9% of children did not reach the daily recommendation.

We noticed that girls tend to have lower values of both cardiorespiratory fitness and moderate-vigorous physical activity. This data can be explained by a set of factors related to the culture of incentive to vigorous physical activities practice, anthropometric, ethnic and physiological variables[21]. Treuth et al.[22] pointed out in a study carried out with girls, that the most performed activity during the week and on most weekend days are sedentary activities (55.4% of the time), in this active time, they have practised mostly activities with low intensity (41.7% light activities) and a little time in moderate (2.2%) and vigorous activities (0.7%).

Regarding associations, our initial results demonstrated a correlation between standardized blood pressure and all indicators of overweight and obesity, as well as moderate-vigorous physical activity and cardiorespiratory fitness. All results showed correlations with moderate or low magnitude ($r < 0.4$). This low magnitude can be explained mainly by the several factors that influence blood pressure, such as height, sex and age,[23] which were not part of this initial analysis. Therefore, from these first analyses, the need for adjusted analyses became clear.

In this perspective, models that can explain part of the standardized blood pressure variance by adjusting associations for the maturity-offset, age and sex were analysed. Thus, we perceive more clearly how much the variables: waist-height ratio, body mass index, body fat percentage, moderate-vigorous physical activity and cardiorespiratory fitness can in fact influence the standardized blood pressure of schoolchildren, both in an individually (through the Beta values) and jointly (through the adjusted R^2 values).

From this, the predictor variables were tested and we arrived at three models that best explain the variance of standardized blood pressure. The first two models (model 1: waist-height ratio, moderate-vigorous physical activity, sex, age and maturity-offset; and model 2: body mass index, moderate-vigorous physical activity, sex, age and maturity-offset) explain 21% and 19% of the variance, respectively. The variable waist-height ratio, which is an indicator of abdominal fat, is the one that most influences the variability of blood pressure. These results are in line with the study by Silva et al.[24] that showed an association of excess visceral fat with blood pressure levels and prevalence of arterial hypertension. However, according to the study by Cauduro et al.,[25] overweight and obese children and adolescents were less likely to have high blood pressure levels regardless of sex, age and socioeconomic status, if they complied with the recommendations for physical activity for their age.

Therefore, the results of Cauduro et al.[25] demonstrate the importance of considering physical activity and some indicator of overweight/obesity in the same association model in the trying perspective for understanding the set of predictors of blood pressure in children. Our results show that, regardless of the overweight/obesity indicator inserted in the model, the associations remain. This is justified by the fact that both variables are independently associated with blood pressure.[6,26,27]

In the last model presented, we observed that cardiorespiratory fitness and body fat percentage explain 18% of the standardized blood pressure variance. It is important to point out, although apparently, the magnitude of the association of cardiorespiratory fitness is low in relation to standardized blood pressure (β: -0.003), we realize that by the unit of measurement of this variable (meters) it is an important result and can easily influence at children's blood pressure.

Finally, it is important to add that cardiorespiratory fitness and moderate-vigorous physical activity are not in the same model because theoretically they are associated[28], just as, when tested for multicollinearity, the relationship found in the present study was $r > 0.7$. It is also important to note that even with three indicators of overweight/obesity performed using different measures (body growth, abdominal fat and image examination) the associations remained and the models maintained a similar percentage of standardized blood pressure explanation. In addition, we also emphasize that in the school environment the use of anthropometric measures to estimate children's nutritional status is an effective strategy and that it has an analysis effect similar to the image examination. This indicates that these variables (body mass index and waist-height ratio) can be added to intervention programs.

Conclusion

We noticed that the body variables: body fat percentage, body mass index and waist-height ratio were shown to be influential to blood pressure. In addition, it was observed that moderate-vigorous physical activity and cardiorespiratory fitness, which are important variables related to exercise, were also shown to influence blood pressure in children. Therefore, it is concluded that all the studied indicators, when analysed together, are associated with the children blood pressure, suggesting that the early prevention of arterial hypertension in children consider the regular practice of moderate-vigorous physical activity, the increases in cardiorespiratory fitness levels and strategies for controlling of overweight and obesity indicators.

Acknowledgments

We are grateful to the Conselho Nacional de Desenvolvimento Científico e Tecnológico (Brazil) for the level D1 research scholarship and for the Institutional Program for Scientific Initiation scholarship. We are grateful to the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (Brazil) for the PhD scholarship.

Author Contributions

Conception and design of the research: Pinheiro G, Gaya A, Gaya AR; Data acquisition: Pinheiro G, Mello J, Gaya AR; Analysis and interpretation of the data: Pinheiro G, Mello J, Gaya A, Gaya AR; Statistical analysis: Pinheiro G, Mello J; Obtaining financing: Gaya AR; Writing of the manuscript: Pinheiro G, Gaya A; Critical revision of the manuscript for intellectual content: Mello J, Gaya A, Gaya AR.

Potential Conflict of Interest

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

Sources of Funding

This study was funded by Conselho Nacional de Desenvolvimento Científico e Tecnológico, number 401969/2016-9

Study Association

This article is from the Programa de Pós-Graduação em Ciências do Movimento Humano submitted by *Júlio Mello*, *Adroaldo Gaya* and *Anelise Reis Gaya*, from Universidade Federal do Rio Grande do Sul.

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Blood Pressure in Children. The Key Role of Physical Activity and Body Fatness

César A. Agostinis-Sobrinho[1] and Katiane Vilan[1]

Klaipeda University - Faculty of Health Sciences,[1] Klaipeda – Lituânia

Short Editorial related to the article: Blood Pressure in Children: Association with Anthropometric Indicators, Body Composition, Cardiorespiratory Fitness and Physical Activity

High blood pressure is the leading global risk factor for chronic kidney disease and cardiovascular diseases and is the leading cause of premature death worldwide.[1] The number of adults with high blood pressure increased from 594 million in 1975 to 1.13 billion in 2015.[2] The World Health Organization (WHO) estimates 1 in 4 men and 1 in 5 women had hypertension and that by 2025, 1.56 billion adults will be living with hypertension.

Childhood raised blood pressure is becoming more common in the general pediatric population, representing a considerable public health challenge worldwide.[3] Studies have suggested that childhood high blood pressure seems to track from childhood to adulthood[4] and is associated with detrimental lifelong cardiovascular events.[3] However, raised blood pressure is one of the most important preventable contributors to disease and death and is considered to be one of the major modifiable risk factors for cardiovascular disease with roots in childhood.[4,5] Studies indicate that high blood pressure levels during childhood are a multifactorial condition.[6] Genetics, age, gender, ethnicity, overweight/obesity, sodium and potassium intake, physical inactivity, and socioeconomic factors have been named as the main risk factors for hypertension.[7]

Physical inactivity and obesity have become a global health issue and the evidence indicate that both are independently associated with raised blood pressure.[8-10] The prevalence of childhood hypertension is rising in parallel with global increases in the prevalence of overweight and obesity.[8] In addition, obesity-related hypertension contributes further to the clustering of cardiometabolic risk factors.[8]

Physical activity and high sedentary behavior play a key role in children and adolescents health.[9,10] Current literature report that physical activity confers benefits for improved physical fitness (cardiorespiratory and muscular fitness), cardiometabolic health (blood pressure, dyslipidemia, glucose, and insulin resistance), bone health, cognitive outcomes (academic performance, executive function), mental health (reduced symptoms of depression); and reduced adiposity.[9] In addition, some studies in children have demonstrated that low levels of cardiorespiratory fitness (CRF) is inversely associated with raised blood pressure.[11,12] As well as a high level of CRF in childhood is associated with normal levels of blood pressure in adulthood.[13,14]

Indeed, the prevalence of a high levels of blood pressure during childhood has also become a significant public health issue.[1] From the public health perspective, reliable studies to identify possible mechanisms associated to hypertension onset serve as a basis for adequate prevention and treatment, as well as evidence-based health resource allocation and policy making. Taking all this into account along with the multifactorial condition of high blood pressure, the study of published in ABC Cardiol,[15] the authors sought to investigate the associations between anthropometric measurements, body composition, moderate-vigorous physical activity, and CRF with blood pressure in children aged 6 to 12 years old. The authors found that body fatness (percentage of fat, body mass index, and waist/height ratio) was negatively associated with blood pressure levels. In addition, they observed that moderate-vigorous physical activity and CRF, also had a great impact on blood pressure. Findings from study[15] are particularly important from a public health perspective, since both physical activity and body weight are modifiable risk factors for the prevention of hypertension, both should be simultaneously considered in future interventions. The early identification of high body fatness, and low levels of CRF and physical activity in childhood may allow early interventions, thereby preventing hypertension at an early age as well as in the adulthood.

The study[15] present some important strengths that should be highlighted, such as the novelty of the analysis of the impact of several variables on blood pressure levels in children of both genders as well as the objectively assessment of physical activity with accelerometers, as these devices do not rely on subjects' recall and may capture the entire daily pattern of physical activity. The study also presents to certain limitations, such as its cross-sectional design, and the authors cannot infer that their observed associations reflect causal relationships. Moreover, there is a lack of data collected regarding food intake, which could provide a more robust predictor model.

In conclusion childhood raised blood pressure represents a considerable public health challenge worldwide. Pediatric hypertension is a condition that has profound effects on later life, increasing the risk for future cardiovascular events in adulthood.[6] Therefore, considering that both physical

Keywords

Blood Arterial; Hypertension/heredity; Risk Factors; Child; Obesity; Overweight; Physical Activity; Exercise; Sedentarism; Public Health.

Mailing Address: César A. Agostinis-Sobrinho •
Klaipeda University - manto gatve Klaipeda 92294 – Lithuania
E-mail: cesaragostinis@hotmail.com

DOI: https://doi.org/10.36660/abc.20210117

activity and obesity/overweight are main modifiable conditions, interacting with epigenetic changes, they should be simultaneously considered in future interventions aiming to improve the health profile of children. The increment of physical activity or exercise to improve physical fitness and decrease obesity/overweight may be an effective preventive strategy for reduction and protection against raised blood pressure. However, taking the findings of study[15] into account, as well as the current literature, scientific experts strongly recommend that children and adolescents should do at least an average of 60 minutes per day of moderate to vigorous-intensity, mostly aerobic, physical activity, across the week to offer significant health benefits and mitigate health risks. In addition, vigorous-intensity aerobic activities, as well as those that strengthen muscle and bone, should be incorporated at least 3 days a week.

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Original Article

The Comparison between Two Risk Scores as for the Prediction of Coronary Microvascular Obstruction during Primary Percutaneous Intervention

Yuyang Xiao,[1,2] Hua Chen,[1] Dongxia Liu,[1] Yanbo Wang,[2] Wenlu Wang,[2] Qian Zhang,[2] Yuping Han,[1] Xianghua Fu[2*]*

Hebei General Hospital - Department of Cardiology,[1] Shijiazhuang, Hebei – China

Second Hospital of Hebei Medical University - Department of Cardiology,[2] Shijiazhuang, Hebei – China

Abstract

Background: For patients with ST-segment elevation myocardial infarction (STEMI) that are suffering from subsequent coronary microvascular functional and structural obstruction (CMVO), no specific and definitive therapeutic approaches of attenuation have been proven valid in up-to-date large-scale tests, which highlights the urge to address its early recognition.

Objectives: This study aimed to compare the performance of two clinical risk scores with an objective measurement of CMVO during percutaneous coronary intervention (PCI) with STEMI.

Methods: The Index of Microcirculatory Resistance (IMR) measurement was conducted and the baseline clinical and angiographic parameters were also recorded. The patients were divided into MO (Microvascular obstruction) or NMO (Non-microvascular obstruction) groups according to the post-procedure IMR value. The CMVO risk was evaluated for all participants by SAK and ATI predictive scores, respectively. Each system was calculated by summing the scores of all variables. The receiver operator characteristic (ROC) curves and the area under the curve (AUC) of two risk models were used to evaluate the discriminatory performance. An echocardiography was performed seven days after the procedure to evaluate left ventricular ejection fraction (LVEF). A two-sided P-value of <0.05 was considered statistically significant.

Results: Among the 65 eligible STEMI patients, 48 patients were allocated in the NMO group and 17 in the MO group, with a CMVO incidence of 26.15%. There was no significant difference in the AUC between both scores. The LVEF evaluated for the NMO group was higher than that of MO group.

Conclusion: Both SAK and ATI scores performed well in estimating CMVO risk after primary PCI for STEMI patients. (Arq Bras Cardiol. 2021; 116(5):959-967)

Keywords: Myocardial Infarction; Percutaneous Coronary Intervention; Coronary Obstruction; Forecasting; Risk Index.

Introduction

For patients with acute ST-segment elevation myocardial infarction (STEMI), the timely reperfusion of the infarct-related artery (IRA) has been shown to be the gold-standard strategy to save the ischemic myocardium and inhibit ventricular remodeling. During the recanalization procedure of the culprit artery, regardless of angiographic grafting patency, many patients develop insufficient perfusion in the myocardial tissue resulting from coronary microvascular functional and structural obstruction (CMVO) in the perioperative period.[1] CMVO, which is a reflection of persistent microvascular injury and has been previously understood as the "no-reflow phenomenon" (NRF), was previously shown to be directly associated with infarcted area extension and cardiovascular events that increase and worsen patients' short and/or long-term prognosis.[2,3] Nevertheless, for STEMI patients suffering from subsequent CMVO, no specific and definitive therapeutic approaches of attenuation have been valid in the present large-scale tests, which highlights the urge to address early recognition and the pretreatment of high-risk patients.

Recently, based on some animal experiments and clinical research, the underlying mechanism of CMVO in an acute STEMI setting has been explored. Although the exact pathophysiology is unclear, multiple mechanisms including ischemia/reperfusion injury, distal embolization, and individual susceptibility are assumed to be responsible for deteriorating microvascular perfusion integrally.[4] Accordingly, despite the fact that numerous trials on the possible influencing factors of CMVO or NRF have been conducted, one single indicator might not be accurate enough in evaluating the perfusion state of the microvasculature. Based on this assumption, we have developed the SAK risk model, composed of six independent

Mailing Address: Yuping Han •
Department of Cardiology, Hebei General Hospital,No. 348 Heping West Road, Shijiazhuang 050000, Hebei Province, China
E-mail: hyp8@hotmail.com
Manuscript received February 13, 2020, revised manscript May 06, 2020,accepted May 06, 2020

DOI: https://doi.org/10.36660/abc.20200115

elements, including symptom onset to balloon (SO-B) time, admission activated clotting time (ACT) level, Killip classification, age, neutrophil/lymphocyte ratio (NLR), and glucose value. The model was proven to have good predictive performance for CMVO risk. Other predicting models have also been recently introduced by various centers, with different variables and conclusions. Among them, the ATI score was capable of evaluating coronary microvascular impairment during primary percutaneous coronary intervention (PCI), in which IMR was an essential parameter.[5]

Since 2003, the index of microcirculatory resistance (IMR) has been described and applied gradually as a new invasive parameter of the coronary microvascular flow.[6] Compared with other noninvasive or invasive methods, IMR has the advantages of good reproducibility, specificity, and independence of epicardial stenosis and dynamics. Therefore, we adopted the IMR as the main means of assessment of the microvasculature in this study. The aim of this paper was to compare the predicting performance of the ATI and SAK scores for CMVO risk during PCI.

Methods

Patient Selection

In this prospective study, candidates admitted to the Cardiology Department of the Second Hospital of Hebei Medical University from January 2018 to April 2018 were enrolled consecutively. All participants met the following criteria: (1) being diagnosed with STEMI according to the guide-recommended standard (typical chest pain symptoms lasting more than 30 minutes without relief, ST-segment elevated 0.1 mV in at least two continuous leads or presumably new left bundle branch block (LBBB) on electrocardiographic examination and increased myocardial biomarker values or positive high-sensitive cardiac troponin)[7]; (2) being scheduled for primary PCI in the emergent catheterization laboratory 24 hours after chest pain onset to admission; and (3) having agreed with IMR examination during the procedure. The participants who met the following features were excluded from the study: (1) having received intravenous thrombolytic agents; (2) having had experienced cardiac shock; (3) refusing primary catheterization or having a selective intervention planned; (4) developing dissection or mechanical complications during procedure; (5) presence of multiple lesions suitable for coronary artery bypass grafting (CABG); (6) presence of severe hepatic or renal insufficiency; (7) Presence of a malignant tumor; and (8) having a contraindication to antithrombotic and anticoagulation therapy. The study protocol was approved by the local ethics committee, as per the Helsinki Declaration. All the selected patients signed an informed consent form prior to the study.

Upon admission, the patients' brief medical histories were immediately taken. An 18-lead electrocardiogram was performed within 10 minutes. All patients were prescribed with loading doses of Aspirin (300mg) and Ticagrelor (180mg) upon receiving the STEMI diagnoses. Venous blood samples were collected for laboratory testing, including blood routine, biochemical assay [high-sensitivity C-reactive protein (hs-CRP), hepatic and renal function, glucose, lipid, electrolyte], myocardial biomarkers [creatine kinase and its MB isozyme (CK, CK - MB)], cardiac troponin I (cTnI), D-Dimer, plasma brain natriuretic peptide (BNP), and ACT. The ACT test was performed with a two-channel mechanical plunger (ACT plus, Medtronic Inc., Minneapolis, Minnesota, USA) with reaction temperature of 37ºC. All participants signed an informed consent form prior to the operation.

Treatment and Evaluation

The interventional procedure was performed according to the standard clinical practice via radial, ulnar or femoral access. The angiographic review and analysis were accomplished by at least two qualified interventional cardiologists. The coronary artery stenosis severity was measured using the Quantitative Coronary Analysis (QCA) system. If the severity degree of the IRA was over 75%, drug-eluting stenting was considered a useful primary reperfusion therapy. The patients received intravenous unfractionated heparin (UFH) 70-100U/kg to maintain the ACT levels of 250-300 seconds conventionally, while Bivalirudin served as an alternative if patients had a high hemorrhage risk. Anticoagulant doses were adjusted based on the individual conditions of patients and on the application of the glycoprotein inhibitor (Tirofiban). Routine devices (stents, balloons, catheters, and wires), interventional procedures (the numbers and the pressure of pre-dilation and post-dilation, thrombus aspiration, and temporary pacemaker implantation), and adjuvant medication were determined by the operators. Reperfusion time data, including symptom onset to balloon time (SO-B) and first medical contact to balloon time (FMC-B) and the initial thrombolysis in myocardial infarction (TIMI) flow grade[8] of the culprit artery were carefully assessed and recorded. As soon as the guidewire crossed or the balloon inflated the culprit lesions, the thrombus burden of the IRA was analyzed and scored.[9] After revascularization, the TIMI flow grade, TIMI myocardial perfusion grade (TMPG),[10] and corrected TIMI frame count (cTFC) of the artery were evaluated, as previously described. The culprit artery cTFC was counted at the rate of 15 frames per second, in accordance with the Gibson's method.[11] All the enrolled patients received anticoagulant and antithrombotic therapy, statins, β receptor blocker, angiotensin-converting enzyme inhibitors/angiotensin receptor blocker, and/or nitrates according to the latest guidelines.

After balloon inflation, all patients were subjected to the IMR measurement upon stenting with the pressure wire (Pressure Wire Certus, C12008, St. Jude Medical System AB, Uppsala, Sweden). The wire and the pressure/temperature sensor on the head were placed on the distal end of the vessel. After the device calibration, 3 mL of saline at room temperature was injected three times through the guiding catheter to collect the baseline data. Adenosine disodium triphosphate was administered by intravenous transfusion at a speed of 140μg/ kg·min to achieve coronary hyperemia. The hyperemic mean transit time (Tmn-Hyp) was obtained by repeated saline injection. The value of the distant artery pressure (Pd) displayed on the screen was carefully recorded and the pressure wire remained in the same position during

IMR assessment to guarantee the reliability of the result. After stent deployment, the IMR value of the culprit artery was measured again to estimate the myocardial perfusion status. Pre- and post-intervention IMR values were calculated using the following formula, without considering the coronary wedge pressure:

$IMR = Pd \times Tmn\text{-}Hyp$[6]

All participants were given ID numbers according to the operation chronological order and were assigned to different groups according to the final IMR values after the intervention, namely the NMO (Non-Microvascular Obstruction) group, with IMR values over 40 U, and the MO (Microvascular Obstruction) group, with IMR values of not more than 40 U. The CMVO risk was evaluated for those participants by two risk models, each score was calculated by summing the points of all variables. The details of the SAK score are presented in Table 1 and the ATI scores are listed in Table 2.

Two-dimension transthoracic echocardiography was performed seven days after the procedure to evaluate the left ventricular function and remodeling for all patients.

Statistical Analysis

The statistical analysis was conducted using the SPSS Software (Version 23.0, SPSS Inc., Chicago, Illinois, USA). Continuous variables were tested for normal distribution with the Kolmogorov-Smirnov's test. Normally distributed data were presented as mean ± standard deviation (SD) and compared by the Student t-test between groups. Non-normally distributed data were presented as median (First Quartile, Third Quartile) and compared by the Mann-Whitney U test. Categorical variables were reported as percentage and compared using the chi-square or the Fisher's exact test. The discriminatory performance of the built model was examined by the receiver operating characteristic (ROC) curve. The illustration of the scores' ROC was conducted using the MedCalc Software (Version 15.2.2, Med Calc Software bvba, Ostend, Belgium). The area under the curve (AUC), cut-off value, sensitivity, specificity, and corresponding Youden Index of each ROC was then obtained (Youden Index = sensitivity+ specificity -1). The comparison between scores was performed using a non-parametric test. A two-tailed *P*-value of <0.05 was considered statistically significant.

Results

Group Enrollment

From January 2018 to April 2018, a total of 65 eligible STEMI patients were enrolled in this study. Based on the final IMR threshold of 40, we allocated 48 patients in the NMO group and 17 in the MO group, with a CMVO incidence of 26.15%.

Baseline Clinical Characteristics

The comparison of demographic data, baseline clinical characteristics, and preoperative laboratory tests between groups are shown in Table 3. No significant difference was observed in the following parameters: gender, body mass

Table 1 – SAK score

Age	Points	SO-B (hrs)	Points	ACT	Points	Killip	Points	NLR	Points	GLU	Points
≤65	0	0-1	1	≤ 60	9	I	0	≤7.0	0	≤12.0	0
>65	2	1-2	2	60-80	8	II	4	>7.0	4	>12.0	2
		2-3	3	80-100	7	III	8				
		3-4	4	100-120	6						
		4-5	5	120-140	5						
		…		140-160	4						
		20-21	21	160-180	3						
		21-22	22	180-200	2						
		22-23	23	200-220	1						
		23-24	24	>220	0						

ACT: activated clotting time; NLR: neutrophil/lymphocyte ratio; GLU: glucose.

Table 2 – ATI score

Age	Points	Thrombus Score	Points	IMR-pre	Points
≤50	0	0-3	0	< 40	0
>50	1	4	1	40-100	1
		5	3	>100	2

IMR: Index of Microcirculatory Resistance.

Table 3 – Baseline clinical characteristics between groups

Variables	NMO group (n=48)	MO group (n=17)	p value
Age (years)	56.51±8.99	64.96±9.43	0.002
Male, n (%)	42(87.50)	13(76.47)	0.434
BMI (kg/m^2)	24.76±3.31	25.52±3.12	0.412
Systolic blood pressure (mmHg)	128.54±19.30	136.67±22.49	0.158
Diastolic blood pressure (mmHg)	79.03±10.22	75.41±14.80	0.271
Heart Rate (bpm)	74.28±18.69	77.35±16.65	0.552
Killip Grade			
Grade I, n (%)	29(60.42)	4(23.53)	0.009
Grade II, n (%)	16(33.33)	4(23.53)	0.452
Grade III, n (%)	3(6.25)	9(52.94)	<0.001
History of CAD, n (%)	25(52.08)	11(64.71)	0.368
Hypertension, n (%)	27(56.25)	10(58.82)	0.854
Diabetes, n (%)	15(31.25)	9(52.94)	0.111
Hyperlipidemia, n (%)	22(45.83)	8(47.06)	0.931
Smoking, n (%)	18(37.50)	9(52.94)	0.267
Laboratory test on admission			
WBC count (10^9/ L)	9.84±2.51	12.45±2.89	<0.001
Neutrophil count (10^9/ L)	7.63(6.18, 9.09)	11.65(10.18, 13.00)	<0.001
Lymphocyte count (10^9/ L)	1.60(1.26, 2.00)	1.46(1.08, 1.70)	0.184
N/L ratio	4.95(3.85, 7.00)	9.52(6.98, 10.56)	<0.001
hs-CRP (mg/L)	4.10(2.10, 6.55)	4.30(2.95, 7.30)	0.565
ACT	154(135, 178)	105(88, 132)	<0.001
CK-MB (U/L)	111 (43, 251)	168(84, 335)	0.044
Cardiac troponin I (ng/mL)	3.5 (1.8, 8.9)	14.0(6.0, 28.5)	<0.001
Serum Creatinine (μmol/L)	77.50(71.35, 86.15)	87.8 (77.5, 93.73)	0.038
Glomerular filtration rate (eGFR) (mL/min/1.73m^2)	98.70±14.62	85.89±17.08	0.004
Serum Potassium (mmol/L)	3.81±0.55	3.83±0.43	0.886
LDL cholesterol (mmol/L)	2.87±0.67	2.80±0.83	0.717
Glucose (mmol/L)	8.57±1.88	11.31±2.41	<0.001
D-Dimer (μg/mL)	0.14(0.10, 0.23)	0.25 (0.16, 0.50)	<0.001
Type B natriuretic peptide, BNP (pg/mL)	50(26,150)	190(78,420)	0.003
Preprocedural medication			
Dual Antiplatelet Therapy, DAPT, n (%)	48(100.00)	15(88.24)	0.065
Statins, n (%)	24(50.00)	7(41.18)	0.531
Beta-blocker, n (%)	3(6.25)	2(11.76)	0.6
GRACE score	137.48±23.91	152.94±27.97	0.032
CRUSADE score	22.75±12.34	29.77±12.29	0.045

NMO: Non-microvascular obstruction; MO: microvascular obstruction; BMI: body mass index; CAD: coronary artery disease; hs-CRP: high-sensitivity C-reactive protein; ACT: activated clotting time;

index (BMI), vital signs, previous history, red blood cell count, platelet count, high-sensitivity C-reactive protein (hs-CRP), electrolyte and lipid (All p>0.05). The mean age of the MO group was higher than that of the NMO group (p=0.002). The patients in the MO group shared a higher proportion of the Killip class 3 and a lower proportion of the Killip class 1. The GRACE and the CRUSADE scores were also significantly higher in the MO group. There were statistical differences in the following laboratory items between groups: white blood count, neutrophil count, lymphocyte count, neutrophil/lymphocyte ratio (NLR), CK-MB, cTNI, ACT, serum creatinine, eGFR, glucose, D-Dimer, and BNP (All p<0.05).

Angiographic Analysis and Invasive Measurement of Microvascular Perfusion

The angiographic features of all participants are summarized in Table 4. The SO-B time of the MO group was apparently delayed compared with that of the NMO group (p=0.002), while there wasn't a significant difference in the FMC to FMC-B time (p=0.843). After the intervention, a significant difference regarding the blood flow perfusion indicators was observed, including TIMI 3 grade proportion (p<0.001), cTFC (p<0.001), and the proportion of TMPG 3 (p<0.001). Other angiographic and procedural information, such as IRA distribution, stenting details, medication, supplementary treatment, and contrast media volume were comparable between groups (All p>0.05).

ROC Curve of Two Scores and Comparison of AUC

The corresponding scores of the two systems were calculated for all participants. Based on the scores and CMVO incidence, the ROC curve was plotted. For the SAK scores, the AUC was 0.855 [95% confidence interval (CI): 0.746 - 0.930], with a cut-off value of 15 and a Youden Index of 0.6078. For the ATI score, the AUC was 0.907 (95%CI: 0.809 - 0.965), with a cut-off value of 3 and a Youden Index of 0.6875. There was no significant difference in the AUC (Z=1.001, p=0.317) (Table 5).

Echocardiography

All patients accepted transthoracic echocardiography after the procedure in the hospital. The left ventricular ejection fraction (LVEF) of the NMO group was higher than that of the MO group (56.03±5.22 vs. 47.79±6.38, p<0.001).

Discussion

Despite the dramatic progress achieved in the therapeutic strategies of myocardial infarction in the past decades, microvascular impairment remains an important issue during primary catheterization. It is estimated that insufficient reperfusion in the myocardial tissue level could be up to 50% in cases, despite successful epicardial recanalization.[12] The benefits resulting from pharmaceutical or mechanical reperfusion strategies would be compromised in the presence of coronary microvascular obstruction, which is associated with poor cardiac function and unfavorable outcomes.

Due to the lack of specific treatment and attenuation of CMVO, early recognition and the pretreatment of high-risk patients are of great importance. The indicators for identification have been intensively examined by sizable previous studies. However, considering that a large number of complicated mechanisms are thought to contribute to microvascular obstruction development, one single element may not be convincing enough in assessing risk prediction and stratification. Therefore, evaluating systems comprising of various indexes to assess the likelihood of this complication provides better detection and diagnosis. Apart from the two models analyzed in this study, previous scores of NFR have also been developed.

Dogan et al.[13] reported that hyperglycemia, prolonged ischemic time, and low neutrophil count attributed to the development of the risk model.[13] Bayramoglu et al.[14] built the predictive model covering age, LVEF value, SYNTAX score, stent length, thrombus burden score, Killip classification, and reperfusion time.[14] The retrospective study conducted by Wang et al.[15] also showed that age, pain to PCI time, neutrophil count, admission glucose level, pre-PCI thrombus score, collateral circulation, and Killip class could be adopted to establish the no-reflow model.[15] Due to the different study protocols, sample size, auxiliary measurements, and consistent conclusions have not been obtained.

Instead of angiographic standards (TIMI blood flow, TMPG or myocardial blush grades) applied in the former clinical trials, the IMR was introduced to determine the microcirculation perfusion in the present study. IMR, a thermodilution-derived quantitative measurement of coronary microvascular function, was first proposed by Fearon in 2003. The Porcine model has also been used to investigate the correlation between the calculated IMR value and true distal resistance, validating the feasibility of this innovative technique in estimating microvascular resistance.[6] Different from other angiographically physiological and functional assessment, IMR shares the advantages of independence of epicardial stenosis, superior reproducibility, and hemodynamic instability. Bulluck reviewed the literature and reported that a post-procedure threshold of 40 U was valid in identifying CMVO for those that underwent IMR measurements.[16]

Apart from being directly related to the perfusion status of myocardial tissue, IMR was also shown to have a strong association with peak creatine kinase levels, patient's prognosis, and ventricular performance recovery in the setting of STEMI,[6,17-20] which laid the foundation for ATI development. The ATI score was first introduced by De Maria et al. mainly consisting of three characteristics including age, thrombus score, and pre-stenting IMR value.,[5] The ATI score was also considered a promising tool for predicting suboptimal myocardial reperfusion in STEMI patients and is correlated with the infarction area measured by cardiac magnetic resonance imaging (MRI) in subsequent studies.[21]

Limited by cost and related insurance regulations, however, IMR is not always available or acceptable in current practices. It could also only be implemented in the emergent Catheterization Laboratory. In this regard, based on the existing evidence and our practical experience, we systematically screened the possible clinical and angiographic

Table 4 – Procedural and angiographic features between groups

Variables	NMO group (n=48)	MO group (n=17)	p value
Onset to balloon (hours)	4.0(3.0, 5.0)	6.5(5.0, 12.0)	0.002
FMC to balloon (hours)	2.0(1.0, 3.0)	1.5(1.0, 2.8)	0.843
Myocardial Wall, n (%)			
Anterior Wall	19(44.19)	9(52.94)	0.339
Others	29(55.81)	8(47.06)	0.339
Stenosed artery number, n (%)			
1	9(18.75)	4(23.53)	0.729
2	18(37.50)	7(41.18)	0.789
3	21 (43.75)	6(35.29)	0.543
Initial TIMI flow, n (%)			
0	27(56.25)	14(82.35)	0.055
1	8(16.67)	2(11.76)	1
2	8(16.67)	1(5.89)	0.426
3	5(10.41)	0(0.00)	0.315
Thrombus score, n (%)			
0-3	24(50.00)	1(5.56)	0.001
4	20(41.67)	7(41.18)	0.972
5	4(8.33)	9(53.26)	<0.001
Final TIMI flow, n (%)			
0	0(0.00)	1(5.88)	0.262
1	0(0.00)	3(17.65)	0.016
2	0(0.00)	11(64.71)	<0.001
3	48(100.00)	2(11.76)	<0.001
IRA-cTFC	24(20, 32)	48(36, 58)	<0.001
TMPG, n (%)			
0	0(0.00)	2(11.76)	<0.001
1	0(0.00)	5(29.41)	<0.001
2	5(10.42)	11(58.83)	<0.001
3	43(89.58)	0(0.00)	<0.001
IMR-pre			
< 40	16(33.33)	1(5.58)	0.029
40-100	20(41.67)	5(29.41)	0.372
>100	12(25.00)	11(64.71)	0.003
Stent number per patient, n (%)			
1	42(87.50)	12(70.59)	0.138
≤2	6(12.50)	5(29.41)	0.138
Stent length (mm)	23(21, 28)	24(18, 31)	0.143
Stent diameter (mm)	2.25(2.20, 3.00)	2.50(2.25, 3.00)	0.859
Pre-dilation pressure (atm)	14(12, 16)	14(12, 15)	0.307
Pre-dilation numbers	3(2, 5)	4(3, 5)	0.422

Continuation

stent expansion pressure (atm)	14(14, 16)	14(12, 16)	0.347
Post-dilation pressure (atm)	16(12, 17)	14(11, 16)	0.776
Post-dilation numbers	2(2, 3)	2(1, 3)	0.689
Thrombus aspiration, n (%)	12(25.00)	3(17.64)	0.741
Temporary pacemaker, n (%)	4(8.33)	1(5.88)	1
Collateral circulation, n (%)	9(18.75)	3(17.65)	1
Contrast media volume (mL)	160(140, 190)	180(150, 210)	0.06
Procedural medication, n (%)			
Tirofiban	43(89.58)	14(82.35)	0.421
Bivalirudin	9(18.75)	5(29.41)	0.493
Anisodamine	8(16.67)	3(17.65)	1

NMO: Non-microvascular obstruction; MO: microvascular obstruction; FMC: first medical contact; TIMI: thrombolysis in myocardial infarction; TMPG: TIMI myocardial perfusion grade.

Table 5 – Comparison of AUC and related details of SAK and ATI Scores

Variables	AUC	95%CI	Cut-off point	Youden Index	Z	p
SAK Score	0.855	0.746 - 0.930	15	0.6078	1.001	0.317
ATI Score	0.907	0.809 - 0.965	3	0.6875		

information, developing SAK predictive scores that incorporate 6 conventional variables, namely age, Killip classification, symptom onset to balloon time, initial ACT levels, NLR, and glucose values. Our former study verified its capability and effectiveness in evaluating the patients at high risk of CMVO.[22] Therefore, we attempted to compare the performance of the SAK and ATI scores in predicting the potential risk of impaired microvasculature during primary intervention, assisting the physicians' prompt pretreatments to minimize the incidence of this condition before the procedure takes place.

Noticeably, an AUC or C-index value over 0.75 in a developed model is recognized as a reliable validation. From the results we obtained, the AUC of the SAK and ATI scores were 0.855 and 0.907, respectively, which proved that both estimating systems were capable of predicting the potential CMVO risk and performed well. The AUC of the ATI scores seemed higher, but there was no obvious difference in the risk evaluation performance.

Though the ATI score had a favorable performance for prediction, there were some distinctions compared to the original report of ATI development. Firstly, the most commonly chosen standard of the thrombus score was established by Gibson. However, according to clinical practice and previous data, only 0.4% of the cases had a score of 5 after the guidewire or balloon passing through the occluded lesions, whereas nearly 30% of the cases shared a score of 4.[23] Consequently, the thrombus burden score was evaluated subsequent to the guidewire passing or small balloon inflation. Secondly, the peak value of myocardial biomarkers and cardiac troponin have not been documented as the original study, taking the echocardiography into consideration that the difference of the LVEF was also precise enough in showing the relationship between microcirculation perfusion and the infarction area. From the echocardiography results, we could derive that patients with CMVO had a poorer cardiac function, which was consistent with the existing evidence, emphasizing the particular significance in improving the perfusion status of microvascular circulation.[24]

Despite its advantages, the IMR is not available or applicable in a majority of local hospitals and many patients refuse this examination due to its cost. Similarly, a SAK score consisting of currently common indexes appeared to be an alternative in the clinical field.

This study, however, has some limitations. First, this was a single-center study with a relatively small sample size. The risk scores were validated by the information from a single-center database. The discriminatory power of the models requires a larger sample scale investigation and validation. Second, ACT was an essential element in the SAK score while the level of ACT is influenced by a series of factors in practice, so the reference range in the score might be different depending on the testing staff and equipment. Third, patients with cardiac shock have not been enrolled since supplementary life-supporting treatment might be needed and the baseline characteristics would be unbalanced for those patients.

Conclusion

In this study, our data showed that both the SAK and ATI scores performed well in estimating CMVO risk after the primary PCI for acute STEMI patients. Therefore, these scores are accurate in predicting CMVO when compared to the invasive measurements obtained from the IMR.

Author Contributions

Conception and design of the research: Xiao Y, Wang Y, Wang W, Zhang Q, Han Y, Fu X; Data acquisition: Chen H, Liu D, Wang W, Han Y; Analysis and interpretation of the data: Xiao Y, Liu D, Wang Y, Zhang Q, Fu X; Statistical analysis: Chen H, Wang Y, Wang W, Zhang Q; Obtaining financing: Xiao Y, Han Y, Fu X; Writing of the manuscript: Xiao Y, Chen H, Han Y, Fu X; Critical revision of the manuscript for intellectual content: Xiao Y, Liu D, Han Y, Fu X.

Potential Conflict of Interest

The authors report no conflict of interest concerning the materials and methods used in this study or the findings specified in this paper.

Sources of Funding

This study was funded by National Key R&D Program of China, number 2016 YFC1301100

Study Association

This study is not associated with any thesis or dissertation.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of the Second Hospital of Hebei Medical University. 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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No Reflow in Acute Coronary Syndromes: An Old Foe or a New Frontier?

Stefano Garzon[1,2]

Hospital Israelita Albert Einstein,[1] São Paulo, SP - Brazil

Universidade de São Paulo Instituto do Coração,[2] São Paulo, SP - Brazil

Short editorial related to the article: The Comparison between Two Risk Scores as for the Prediction of Coronary Microvascular Obstruction during Primary Percutaneous Intervention

According to the World Health Organization (WHO), ischemic heart disease is the leading cause of death worldwide, accounting for 16% of the world's deaths in 2019.[1] However, due to continuous evolution in medical treatment and revascularization techniques, a steady decline in death rates in acute coronary syndromes (ACS) has been observed in recent years.[2]

Currently, percutaneous coronary intervention (PCI) is the gold-standard treatment for ST-elevation myocardial infarction (STEMI)[3] and a mainstay therapeutic option for non-STEMI ACS[4] and stable coronary artery disease.[5] Nonetheless, and particularly in STEMI patients, PCI can be very challenging at times. One of the most dreaded events during PCI in STEMI is the phenomenon commonly referred as "no-reflow", an impaired myocardial perfusion secondary to microvascular obstruction without angiographic evidence of coronary obstruction(6). Initially described in animal models,[6,7] it was also recognized in humans in the following decades,[8,9] being first described after PCI for STEMI by Feld in 1992.[10] Its occurrence is related to poorer short- and long-term outcomes following PCI,[11,12] and it is present in more than 20% of patients undergoing primary PCI for STEMI.[13]

In a recent publication,[14] Rezkalla et al. thoroughly reviewed the management of no-reflow, identifying many risk factors, which include longer time to reperfusion, high-pressure balloon dilation, longer stents, and also clinical characteristics of the patient, many of which overlap with those of coronary artery disease and ACS. If no-reflow is anticipated, pharmacological and technical measures can be taken in an attempt to prevent it, potentially minimizing its occurrence and alerting the operator to promptly act in case it occurs.

Keywords

Myocardial Ischemic; Cardiovascular Diseases/mortality; Percutaneous Coronary Interventions; Myocardial Infarction; Coronary Artery Disease; Risk Factors; Vascular Resistance.

Mailing Address: Stefano Garzon •
Hospital Israelita Albert Einstein - Av. Albert Einstein, 627.
Postal Code 05652-900, São Paulo, SP – Brazil
E-mail: stefano.lemos@einstein.br

DOI: https://doi.org/10.36660/abc.20210118

According to this idea, the article "The Comparison between Two Risk Scores as for the Prediction of Coronary Microvascular Obstruction during Primary Percutaneous Intervention,"[15] published in the current edition of this journal, explores the ability of two risk scores in predicting the occurrence of no-reflow. It compares the SAK score, which uses purely clinical parameters (symptom onset to balloon inflation time, ACT level on admission, Killip classification, age, neutrophil/lymphocyte ratio, and glucose levels), with the ATI score, whose parameters are an invasive measure of microvascular resistance (IMR) obtained via coronary microcatheter, age and thrombus score in the culprit artery. In this study, both scores performed well, with the SAK score presenting an AUC of 0.855. In this study, no-reflow was more commonly associated with older patients with longer reperfusion times, higher glucose levels, higher serum creatinine levels, higher leucocyte counts, Killip III classification and increased myocardial necrosis biomarkers, which is in accordance with current medical literature. However, other factors, such as hypertension, dyslipidemia, diabetes, and smoking were not related to the occurrence of the phenomenon, suggesting that its physiopathology is not yet fully understood. Also, there are no data regarding how no-reflow was treated and whether the treatment resulted in improvement of microvascular resistance and possibly better outcomes.

In a study recently published,[16] Viana et al. compared the SYNTAX and GRACE scores in predicting cardiovascular mortality and recurring non-fatal coronary events after ACS. Both were effective in predicting cardiovascular death (C-statistic 0.80 vs. 0.89, p=0.19, for the SYNTAX and GRACE scores, respectively), but the anatomical SYNTAX score was the only one capable of predicting recurring non-fatal coronary events (C-statistic 0.64 vs. 0.50, p=0.027), suggesting that intra-procedural complications and outcomes, such as no-reflow, are not accounted for when using purely clinical ACS risk scores.

Understanding the full complexity of ACS still seems to be out of our reach at the moment. However, realizing that prognosis and outcomes of such patients result from numerous clinical and intra-procedural factors might be the beacon to help us navigate these troubled and not-yet-fully-charted waters.

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Vitamin D Supplementation Induces Cardiac Remodeling in Rats: Association with Thioredoxin-Interacting Protein and Thioredoxin

Priscila P. dos Santos,[1,2] Bruna P. M. Rafacho,[1] Andrea F. Gonçalves,[1] Vanessa C. M. Pires,[1] Meliza G. Roscani,[1] Paula S. Azevedo,[1] Bertha F. Polegato,[1] Marcos F. Minicucci,[1] Ana Angélica H. Fernandes,[2] Suzana E. Tanni,[1] Leonardo A. M. Zornoff,[1] Sergio A. R. de Paiva[1,3]

Faculdade de Medicina de Botucatu – UNESP,[1] Botucatu, SP - Brazil
Instituto de Biociências de Botucatu-UNESP,[2] Botucatu, SP - Brazil
Centro de Pesquisa em Alimentos,[3] São Paulo, SP - Brazil

Abstract

Background: Vitamin D (VD) has been shown to play an important role in cardiac function. However, this vitamin exerts a biphasic "dose response" curve in cardiovascular pathophysiology and may cause deleterious effects, even in non-toxic doses. VD exerts its cellular functions by binding to VD receptor. Additionally, it was identified that the thioredoxin-interacting protein (TXNIP) expression is positively regulated by VD. TXNIP modulate different cell signaling pathways that may be important for cardiac remodeling.

Objective: To evaluate whether VD supplementation lead to cardiac remodeling and if TXNIP and thioredoxin (Trx) proteins are associated with the process.

Methods: A total of 250 Male Wistar rats were allocated into three groups: control (C, n=21), with no VD supplementation; VD3 (n = 22) and VD10 (n=21), supplemented with 3,000 and 10,000 IU of VD/ kg of chow respectively, for two months. The groups were compared by one-way analysis of variance (ANOVA) and Holm-Sidak post hoc analysis, (variables with normal distribution), or by Kruskal-Wallis test and Dunn's test post hoc analysis. The significance level for all tests was 5%.

Results: TXNIP protein expression was higher and Trx activity was lower in VD10. The animals supplemented with VD showed increased lipid hydroperoxide and decreased superoxide dismutase and glutathione peroxidase. The protein Bcl-2 was lower in VD10. There was a decrease in fatty acid β-oxidation, tricarboxylic acid cycle and electron transport chain with shift to increase in glycolytic pathway.

Conclusion: VD supplementation led to cardiac remodeling and this process may be modulated by TXNIP and Trx proteins and consequently oxidative stress. (Arq Bras Cardiol. 2021; 116(5):970-978)

Keywords: Vitamin D; Ventricular Remodeling; Rats; Thioredoxins; Oxidative Stress.

Introduction

Vitamin D (VD) is a fat-soluble compound known to affect classical target organs, like bones, intestines and kidneys, and stimulates calcium transport from these organs to the blood.[1] However, increasing evidence has shown that VD affects other organs including the heart and may play an important role in cardiac development and function.[2,3]

The prevalence of VD deficiency has increased in recent years, becoming a public health problem worldwide.[4] Furthermore, VD deficiency is associated with an increased risk of developing several chronic diseases including cardiovascular diseases.[5] Therefore, researchers have recommended increased sun exposure, food fortification and VD supplementation, both for people at higher risk for hypovitaminosis D and for the general population.[6-9] However, further research with different doses of VD supplementation is urgently needed,[10-12] due to increasing reports of deleterious cardiovascular effects of VD in non-toxic doses.[10,11,13-15] Uremic rats and infarcted rats, both supplemented with VD at non-hypercalcemic dosages presented hypertension,[13] changes in the aorta,[13] left ventricular hypertrophy,[13,14] cardiac dysfunction, and changes in cardiac energy metabolism.[14] Additionally, study with normotensive rats showed that VD supplementation at non-hypercalcemic doses led to increased blood pressure and changes in vascular structure and function, mediated by generation of reactive species and changes in nitric oxide bioavailability.[15] These data indicate that VD exerts a biphasic "dose response" curve on cardiac remodeling.[10]

Cardiac remodeling is caused by an injury to the heart, which can lead to progressive cellular, interstitial, and molecular changes.[16] The cellular and molecular alterations include oxidative stress, apoptosis, and cardiac energy

Mailing Address: Priscila Portugal dos Santos •
Faculdade de Medicina de Botucatu, Rubião Júnior s/n. Postal Code 18618-970, Botucatu, SP - Brazil
E-mail: prilpolmed@yahoo.com.br, priscila.portugal@unesp.br
Manuscript received March 21, 2019, revised manuscript April 14, 2020, accepted June 10, 2020

DOI: https://doi.org/10.36660/abc.20190633

metabolism change, which can progress to hypertrophy and ventricular dysfunction.[14]

VD exerts its cellular functions by binding to VD receptor and leading to transcriptional regulation of target genes.[17] Additionally, Chen and DeLuca[18] identified a VD3-up-regulated protein1 (VDUP1) gene that is up-regulated in the human HL-60 promyelocytic cell line by 1,25-dihydroxyvitamin D3 (1,25(OH)2D3) treatment.[18] Since then, VDUP1 has been identified in various tissues, including the heart.[19]

The protein encoded by VDUP1 is known as thioredoxin-interacting protein (TXNIP) and was identified as a negative regulator of thioredoxin (Trx). TXNIP binds to the catalytic center of Trx forming a stable disulfide-linked complex, reducing its activity.[20] This causes an antioxidant imbalance, since the Trx system is an important antioxidant thiol reducing system in the heart.[21,22] Indeed, studies with cancer cell showed that VD treatment enhanced reactive oxygen species (ROS) production.[23-25]

Studies have shown that both Trx as TXNIP modulate different pathways by direct interaction with intracellular signaling molecules. These proteins participate in the regulation of apoptotic and hypertrophic pathways and modulate energy metabolism in both cardiomyocytes and other cell types[21,22,26]. Therefore, VD supplementation at non-hypercalcemic doses could lead to an imbalance of TXNIP and Trx in the heart, resulting in cardiac remodeling.

Thus, the aim of the present study was to evaluate whether VD supplementation at non-hypercalcemic doses leads to cardiac remodeling and whether TXNIP and Trx proteins are associated with this process.

Materials and Methods

Experimental protocol

All experiments were performed in accordance with the National Institutes of Health's Guidelines for the Care and Use of Laboratory Animals and were approved by the Ethics Committee for Animal Experimentation of the Botucatu Medical School, UNESP, São Paulo, Brazil (2008/694). Male Wistar rats of 250 g were randomly allocated into three groups and fed a cereal-based chow for two months. The groups were: 1) control group (C, n=21), with no supplementation of VD (cereal-based diet -Nuvilab CR1, with the approximate composition [kg mixture]: protein, 220g; fat, 40g; mineral, 100g; fiber, 80g and VD, 1,800 IU); 2) VD3 (n=22), supplemented with 3,000 IU VD/kg of chow; and 3) VD10 (n=21), supplemented with 10,000 IU VD/kg of chow.

The sample size was determined based on our experience with experimental models used and analyzes; it was also used on a previous study carried out in our laboratory, to assess the influence of VD supplementation on systolic arterial pressure, vascular reactivity, and mechanical properties.[15] The animals were randomly placed in individual boxes. Subsequently the boxes are chosen at random to compose the different groups.

All animals were fed the same amount of chow. VD supplementation was performed by adding cholecalciferol (Sigma-Aldrich, St. Louis, MO, USA) diluted with corn oil, to the chow. All animal groups received 10 mL of corn oil per kg of chow.

The National Research Council recommended the amount of 1,000 IU of VD per kg of chow for the rats.[27] However, the council has not established an upper intake level. Therefore, we used 10 times the recommended daily dose as our tolerable upper intake level. Shepard and DeLuca[28] showed that rats supplemented with doses above 1,000 IU of VD/day (~ 30,000 IU/kg of chow) presented toxicity signs such as diarrhea, loss of appetite, decrease in weight gain, and kidney calcification. The doses used in our study were 4.8 and 11.8 times higher than the recommended dose for rats and did not reach the 1,000 IU/day. Furthermore, in our previous study,[15] these VD doses did not cause toxicity signs or hypercalcemia. Therefore, the doses used in the present study were considered non-toxic in terms of calcium metabolism.

Echocardiographic study

All animals were evaluated by transthoracic echocardiography,[29] using a commercially available echocardiographic machine (General Electric Medical Systems, Vivid S6, Tirat Carmel, Israel) equipped with a 5-12 MHz phased array transducer. All measurements were obtained by the same observer according to the American Society of Echocardiography and the European Association of Echocardiography's recommendations.[30]

After the echocardiographic study, euthanasia of animals was performed with intraperitoneal injection of sodium thiopental at excessive dose (180 mg/kg), and the animals were decapitated. The blood and the hearts of animals were collected.

Assessment of 25-hydroxyvitamin D_3 (25 (OH) D_3) and calcium[31]

Plasma concentrations of 25 (OH) D_3 were measured by high performance liquid chromatography (HPLC) as described by Asknes[31] with slight modification.[31] The apparatus used was the Waters 2695 chromatograph with photodiode detector Waters 2996. 25 (OH/) D_3 was quantified by determining peak areas on high-performance liquid chromatograms, calibrated against known amounts of standards (H4014 Sigma-Aldrich, St. Louis, MO, USA).

Serum concentration of calcium was measured through arsenazo III method (test kit, Labor Lab, SP, Brazil).

Cardiac lipid hydroperoxide, antioxidant enzyme and cardiac energy metabolism

Left ventricular samples (200 mg) were used for the measurements of total protein and lipid hydroperoxide (LH) concentration and for determination of glutathione peroxidase (GPx), superoxide dismutase (SOD) and catalase (CAT) activity.[14] Cardiac energy metabolism was assessed by 3-hydroxyacyl coenzyme-A dehydrogenase (HADH), phosphofructokinase, lactate dehydrogenase (LDH), pyruvate dehydrogenase, citrate synthase (CS), complex II (succinate dehydrogenase), and ATP synthase activities. The enzyme activity assays were performed at 25°C with the absorbance measured using a Pharmacia Biotech spectrophotometer (UV/

visible Ultrospec 5000 with Swift II Applications software). All of the reagents were from Sigma (Sigma-Aldrich, St. Louis, MO, USA).

Western blot

Western blot was performed to analyze protein expression in the left ventricle. Samples were separated on 10% SDS-polyacrylamide gel and the proteins were transferred to a nitrocellulose membrane. The membrane was blocked with 5% nonfat dry milk and incubated with primary antibody (Santa Cruz Biotechnology, Inc, Europa): VDUP1 (mouse monoclonal IgG1, sc271238); Trx-1 (rabbit polyclonal IgG, sc20146); peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α - rabbit polyclonal IgG, sc13067); peroxisome proliferator-activated receptor-α (PPAR-α - rabbit polyclonal IgG, sc9000); Bcl-2 (rabbit monoclonal IgG, sc492); caspase 3 (rabbit monoclonal IgG - Cell Signaling Technology, Inc, Beverly, MA, USA, 9664), and secondary peroxidase-conjugated antibody. Super Signal® West Pico Chemiluminescent Substrate (Pierce Protein Research Products, Rockford, USA) was used to detect bound antibodies. GAPDH (mouse monoclonal IgG1, Santa Cruz Biotechnology, Inc, Europe, sc 32233) was used for blot normalization.

Insulin reduction assay for Trx and thioredoxin reductase (TrxR)

The activity of Trx in the heart was determined by the insulin reduction assay, according to the method described by Yamamoto et al. 2003[32] with slight modification. The activity of TrxR in the heart was determined by the insulin reduction assay, according to the method described by Schutze et al.[33] with slight modification.

Statistical analysis

The normality of the data was verified by Kolmogorov–Smirnov statistical test. The groups were compared by one-way analysis of variance (ANOVA) and Holm-Sidak post hoc analysis, for variables with normal distribution, and data are expressed as mean ± standard deviation (SD). Otherwise, the groups were compared using the Kruskal-Wallis test and Dunn's post hoc analysis and the data are expressed as medians (including the lower and upper quartiles). The statistical analyses were performed using Sigma Stat for Windows v3.5 (SPSS Inc. Chicago, IL, USA). To assess the dose-response of VD, test for trend was used: Trend test of the statistical package GraphPad Prism software was used for variables with normal distribution; and the Spearman correlation used for variables without normal distribution.[34] The significance level for all tests was 5%.

Results

As shown in Table 1, VD supplementation was effective, since daily intake of cholecalciferol was different between the three groups, and 25-hydroxycholecalciferol concentrations were higher in VD10 than in C, and VD3 had an intermediary value. Additionally, the animals receiving both VD doses showed a slight increase in serum calcium level. However, the supplemented groups were in normocalcemic range. These variables showed a dose-dependent response. The final body weight and food consumption did not differ among groups and did not present a dose-dependent response.

As shown in Figures 1A and 1B and Table 2, VD supplementation changed were TXNIP, Trx activity and Trx protein, without TrxR participation. Protein expression of TXNIP was higher and Trx activity was lower in VD10. These variables showed a dose-dependent response. Additionally, there was a decrease in the protein expression of Trx in a dose-dependent manner.

Table 3 summarizes the oxidative stress and apoptosis data. In this study, the animals supplemented with VD presented an increase in oxidative stress, shown by the higher lipid peroxidation values in the VD10; in addition, we observed a lower activity of antioxidant enzymes. SOD and GPx

Table 1 – Body weight, vitamin D and food ingestion, serum calcium and plasma 25-hydroxycholecalciferol (OH) D3 in the groups of rats supplemented with vitamin D and control group

Variable	C	VD3	VD10	P1 Comparison test	P2 Trend test
Body weight (g)	422±26.8 (21)	429±35.6 (22)	421±31.7 (21)	0.646	0.923
Food ingestion (g/day)	25.7±1.54 (21)	25.9±1.91 (22)	24.9±1.98 (21)	0.166	0.154
VD ingestion (IU/day)	45.5 (44.8-48.1) (21)	123 (118-128)* (22)	290 (283-310)*# (21)	<0.001	<0.001
25 (OH) D_3 (ng/mL)	14.6 (9.40-16.4) (7)	19.0 (17.2-32.4) (7)	35.6 (33.2-37.8)* (7)	0.007	<0.001
Ca (mg/dL)	8.25±1.10 (9)	9.32±1.15* (10)	9.44±0.54* (10)	0.023	0.011

*Data expressed as mean±SD or median with 25 and 75 percentiles. Numbers in parentheses indicate the numbers of animals in each group. C: control group, with no supplementation of VD; VD3 and VD10: supplemented with 3,000 and 10.000 IU VD/kg of chow, respectively; VD: vitamin D; 25 (OH) D3: plasma 25-hydroxycholecalciferol; Ca: serum calcium. P1: p value of 1-way ANOVA or Kruskal Wallis and Holm-Sidak or Dunn's test post hoc analysis; P2: p value of Trend test or Spearman correlation. Bold numbers represent the significant effects that were considered. * ≠ C group; # ≠ VD3 group.*

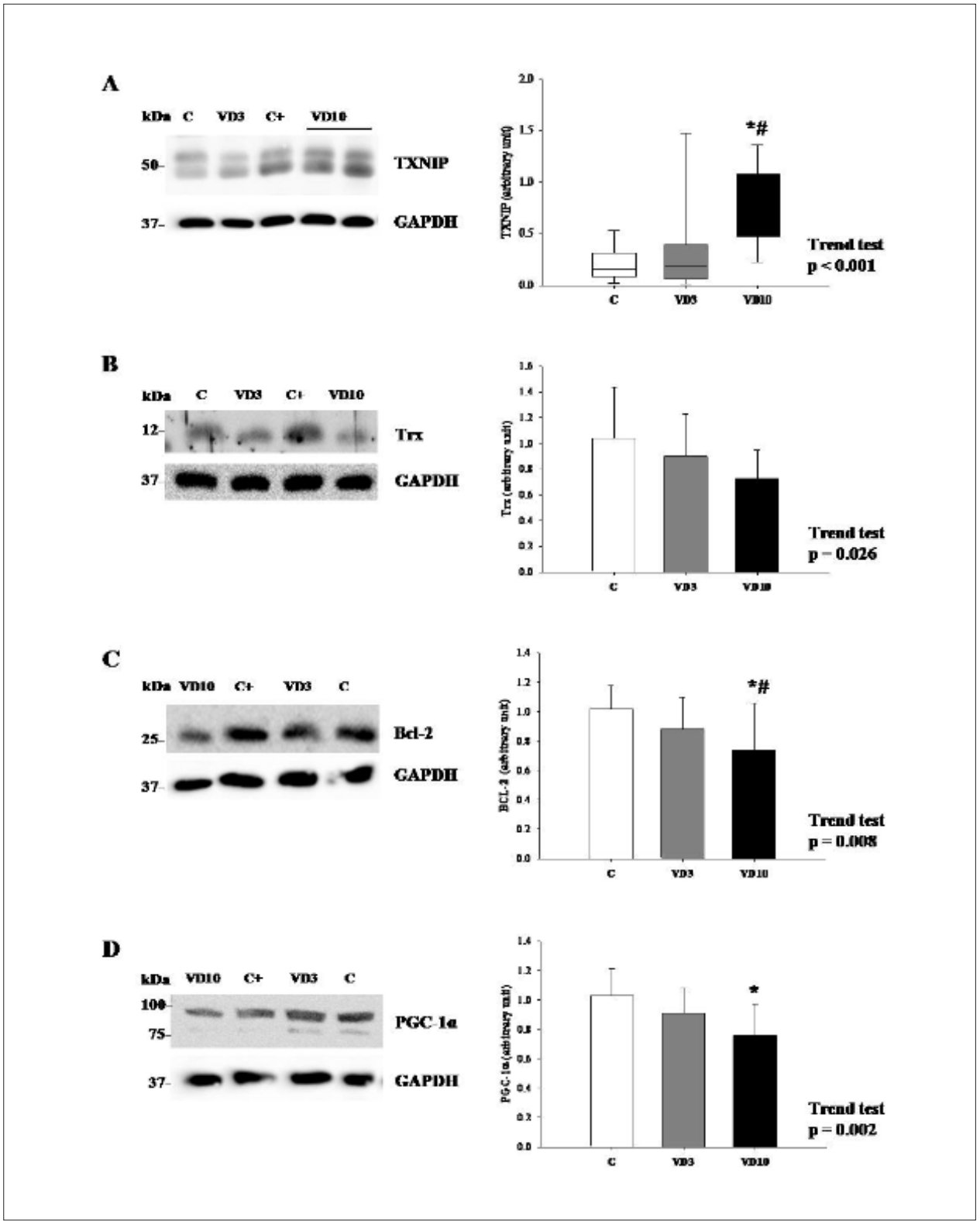

Figure 1 – *Western blot. A: Left: representative western blots showing thioredoxin-interacting protein (TXNIP). Right: median TXNIP/GAPDH ratio band density; p= 0.002. B: Left: representative western blots showing thioredoxin (Trx). Right: median Trx/GAPDH ratio band density; p= 0.082. C: Left: representative western blots showing Bcl-2. Right: median Bcl-2/GAPDH ratio band density; p= 0.027. D: Left: representative western blots showing peroxisome proliferator-activated receptor-γ coactivator 1α (PGC-1α). Right: median PGC-1α/GAPDH ratio band density; p= 0.006. Number of animals: 11-12. C: control group, with no supplementation of VD; VD3: supplemented with 3,000 IU VD/Kg of chow; VD10: supplemented with 10,000 IU VD/kg of chow. Statistical analysis 1-way ANOVA. * C group; # ≠ VD3 group. C+ is a control animal for adjustment for gel running.*

Table 2 – Thioredoxin (Trx) and thioredoxin reductase (TrxR) enzymatic activity in the groups of rats supplemented with vitamin D and control group

Variables	C	VD3	VD10	P1 Comparison test	P2 Trend test
Trx activity (OD 340 nm x minute)	0.251±0.08 (10)	0.226±0.06 (10)	0.115±0.07*# (10)	**<0.001**	**<0.001**
TrxR activity (mU/mg protein x minute)	0.097 (0.096-0.098) (8)	0.097 (0.096-0.097) (9)	0.096 (0.085-0.098) (10)	0.383	0.117

*Data expressed as mean ± SD or median with 25 and 75 percentiles. Numbers in parentheses indicate the numbers of animal in each group. C: control group, with no supplementation of VD; VD3 and VD10: supplemented with 3,000 and 10.000 IU VD/kg of chow. Trx activity: thioredoxin enzymatic activity; OD: optical density; TrxR: thioredoxin reductase. P1: p value of 1-way ANOVA or Kruskal Wallis and Holm-Sidak or Dunn's test post hoc analysis; P2: p value of Trend test or Spearman correlation. Bold numbers represent statistically significant effects. * ≠ C group; # ≠ VD3 group.*

Table 3 – Variables of oxidative stress and apoptosis in the groups of rats supplemented with vitamin D and control group

Variables	C	VD3	VD10	P1 Comparison test	P2 Trend test
LH (nmol/g tissue)	143.8±13.9 (8)	134.1±20.1 (8)	179.6±11.8*# (8)	<0.001	<0.001
SOD (nmol/mg protein)	19.9 (18.6-24.5) (8)	13.0 (11.8-14.0)* (8)	13.0 (11.8-14.2)* (8)	<0.001	0.001
GPx (umol/g tissue)	40.4±6.2 (8)	31.5±4.6* (8)	29.7±3.1* (8)	<0.001	<0.001
CAT (µmol/g tissue)	120.9±15.5 (8)	124.6±11.1 (8)	110.9±15.8 (8)	0.165	0.178
LH/(SOD+GPx+CAT)	0.79±0.09 (8)	0.80±0.14 (8)	1.18±0.09*# (8)	<0.001	<0.001
Caspase-3 (arbitrary unit)	1.01±0.49 (12)	0.84±0.48 (12)	1.54±0.56# (12)	0.023	0.060

*Data expressed as mean±SD or median with 25 and 75 percentiles. Numbers in parentheses indicate the numbers of animals in each group. C: control group, with no supplementation of VD; VD3 and VD10: supplemented with 3,000 and 10.000 IU VD/Kg of chow, respectively. SOD: superoxide dismutase; GPx: gluthathione peroxidase; CAT: catalase; LH: lipid hydroperoxide; Caspase-3: Caspase-3-cleaved. P1: p value of 1-way ANOVA and Holm-Sidak or Dunn's test post hoc analysis; P2: p value of Trend test or Spearman correlation. Bold numbers represent statistically significant effects. * ≠ C group; # ≠ VD3 group.*

activity were lower in VD-supplemented animals and the LH/(SOD+GPx+CAT) ratio was higher in VD10. These alterations in variables showed a dose-dependent response. For apoptosis data, the expression of anti-apoptotic Bcl-2 protein was lower in VD10 and showed a dose-dependent response (Figure 1-C). The apoptotic factor, caspase-3-cleaved, was lower in VD3 than in VD10 (Table 3).

Table 4 summarizes data of cardiac energy metabolism. In relation to fatty acids β-oxidation, protein expression of PGC-1α (Figure 1-D) and OHADH activity were lower in VD10. Both variables showed a dose-dependent response. The protein expression of PPARα did not differ among the groups and did not present a dose-dependent response. For the glycolytic pathway, the activity of PFK and LDH enzymes showed higher values in the VD10 group. The LDH enzyme and PDH complex showed an increase in a dose-dependent manner. The tricarboxylic acid cycle (TCA) was evaluated by the activity of CS, and the electron transport chain (ETC) was evaluated by the activity of complex II and ATP synthase activity. The activity of CS and complex II was lower in VD10. Both enzymes showed a dose-dependent response. The activity of ATP synthase differed between the groups, with higher values in the VD3 group. These alterations indicate that the animals supplemented with VD presented impairment in fatty acids oxidation, TCA, and ETC, with a shift to an increase in the glycolytic pathway.

No differences were observed between the three groups in relation to structural variables, or in systolic and diastolic function by echocardiogram after two months of VD supplementation. Echocardiographic variables are provided in the supplementary material (Table S1).

Discussion

This study showed that VD supplementation, in non-hypercalcemic doses, for two months in normal rats was associated with higher expression of TXNIP and lower Trx activity. In addition, the animals presented molecular alterations compatible with the cardiac remodeling process, such as oxidative stress, decreased anti-apoptotic markers, and alterations in cardiac energy metabolism, without changes in cardiac structure and function. Changes in the expression of

Table 4 – Variables of cardiac energy metabolism in the groups of rats supplemented with vitamin D and control group

Variable	C	VD3	VD10	P1 Comparison test	P2 Trend test
PPARα (arbitrary unit)	1.06±0.40 (12)	0.87±0.44 (12)	0.95±0.50 (11)	0.593	0.562
OHADH (nmol/mg protein)	69.9±10.8 (8)	65.8±13.1 (8)	34.4±5.14*# (8)	<0.001	<0.001
PFK (nmol/g tissue)	131±23.6 (6)	123±34.8 (6)	170±36.4 (6)	0.048	0.053
LDH (nmol/mg protein)	220±18.1 (8)	209±10.0 (8)	256±9.60*# (8)	<0.001	<0.001
PDH (nmol/g tissue)	317±57.9 (6)	337±42.9 (6)	382±41.6 (6)	0.088	0.034
CS (umol/g tissue)	39.7±3.22 (8)	40.4±2.75 (8)	34.5±4.02*# (8)	0.004	0.005
Complex II (umol/mg tissue)	6.36±0.90 (6)	6.27±1.18 (6)	3.40±0.67*# (6)	<0.001	<0.001
ATP synthase (umol/mg tissue)	45.4±2.96 (6)	53.0±5.42 (6)	44.6±8.04 (6)	0.049	0.824

*Data expressed as mean ± SD. Numbers in parentheses indicate the number of animals in each group. C: control group, with no supplementation of VD; VD3 and VD10: supplemented with 3,000 and 10,000 IU vitamin D/kg of chow, respectively. PPARα: peroxisome proliferator-activated receptor α; OHADH: 3-hydroxyacyl coenzyme-A dehydrogenase; PFK: phosphofructokinase; LDH: lactate dehydrogenase; PDH: pyruvate dehydrogenase; CS: citrate synthase; Complex II: respiratory complex II; ATP: adenosine triphosphate. P1: p value of 1-way ANOVA and Holm-Sidak post hoc analysis; P2: p value of Trend test. Bold numbers represent statistically significant effects. * ≠ C group; # ≠ VD3 group*

TXNIP and Trx may be one of the mechanisms involved in the cardiac remodeling in animals supplemented with VD.

A previous study showed that $1,25(OH)_2D_3$ upregulates the expression of TXNIP.[18] TXNIP interacts with Trx and acts as a negative regulator of Trx, by decreasing its expression and its activity.[20] In this study, we observed that VD supplementation led to higher expression of TXNIP and lower activity of Trx. TXNIP and Trx are important signaling molecules, thereby modulating various cellular functions in the heart such as the redox balance (by a direct action on ROS or acting on homeostasis of proteins and antioxidant enzymes), apoptosis and energy metabolism.[21,22,35] In our study, we observed that all these cellular functions were affected by VD supplementation.

In relation to redox balance, we observed an increase in lipid peroxidation and decrease in the activity of antioxidant enzymes: SOD and GPx. These alterations characterize oxidative stress.[36] A decrease in these antioxidant mechanisms can induce severe cell damages due to imbalances between the production and the removal of free radicals, as indicated by the LH/SOD+GPx+CAT ratio in VD10 animals.[37] The SOD-CAT-GPx system is considered the first line of defense against oxyradical formation.[36] Studies *in vitro* (with tumor cells, adipocytes, and human bone cells) have also shown a potential prooxidant role of VD. Treatment with VD in these cells led to changes in redox balance, such as an increase in ROS, and SOD and glutathione reduction.[24,25,38]

Apoptosis is the biological process by which programmed cell death occurs, requiring the interaction of pro- and anti-apoptotic factors, such as the Bcl-2 protein.[39] In this study, we showed lower expression of Bcl-2 in animals supplemented with VD, in a dose-dependent manner. Studies with tumor cells also showed that VD treatment led to increased apoptosis,[24,40] and the mechanisms involved are decreased Bcl-2[41] and increased oxidative stress.[24,40]

TXNIP and Trx proteins have been shown to participate in the regulation of apoptosis pathways.[26] An *in vitro* study performed by Min et al.[42] showed that TXNIP down-regulates Bcl-2 gene expression. Another study, with human epithelial cells, showed that treatment with VD increases TXNIP and decreases Trx activity. In addition, the authors observed increased in oxidative stress, decreased Bcl-2 expression and apoptosis activation.[26]

In our study, the animals supplemented with VD showed a decrease in the flow of oxidizable substrates for β-oxidation, TCA, and ETC. On the other hand, the animals presented an increase in the glycolytic pathway. Changes in metabolism may be mediated by two important transcription factors, PGC-1α and PPAR α. PGC-1α binds to PPARα and retinoid receptor, forming a complex that regulates the transcription of enzymes of fatty acids β-oxidation and ETC, and inhibits pyruvate oxidation.[43] In this study, VD supplementation led to lower PGC-1α expression. Studies have shown that TXNIP and Trx proteins regulate energy metabolism pathways,[44] for example, modulating the PGC-1α.[45,46] Transgenic mice that overexpress Trx in the heart presented increased expression of PGC-1α and improvement of mitochondrial function.[45,46]

Our findings allow us to suppose that one of the mechanisms involved in metabolic and molecular alterations observed in animals supplemented with VD for two months are changes in the TXNIP/Trx complex.

All these metabolic and molecular changes precede the changes in the structure and function of the heart.[47] The animals supplemented with VD for two months showed no

changes in cardiac structure and function. However, studies with prolonged supplementation are necessary to assess whether VD can lead to such changes.

For most of the changes observed in our study, VD showed a dose-dependent response, and the intensity of these changes increased at the highest dose of VD.

Limitations

VD supplementation in this study was carried out for two months, which allowed us to observe only biochemical, cellular, and molecular changes. Studies with longer supplementation periods could show changes in cardiac structure and function, which is clinically more relevant.

Conclusion

In conclusion, in our study, VD supplementation in non-hypercalcemic doses lead to early process of cardiac remodeling. The possible mechanism of cardiac changes by VD supplementation is by TXNIP and Trx modulation and consequently oxidative stress.

Author Contributions

Conception and design of the research: Santos PP, Azevedo PS, Polegato BF, Minicucci MF, Minamoto SE, Zornoff LAM, Paiva SAR; Acquisition of data: Santos PP, Rafacho BPM, Gonçalves AF, Pires VCM, Roscani MG, Polegato BF, Fernandes AAH; Analysis and interpretation of the data: Santos PP, Azevedo PS, Minicucci MF, Fernandes AAH, Zornoff LAM, Paiva SAR; Statistical analysis: Santos PP, Minamoto SE, Paiva SAR; Obtaining financing: Paiva SAR; Writing of the manuscript: Santos PP, Azevedo PS, Zornoff LAM, Paiva SAR; Critical revision of the manuscript for intellectual contente: Santos PP, Rafacho BPM, Gonçalves AF, Azevedo PS, Polegato BF, Minicucci MF, Fernandes AAH, Zornoff LAM, Paiva SAR.

Potential Conflict of Interest

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

Sources of Funding

This study was partially funded by FAPESP and CAPES.

Study Association

This article is part of the thesis doctoral submitted by Priscila Portugal dos Santos from Faculdade de Medicina de Botucatu – UNESP.

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*Supplemental Materials

For additional information, please click here.

Supplementation of Vitamin D

Marina P. Okoshi,[1] Rosana M. Cortez,[1,2] Luana U. Pagan,[1] Paula F. Martinez,[3] Filipe W. L. Pereira[1]

Departamento de Clínica Médica - Faculdade de Medicina de Botucatu (UNESP),[1] Botucatu, SP - Brazil

Unimed Sorocaba,[2] São Paulo, SP - Brazil

Instituto Integrado de Saúde, Universidade Federal de Mato Grosso do Sul (UFMS),[3] Campo Grande, MS - Brazil

Short Editorial related to the article: Vitamin D Supplementation Induces Cardiac Remodeling in Rats: Association with Thioredoxin-Interacting Protein and Thioredoxin

Vitamin D (Vit D) is a fat-soluble vitamin that is essential in mineral and bone metabolism. Vit D status is evaluated by measuring serum 25-hydroxyvitamin D [25(OH)D]) levels. Currently, Vit D supplementation is mainly indicated in cases of vitamin deficiency. However, there are two main issues concerning Vit D supplementation. The first is related to the definition of the lower limit of normal for serum 25(OH) D. In recent years, extensive clinical research has revealed that large percentages of global populations have low Vit D levels, i.e., serum [25(OH)D] concentrations below 20 ng/mL.[1] However, several investigators have considered that this value is probably overestimated, therefore putting more people in need for supplementation. Several medical societies are now intensively debating on when to screen for Vit D deficiency and when to supplement Vit D.[1,2]

The other issue concerning Vit D supplementation relates to the fact that convincing experimental and epidemiological studies have suggested that Vit D deficiency is associated with increased risk of chronic cardiovascular and immunological diseases and cancer. Therefore, Vit D has been supplemented in the general population without a specific indication. However, more recent studies have reported that Vit D supplementation for preventing or controlling chronic diseases such as cancer, diabetes mellitus, dementia or cardiovascular disease has failed to provide benefits.[3-5] Furthermore, not only were no benefits found. In advanced heart failure, a daily Vit D supplement was associated with a greater need for mechanical circulatory support devices, which indicates caution regarding long-term supplementation.[6]

Experimental studies are important as they allow the establishment of better control parameters involved in vitamin supplementation.[7-9] In the current issue of ABC, Santos et al.[10] confirmed their hypotheses that Vit D supplementation at non-hypercalcemic doses induces detrimental myocardial changes in rats and that this process may, at least in part, be modulated by thioredoxin-interacting protein (TXNIP), thioredoxin (Trx), and oxidative stress. In an elegant study, male Wistar rats were subjected to two different non-hypercalcemic Vit D doses for two months. Supplementation decreased the activity of enzymes involved in oxidative metabolism and increased the glycolytic pathway. Increased oxidative stress was characterized by higher lipid peroxidation and reduced antioxidant enzyme activity in myocardium of the supplemented rats. Additionally, higher TXNIP expression and lower Trx activity, associated with reduced antiapoptotic markers, were also observed with the higher dose of Vit D, in a dose-dependent manner. Considering the increased oxidative stress and reduced antiapoptotic markers, we can hypothesize that in the long-term the myocardial changes could induce cardiac remodeling or predispose healthy hearts to deleterious effects of cardiac injury, such as myocardial ischemia and arterial hypertension. As pointed out by the authors, one limitation of the study is the short treatment period, which did not allow to determine whether chronic Vit D supplementation causes pathological cardiac remodeling.

Although epidemiological data link Vit D to cardiovascular outcomes and support a role for Vit D in pathogenic processes, mechanistic data are insufficient to recommend Vit D supplementation for prevention or treatment of diseases other than bone metabolic disease.[11]

Keywords

Vitamin D; Nutritional Status; Bone and Bones/metabolism; Dietary Supplements/adverse effects.

Mailing Address: Marina P. Okoshi •
Departamento de Clínica Médica, Faculdade de Medicina de Botucatu. Rubião Junior, S/N. Postal Code 18618 687, Botucatu, SP – Brazil
E-mail: mpoliti@fmb.unesp.br

DOI: https://doi.org/10.36660/abc.20210181

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Review Article

Dysautonomia: A Forgotten Condition — Part II

Eduardo Arrais Rocha,[1] Niraj Mehta,[2,3] Maria Zildany Pinheiro Távora-Mehta,[2,3] Camila Ferreira Roncari,[4] Alan Alves de Lima Cidrão,[5] Jorge Elias Neto[6]

Hospital Universitário Walter Cantídio da Universidade Federal do Ceará (UFC) - Programa de Pós-graduação em Ciências Cardiovasculares da Faculdade de Medicina da UFC,[1] Fortaleza, CE - Brazil
Universidade Federal do Paraná, Curitiba,[2] PR - Brazil
Clínica de Eletrofisiologia do Paraná,[3] Curitiba, PR - Brazil
Departamento de Fisiologia e Farmacologia - Faculdade de Medicina da Universidade Federal do Ceará (UFC),[4] Fortaleza, CE - Brazil
Programa de Pós-graduação em Ciências Cardiovasculares da Faculdade de Medicina da UFC,[5] Fortaleza, CE - Brazil
Serviço de Eletrofisiologia do Vitória Apart Hospital,[6] Vitória, ES - Brazil

Clinical Series of the Brazilian Society of Cardiac Arrhythmias

General and Cardiovascular Clinical Manifestations

The pathologies that affect the autonomic nervous system (ANS) can manifest in different ways, depending on the etiology, degree of impairment, disease duration, presence of comorbidities, age or use of associated drugs. Many symptoms can be completely debilitating, such as severe pain in peripheral neuropathy and falls or syncope in autonomic neuropathies. Progression to severe orthostatic intolerance may occur in more advanced cases of dysautonomies, with severe early orthostatic hypotension and supine hypertension, making treatment difficult (Table 1). [1-7]

Investigation methods

The Autonomic Nervous System (ANS) is reasonably complex, which makes it hard to investigate it and interpret it at first. However, some tests are simple, easy to perform and provide valuable information about its shortcomings. They can be performed using modern computerized equipment or through simple digital electrocardiograms that can record the tests, the RR intervals, allowing for adequate measurements of the relationships between their variations.

The objectives of this evaluation are:

a) To confirm diagnosis;

b) To stage the severity of dysfunction;

c) To identify subclinical abnormalities;

d) To monitor evolution of the disease.

For the effective performance of autonomic tests, the patient must be rested and calm. The autonomic evaluation laboratory should be a quiet properly heated and lightly darkened place.[8,9]

Keywords

Primary Dysautonomias; Hypotension,Orthostatic; Hypothension, Postural; Fatigue; Diabetes; Autonomic Nervous System; Syncope; Cardiovascular Autonomic Neuropathy.

Mailing Address: Eduardo Arrais Rocha •
Av. Padre Antônio Tomás, 3535/ 1301. Postal Code 60190-120, Fortaleza, CE - Brazil
E-mail: eduardoarraisrocha@gmail.com
Manuscript received May 04, 2020, revised manuscript October 06, 2020, accepted November 04, 2020

DOI: https://doi.org/10.36660/abc.20200422

Cardiovascular Autonomic Reflex Tests (Cardiovagal Function Tests)

These tests were described by Ewing, in the 70s, and today, they are the gold standard tests for the diagnosis of cardiovascular autonomic neuropathy (CAN).[7,10-13] They have good sensitivity and specificity and must be performed in the presence of symptoms suggestive of dysautonomia, and early in patients with pathologies that include diabetes, which may progress to CAN, even in their glucose intolerance phase (Figure 1).[8-10]

The tests are divided into methods that assess sympathetic and parasympathetic function, which are usually abnormal earlier, especially in diabetes.

Abnormal results in one method of the 3 cardiovascular tests implies early or uncertain autonomic neuropathy. The test must be repeated after 1 year for confirmation and evaluation of evolution. The presence of 2 positive tests is confirmatory for CAN. The association of orthostatic hypotension with 2 positive tests implies advanced dysautonomia and worse prognosis.

These tests require proper assessment and preparation, with the suspension of several drugs that can alter the analysis of heart rate and ANS. Proper evaluation of this test is not possible in patients with frequent arrhythmias (more than 6 ectopic beats per minute), atrial fibrillation, cardiac pacemaker, and accentuated tremors and non-collaborative patients.

Cardiovascular Autonomic Reflex Tests (Cardiovagal Function Tests)

These were described by Ewing in the 70s. They are the gold standard tests in the diagnosis of Cardiovascular Autonomic Neuropathy (CAN). They have good sensitivity and specificity and should be performed in the presence of symptoms suggestive of dysautonomia, and early in patients with pathologies such as diabetes, which may progress to CAN, even in their glucose intolerance stage.[7,11-13]
They can be performed using modern computerized equipment or through simple digital electrocardiograms, which can record the tests, the RR intervals, allowing for adequate measurements of the relationships between the variations of the longest and shortest RR intervals.[14-16]

Breathing Test (E/I Respiratory Quotient)

This method analyzes the ratio (quotient) between the highest RR cycle on exhalation divided by the largest RR cycle

Table 1 – Clinical and Cardiovascular Signs and Symptoms of Dysautonomia and/or Cardiovascular Autonomic Neuropathy (CAN)

Clinical symptoms	Cardiovascular signs and symptoms
Impotence in men and reduced libido	Fatigue and exercise intolerance
Abnormal menorrhea	Pre-syncope/syncope
Urinary urgency and incontinence	Visual darkening and intolerance to prolonged orthostasis
Diarrhea / Constipation / Indigestion	Unexplained falls
Exacerbated responses to hypoglycemic agents	Exacerbated responses to antihypertensive drugs
Difficult control of diabetes (due to gastroparesis)	Supine hypertension
Hypohidrosis or anhidrosis	Non-dipper pattern on Ambulatory Blood Pressure Monitoring (ABPM)
Abnormal vision, pupil atrophy	Tiredness, shortness of breath (due to chronotropic incompetence)
Pain, numbness or burning feeling in the extremities	Bradycardia
Forgetfulness, decreased cognitive function	Paleness, cold extremities
Tremors, unbalance	Orthostatic hypotension
Sleep abnormalities/apnea	Postprandial syncope or pre-syncope (up to 2 hours after a copious or high-carbohydrate meal)
Severe pain in the posterior cervical region (trapezius ischemia)	Palpitations and tachycardia on rising

Source: Author.

on inspiration — 3 cycles of 1 minute each are performed, with 1-minute intervals between tests, allowing to evaluate the parasympathetic system.

Inhalation and exhalation cycles are slow and deep, with a total respiratory cycle lasting 10 seconds. It accentuates the sinus respiratory arrhythmia seen in normal individuals. The normal response is an acceleration of the heart rate during inspiration and deceleration on exhalation. In summary, heart rate is recorded for 1 minute (6 slow, deep breathing cycles lasting 10 seconds each). The difference between the maximum and minimum heart rate, or the ratio of these two (E:I ratio), is recorded and measured in milliseconds.

Usually, respiratory amplitudes are averaged over the 6 cycles. This is a test that assesses parasympathetic response to respiratory stimulus. Patients with dysautonomia may experience reduced or no heart rate oscillation on deep breathing. Loss of respiratory sinus arrhythmia may be one of the first signs of diabetic autonomic neuropathy.

Normal physiological values of the amplitude difference are considered above 15 bpm. Between 11–14 bpm, borderline and below 10 beats would be pathological. The E:I ratio (maximum heart rate measured in milliseconds during exhalation divided by the maximum heart rate during inspiration) in normal individuals must be greater than 1.2.[11-15] These values must be adjusted for age and sex.

Valsalva Test — (Valsalva Quotient)

In this test, the relationship between the largest RR cycle in the relaxation phase divided by the largest RR cycle in the Valsalva maneuver phase is measured, allowing to assess particularly the parasympathetic system and also the sympathetic system, when associated with continuous blood pressure measurements.

The Valsalva maneuver is particularly interesting because it tests the integrity of both the cardiovagal parasympathetic response, by analyzing heart rate, and the sympathetic response, by analyzing blood pressure. The technique basically consists of making the monitored patient blow for 15 seconds through a small tube, with a discreet air outlet to avoid closing the glottis. The expiratory air pressure generated should be around 40 mmHg.

There are 4 distinct phases: blood pressure deflections in phases I and III represent mechanical disturbances generated by changes in intrathoracic pressure, at the beginning and at the end of the Valsalva maneuver. On the other hand, phase II and phase IV are the clinically relevant phases.

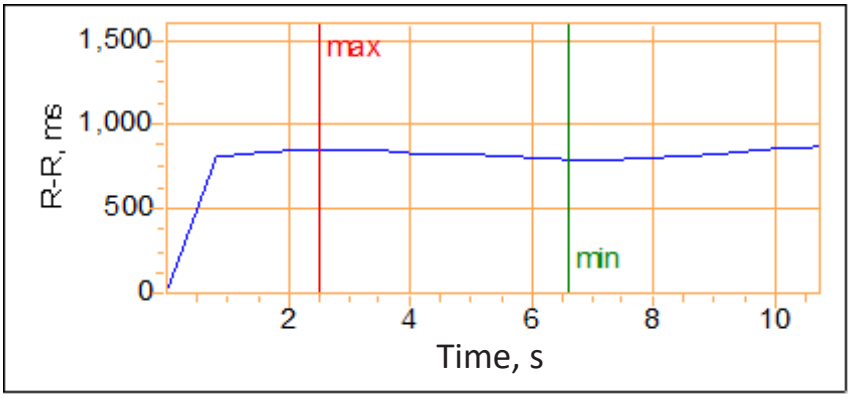
In healthy individuals, during expiratory effort, in phase I, blood pressure drops due to decreased venous return. This pressure drop is perceived by intact baroreceptors, which trigger a response with increased sympathetic tone, leading to vasoconstriction and increased heart rate.

This action recovers pressure in late phase II. On release of intrathoracic pressure at the end of the maneuver, there is increased venous return and, with the maintenance of peripheral vasoconstriction, there is blood pressure overshoot (perfect combination of increased venous return and vasoconstriction).

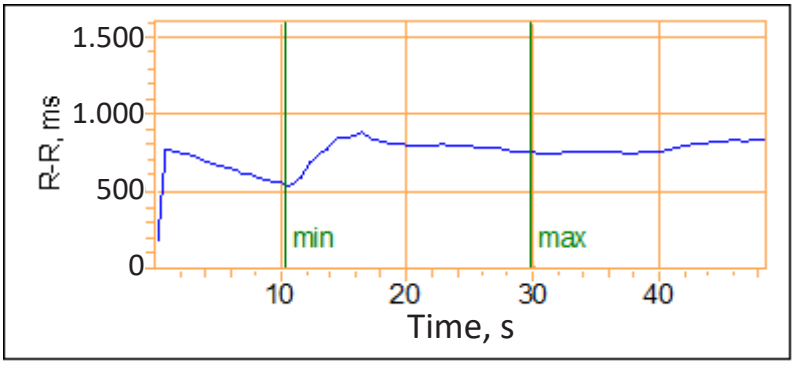
Patients with autonomic dysfunction are unable to react with increased sympathetic tone to the initial pressure drop caused by the maneuver. Therefore, there is no pressure increase in late phase II and, typically, there is no blood pressure overshoot in phase IV. Instead, pressure response in patients with dysautonomia reveals a gradual return of blood pressure to baseline levels after induction of hypotension caused by the forced expiration.[17-19]

With regard to heart rate, the Valsalva quotient is derived from the maximum heart rate measured in milliseconds and generated by the Valsalva maneuver, divided by the lowest heart rate in the first 30 seconds of the peak heart rate. Heart rate responses are mediated by baroreceptors.

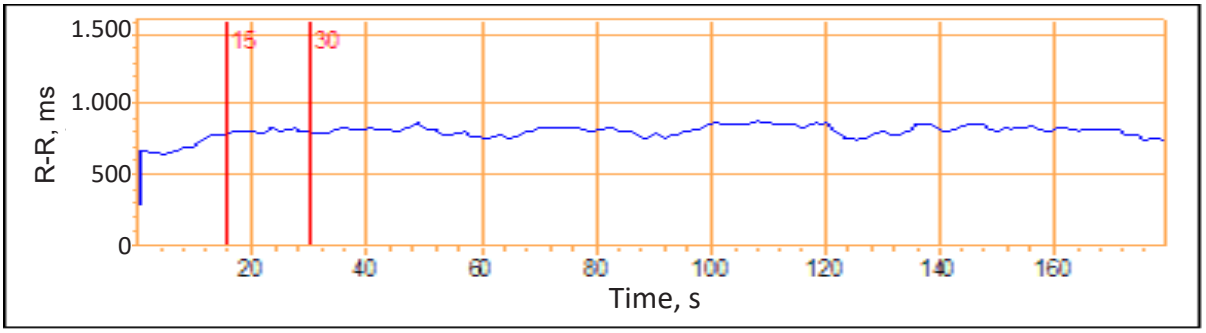
1.1 – Respiratory Test



1.2 – Valvalva Coefficient



1.3 – Orthostatic Test 30:15



1.4 – Table of results

Parameter	Value
Respiratory Coefficient	1.08
30/15 Coefficient	1.03
Valsalva Coefficient	1.44

Figure 1 – *Cardiovascular Autonomic Reflex Tests. Clinical case of a patient with advanced disautonomia with abnormal breathing tests (1.08) and abnormal orthostatic coefficient 30/15 (1.03). Values need to be adjusted for age and sex.*[11-13]

Increase in heart rate is due to the blood pressure drop. Besides, baroreceptor response to the blood pressure overshoot in phase IV is responsible for the transient bradycardia at the end of the maneuver.[17-19]

In patients with dysautonomia, there is a loss of both blood pressure overshoot and reflex bradycardia. Therefore, heart rate does not respond either, due to the absence of increased sympathetic response, showing a straight curve (absence of heart rate oscillation).

The normal Valsalva quotient (maximum RR value in ms divided by the lowest RR value) during the maneuver must be greater than 1.21. Borderline values would be between 1.11 and 1.20, while pathological values would be considered if less than or equal to 1.10.[13-15] These values must also be adjusted for age and sex.

30/15 Quotient Test with Orthostasis

RR interval is evaluated after orthostasis around the 15th beat (usually higher frequency — lower RR interval) and around the 30th beat (lower frequency — higher RR interval), indicating a predominant evaluation of the parasympathetic system.

The simplest and most commonly used method for testing cardiovascular feedback is by measuring cardiovascular parameters (heart rate, blood pressure, noradrenaline dosage) during postural change from horizontal posture to orthostatic posture.[16-19]

Due to changes in hydrostatic pressure, when standing, 500–800 ml of volume is redistributed to the lower limbs. However, when actively standing the lower limb veins are compressed (the so-called skeletal-muscle pump), immediately increasing venous return.

Compensatory mechanisms act quickly, causing blood pressure to change very little in healthy individuals. However, in 10 to 15% of individuals, orthostatic circulatory disorders are observed due to insufficient compensatory mechanisms.

Evaluation of response to orthostasis can be performed by active inclination or by response to the tilt test. In the first, with regard to heart rate, there is a rapid and maximum increase around the fifteenth heart beat in normal people. After that, there is relative maximum bradycardia around the thirtieth beat. Pharmacological studies indicate that this response is mediated by the vagus nerve.

Patients with diabetes-associated cardiovascular autonomic neuropathy show only a slight progressive increase in heart rate.[19] The 30:15 ratio (or Ewing's ratio) is used as a measure of parasympathetic integrity. The longest RR interval at the 30th beat and the shortest RR interval at the 15th beat is called the Ewing ratio or 30:15 ratio, where a normal value would be above 1.04.

Current software packages no longer calculate pure 30:15 ratio. Instead, they use the measurement of the longest RR interval between the 20th and 40th heartbeat and the shortest RR interval, between the 5th and 25th heartbeat.[14-19]

Protocol of the 7 Tests for Dysautonomia

Association of 3 cardiovascular function tests with 3 tests of analysis of RR variability in the frequency domain and orthostatic hypotension investigation represents the protocol of the 7 tests (figures 1 and 2) for investigation of CAN, with high sensitivity and specificity.

This test may have a better diagnostic capacity according to some authors.[12] It is considered positive if 3 methods out of the 7 tests are abnormal, or uncertain or early if 2 abnormal methods. Similar to the isolated cardiovagal tests, the presence of associated orthostatic hypotension implies greater CAN severity.

These tests can be performed together using specific software such as the VNS-Rhythm poly-spectrum analysis® or Neuro-Diag. Ansar®, which are inexpensive compared to equipment used with hemodynamic measures.

Tilt test

The tilt test is a very useful diagnostic tool for patients with dysautonomia. On orthostatic position, 500–800ml of central volume is transfered to the periphery (pelvis, abdomen and lower limbs). This volume movement leads to a drop in systolic volume and, consequently, cardiac output. This drop, in turn, is felt by the baroreceptors of the aortic arch and carotid sinus which, after interaction with vasomotor centers, trigger a response with a reduction in parasympathetic activity and an increase in sympathetic activity. This translates into peripheral vasoconstriction and increased heart rate.

This diagnostic test can be particularly useful to detect and confirm the autonomic failure seen in orthostatic hypotension, orthostatic postural tachycardia, late orthostatic hypotension and, obviously, reflex changes in vaso-vagal reaction.[19-20]

The tilt test is performed in a quiet room with minimal distractions. The patient is initially instructed to fast for 3 hours and lie down in the supine position for at least 10–15 minutes. Although there are several protocols, the current recommendation and the most commonly used protocol is inclination at 70 degrees for about 30–40 minutes.[21]

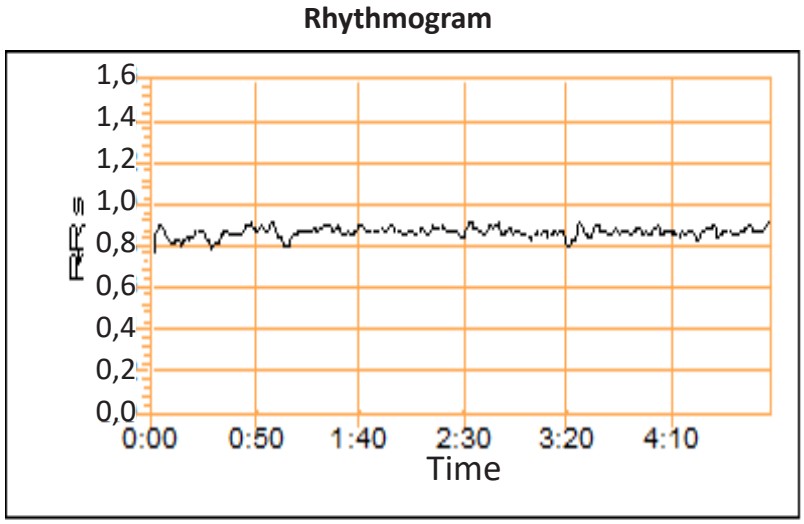
Provocative test with isoproterenol or 1.25 mg sublingual isosorbide can be useful for investigating syncope of vaso-vagal origin as it increases test sensitivity.[22] However, drug sensitization does not apply when the goal is to evaluate dysautonomia, because it is necessary to evaluate spontaneous cardiovascular physiological response to prolonged orthostatic stress.

Although intermittent blood pressure measurements (every 2–3 minutes) can be performed, continuous monitoring of blood pressure and electrocardiographic recording would be preferable, however at a much higher cost.

Tilt test associated with hemodynamic measurements

The use of additional modules to measure continuous blood pressure (Finapress® modelflow and Task Force Monitor® impedance cardiography) allows to determine stroke volume indirectly. From this parameter, other hemodynamic parameters can be estimated with reasonable precision, such as peripheral vascular resistance and cardiac output.

Finapress® modelflow uses the analysis of arterial pulse contour, which is a technique for determining stroke volume. In modelflow, the arterial pulse flow wave is calculated from the arterial pulse pressure contour. Integration of this flow wave with each beat generates the stroke volume.[22,23]



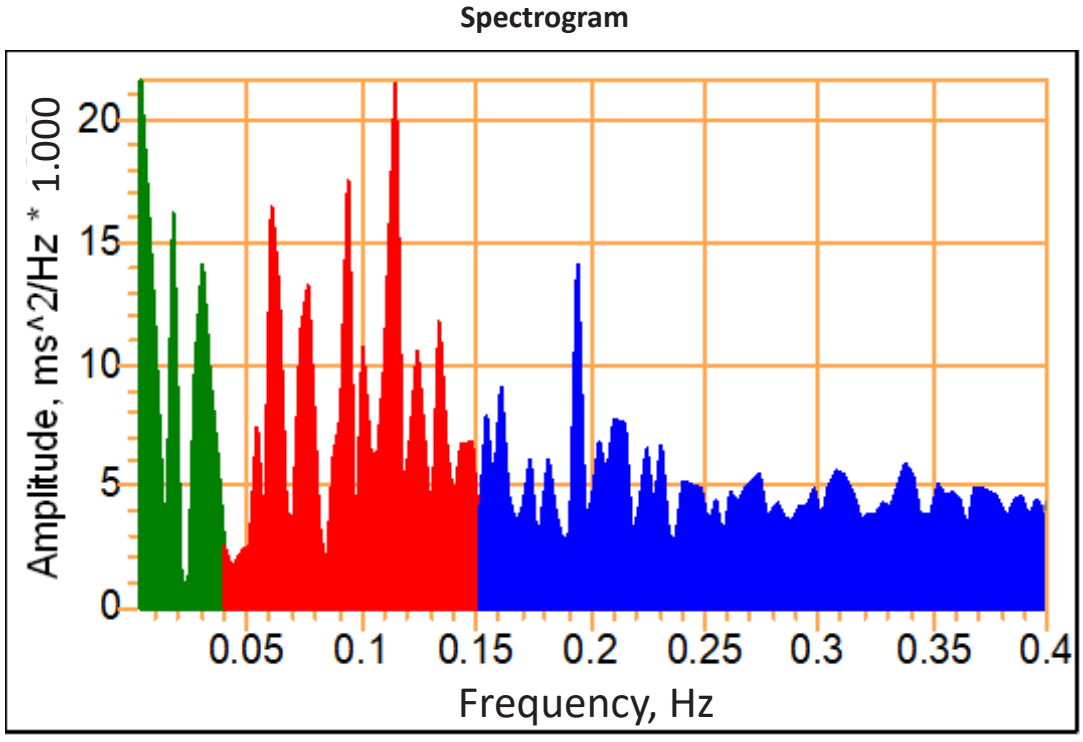


Figure 2 – ***Analysis of RR Variability in the frequency domain*** *during a 5-minute cycle. Any drugs that interfere with heart rate analysis must be discontinued. The presence of frequent arrhythmia, atrial fibrillation or pacemaker makes it impossible to analyze the test.*
Very low frequency component — 0.01–0.04 Hz (FMB – VLF) — *Assessment of vasomotor tone fluctuations related to thermoregulation and sweating — (predominant sympathetic action)*
Low Frequency Component — 0.04–0.15 Hz (FB-LF) — *Baroreceptor evaluation (predominant sympathetic component with vagal modulation)*
High Frequency Component — 0.15–0.5 Hz (FA — HF) — *Related to sinus control (parasympathetic action)*
It can be carried out in the protocol with the tests in figure 1 (characterizing the protocol of the 7 Cardiovascular Autonomic Reflex Evaluation Tests).

Impedance cardiography (Task Force Monitor®), on the other hand, measures abnormalities in chest impedance generated by fluctuating blood volumes during the cardiac cycle, allowing to calculate stroke volume, cardiac output and other parameters.[23] Although these noninvasive cardiac output determination techniques are not completely accurate, they have been validated compared to invasive techniques and are quite reliable to monitor the relative changes in cardiac output.

Therefore, the tilt test with hemodynamic parameters, in addition to measuring continuous blood pressure, allows to evaluate stroke volume, cardiac output and peripheral vascular resistance. Analysis of hemodynamic parameters during the tilt test is very important, as it allows to record the drop in peripheral vascular resistance and reveal the presence of dysautonomia, often without a significant drop in blood pressure due to borderline compensatory mechanisms (mild to moderate dysautonomia).

Besides, it allows to determine whether there is a significant reduction in stroke volume, which may be a non-neurogenic component of orthostatic hypotension (due to chronic dehydration, for example).

Thus, the tilt test with hemodynamic parameters allows to identify subclinical abnormalities in ANS integrity even without any evident pressure drop, hence increasing test sensitivity. The limitation of the method is its high cost. It is restricted to few centers, especially for dysautonomia research.

24 hours Ambulatory Blood Pressure Monitoring (ABPM)

Daytime and nocturnal autonomic balance does not only affect heart rate, but also blood pressure. Normally, blood pressure fluctuates, with higher levels during wakefulness, declining at night (nocturnal decrease). Proportional blood pressure drops at night based on the daytime period determine the expected nocturnal decrease responses: attenuated response (0–10% nocturnal decrease), normal response (10–20% nocturnal decrease), marked response (above 20% decrease) and reverse response (increase in blood pressure instead of expected nocturnal decrease).

Attenuated or reverse response shows exacerbated sympathetic activity, which may be present in dysautonomia, and has been associated with increased mortality. In addition, the presence of nocturnal hypertension may increase the risk of daytime hypotension (as a result, among other things, of increased nocturnal excretion of natriuretic hormone).

ABPM can indicate cardiovascular autonomic dysfunction abnormalities and is able to select patients for a deeper assessment of dysautonomia. More specifically, ABPM can be especially useful in detecting nocturnal hypertension (an important predictor of cardiovascular events) and forms of early or postprandial orthostatic hypotension, usually not detected with the usual blood pressure measurements.

Supine Hypertension – Warning Sign

The presence of supine hypertension or non-dipper pattern on 24-h ABPM, especially in patients with pathologies that are known to involve dysautonomia must consider suspicion and investigation with clinical and laboratory screening for dysautonomia.

Holter Monitoring and RR Variability Analyses

The sinus node is subject to both sympathetic and parasympathetic (vagal) action, depending on the situation evaluated. Standing position, mental stress and exercise are associated with increased sympathetic tone. On the other hand, vagal tone is increased in resting conditions. In normal individuals, both sympathetic and parasympathetic tone fluctuate throughout the day, generating a variation in RR intervals or simply RR variability. In normal individuals, RR variability declines 3–5 beats every decade.

24-h Holter can be used to analyze average heart rate, chronotropic incompetence and cardiac arrhythmias, and when coupled with specific software, it allows analyzing RR variability.

High mean heart rates may suggest autonomic dysfunction, such as in diabetic patients, or indicate inappropriate sinus tachycardia (IST), or even allow the identification of chronotropic incompetence. The detection of arrhythmias may suggest other etiologies as a justification for the symptoms, and helps in the selection for the performance of cardiovascular tests.

There are several methods for analyzing RR variability data, including time and frequency domain analysis. In the time domain analysis, each QRS is detected to determine the "normal to normal" interval. This interval also provides additional information, including standard deviation. More complex statistical analyses require extended periods of time. Spectral analysis can provide evaluation in the frequency domain, giving information on how variance is arranged as a function of frequency.

Heart rate abnormalities occur continuously during daily activities, reflecting autonomic balance, reflex cardiovascular mechanisms and external stimuli. In normal people, increased RR variability of heart rate is considered a measure of autonomic integrity, while reduced heart rate variation is an early sign of autonomic imbalance.

Analysis of RR variability can be done in the time domain and in the frequency domain for short periods of a few minutes or longer periods (24-hour Holter). Time domain analysis includes evaluation of many parameters, such as: mean normal intervals; mean heart rate, difference in maximum heart rate, standard deviation of the average normal-to-normal intervals (SDANN); root mean square of successive differences between normal heartbeats (rMSSD).

Prolonged monitoring (24-h Holter) also allows to calculate the number of instances per hour in which a difference greater than 50 ms was measured between two consecutive RR intervals (pNN50). Essentially, all of these indexes explore parasympathetic activity.

The spectral analysis of RR variability (frequency domain), in turn, reveals 3 main frequency components:

Very low frequency component (<0.04Hz) related to fluctuations in vasomotor tone linked to thermoregulation and sweating (sympathetic control);

Low frequency component (0.04–0.15 Hz) connected to the baroreceptor reflex (sympathetic control with vagal modulation);

High frequency component (0.15–0.4 Hz) influenced by breathing (respiratory sinus arrhythmia), being a component of parasympathetic activity.

In diabetic patients with predominantly vagal (earlier) dysfunction, the range of high frequencies is reduced or absent. On the other hand, in later sympathetic dysfunctions, the amplitudes of low and very low frequencies are reduced.

Time domain parameters, total spectral power of RR variability and the high frequency spectral component are parasympathetic parameters. Although the low frequency component is controlled by sympathetic activity, extreme sympathetic activation (as in exercise, in heart failure) attenuates RR variability, making it difficult to record it, and may, therefore, not correlate with the real sympathetic activity.

Thus, it is now accepted that the absolute "spectral power" of low frequencies does not reflect sympathetic activity. However, when measured in relative terms (as a percentage of the overall RR variability), the relative ratio of low to high frequencies provides a relative and approximate indication of sympathetic modulation of the heart.

Therefore, the ratio of low to high frequency component best represents sympathetic status. As RR variability is influenced by age, sex and respiratory rate, adjustment for these variables is recommended. Results of spectral analysis correlate well with the tests of autonomic function in clinical situations.

Spectral analysis is more sensitive in the early stages of CAN. In diabetic patients in the early stages of CAN, a progressive deterioration of the parameters of spectral analysis related to the parasympathetic system is documented. The expected nocturnal increase in the high frequency band of RR variability, representing vagal modulation of the heart, seems to be the earliest abnormality detected. During advanced stages of CAN, all components are eliminated.

Electromyography and Small Fiber Neuropathies

Postganglionic autonomic fibers are type C, non-myelinated. With the Aδ fibers, little myelinated, they make up the group of fine fibers. They differ from thick myelinated fibers by their thickness and conduction speed: they conduct nerve impulses at a speed of 0.5 to 1 m/s, while in the latter, speeds of up to 120 m/s are observed.[24,25]

Aδ fibers are of the somatic sensory type and participate in skin innervation, mediating the perception of pain and thermal stimuli, whereas type C autonomic fibers innervate the cardiac musculature, smooth muscles (present in the blood vessel wall, gastrointestinal and genitourinary tracts) and salivary, lacrimal and sweat glands.[24]

Neuropathic involvement of small fibers can occur without the involvement of thick fibers, characterizing small fiber neuropathy, or in the context of a polyneuropathy, where there is a clear involvement of those. In the context of small fiber neuropathies, involvement of Aδ fibers is more commonly observed.

Typical symptoms include paresthesia, pain, a burning sensation or cold, with clear worsening at night. Dysautonomic signs and symptoms occur in approximately 50% of these patients. More rarely, small fiber neuropathy may appear predominantly with autonomic symptoms.[26,27]

Skin biopsy and quantitative sensory testing (QST) are useful mainly for the assessment of Aδ fibers. Other tests are for the evaluation of autonomic fibers and, when performed, they increase diagnostic sensitivity.[26-31]

Conventional electroneuromyography, through conduction and electromyography studies, is a key test for the initial evaluation of these cases, not to confirm diagnosis, but mainly to rule out polyneuropathy (involvement of thick fibers) and conditions that may appear like small fiber neuropathy, such as bilateral S1 radiculopathy which characteristically involves paresthesia of the feet.

Conduction studies by this method evaluate only the fastest nerve fibers and is not able to identify impairment of small fibers. Therefore, in pure cases of small fiber neuropathy, conduction studies, including evaluation of sural nerves, which are classically altered in cases of polyneuropathies, will be normal.[26,27,31,32]

Skin biopsy is still considered the gold standard for the diagnosis of small fiber neuropathy. It is a low-invasive procedure, performed on an outpatient basis, with local anesthesia. In general, a 3-mm tissue fragment is removed from the distal region of one of the lower limbs, 7 to 10 cm proximal to the lateral malleolus. Other fragments can be removed 7 to 10 cm proximal to the knee and 7 to 10 cm distal to the greater trochanter, of the same limb, to define the pattern — length-dependent (distal to proximal pattern) or not length-dependent, or biopsy of specific sites if focal symptoms are detected.

As mentioned before, evaluation of the density of intra-epidermal fibers predominantly focuses on the Aδ fibers.[28] The expected normal values vary according to age, gender and biopsy site. Recent studies have sought to standardize these values.[33,34] When the values are unknown for a given site, comparative analysis with the contralateral side may be a valid alternative.

Limitations of this method are: difficulty accessing specialized laboratories, especially in developing countries such as Brazil; the possibility that the test may still be normal at the beginning of the condition; no standardization of expected values for many anatomical sites and no standardization for the evaluation of autonomic fibers.

Quantitative Sensory Testing and Sudomotor Test

The Quantitative Sensory Testing (QST Testing) assesses the pain sensation threshold mainly through controlled thermal stimulus, usually by heat. It therefore assesses the integrity of Aδ fibers. It is a test that depends on the patient's collaboration, since they need to be able to share their perceptions. Thus, it can be distorted by the difficulty of understanding instructions, patient's difficulty to concentrate or even by volitional action.

Other limitations to the method are: low availability and the fact that it does not distinguish peripheral from central injuries. Involvement of the spino-thalamic pathways and brain areas related to this sensory modality will also lead to an abnormal pattern in the test. For these reasons, it is not recommended that it be used as a single test to diagnose small fiber neuropathy.[26,30]

Tests of the autonomic fibers are mainly directed to the evaluation of sudomotor function. Sweat production by the sweat glands is mediated by cholinergic sympathetic innervation. It is observed, in general, in the presence of impairment of such fibers in a length-dependent pattern (distal to proximal), anhidrosis in the distribution of boots and gloves, with compensatory proximal hyperhidrosis.[26,27] Severe and diffuse loss of this function may lead to thermoregulation and hyperthermia disorders.

Of the available methods, Thermoregulatory Sweat Testing (TST) and Quantitative Sudomotor Axon Reflex Testing (QSART) can be performed.

TST is carried out in a room where it is possible to control temperature and humidity. The patient lies supine on a stretcher, their temperature is monitored by 2 sensors (one for the skin and another one for the oral cavity) and have their body covered by a compound that changes color when the local pH changes by sweat.

The room temperature is increased to 45–50ºC, maintaining a relative humidity of about 35–40%. Skin temperature is maintained between 38.5 and 39.5 ºC and the oral temperature must rise by 1 ºC from the baseline value or reach 38 ºC (whichever is greater). Observation should take place between 30 and 65 minutes. The color change of the reagent on the patient's body indicates the local production of sweat. Digital photographs are taken and an anatomical map of the sweat density is generated, which is then interpreted.

The main limitations of the method are the low availability and inability to distinguish pre- or post-ganglionic impairment. Thus, combining it with a test that is directed at post-ganglionic fibers can help to make this distinction.[31,34]

QSART evaluates the function of post-ganglionic autonomic fibers related to sudomotor function. It evaluates the production of sweat through the cholinergic stimulus by iontophoresis. Usually, four segments are evaluated — forearm, proximal leg, distal leg and dorsum of the foot; this can provide information about the pattern of involvement: length-dependent or non-length-dependent.

The system consists of a special multi-compartmentalized capsule (a compartment for iontophoretic stimulation, another to measure humidity and a third one that separates the first two), which is in direct contact with the skin, a continuous flow system of dry nitrogen, which passes through the capsule at constant temperature and goes to a hygrometer, which records humidity fluctuation due to local sweat production.

Humidity variation is recorded in a chart on a computer attached to the system. The chart is analyzed mainly for its latency and the area under the curve, with standard values for men and women. The limitations of this method are the difficulty of access and the impossibility of evaluating pre-ganglion fibers.[26]

Magnetic Resonance Imaging of the Brain and MIBG Scintigraphy

Magnetic resonance imaging can be useful in the diagnosis of multisystem atrophy (MSA) by identifying specific structural changes in the brain, focused on identifying gray matter atrophy patterns.[35,36]

T1- and T2-weighted images viewed by experienced neuroradiologists have identified classical signs, such as the hot cross bun sign (which represents degeneration of the pons fibers and pontocerebellar fibers, with preservation of the corticospinal tract). This sign appears as a hyperintense cross on the pons, with high specificity (97%), although with low sensitivity (50%). Another observation is the hyperintense signal at the putamen edge with high specificity (90%), although also with less sensitivity (72%).[35,36]

Over the past few years, there has been significant progress in neuroimaging techniques, using new connectivity and functional techniques, which can improve diagnostic accuracy and determine new markers of disease progression. A multimodal approach with innovative technologies, as part of the diagnostic arsenal, will allow future progress in the diagnosis and research of multisystemic atrophy (MSA).[35,36]

Regarding Parkinson's disease, the morphological analysis of the midbrain by magnetic resonance imaging, particularly of the substantia nigra and the basal nuclei, presents findings that support the diagnosis of parkinsonian syndromes.[36]

A new and exciting area in MRI is the analysis of brain inflammation. In patients with chronic fatigue syndrome, brain inflammation has been investigated with spectroscopy, measuring levels of various metabolites related to neuroinflammation, including compounds containing choline, myo-inositol, lactate and N-acetylaspartate.[37] A study evaluating magnetic resonance spectroscopy applied to the entire brain area demonstrated abnormalities of metabolites and temperature distributed throughout the brain, rather than regionally limited.[37]

This finding suggests that chronic fatigue syndrome is a diffuse pathological process that affects the entire brain, which is consistent with the heterogeneous clinical symptoms of the syndrome. These findings, according to the authors, support the hypothesis that the chronic fatigue syndrome is the result of low intensity chronic neuroinflammation.

Another interesting aspect of magnetic resonance imaging is the analysis of cognitive disorders in alpha-synucleinopathies.[38] Many of these patients have orthostatic hypotension, which leads to transient cerebral hypoperfusion. A suggested hypothesis is that transient or repetitive cerebral hypoperfusion may be responsible for cognitive deficits in these patients.

Structural magnetic resonance imaging demonstrates hyperintensity of the white matter, which may contribute to cognitive defects. There is evidence that orthostatic hypotension is associated with white matter hyperintensity in α-synucleinopathies, partially explaining the relationship between orthostatic hypotension and cognitive impairment.

New applications of functional magnetic resonance imaging show that physiological fluctuations in the white matter observed on the resonance precede the structural changes in white matter hyperintensity, therefore they are more sensitive measures to assess brain impairment.[38]

MIBG (metaiodobenzylguanidine) scintigraphy images can be used to directly quantify cardiac sympathetic innervation in various pathologies, including cardiovascular autonomic neuropathies. Innervation asymmetry may be responsible for predisposition to arrhythmias and sudden

death. It can also be used to assess sympathetic reinnervation after adequate treatment.[39]

Laboratory tests

The most important plasma catecholamines in humans are epinephrine and norepinephrine, both reflecting sympathetic activity. Norepinephrine is released in neuronal sympathetic terminals, and a small portion only reaches systemic circulation. Epinephrine, in turn, is released by sympathetic pre-ganglionic stimulation of the adrenal medulla. Plasma epinephrine and norepinephrine respond differently to stressors. While norepinephrine responds more to cold stimuli, epinephrine is more responsive to hypoglycemia and hypotension.[40]

Standing after resting in a lying position, or tilting the patient on the tilt test, results in blood accumulation in the lower limbs, resulting in a drop in cardiac output. Reflex activation of the sympathetic nervous system results, among other actions, in increased release of norepinephrine by terminals of the sympathetic nerves, reflecting an increase of up to 100% in the plasma circulation of norepinephrine in 5 minutes.

Patients with autonomic failure secondary to dysfunction of the sympathetic post-ganglionic neurons may have reduced concentrations of norepinephrine in the supine position. On the other hand, individuals with autonomic failure for any reason often fail to raise their plasma norepinephrine levels when standing or leaning on the tilt test.

This is due to reduced or no triggers of sympathetic efferents in response to orthostatic stimulus. A subnormal increase in norepinephrine on orthostatic stress is a very specific, although not very sensitive, factor of sympathetic response attenuated by baroreflex-sympathoneural failure or sympathetic denervation.[40]

On the other hand, in patients with hyperadrenergic autonomic dysfunction (such as some patients with mitral valve prolapse or some subtypes of postural orthostatic tachycardia syndrome — POTS — there may be an exaggerated supranormal increase in norepinephrine when subjected to orthostatic stress (standing or when tilting).

In neurogenic orthostatic hypotension, caused by autonomic disorders including cardiovascular autonomic neuropathy (CAN), orthostatic increase in norepinephrine is attenuated. Therefore, an increase in plasma norepinephrine smaller than 60% after 5 minutes of orthostasis supports diagnosis of neurogenic orthostatic hypotension.[40]

Other specific laboratory tests may be requested to investigate various etiologies that may potentially cause dysautonomia, depending on the symptoms and clinical suspicion. Pathologies such as diabetes, amyloidosis, renal failure, autoimmune diseases, neoplasms, mainly of the lung, may require specialized investigation.

Peripheral Neuropathy — Warning Sign

The presence of symptoms or diagnosis of peripheral neuropathy may represent a warning sign for Disautonomia investigation. In diabetic patients, more than 50% will have cardiovascular autonomic neuropathy (CAN) when diagnosed with peripheral neuropathy, while almost 100% of patients with CAN will have peripheral neuropathy.

Treatment

Treatment of dysautonomia and particularly orthostatic hypotension (OH), its main clinical symptom in most cases, must follow a progressive approach that involves both non-pharmacological treatment and use of drugs (Figures 3 and 4).[41-44]

The goal of treating patients with OH is to improve debilitating clinical symptoms (specially to reduce the risk of falls) and quality of life, increasing tolerance to longer periods of orthostasis and physical capacity. Having normal blood pressure levels is hardly attainable.

The need for treatment must be based on an individualized analysis of the cases, taking as a reference the severity of the condition and the comorbidities involved. In most cases, particularly in elderly and/or dysautonomic patients, better control of symptoms and vital signs in orthostasis should be sought to help optimize the established therapy.

There is a lack of studies on the treatment of OH, and the existing recommendations are mainly based on small studies. A potential limitation of these studies is that they have not been validated by randomized studies, with a more significant number of patients. Besides, they have the limitation of reflecting mainly the result of acute treatment of OH and, in general, in a heterogeneous group of patients, an aspect that is fundamental since OH involves a range of pathologies that are different to each other in terms of presentation and clinical course.[42-44]

A consensus of experts in neurogenic OH (NOH) has proposed a stepwise treatment based on 4 steps:

(1) evaluating and adjusting pre-existing medications

(2) non-pharmacological treatment

(3) implementing monotherapy

(4) Trying to combine drugs.

According to these authors, there is a recommendation that for each proposed treatment stage there should be a minimum period of 2 weeks of observation to define the symptomatic benefit before migrating to another strategy.[45,46]

Those involved in the treatment of patients with dysautonomia should always remember that educating the patient, family and caregivers about the mechanisms involved in the genesis of OH and the situations of daily activity that can lead to a drop in blood pressure are the cornerstones of clinical treatment. Staying in hot environments, having hot showers, type and intensity of physical effort, prolonged or quickly achieved orthostatic position, drinking alcohol or having large meals, particularly with carbohydrates, can precipitate or worsen the symptoms.

Non-pharmacological treatment

Analysis of the medications in use

Regardless of the etiology of dysautonomia, whenever possible, discontinuation or dose adjustment of drugs that may worsen OH should be considered.[42,43,47] A substantial number of these agents are drugs regularly used by cardiologists.

As the medication is adjusted, it is important to monitor the symptoms of NOH continuously. Some studies recommend using questionnaires created for this purpose.[43,44,47] In cases with a defined indication, antihypertensive drugs with a shorter half-life, preferably with a single nocturnal intake, must be chosen.

Medicines such as nitrates and diuretics, which decrease the preload, must be discontinued or avoided. Other drugs that also worsen or contribute to OH include dopaminergic drugs, anticholinergics, tricyclic antidepressants, α1-blockers (e.g.: tamsulosin) and other antihypertensives.

Non-pharmacological measures

The next step in treatment is the incorporation of a range of non-pharmacological measures in the patient's daily routine, all with the objective of minimizing the symptoms resulting from NOH. From a practical point of view, these measures are incorporated while a careful review of the pharmacological treatment previously in use is conducted.

For patients with syncope, pre-syncope or recurrent falls, postural instability resulting from OH must be eliminated with greater urgency, and patients must be guided on maneuvers that may reduce venous retention in the lower limbs and digestive tract.[48]

Non-pharmacological measures can be used individually, but are most effective when used in combination or during concomitant titration of pharmacological treatments. Although they are cost-effective and can be combined with pharmacological interventions, non-pharmacological instructions may have low compliance by patients.

Increased circulatory volume

Patients with NOH need interventions to normalize or expand blood volume. Many of these patients, especially the elderly, present volume decrease secondary to inadequate intake of oral fluid. This may be due to a voluntary restriction of fluid intake, to avoid common conditions such as urinary urgency in the elderly or in patients with neurological diseases.[49]

Adjusting the volume of fluid intake should also consider the geographical area and climatic fluctuations. Water intake is considered a first-choice "drug" in the treatment of NOH.[49-53]

Also, in acute situations (e.g.: syncope or very symptomatic OH), or when long periods of orthostasis or exposure to heat are expected, rapid water intake is recommended, preferably cold water (500 ml in 2–3 minutes), due to its action in promoting increased sympathetic tone and consequent BP increase.[53-56]

This acute pressure response starts 5–10 minutes after drinking water, peaking at 20–40 minutes, that is, producing an effect that mimics the use of drugs with a fast short-term effect. The effect of this rapid water intake is due to the hypo-osmolar reflex in the portal circulation and can last for up to 1 hour, enabling an improvement in the symptoms of NOH. The intake of other liquids is ineffective in generating a significant pressure response. Proper hydration can produce acute and chronic effects, with a beneficial clinical impact on patients with NOH.[51-56]

Sodium intake

Another important non-pharmacological treatment is monitoring and adjusting the daily supply of salt. Because sodium is considered a negative component of the diet, many patients eliminate or significantly reduce the salt content in the diet, which makes orthostatic symptoms get worse.

For patients with NOH, an intake of 2 to 3 servings of sodium a day (5 to 7.5 g of salt) is recommended. Some cases may require larger intakes, reaching 10 g of sodium. Patients at risk for heart failure, supine hypertension or peripheral edema must be monitored closely as symptoms may get worse and may require adjustments or lower intakes. Excessive salt deprivation should be avoided.[57,58]

Diet

In patients with OH, sympathetic activation is not able to compensate for the accumulation of blood in the splanchnic circulation after a meal. In NOH, vasoconstrictive sympathetic activity is deficient and many patients have significant hypotension after food intake.

In individuals with postprandial hypotension, smaller and more frequent meals are recommended.[59,-60] This type of diet has been shown to be effective in reducing orthostatic symptoms in patients with pure autonomic failure and multisystemic atrophy. There is evidence that a low glycemic diet may have a beneficial effect on OH symptoms. Postprandial hypotension can also be reduced with the caffeine or acarbose.[61]

Anemia leads to decreased blood viscosity and oxygen-carrying capacity with a potential increase in OH symptoms and, therefore, must be prevented and treated.[62] Vitamin B12 deficit may be associated with postural instability and cause OH, being a reversible cause of some polyneuropathies.[63] Therefore, changes in diet, as well as supplementation with vitamins and iron in patients with deficiencies of these minerals can be useful in patients with NOH.

Physical maneuvers to raise blood pressure

OH patients should be informed about simple measures that can be used to increase BP during daily activities. These physical counter-maneuvers include: crossing the legs, squatting and tightening leg, arm, abdomen, bottom or whole-body muscles.[64] These maneuvers increase cardiac preload, with consequent increases in cardiac output, blood pressure and cerebral perfusion.[64]

The most basic maneuver is activation of the calf muscle pump ("anti-gravity" muscles). If venous valves are competent, muscle activation increases cardiac venous pressure and cardiac filling pressure. Even small BP increases can alter self-regulation and prevent presyncope and syncope.[65]

Patients should be warned that sitting or lying down improves symptoms, but they can recur after returning to orthostatic position. Some evidence points to the beneficial effect of voluntary contraction of the lower limbs for 40 seconds after orthostasis.[47,48]

It is also useful to train respiratory counter-maneuvers that facilitate venous return of the abdomen and lower limbs to the

heart. These respiratory maneuvers use slow deep breathing and inspiratory resistance.

Many patients, particularly those with more severe dysautonomia, need help from others to perform physical counter-maneuvers. They should be advised to get up slowly (over 15 seconds or more), as it has been shown to mitigate blood pressure drop.

Physical activity

Physical activity and exercise should be encouraged to avoid poor fitness, which is known to worsen orthostatic intolerance.[66] The mechanisms underlying exacerbation are related to hypovolemia and left ventricular remodeling, leading to deteriorated left ventricular chamber performance. These cardiac abnormalities are reversed by physical training and physical fitness.[67-69]

However, physical exercise, particularly in cases of OH due to dysautonomy, demonstrated that orthostatic posture, immediately after exercising in the supine position, may exacerbate OH in these patients. This observation is not reproducible in healthy individuals.[67-69]

As a result, especially in elderly patients with NOH, physical exercise must be supervised by family members or specialized professionals to avoid injuries or falls. In this subgroup of patients, moderate physical training should be prioritized, especially for the lower limbs and physical exercises that do not generate greater gravitational stress, such as cycling in the supine position or water exercises.

Patients should avoid strenuous exercises due to increased body temperature and peripheral vasodilation, with a consequent risk of orthostatic hypotension.[70,71]

To minimize OH, the patient must be hydrated before and throughout the exercise session and must be warned about the initial risk of OH worsening right after interruption of physical effort.

Avoiding increased body temperature

Increasing body temperature causes peripheral vasodilation. Patients with NOH should avoid situations that cause an increase in body temperature, such as high-intensity physical exercise, exercise in environments with high temperature and humidity, saunas or hot baths.[72] Also, as individuals with autonomic failure have an impaired thermal-regulatory capacity, they have higher risk of hyperthermia.

Head-up tilt sleeping

Head-up tilt sleeping is an important measure. It can be done by sliding a wedge under the mattress or by placing blocks under the legs under the bed head so that the patient's head is 20 to 30 cm higher than the feet, reducing supine hypertension. Smaller tilt angles may not be as successful. Folded pillows placed under the head may not be enough.

Supine hypertension commonly leads to increased nocturia and nocturnal volume depletion. This increase in nocturnal diuresis decreases by raising the bed head. Also, although small, increase in nocturnal gravity stress maintains activation of the renin-angiotensin-aldosterone system, allowing higher pressure in the morning.

The effectiveness of this intervention was questioned in a recent randomized study. However, this study failed to make any distinction between the causes of OH and did not properly monitor hydration and the bed head raising degree, which may have contributed to a negative result. As a result, it should be recommended that at least patients with autonomic failure be told to head-up tilt sleeping. This specific action is not exempt from adverse effects, and may be associated with ankle edema and sliding of the body in bed and consequent feet pain.[73-75]

Compressive clothing

Elastic stockings to generate some pressure gradient may be beneficial in the treatment of OH. Compression stockings or bandages reduce the accumulation of peripheral blood in the lower limbs, decrease orthostatic hypotension and reduce symptoms.

Compression must preferably extend to the waist, as most of the stasis occurs in the splanchnic circulation, which contains up to 25% of the resting blood volume. It is necessary to put on the stockings in the morning while lying down, before getting out of bed.

These non-invasive procedures are usually challenging, of low acceptability and require help from third parties, especially in elderly patients and those with neurological diseases. The long-term benefits of these interventions have not been studied. Some authors suggest that an acceptable alternative, due to the low long-term adhesion of compressive clothing, would be wearing cycling clothing, which can offer satisfactory abdominal compression.

In any case, the association between compression techniques (particularly of the abdomen) and physical counter-maneuvers has been shown to be very effective in patients with neurogenic etiology.

An increase in abdominal pressure of 20–40mmHg promoted by abdominal straps combined with physical counter-maneuvers of lower limb contraction results in a significant increase in pressure response to gravitational stress. Studies evaluating non-pharmacological treatment of dysautonomia have found evidence on the use of compressive clothing.[76-79]

Pharmacological Treatment

Addition of pharmacological treatment may be necessary in patients with severe OH when non-pharmacological approaches are insufficient to prevent pre-syncopal or syncopal symptoms (figures 3 and 4). This requires probable patient diagnosis, such as NOH, POTS or chronic fatigue syndrome, to be properly considered.

Previous hypertension or supine hypertension, common in patients with dysautonomia and an underlying cardiovascular disease, should also be considered. The treatment of OH is challenging because of the few therapeutic options. Only midodrine and droxidopa (approved in the USA and Japan) have evidence from randomized clinical trials supporting their use in the treatment of OH. Neither of these two drugs is normally available in Brazil.

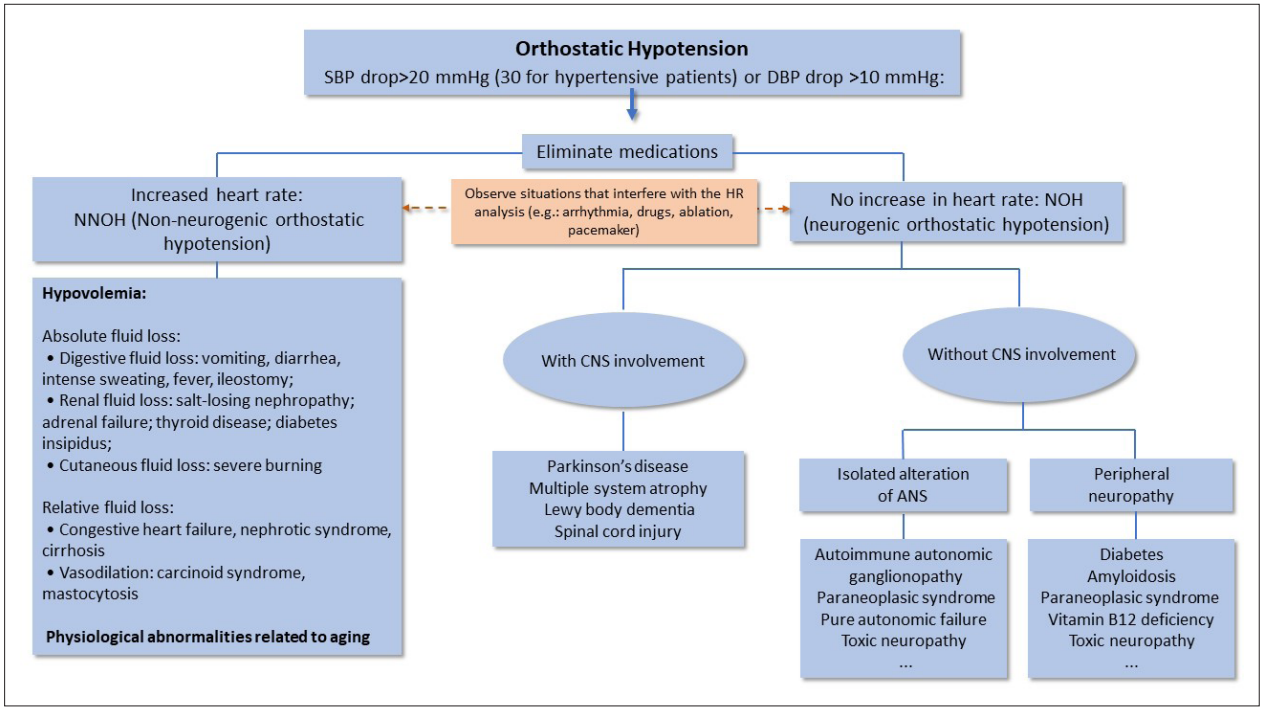


Figure 3 – *Flowchart on the management of orthostatic hypotension and its differential diagnoses. Divided into groups with increased heart rate in orthostasis, usually observed in OH due to hypovolemia or medication and without increase, as seen in neurogenic hypotension, excluding the use of bradycardic drugs or patients with sinus node disease.*

Therapeutic Approach to Dysautonomia
Neurogenic Orthostatic Hypotension - Non-Pharmacological Interventions: Reduced venous retention in lower limbs
• Physical counter-maneuvers (e.g.: crossing the legs, squatting, moving the legs, hand compression); Slow change in position • Compressive clothing (elastic stockings, preferably waistline-high — 30–40 mmHg and/or abdominal straps 20–30 mmHg)
Increased central blood volume
• Increasing sodium intake (2-3 g/day or 5–7.5 g NaCl) or higher doses, in the absence of supine hypertension, edema or heart failure • Increasing water intake (2–3 liters/day) • Head-up tilt sleeping (20-30 cm)
Other lifestyle changes
• Learning to identify prodromal symptoms of orthostatic hypotension • Light, fractional meals • Regular daily physical activity, such as water exercises, sitting bicycle with support, short-term walks with a companion and gradual increases • Avoiding alcohol and carbohydrate-rich foods • Avoiding situations that may increase body temperature (such as sauna, hot bath) • Drinking 400–500 ml of water before getting up or after prolonged decubitus or before exercising (acute osmotic effect) • Head-up tilt sleeping • Avoiding drugs that may worsen the condition
Pharmacological interventions:
• Reviewing the whole pharmacological therapy, avoiding drugs that may worsen orthostatic hypotension • Increasing intravascular volume – Fludrocortisone (0.1–0.3 mg/day – once a day)/Erythropoietin (25–75 U/Kg — 3 times a week) • Increasing vascular resistance – Midodrine (2.5–10 mg, 3 times a day)/Droxidopa (100–600 mg, 3 times a day) / Atomoxetine (18–40 mg per day) / Pyridostigmine (30–60 mg, 2 to 3 times a day) / Pseudoephedrine (30 mg, 3 times a day) / Ergotamine / caffeine (1 mg/100 mg/day) • Octreotide (12.5–25 mcg subcutaneously), 30 min to 1 hour before a meal), especially for postprandial OH or Acarbose 100 mg.
Combined therapy
• Fludrocortisone (0.1–0.3 mg/day, orally) and midodrine (2.5–10 mg, orally — 3 times a day)

Figure 4 – *Therapeutic approach to dysautonomia. Source: Author.*

There are no comparative studies to guide the initial choice of the drug in NOH. Selection of a medication or another, in many situations, will be related to the clinician's preference and experience and the patient's possibility of having access to the medication. Severity and comorbidities (especially heart or kidney failure) should always be taken into account.

These agents can increase BP and blood volume, which may worsen supine hypertension. As a result, the expected improvement in orthostatic hypotension (and the decreased risk of syncope and falls) must be weighed against the long-term risks of hypertension.

Other treatment challenges are the limited availability of clinical evidence and the lack of comparative effectiveness research studies. Below, we present an overview of the main drugs used in the treatment of OH and the recommendations of use.[79]

Midodrine

Midodrine was the first drug approved by the U.S. Food and Drug Administration (FDA) for OH. It is a prodrug that is quickly converted into its active metabolite, desglimidodrine. This is a selective α1-adrenergic agonist, with short half-life (peak action at 1 hour) and duration of action of about 3–4 hours. Midodrine has been shown to significantly increase blood pressure in orthostasis, while decreasing symptoms of orthostatic intolerance.

A recent meta-analysis also found that midodrine improves clinical outcomes with minimal significant side effects. The dose usually starts at 2.5 mg, and may get to 10–15 mg per dose, up to 3 times a day. Due to the short half-life, a typical dosing schedule is every 4 hours, starting on waking up. It should not be administered at bedtime and patients should avoid lying down for 4 hours after the last dose of midodrine to avoid worsening of supine hypertension.[79-81]

Given the short half-life, it can also be used as needed, before specific activities related to symptomatic orthostatic hypotension. Side effects of midodrine include supine hypertension, piloerection, tingling of the scalp, urinary urgency or retention and headache.

Midodrine is contraindicated in cases of severe heart disease, bradycardia, history of angina, closed-angle glaucoma, severe occlusive arterial disease, thyrotoxicosis, pheochromocytoma, severe renal failure, Raynaud's disease and proliferative diabetic retinopathy. Care should also be taken in patients with heart failure and chronic renal failure.

Fludrocortisone

In patients without hypertension or heart failure, fludrocortisone is included in the treatment based on expert opinion and it is the most widely used, especially in countries that do not have the other recommended drugs. Fludrocortisone is a synthetic mineralocorticoid that increases intravascular volume and renal sodium reabsorption. The long-term effects of fludrocortisone on BP, however, are attributed to the increased sensitivity of blood vessels to noradrenaline and angiotensin II. The starting dose is typically 0.05 mg per day and can be increased to 0.3 mg (in a single or divided dose).

Onset of action occurs in 3 to 7 days. Its side effects may include hypokalemia, headaches, peripheral edema, heart failure and supine hypertension. At higher doses, patients may be at increased risk of hypothalamic-pituitary-adrenal axis suppression. 30% of patients stop using the drug due to side effects.

In patients with pre-existing supine hypertension, fludrocortisone is generally not chosen as a first-line medication, with midodrine being the most appropriate one. Formal clinical evidence supporting the use of fludrocortisone for the treatment of neurogenic OH is scarce.[82-84]

Droxidopa

The FDA has recently approved droxidopa for the treatment of neurogenic orthostatic hypotension in the United States, especially in Parkinson's disease, multisystemic atrophy and pure autonomic failure. Droxidopa is a synthetic prodrug that is converted into norepinephrine in the brain and peripheral tissues. Circulating levels of norepinephrine increase in 6 hours after droxidopa. The drug has a plasm peak between 1-4 hours, with a average of 2 hours in healthy individuals.

Droxidopa is well tolerated and improves orthostatic tolerance in NOH controlled trials (100–600 mg VO, 3 times a day). Similar to midodrine, droxidopa should not be taken within 5 hours before bedtime. Caution is recommended in patients with congestive heart failure and chronic renal failure. Its side effects include headache, dizziness, nausea and fatigue.[85]

Other medications

Other drugs include pseudoephedrine, atomoxetine (norepinephrine reuptake inhibitor), yohimbine (α2-adrenergic receptor antagonist), octreotide (somatostatin analogue), ergotamine, erythropoietin and pyridostigmine (cholinesterase inhibitor).[86-89]

Atomoxetine is a norepinephrine transporter inhibitor approved for the treatment of attention deficit hyperactivity disorder (ADHD). However, in patients with autonomic impairment who have intact peripheral noradrenergic function, this medication can cause a powerful peripheral vasoconstriction, leading to blood pressure increase. This medication is little effective in pure autonomic failure (PAF) due to peripheral impairment of the noradrenergic system.

Pyridostigmine, an acetylcholinesterase inhibitor that increases availability of acetylcholine in nerve endings is supposed to prevent OH. However, it does so by increasing sympathetic nerve activity in response to orthostatic stress, causing changes in baroreceptor sensitivity. It is probably more useful in less severe patients with residual sympathetic function and has the advantage of not worsening supine hypertension. A study has found it is less efficient than fludrocortisone in the OH of Parkinson's disease, but causes less supine hypertension, although this increase in peripheral supine hypertension is not accompanied by a similar increase in central blood pressure with fludrocortisone.[90,91]

Acarbose, an agent that prevents glucose absorption in the small intestine, decreases the release of gastrointestinal hormones and delays gastric emptying when administered

20 minutes before a meal. This pattern has been shown to be efficient in those cases of postprandial hypotension. It is contraindicated for patients with diabetic ketoacidosis, cirrhosis, inflammatory bowel disease, ulcerative colitis, intestinal obstruction or any chronic intestinal disease that may disrupt digestion or absorption.

Caffeine (200–250 mg or 1 cup of 200 ml coffee per day) in patients who are not chronic users may help by inhibiting peripheral vasodilation. Therefore, it may increase blood pressure in orthostasis.

A recent study showed that dihydroergotamine, in combination with caffeine, can be used as an alternative treatment in patients with autonomic failure and without underlying vascular coronary artery disease.[87]

Combined pharmacological treatment

There is little data to determine the effectiveness and safety of different combinations of therapy compared to monotherapy for OH. It is recommended to seek the maximum tolerable dose of a single agent and then, if no symptomatic benefit is obtained, consider switching to a different therapy or adding a second agent and titrate from the lowest effective dose.

The most common association in refractory cases is between midodrine and fludrocortisone. The use of water, salt and the preventive measures discussed can also be effective when combined with drugs. A combination with other drugs is possible, always paying attention to dose flexibility (particularly the dose of drugs with short half-life such as midodrine) and strict control of adherence to non-pharmacological treatment.[92,93]

Peculiarities of the management of supine hypertension and postprandial hypotension

Supine and nocturnal hypertension

In patients with OH, especially NOH, we commonly observe an association with supine and nocturnal hypertension, with the severity of nocturnal hypertension correlating with the magnitude of OH. Supine hypertension is distinct from essential hypertension, since most patients are normotensive while sitting and can be severely hypotensive while standing. Approximately 50% of patients with PAF and MSA have supine hypertension.

Evaluation of supine and nocturnal hypertension should be performed routinely in patients with NOH, as its presence is a limiter for therapeutic options due to the possibility of adverse effects. ABPM can also be used for diagnostic evaluation and clinical follow-up.

In most patients, there are strong reasons to prioritize the treatment of NOH over supine hypertension. Symptomatic OH carries a variety of posture-related symptoms including dizziness, pre-syncope or syncope, fatigue, cervical spine pain, weakness and visual impairment on orthostasis. All symptoms that can contribute to increased occurrence of falls must be well evaluated, as falls represent some of the most common causes of hospitalization, and it leads to high morbidity and mortality.

To prevent and treat supine hypertension, one should:

(1) head-up tilt sleeping;

(2) Have carbohydrate-rich meals just before going to bed;

(3) Avoid liquids before going to bed;

(4) Avoid supine position during the day, especially those patients wearing compression garments or vasopressor drugs.

There are no drugs approved for the treatment of supine hypertension, but there are several potentially useful agents.

In patients who still have some sympathetic tone, a central alpha-2 agonist (clonidine) reduces sympathetic flow when administered late in the afternoon, without exacerbating orthostatic hypotension during the day. It is important to avoid the use of long-acting diuretics and antihypertensive drugs, even if they can control supine hypertension.[89,92,93]

Supine hypertension therapy in dysautonomia

The cut-off point for BP to start antihypertensive therapy has not been defined and treatment decisions must be made individually. However, antihypertensive drugs may be prescribed with caution if nocturnal BP is predominantly ≥160/100 mmHg (table 2) with administration of short-acting drugs.[89,92,93]
Supine hypertension is different from essential hypertension, since most patients are normotensive while sitting and can be severely hypotensive while standing.

Postprandial hypotension

Postprandial hypotension (PPH) is commonly observed in patients with OH, but it can occur in isolation, particularly in

Table 2 – Treatment of Supine Hypertension

Drugs*	Mechanism of action	Usual dose
Captopril	Angiotensin-converting enzyme inhibitor	25 mg at night
Clonidine[a]	Central alpha-2 agonist	0.1–0.2mg after a night meal
Hydralazine	Peripheral smooth muscle relaxation	10–25 mg at night
Losartana	Angiotensin II receptor antagonist	50 mg at night
Nitroglycerin (patch)	Vasodilator	0.1 mg/h (patch — remove in the morning)

**Short-lived antihypertensive drugs should preferably be used to treat supine hypertension. Administration should only be done at night. Remember that many of these medications are usually taken 2–3 times a day and, if taken inadvertently this way, or while awake, they may worsen the symptoms of NOH*
a - Use of clonidine increases the risk of morning hypotension.

institutionalized elderly patients. The mechanisms leading to blood pressure drops are not clear. Postprandial hypotension and its extension are favored by glucose intake.

Treatment strategies include: small, frequent meals with low carbohydrate content; drinking water before and during the meal (it is recommended to take 400–500 ml of cold water 30 minutes before meals); minimizing or preferably avoiding alcohol intake; eliminating iatrogenic causes (administration of antihypertensive drugs between meals and not during meals) and caffeine (200–250 mg or 200 ml of coffee), and acarbose (100 mg).

Author Contributions

Conception and design of the research: Rocha EA, Elias Neto J; Acquisition of data, Analysis and interpretation of the data, Writing of the manuscript and Critical revision of the manuscript for intellectual content: Rocha EA, Mehta N, Távora-Mehta MZP, Roncari CF, Cidrão AAL, Elias Neto J.

Potential Conflict of Interest

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

Sources of Funding

There were no external funding sources for this study.

Study Association

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

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Persistent Aneurysm of the Right Coronary Artery, Even after Correction of a Fistula with the Right Ventricle

Edmar Atik

Instituto do Coração do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, São Paulo, SP - Brazil

Introduction

Among the coronary-cavitary fistulas, the most commonly found type corresponds to that involving the right coronary artery and the right cardiac cavities, with corresponding volume overload due to arteriovenous deviation.[1] The clinical manifestations correspond to heart failure, angina with myocardial infarction and arrhythmias. A continuous murmur easily suggests the diagnosis of a congenital defect, which is consolidated by the imaging examinations. Other fistulas should always be suspected in the differential diagnosis, such as the patent ductus arteriosus, aortopulmonary window, systemic-pulmonary collaterals, and fistulas of the sinus of Valsalva with the right ventricle cavity. Cardiac surgery and / or percutaneous interventions comprise the therapeutic basis for fistula resolution. Little is said, however, about the evolution after the procedures, given that the previous coronary dilation persists and may constitute another evolution problem in the longer term.

This aspect comprises the main reason for this assessment.

Case description

Clinical data: Heart murmur auscultated at two days of age was due to a small 3-mm diameter interventricular septal defect, evidenced at the time by the echocardiogram. At a few months of life, the murmur was no longer heard in the presumption of spontaneous closure of this defect. At 8 months of age, a continuous murmur was heard on the right external border for the first time. On this occasion, the echocardiogram disclosed the presence of a fistula between the dilated right coronary artery, with a diameter of 6.5 mm, and the right ventricular cavity at the inlet portion. The patient remained asymptomatic, with a slightly enlarged cardiac area on the chest X-ray and with a mild conduction disturbance through the right branch on the electrocardiogram. This fistula was surgically sectioned at 10 months of age, without extracorporeal circulation. The patient had a good clinical evolution after the age of 14 and remained asymptomatic.

Keywords

Arteriovenous Fistula/surgery; Artery Coronary Cavitary, Fistula/surgery; Clinical Evolution; Coronary Fistula Right; Ventricular Dysfunction, Right; Heart Defects, Congenital.

Mailing Address: Edmar Atik •
Rua Dona Adma Jafet 74 cj 73. Postal Code 01308-050, São Paulo, SP - Brazil
E-mail: edmar.atik@incor.usp.br
Manuscript received September 11, 2020, revised manuscript October 14, 2020, accepted October 14, 2020

DOI: https://doi.org/10.36660/abc.20201010

Physical examination: good general condition, eupneic, acyanotic, normal pulses in the four limbs. Weight: 54 Kg, Height: 170 cm, BP: 110/60 mm Hg, HR: 68 bpm, oxygen saturation = 98%. Aorta not palpable at suprasternal notch.

Precordium: apical impulse was not palpable, without systolic impulses on the left external border. Normal-intensity heart sounds, mild and discrete systolic murmur, ejection type, +/4 intensity, on the left sternal edge. Liver was not palpable and lungs were clear.

Complementary Exams

Electrocardiogram: sinus rhythm, PR: 0.17, QRS: 0.08, with polyphasic complexes in V1 (rsr´s´) and RS in V6, with thickened S waves in the left precordial area, indicative of final conduction disturbance by the right branch. The T wave was isoelectric in V1. AP= +60º, AQRS= +120º, AT= +40º (Figure 1).

Chest radiography: normal cardiac area (cardiothoracic index = 0.46) with rectified middle arch, normal aortic arch and normal pulmonary vascular network (Figure 1).

Echocardiogram: Cardiac cavities were normal, with LV = 50, LA = 37, RV = 26 mm, LVEF = 68%, ventricular septum and LV posterior wall = 8 mm. The right coronary artery was dilated, measuring 9 mm in diameter (Z score = +12.6) (Figure 2).

Exercise test: it did not disclose changes in ventricular repolarization with T-wave remaining positive and without changes in the ST-segment, even with increased heart rate. There were no arrhythmias during the examination.

Myocardial scintigraphy: there was no demonstration of myocardial ischemia until it was induced by stress at 171 bpm.

24-hour Holter: heart rate ranged from 53 to 150, with an average of 83 bpm. Rare ventricular extrasystoles were observed during the examination.

Angiotomography of the coronary arteries: dilated right coronary artery, with a diameter of 9x12 mm in the ostium, in an extension of 30 mm, being occluded in the middle third (surgical ligation). The right marginal artery was of minor importance and the posterior descending artery was slightly opaque. The left coronary artery was normal. The anterior descendant artery outlined the apex and the other arteries had no luminal obstruction.

Cardiac catheterization and angiography prior to surgery: intracavitary pressures were normal. RA = 8; RV = 30/4-11; PT = 28/15/19; LV = 70/2-10; Ao= 65/30/42 mm Hg. The angiography in the aorta and selective procedure in the coronary arteries showed marked right coronary artery dilation that ended in the lateral wall of the right ventricle (figure 2).

Clinical Diagnosis: Fistula of the right coronary artery in the right ventricular inlet region with mild clinical manifestation

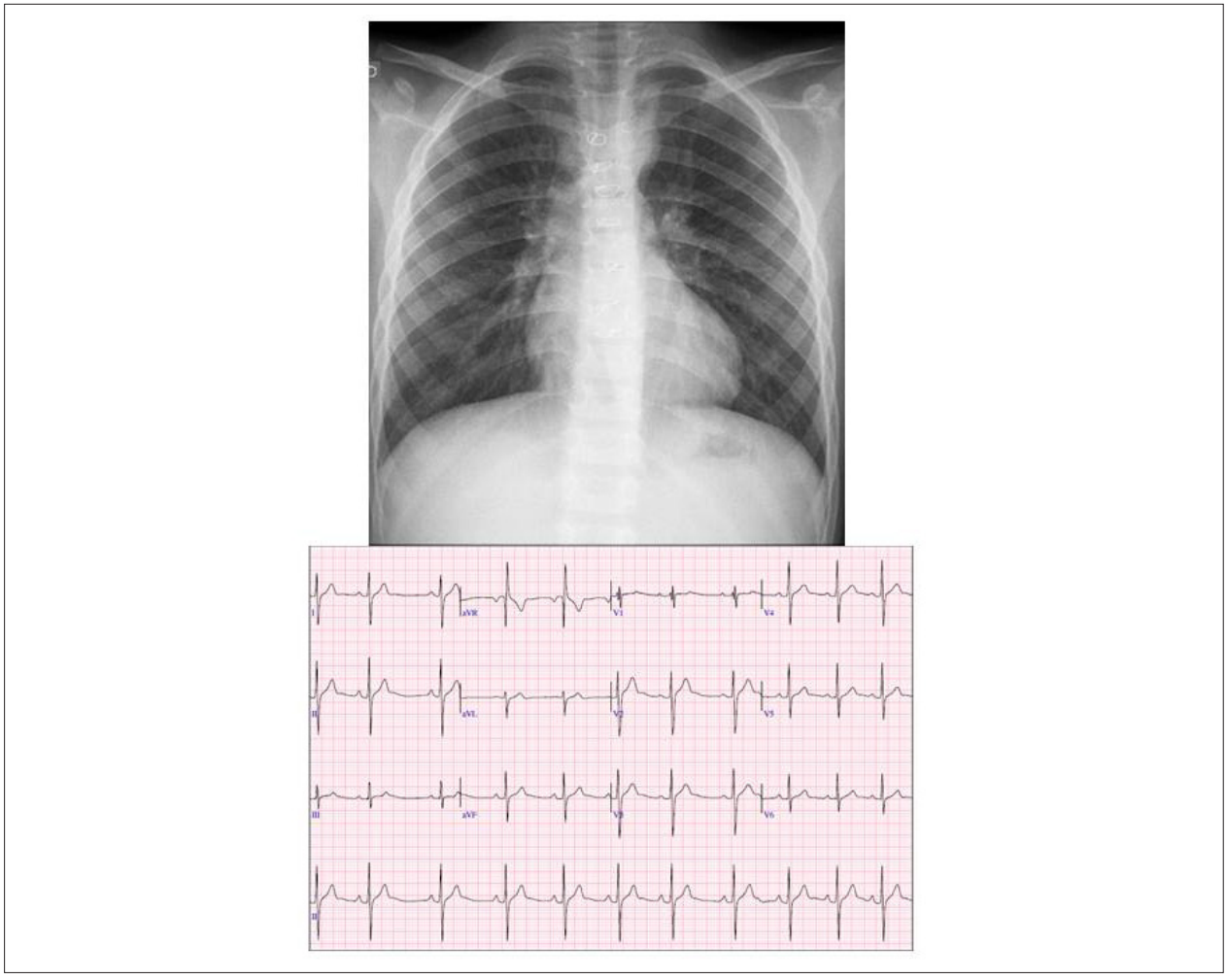

Figure 1 – *Chest X-ray highlights normal cardiac area and pulmonary vascular network. Electrocardiogram highlights the signs of conduction disturbance through the right branch, with a polyphasic V1 complex in V1 and thickened S waves, without cavitary overload.*

but marked coronary dilation, which persisted in the long term after surgical correction.

Clinical characteristics

A) Clinical reasoning: in this symptom-free infant, the clinical elements guided the diagnosis of arteriovenous fistula to the right cavities, in the atrium or ventricle. They were externalized by continuous murmur on the right sternal edge, slightly enlarged cardiac cavities and pulmonary vascular network on chest X-ray and also with conduction disturbance at the right branch on the electrocardiogram. This impression was consolidated by the echocardiogram, in a clear demonstration of the dilation of the right coronary artery, confirmed by coronary angiography.

B) Differential diagnosis: continuous murmur, when heard, suggests the presence of an arteriovenous fistula in some organic location. Thus, if present on the upper left sternal border, it suggests the presence of a patent ductus arteriosus. If it is audible on the left outer edge, but in a lower region, for the aortopulmonary window. In the region of the armpit for coronary fistulas to the left atrium and also on the right sternal border for coronary fistulas or even from the ascending aorta to the right cardiac cavities. If the continuous murmur is audible on the back, to the right or left of the spine, it suggests the presence of systemic-pulmonary collaterals that occur in pulmonary atresia associated with ventricular septal defect.

Management: There was an indication for immediate relief from the overload of the right heart cavities, as soon as the coronary anomaly was diagnosed, still without symptoms and with normal ventricular function. The surgical intervention was successful at 10 months of age, simply performed through surgical ligation of the dilated right coronary artery, and without extracorporeal circulation. The subsequent evolution was adequate, with preservation of good dynamic condition and good cardiac function. However, there was a persistence of aneurysmatic dilation of the right coronary artery over a 14-year period, suggesting the presence of congenital changes in the structure of the arterial wall, which will undoubtedly persist, raising the concern of complications that may arise from it as a result.

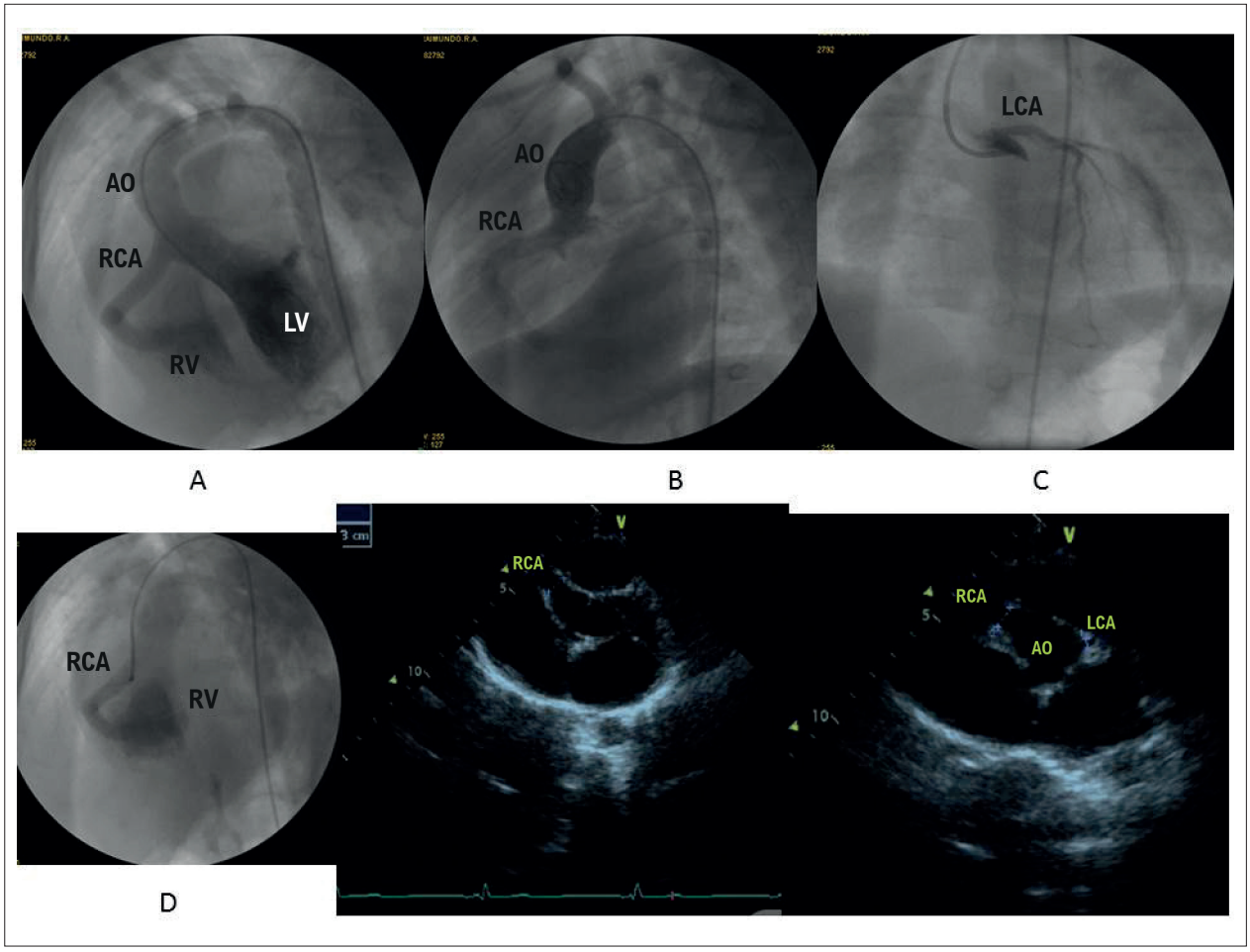

Figure 2 – *Angiography highlights the dilated right coronary artery in connection with the right ventricular cavity in A, B and D and the normal-sized left coronary artery in C, in the period prior to cardiac surgery. Recent cross-sectional echocardiogram images also show the large dilation of the right coronary artery in the emergence of the aorta. Ao: aorta; RCA: right coronary artery; LCA: left coronary artery; RV: right ventricle; LV: left ventricle.*

Discussion

The most common site of the coronary fistula is the right ventricle (41%), being found in the right atrium in 26%, left atrium in 5%, left ventricle in 3%, coronary sinus in 7%, superior vena cava in 1% and in pulmonary arteries in 17%.[1] The fistula in the right coronary artery is the most often affected (50%) and causes symptoms, whereas the left coronary artery (42%) usually evolves without symptoms. These fistulas are generally not associated with other heart diseases, and most of them are simple and can be more rarely multiple. Clinical exteriorization is manifested by continuous murmur, cavity volume overload with heart failure, arrhythmia, myocardial infarction and syncope. In some cases it can even evolve with pulmonary arterial hypertension. Surgical management by ligation or intervention by cardiac transcatheterization embolization are the most often accepted.[2] In the subsequent evolution, the hemodynamic disorder normalizes. However, this anomaly concerns the persistence of coronary artery dilation over time, even after adequate correction of the defect. Hence, the use of platelet anti-adhesive agents has been recommended in these patients, in addition to the routine referral to periodic medical controls. During this evolution, likewise, the aneurysmatic artery wall should always be evaluated in order to prevent possible rupture of this structure. Infectious endocarditis is also described in some cases, thus constituting another evolutionary concern.

Careful descriptions of the evolution after corrective interventions for coronary fistulas are rare,[3-6] but conclusive of coronary obstruction phenomena due to thrombosis, in addition to the continuation of coronary dilation and hence, even the need for these patients to use anticoagulants.[7] As a premise of this therapeutic approach, in a group of 13 of these patients followed after surgical correction, nine of them received anticoagulants.[7] It is observed that the greatest possibility of an unfavorable evolution, due to the greater coronary dilation, lies in the group of patients with more distal fistulas, and whose diagnosis has been late.

In short, the follow-up after the correction of cavitary coronary fistulas must be rigorous, with coronary evaluation by anatomical and functional viewpoints, through sequential, routine and rigorous assessments.

Author Contributions

Conception and design of the research, Acquisition of data, Analysis and interpretation of the data, Writing of the manuscript and Critical revision of the manuscript for intellectual content: Atik E.

Potential Conflict of Interest

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

Sources of Funding

There were no external funding sources for this study.

Study Association

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

Ethics approval and consent to participate

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

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Reduction in the Number of Patients with Suspected and Confirmed Acute Coronary Syndrome during the early months of the Covid-19 Pandemic: Analysis of a Brazilian Network

Pedro Gabriel Melo de Barros e Silva,[1,2] Ana Amaral Ferreira Dutra,[3] Adriana Bertolami Manfredi,[4] Pedro Paulo Nogueres Sampaio,[5] Celso Musa Correa,[6] Hemilo Borba Griz,[7] Daniel Setta,[3] Valter Furlan[1,2]

Hospital Samaritano Paulista,[1] São Paulo, SP - Brazil
Cardiologia Americas,[2] São Paulo, SP - Brazil
Hospital Pró-Cardíaco,[3] Rio de Janeiro, RJ - Brazil
Hospital Alvorada Moema,[4] São Paulo, SP - Brazil
Hospital Samaritano Botafogo,[5] Rio de Janeiro, RJ - Brazil
Americas Medical City,[6] Rio de Janeiro, RJ - Brazil
Hospital Santa Joana Recife,[7] Recife, PE - Brazil

Introduction

The first reports of infections by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) occurred in December of 2019 in Wuhan, China.[1,2] This disease (named as coronavirus disease-2019, Covid-19) rapidly spread globally and, on March 11, 2020, the World Health Organization (WHO) declared the state of pandemic.[1,2] Lockdown was a common recommendation for countries affected by the outbreak.[3]

Despite all the attention put on Covid-19 by the health authorities, other diseases could also be impacted by this new circumstance. Rates of acute cardiovascular diseases changed in countries such as Italy and United States, with a reduction in hospital admissions.[4-6] Previous national data regarding acute coronary syndrome (ACS) is already well and largely described, but these studies did not include the Covid-19 period.[7,8] Thus, despite the fact that Brazil was the second most affected country when it comes to number of Covid-19 cases,[9] the impact in hospital admissions due to suspected or confirmed ACS is still not well defined in both private and public Brazilian healthcare systems.

The objective of this report was to compare the number of patients with suspected and confirmed ACS before and during the early months of the Covid-19 pandemic in a network of private hospitals in Brazil.

Methods

Study design

Analysis of a registry of patients included in the same Chest Pain Protocol in a network of 16 hospitals in 6 different States in Brazil. The study was approved by the institutional review board (20710119.4.0000.5533).

Study participants and study variables

In 2019, a private network of hospitals implemented a Chest Pain Protocol aiming to standardize investigation and treatment of patients with suspected symptoms of ACS and to provide metrics for quality improvement initiatives. Subjects were included in the Chest Pain Protocol based on the following criteria: acute chest pain regardless of risk factors and/or anginal equivalent symptom, such as shortness of breath (dyspnea), in patients at high cardiac risk (age >65 years old or history of risk factors). Patients with a confirmed diagnosis of ACS were classified according to presence or absence of ST-elevation. The same criteria were used before and during the Covid-19 outbreak for inclusion in the Chest Pain Protocol. The treatment options were also the same in both periods, that is, preference for primary percutaneous coronary intervention in cases of ST-elevation myocardial infarction (STEMI). The only differences were regarding the routine use of personal protective equipment (PPE) and the location for investigation according to Covid-19 probability, since patients with infectious or respiratory symptoms were evaluated in specific units.[10] Clinical outcomes of in-hospital mortality and low ejection fraction (EF<40%) were also routinely collected from all ACS patients in both periods.

The variables related to the first three months of Covid-19 outbreak in Brazil (March to May, 2020) were compared to those of the same period in 2019, and also to the two months just before the Covid-19 outbreak in Brazil (January and February, 2020) and the average of previous 12-month results. These different comparisons were chosen so one could assess a larger number of cases in a longer period of observation and also to avoid seasonal variations that may occur along different periods of a calendar year.

Statistical analyses

Categorical variables were reported as absolute and relative frequencies, while continuous variables were described as mean and standard deviation (SD). Groups were compared by the t-test for continuous variables and the Chi-square test for categorical variables. P values were two-tailed, and values

Keywords

Hospitals, Public; Chest Pain; Hospitals, Private; Acute Coronary Syndrome Pandemics; Epidemiology; Comparative Study.

Mailing Address: Pedro Gabriel Melo de Barros e Silva •
Hospital Samaritano Paulista - R. Dr. Fausto Ferraz, 204-232. Postal Code 01333-030, Bela Vista, SP – Brazil
E-mail: pgabriel@prestadores.samaritanopaulista.com.br
Manuscript received August 05, 2020, revised manuscript October 26, 2020, accepted November 11, 2020

DOI: https://doi.org/10.36660/abc.20200873

below 0.05 were considered statistically significant. The analysis was performed using the R software, version 3.6.1 (R Foundation for Statistical Computing).

Results

Analysis of patients with Suspected ACS before and during the early months of the Covid-19 pandemic

The mean age (52.9 ± 7.2 vs. 53.2 ± 6.9; P =0.16) and percentage of women in the samples (45.3%, 749/1,653 vs. 46.9%, 1,427/3,040; P= 0.29) did not change comparing patients with suspected ACS in the early months of Covid-19 with the same period in the previous year (March to May, 2019). The number of patients seen to the emergency department with suspected ACS symptoms (and included in the Chest Pain Protocol) dropped in the first three months of the pandemic (Figure 1). This decrease was more pronounced in the first two months in Sao Paulo and Rio de Janeiro, while it was more gradual in the hospitals from the Northeast of Brazil (Figure 1). In the Federal District, the curve did not show a relevant change during the start of the pandemic, but the analysis was limited to only one hospital (Figure 1). Overall, the monthly average of patients with suspected symptoms of ACS in the first three months of the pandemic reduced 42.1% compared to the previous 12 months (934.0 ± 81.2 vs. 541.3 ± 134.7; $p < 0.01$), 46.6% compared to the same three months in 2019 (1013.3 ± 74.2 vs. 541.3 ± 134.7; $p < 0.01$), and 39.6% compared to January and February of 2020 (895.0 ± 4.2 vs. 541.3 ± 134.7; $p = 0.03$).

Analysis of Patients with Confirmed ACS before and during the Early Months of the Covid-19 pandemic

Comparing the first three months of the Covid-19 outbreak with the monthly average in the 12 previous months, a reduction of 36.5% in the number of ACS patients was seen, being more pronounced in non-ST elevation ACS (Table 1). These results were similar to those of three international reports (Table 1). The rates of In-hospital mortality in this Brazilian network in the 12 previous months were also checked against the current ones and, unlike the Italian Registry's data, they were not higher (Table 1). In spite of no increase in mortality, the percentage of patients being discharged after an ACS with low ejection fraction was higher in the first three months of the pandemics when compared to the 12 previous months (7.1%, 127/1,777 vs. 11.1%, 34/306; p = 0.02). During 15 months of analysis (March, 2019 to May, 2020), all eligible patients with ACS received double antiplatelet therapy and all STEMI patients received reperfusion therapy. The mean door-to-balloon time of the 12 previous months did not change when checked against that of the early months of the Covid-19 pandemic (70.3±18.1 vs.72.1±19.8; p=0.60).

Discussion

This paper aimed to evaluate the numbers related to ACS in Brazil, including the number of patients seeking medical care and the rate of confirmed diagnosis and major clinical outcomes. We found a reduction not only in the number of patients with confirmed ACS diagnosis, but also in the number of patients seeking medical care due to suspected ACS. Most of the previous publications were focused on patients with confirmed diagnosis, not on clinical suspicion.[4-6] This varied according to the region, being more pronounced in the first two months in Sao Paulo and Rio de Janeiro, with a more gradual decline in the northeast of Brazil. This probably stems from the total number of cases of Covid-19, which was more pronounced in Sao Paulo, especially in the early phase of the pandemic.

The data identified in this network of 16 hospitals from six different States reinforce the findings from previous international reports about reduction of in-hospital ACS diagnosis. The drop in the number of confirmed cases may indicate that more severe cases that did not immediately seek medical care may have been fatal outcomes out of the hospital. This was identified in previous publications,[11,12] but could not be assessed in our national database, since it includes only in-hospital information.

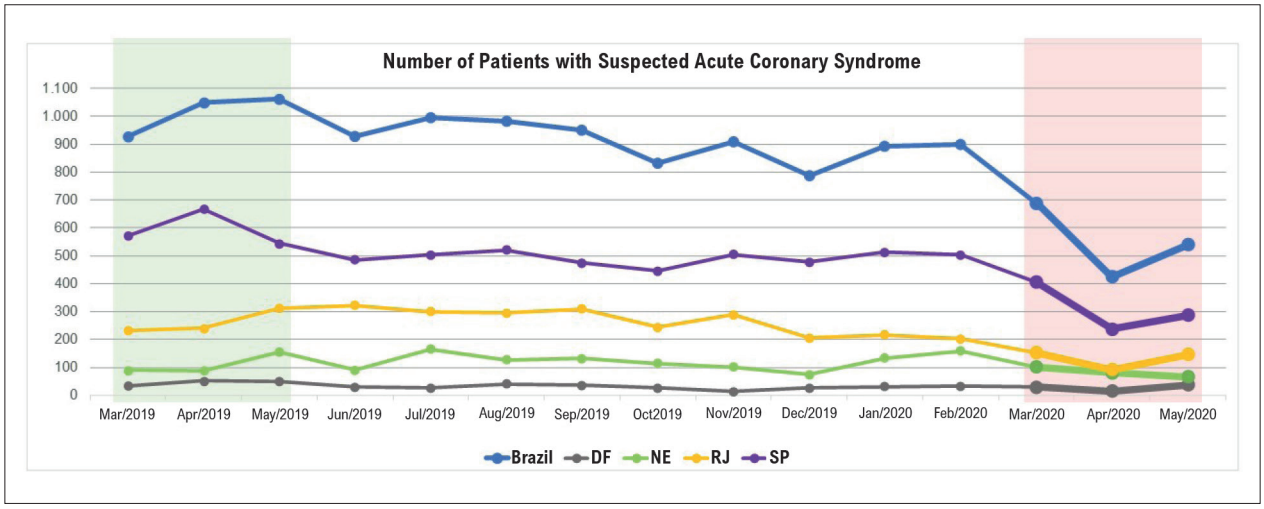

Figure 1 – *Number of patients with suspected Acute Coronary Syndrome before and during the first three months of the Covid-19 outbreak in Brazil (overall and in four different regions). DF: Federal District (1 hospital); NE: Northeast (3 hospitals from 3 different States: Pernambuco, Rio Grande do Norte and Ceará); RJ: Rio de Janeiro (4 hospitals); SP: São Paulo (8 hospitals).*

Table 1 – Relative changes in Acute Coronary Syndrome diagnoses and in-hospital mortality before and during initial period of Covid-19 outbreak in the current analysis and in the international literature (North Italy[4], Kaiser Permanente[5], Italian Registry[6])

	Total ACS[a]	STEMI	NSTEMI	In-hospital mortality
North Italy[b]	28% reduction	24% reduction	43% reduction	Not available
Kaiser Permanente[c]	48% reduction	40% reduction	49% reduction	Not available
Italian Registry[d]	48.4% reduction	26.5% reduction	65.1% reduction	$RR_{overall}$= 3.6 (2.0–6.4) RR_{STEMI}= 3.3 (1.7–6.6)
Brazilian Network[e]	36.5% reduction[e]	28.9% reduction[e]	39.5% reduction[e]	$RR_{overall}$= 0.85 (0.4-1.7)[e] RR_{STEMI}= 1.2 (0.3-4.0)[e]

ACS: Acute Coronary Syndrome; STEMI: ST-Elevation Myocardial Infarction; NSTEMI: Non-ST-Elevation Myocardial infarction; RR: Risk Ratio.
[a] In the reports from Kaiser Permanente and Italian Registry, only acute myocardial infarction was evaluated.
[b] Retrospective analysis of consecutive patients who were admitted for acute coronary syndrome at 15 hospitals in northern Italy, comparing February and March to two control periods: a corresponding period in the previous year (2019) and an earlier period in the same year (2020)[4]. We reported the average from both analyses.
[c] The comparison reported was based on a database of a health care delivery system from January through March 2020, compared to data from April 2020[5].
[d] Data based on a nationwide survey regarding admissions for acute myocardial infarction at Italian coronary care units in a one-week period during the Covid-19 outbreak, and compared with the equivalent week in 2019[6].
[e] Comparison between the average of the first three months of the Covid-19 pandemic (94 ACS per month; 21 STEMI per month; 53.3 NSTEMI per month) and the average of the previous 12 months (148.1 ACS per month; 29.5 STEMI per month; 88.1 NSTEMI per month). Overall, the mortality rate was 3.4% (61/1777) in the previous 12 months and 2.9% in the first three months of the pandemic (9/306). The mortality was 3.9% among STEMI patients (14/354) in the previous 12 months and 4.7% (3/63) in the first three months of the pandemic.

In addition, the >40% reduction in the number of patients who sought medical care in the early months of the pandemic was associated to a higher rate of patients with low ejection fraction despite adequate medical care, indicating that the population affected by ACS in the pandemic phase were composed of more severe patients. This may indicate that patients with less severe and transitory presentations may not have sought medical care in the early phase of the pandemic for fear of contamination. Thus, the drastic drop in ACS cases may be justified not only by more critical cases with potentially fatal outcomes out of the hospitals, but also by patients with less severe manifestations that would normally seek medical evaluation, but did not do so in the context of the pandemic. This last situation accounts for the group of patients that may have survived the acute event, but they would be at a greater risk in the future due to the lack of treatment.

In summary, the small number of patients admitted for emergency evaluation raises a concern as to patients who had an ACS event at home and could present worse outcomes in the short and long terms. Our findings, along with previous data from the international literature, reinforce how necessary it is to seek medical care in suspected cardiovascular events even during a lockdown period like the start of the Covid-19 pandemic.

Limitations

This is a report based on a specific database developed for monitoring quality improvement initiatives related to the Chest Pain Protocol. Information such as symptom duration and baseline characteristics of patients, other than age and gender, were not included in the registries and could not be assessed. Finally, the lack of information about concomitant or recent Covid-19 infection does not allow an analysis of a possible relation with lower ejection fraction after myocardial infarction in patients with recent history of SARS-CoV-2 infection.

Conclusion

In a network of hospitals in Brazil, we identified a reduction of more than 40% of patients with suspected ACS and 36.5% in admissions due to confirmed ACS when comparing the early months of the Covid-19 pandemic to the average of previous months. These findings raise an alert of a smaller number of patients seeking emergency departments during the Covid-19 outbreak in Brazil. National medical societies and healthcare systems should monitor potential adverse consequences in the public health such as an increase in cases of heart failure following myocardial infarction.

Acknowledgments

We would like to thank Alexsandro Vieira dos Santos, Fabiola de Fátima Ribeiro de Souza, Katrin Fenzl and Nilson Lopes de Araujo for their support in data analysis and the creation of graphs.

Author Contributions

Conception and design of the research: Barros e Silva PGM, Dutra AAF, Manfredi AB, Furlan V; Acquisition of data: Dutra AAF, Sampaio PPN, Correa CM, Griz HB, Setta D; Analysis and interpretation of the data and Critical revision of the manuscript for intellectual contente: Barros e Silva PGM, Dutra AAF, Manfredi AB, Sampaio PPN, Correa CM, Griz HB, Setta D, Furlan V; Statistical analysis and Writing of the manuscript: Barros e Silva PGM.

Potential Conflict of Interest

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

Sources of Funding

There were no external funding sources for this study.

Study Association

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

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Hospital Pró-Cardíaco under the protocol number 20710119.4.0000.5533. 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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The Evolution of Percutaneous Coronary Intervention in Latin America

Costantino Roberto Costantini,[1] Rafael Michel de Macedo,[1] Marcos Antônio Denk,[1] Sergio Gustavo Tarbine,[1] Lazaro Garcia,[2] Mario Fernando Camargo Maranhão,[1] Costantino Ortiz Costantini[1]

Hospital Cardiológico Costantini Ltda,[1] Curitiba, PR - Brazil

Santa Casa de Curitiba,[2] Curitiba, PR - Brazil

In August 1979, two years and one month after the first percutaneous coronary intervention (PCI) was performed in the world by Andreas Grüntzig,[1] we received at Santa Casa de Misericordia in Curitiba (SCMC) a 55-year-old male patient (A.S.O.) with Canadian Cardiovascular Society (CCS) class 2 stable angina. Coronary angiography showed a severe (75-80 DS%) lesion in the middle segment of the Right Coronary Artery (RCA). The left coronary artery system did not have any significant atherosclerotic lesion and the left ventriculogram showed mild inferior wall hypokinesia with competent mitral and aortic valves.

That was the opportunity to put into practice the technique described by Gruntzig et al.[1] for the first time in Latin America. The clinical presentation and the angiographic characteristics of the lesion met all the criteria described by Gruntzig: Single lesion, short length (<10mm), proximal arterial segment, without vasospasm, concentric, non-calcified and feasible for CABG. Thus, after discussing it with the clinical and cardiovascular surgery staff, it was decided to propose the dilation of the RCA obstruction to the patient as an attempt to treat his coronary disease.

After patient consent was obtained, on August 10, 1979 he was submitted to PCI as described by Costantini et al.[2]. After the PCI, the severe RCA lesion was reduced to a mild lesion (15-20 DS%). Despite the good angiographic result, there was concern about the heart muscle metabolism. Thus, in the absence of another method for myocardial ischemia assessment, a metabolic evaluation was performed by extracting a blood sample from the coronary sinus during temporary pacemaker-induced tachycardia pre- and post-PCI for evaluation of lactic acid levels. This evaluation confirmed the adequate oxygen supply to the heart muscle after PCI as demonstrated in Figure 1.[2]

During the subsequent years, the patient (A.S.O) was closely monitored regarding the coronary heart disease evolution. Other treatments were performed over time and new techniques and technologies were used. Figure 2 and Table 1 show patient evolution between 1982 and 2009.

In March 2010, the patient returned with CCS 2 stable angina, being submitted to the 9th cardiac catheterization, of which images are shown in Figure 03. The LV gram showed slightly increased LV volumes due to diffuse hypokinesia and a 46% ejection fraction (A) and significant progression of the proximal 1/3 lesion submitted to angioplasty in 1979 (B). The IVUS showed a luminal area of 3.22 mm² (C). The LMT, LAD and LCX presented with an excellent angiographic evolution in sites submitted to stent implantation (D,E). Because of angina limitations and the progression of the atherosclerotic plate in the proximal RCA, it was opted to perform the IVUS-Guided DES PCI with two Taxus stents (4.0x16 mm and 4.0x12 mm) (F, G,H). The two previous stents in the middle and distal segments of the RCA showed mild neointimal hyperplasia in the IVUS assessment (I,J). In the angiographic and IVUS evaluation of previously implanted stents in the LMT and LAD, an optimal evolution was observed with the presence of a mild degree of neointimal hyperplasia (L-O).

Forty-one years after a pioneering intervention, enthusiastically following the technique that Grüntzig taught us, we can offer our patients the newest technology in interventional cardiology, always seeking new methods to improve the treatment of coronary heart disease.

By following the trajectory of patient A.S.O., we had the great opportunity to learn about the morphological aspects of this coronary pathology, which is progressive and has no cure. It was possible to monitor all therapeutic and diagnostic imaging advances (angiography, IVUS and OCT) starting with the use of the first balloon-catheter to the first generation of drug-eluting stents.

After 34 years of evolution of the first angioplasty performed in Latin America, patient A.S.O. died in 2013 from neurological causes. To his family and in his memory, our eternal gratitude for the trust placed in our team.

Keywords

Angina Pectoris; Cineangiography/history; Angioplasty, Balloon, Coronary/history; Angioplasty Balloon, Coronary/trends; Stents; Myocardium/metabolism; Clinical Evolution.

Mailing Address: Costantino Roberto Costantini •
Hospital Cardiológico Costantini Ltda – Hemodinâmica - Rua Pedro Collere, 890. Postal Code 80320-320, Curitiba, PR – Brazil
E-mail: crcostantini@hospitalcostantini.com.br
Manuscript received August 20, 2020, revised manuscript December 02, 2020, accepted December 02, 2020

DOI: https://doi.org/10.36660/abc.20200927

Author Contributions

Conception and design of the research and Writing of the manuscript: Costantini CR, Macedo RM, Denk MA; Acquisition of data and Analysis and interpretation of the data: Costantini CR; Critical revision of the manuscript for intellectual contente: Costantini CR, Macedo RM, Denk MA, Tarbine S, Garcia L, Maranhão MFC, Costantini CO.

Potential Conflict of Interest

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

Sources of Funding

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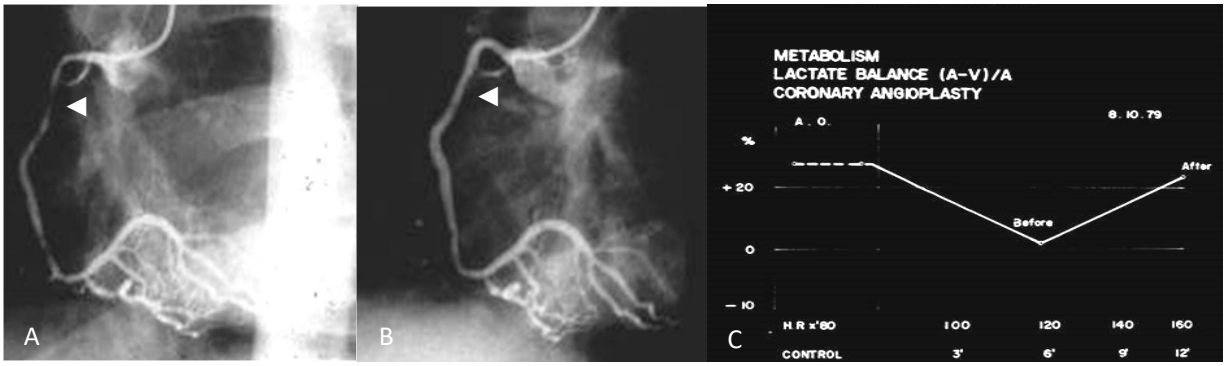

Figure 1 – *A) Proximal RCA lesion before PCI, B) Proximal RCA lesion post-PCI, C) Coronary Sinus Lactate level assessment pre- and post-PCI.*

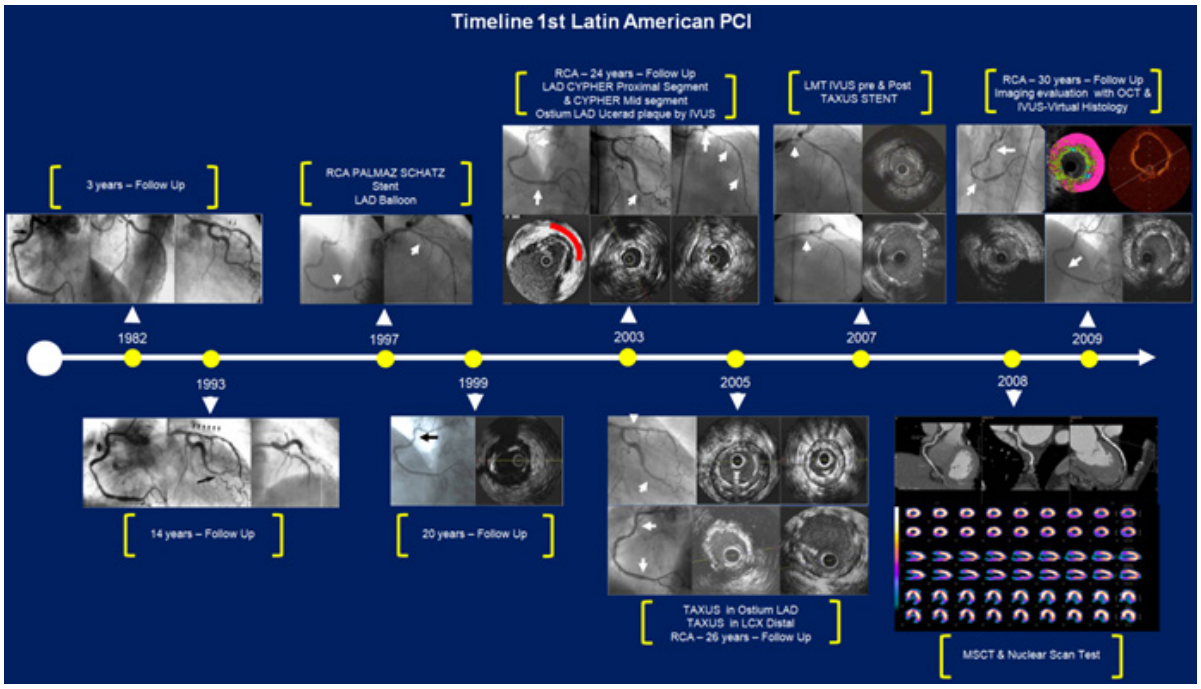

Figure 2 – *Therapeutical evolution between 1982 and 2009 (A.S.O)*

Table 1 – Description of the patient's evolution and treatment (A.S.O.) between 1982 and 2009

Date	Exam	Diagnostics	Conduct
1982	Cardiac Catheterization 3 years of FU	LV: RCA preserved systolic function with maintained angiographic result, LMT: mild lesion, LAD and LCX: mild lesions;	Clinical Treatment
1993	Cardiac Catheterization 14 years of FU	LV: preserved systolic function, RCA: mild lesion in proximal LMT segment: mild lesion, LAD: moderate lesion in the proximal segment and severe lesion in the mid segment, LCX: severe lesion in the distal segment.	Rotational atherectomy PCI of LAD lesion and balloon PCI of LCX lesion
1997	Cardiac Catheterization 14 years of FU	LVEF: preserved systolic function, RCA: mild lesion in the proximal segment and severe lesion in the distal segment with ulcerated plaque on IVUS assessment, LMT: mild lesion, LAD: angiographic restenosis of rotational atherectomy PCI LCX: mild lesion in the distal segment;	PCI with 4.0x15 mm Palmaz-Schatz stent implantation in the distal RCA; Balloon PCI of LAD
1999	Cardiac Catheterization 20 years of FU Stable Angina	LV: preserved systolic function, RCA: mild lesion in the proximal segment; good angio and IVUS outcome of the distal stent, LMT: mild lesion, LAD: good angiographic outcome, LCX: good angiographic outcome;	Clinical treatment
2003	Cardiac Catheterization 24 years of FU Stable Angina	LV: preserved systolic function, RCA: mild lesion in the proximal segment, good angio and IVUS outcome of the distal stent, LMT: mild lesion, LAD: angiographic restenosis, ulcerated plaque in the LCX ostium: in stent 40% DS;	Proximal and mid LAD IVUS-guided DES PCI (CYPHER 2.75x18 & 2.75x33 mm). Ulcerated ostial plaque evaluated by IVUS and maintained in clinical treatment because it had preserved luminal area.
2005	Cardiac Catheterization 26 years of FU Stable Angina	LV: preserved systolic function, RCA: mild lesion in proximal segment; good angio and IVUS outcome of the distal BMS, LMT: moderate lesion LAD: severe ostial lesion, good angiographic and IVUS evolution of DES, LCX: angiographic restenosis;	Distal LCX (TAXUS stent) & ostial LAD (TAXUS stent) IVUS-Guided DES PCI
2007	Cardiac Catheterization 28 years of FU Stable Angina	LV: preserved systolic function, RCA: Moderate lesion in the proximal RCA and good angio and IVUS outcome of the distal BMS, LMT: severe lesion LAD: good angiographic and IVUS evolution of DES LCX: good angiographic and IVUS evolution of DES;	LMT IVUS-Guided DES PCI (TAXUS 4.0x28 mm)
2008	Check-up Multi-Slice Computed Tomography/ Cardiac Nuclear Scan Test	Normal perfusion, LV with preserved systolic function, RCA: moderate to severe lesion (60-70%) in the proximal segment and good evolution of the distal BMS;	Clinical Treatment
2009	Cardiac Catheterization 30 years of FU Stable Angina	RCA: Virtual Histology and OCT assessment of the proximal segment showing intermediate luminal area stenosis with a large Necrotic core and TCFA. Severe stenotic and ulcerated lesion in the mid segment.	Mid RCA IVUS-Guided BMS (3.5x18mm) PCI (3.5x18 mm). The proximal RCA lesion was not submitted to any intervention and maintained on clinical treatment.

RCA: right coronary artery; LMT: left main trunk; LCX: left circumflex artery; LAD: left anterior descending artery; PCI: percutaneous coronary intervention; IVUS: intravascular ultrasound; OCT: optical coherence tomography; BMS: bare metal stent; DES: drug-eluting stent; TCFA: thin-cap fibroatheroma.

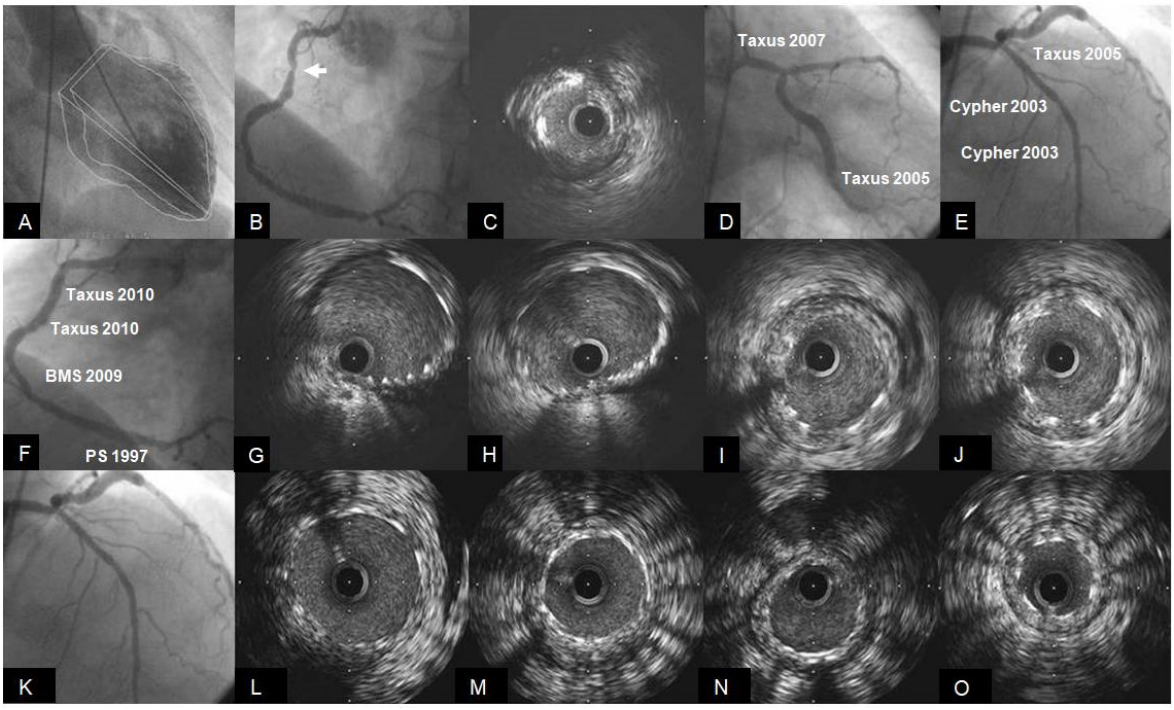

Figure 3 – *A) LV; B) pre-intervention RCA; C) RCA IVUS assessment; D) LMT/LCX angiography; E) LAD angiography; F) post-intervention RCA; G,H) post-intervention RCA IVUS; I,J) RCA IVUS assessment of the mid and distal segments in previous stents; K-O) LMT/LAD angiographic and IVUS previous stents.*

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Percutaneous Treatment of Secondary Mitral Regurgitation by MitraClip: Mitra-FR vs. COAPT

Sergio Barros-Gomes,[1,2] Flávio Tarasoutchi,[2] Ana Clara Tude Rodrigues,[1] Lara Ferreira Nhola,[1] Pedro Alves Lemos,[1] Samira Saady Morhy,[1] Claudio Henrique Fischer,[1,3] Marcelo Luiz Campos Vieira[1,2]

Hospital Israelita Albert Einstein,[2] São Paulo, SP - Brazil

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

Universidade Federal de São Paulo,[3] São Paulo, SP - Brazil

Introduction

Secondary or functional mitral regurgitation (MR) is due to changes in the geometry of the left ventricle (LV) secondary to ventricular dysfunction.[1] It occurs when an ischemic heart disease or a dilated cardiomyopathy of any etiology causes dilation of the LV, dilation of the mitral ring, and/or displacement of the papillary muscle, resulting in poor coaptation of the valve cusps and valve regurgitation.[2] the American Heart Association indicates that 16,250 per million North Americans have secondary MR,[3,4] totaling more than 5 million cases in the United States of America alone, and this number is estimated to be even greater due to the continued growth and aging of the population. This is noteworthy, as secondary MR causes a poor prognosis and is an independent predictor of mortality.[5,6]

For many years, the mechanical intervention of secondary MR (surgical or percutaneous) has been restricted to cases refractory to conventional clinical treatment,[7,8] with evidence mainly supported by two important studies conducted by the Cardiothoracic Surgical Trials Network group.[9,10] The first study[9] randomized 301 patients with moderate ischemic MR and found no differences in ventricular geometry between patients who undergone surgical myocardial revascularization versus the combination of surgical revascularization and mitral valve repair. The second study[10] surveyed 251 patients with severe MR and found no differences regarding mortality, in addition to the greater recurrence of mitral regurgitation and complication rates among patients treated with mitral valve repair versus valve replacement. Considering these two studies, the recommendations of the American Heart Association/American College of Cardiology[7] and the Brazilian Guidelines for Valvular Heart Disease[8] classified surgical or percutaneous mitral valve intervention as a Class IIb indication.

Keywords

Heart Failure; Mitral Valve, Insufficiency; Echocardiography/methods; Clinical Trials.

Mailing Address: Sergio Barros-Gomes •
Instituto do Coração da Universidade de São Paulo – Ecocardiograma - Av Dr. Eneas Carvalho de Aguiar, 44. Postal Code 05403-900, São Paulo, SP – Brazil
E-mail: sergiomed2@hotmail.com

Manuscript received January 26, 2020, revised manuscript October 16, 2020, accepted December 02, 2020

DOI: https://doi.org/10.36660/abc.20200063

Until recently, no randomized trial had compared percutaneous secondary MR intervention with the conventional clinical treatment. In 2018, the conduct towards secondary MR decisively changed with the presentation of two randomized clinical trials: the *Multicentre Study of Percutaneous Mitral Valve Repair MitraClip Device in Patients With Severe Secondary Mitral Regurgitation* (MITRA-FR)[11] and the *Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation* (COAPT).[12] These studies evaluated the efficacy and safety of two therapeutic strategies in patients with severe secondary MR – percutaneous therapy with MitraClip® together with optimized clinical treatment versus optimized clinical treatment alone.

In this article, the main similarities and differences between both studies will be addressed, in addition to considering the application of this procedure to the clinical practice, including the ideal profile of the candidate for the procedure. Table 1

MITRA-FR

MITRA-FR was a multicenter study conducted in 37 French centers that randomized 304 patients with severe secondary MR, symptomatic systolic heart failure (HF), and left ventricular ejection fraction (LVEF) between 15% and 40% in two therapeutic strategies, in a 1:1 ratio, allocated for percutaneous treatment with MitraClip® together with optimized clinical treatment (intervention group; 152 patients) versus isolated optimized clinical treatment (control group; 152 patients).[11] Severe secondary MR was defined as having an effective regurgitant orifice area (ERO) > 20 mm^2 or regurgitant volume (RV) > 30 mL per beat. The primary endpoint was mortality from any cause or hospitalization for HF within 12 months. Patients in both groups showed an improvement in the functional class, but with no significant difference between the two groups. Finally, there was no significant difference in the composite primary endpoint (54.6% vs. 51.3%, respectively; $p = 0.53$), mortality rate (24.3% vs. 22.4%; $p > 0.05$), and hospitalization rate (48.7% vs. 47.4%; $p > 0.05$) between the intervention versus control group during 1 year of follow-up. Likewise, there was no significant difference in the composite primary endpoint (63.8% vs. 67.1%, respectively; $p > 0.05$), mortality rate (34.9% vs. 34.2%; $p > 0.05$), and hospitalization rate (55.9% vs. 61.8%; $p > 0.05$) between the intervention versus control group during 2 years of follow-up.[13] The authors concluded that MitraClip® is safe and effective in secondary MR compared with optimized clinical treatment, but with no

Table 1 – Characteristics of recruitment, randomization and clinical follow-up

Variable	MITRA-FR	COAPT
Patients, n	304	614
Patients Intervention/ Control, n	152/152	302/312
Study period, years	2013-2017	2012-2017
Inclusion criteria		
ERO, mm^2	> 20	> 30
RV, mL/beat	30	45
LVEF, %	15-40	20-50
LVESD, mm	NA	≤ 70
Daily medications	Adjusted in each group according to clinical practice	Maximum stabilized dose and resynchronization therapy if appropriate
Symptoms	NYHA II, III, IV	NYHA II, III, IV

LVESD: left ventricular end-systolic diameter; ERO: effective regurgitant orifice area; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association; RV: regurgitant volume.

improvement in survival or reduced hospitalization for HF in patients with secondary MR and systolic HF.

COAPT

COAPT was a multicenter study that randomized 614 patients in 78 North American and Canadian centers with symptomatic systolic HF and moderate to severe (3+) or severe (4+) secondary MR, defined as ERO > 30 mm^2 or RV > 45 mL per beat, with LVEF ≥of 20% (mean LVEF of 31.3 ± 9.3%), in the ratio of 1: 1, allocated for percutaneous treatment with MitraClip® together with optimized clinical treatment (intervention group; 302 patients) versus isolated optimized clinical treatment (control group; 312 patients).[12] Symptomatic HF was defined as symptoms of HF despite the maximum tolerated drug dose. The primary efficacy endpoint was hospitalization for HF within 24 months and the primary safety endpoint was an event free of complications related to MitraClip® at 12 months. The annual rate of hospitalization for HF within 24 months was 35.8% per patient/year in the intervention group versus 67.9% in the control group (*hazard ratio* 0.53; 95%CI 0.40-0.70; p <0.001). The percentage of event-free complications related to the device in 12 months was 96.6% (p < 0.001), whereas death from any cause in 24 months occurred in 29.1% in the intervention group compared with 46.1% in the control group (*hazard ratio* 0.62; 95%CI, 0.46-0.82; p < 0.001). The intervention group not only reduced the rate of hospitalizations for HF by 47%, but also reduced mortality by 38%. Reduction in the absolute risk of all-cause mortality in the MitraClip® group was 17%, and the number necessary for treatment in order to prevent death in 2 years was 5.9; to prevent hospitalization for HF in 2 years, it was 3.1. The authors concluded that the MitraClip® combined therapy and optimized clinical treatment for patients with symptomatic systolic HF and moderate to severe or severe MR reduces the number of hospitalizations for HF and all-cause mortality in 2 years when compared with exclusively optimized clinical treatment. Tables 2 and 3 compare the characteristics and clinical outcomes between both studies.

Main Similarities and Differences

Both trials had conflicting results, with COAPT showing benefit from MitraClip® versus drug therapy, whereas MITRA-FR showed no benefit related to MitraClip®. Undoubtedly, these two studies have changed the researchers' understanding of secondary MR. But why did they show significantly different results? Why did the COAPT study have a positive result, whereas the MITRA-FR was neutral? The answer to this question is probably multifactorial and includes differences in patients' selection, optimization of drug therapy, grade of MR, and ventricular remodeling.

Recruitment: The COAPT recruitment was more selective compared with MITRA-FR, considering that its recruitment was slower and more prolonged. The number of patients was different in both studies: COAPT recruited about 300 patients in each group, and MITRA-FR, around 150 patients. Perhaps the sample size of the MITRA-FR population, after excluding patients with incomplete follow-up, may not have been sufficient to detect statistical significance and thus avoid type II error, especially in relation to secondary endpoints. In the COAPT study, the number of hospitalizations between the two therapeutic strategies has diverged since the beginning of the follow-up, partially explained by the more rigorous drug treatment.

Grade of MR: In MITRA-FR, the mean ERO was 31 mm^2, whereas COAPT had a mean ERO of 41 mm.[2] Although the inclusion criterion for both studies was MR with grade from moderate to severe, the COAPT study followed the North American recommendations of 2008,[14] which classifies moderate to severe MR when the ERO is ≥ 30 mm^2 and/or 45 mL RV; MITRA-FR followed the European recommendations of 2012:[15] ERO ≥ of 20 mm^2 and/or 30 mL RV classified as moderate to severe MR. This disagreement is based on the concept that mortality in patients with secondary MR is significantly higher for lower levels of ERO and RV.[16,17] However, the mechanism of functional MR is complex and it is unknown whether moderate ERO or RV actively work as

Table 2 – Clinical and echocardiographic characteristics

Variable[a]	MITRA-FR	COAPT
Clinical		
Age, years		
– MitraClip group	70 ± 10	72 ± 12
– Control group	71 ± 10	73 ± 10
Sex, male, n (%)	120 (79)	201 (67)
	107 (70)	(62)
NYHA, %		
-I	0	0.2
-II	32.9	39
-III	58.5	52.5
-IV	8.6	8.3
Ischemic cardiomyopathy		
– MitraClip group	95 (62.5)	184 (60.9)
– Control group	85 (56.3)	189 (60.6)
Previous myocardial revascularization		
– MitraClip group	71 (46.7)	PCI: 130 (43.0) CABG: 121 (40.1)
– Control group	62 (42.4)	PCI: 153 (49.0) CABG: 126 (40.4)
Previous cardiac resynchronization		
– MitraClip group	46 (30.5)	115 (38.1)
– Control group	35 (23.0)	109 (34.9)
Surgical Risk		
- STS score	NA	8.2 ± 5.9%
- EuroScore II	6.2 (3.5-11)	NA
Echocardiography		
MR severity, %		
- ERO 20-29 mm^2 (moderate)	157 (52.2)	80 (13.5)
- ERO 30-39 mm^2 (moderate/severe)	95 (31.6)	270 (45.7)
- ERO ≥ 40 mm^2 (severe)	49 (16.3)	241 (40.8)
ERO, mm^2	31 ± 10	41 ± 15
LVEDVI, mL/m^2	135 ± 35	101 ± 34
LVEF, %	33 ± 7	31 ± 9

ERO: effective regurgitant orifice area; LVEF: left ventricular ejection fraction; NA: not applicable; NYHA: New York Heart Association; STS: Society of Thoracic Surgeons – risk of death within 30 days after mitral valve replacement; LVEDVI: left ventricular end-diastolic volume index. [a] Categorical variables are reported in numbers (percentages); continuous variables are reported as mean ± standard deviation [SD] and median (interquartile range).

causes of ventricular remodeling and dysfunction, or if they are mere markers resulting from incipient cardiomyopathy. Subsequent guidelines returned ERO and RV to their usual values; based on current recommendations, ERO of 30 mm^2 is considered moderate, whereas ERO of ≥ 40 mm^2 is considered severe.[8,18] New studies suggest that the unified approach, based on the integration of ERO, RV, and regurgitant fraction (RF), may be an excellent discriminator of severe secondary MR when compared with the algorithms established in the latest guidelines and, therefore, an excellent identifier of patients at high risk.[19] Hence, a significant number of patients (52%) with moderate MR (ERO of 20-30 mm^2) were recruited for MITRA-FR, whereas only 14% of patients with these characteristics were recruited for COAPT. Regarding severe MR, (ERO ≥ of 40 mm^2), only 16% of MITRA-FR patients had severe MR versus 41% of COAPT. The findings of both studies suggest that the benefit of MitraClip® is greater for patients with ERO > 40 mm^2 (i.e., truly severe MR).

Ventricular Remodeling: The mean left ventricular end-diastolic volume index (LVEDVI) of the patients in the MITRA-FR study was 135 mL/m^2 compared with 101 mL/m^2 of the COAPT. The LV was significantly greater in MITRA-FR, characterizing more remodeled ventricles, in more advanced

Tabela 3 – Desfecho clínico

Variable [a]	MITRA-FR	COAPT
MitraClip Group only, n		
- Complications in the procedure	21 (14.6)	25 (8.5)
- MR ≥ +2 on discharge	93 (24.4)	214 (17.7)
- MR ≥ +2 in 2 years	48 (49.5) [b]	26 (22.8)
Mortality from any cause in 2 years, n		
– MitraClip group	53 (34.9)	80 (29.1)
– Control group	52 (34.2)	121 (46.1)
p value	>0.05	<0.001
Hospitalizations for CHF in 2 years, n		
– MitraClip group	85 (55.9)	92 (35.7)
– Control group	94 (61.8)	151 (56.7)
p value	>0.05	<0.001
Mortality from any cause or hospitalizations associated with HF in 2 years, n		
– MitraClip group	97 (63.8)	129 (45.7)
– Control group	102 (67.1)	191 (67.9)
p value	>0.05	<0.001

HF: heart failure; CHF: congestive heart failure; MR: mitral regurgitation. [a] Categorical variables are reported in numbers (percentages). [b] MR +2 in 1 year.

stages of cardiomyopathy. This difference is probably due to the exclusion of patients with severe dilation/dysfunction in COAPT (LV systolic diameter > 70 mm), whereas in MITRA-FR there was no such limitation. The inclusion criterion for LVEF between the two studies was also different: COAPT included patients with LVEF of 20-50% versus LVEF of 10-40% in MITRA-FR. Interestingly, a subgroup of patients in the COAPT study who did not benefit from treatment with MitraClip® (number of hospitalizations associated with HF within 12 months) consisted of patients with ERO and LVEDVI relatively similar to those recruited in the MITRA-FR study (ERO ≤ of 30 mm^2 and LVEDVI > 96 mL/m^2).[20] These facts suggest that patients with moderate MR, markedly more dilated LV, and with greater dysfunction may not be ideal candidates for the treatment with MitraClip®. In fact, the high recurrence of MR and the worst clinical outcome had been previously reported in the surgical correction of patients with ischemic MR, ventricular dilation (LV diastolic diameter > 65 mm), and severe LV dysfunction (LVEF < 20% and LV systolic diameter > 55 mm).[21,22] In the MITRA-FR study, cardiomyopathy was possibly the main cause of HF symptoms and, consequently, the determinant of the unfavorable clinical outcome, i.e., MR was merely a factor secondary to ventricular remodeling. On the other hand, in the COAPT study, HF was partly due to MR and, therefore, the grade of MR in the COAPT trial was higher, while cardiomyopathy was less advanced (smaller LV and greater LVEF).

Drug Therapy and Therapeutic Optimization: In the COAPT study, the patient inclusion criterion was symptomatic systolic HF despite the maximum tolerated drug dose, use of cardiac resynchronization therapy, use of defibrillators, and myocardial revascularization therapy (if appropriate). Patients were clinically optimized prior to recruitment and only a few medication adjustments were made during follow-up. Conversely, in the MITRA-FR study, it was not possible to optimize the medication in all patients before randomization and multiple readjustments during follow-up. In MITRA-FR, the medication was adjusted by the researchers, whereas in COAPT the medication was more rigorously adjusted by a group of specialists who supervised the maximum tolerated dose, before and after the intervention. The initial dosage and adjusted doses of each medication were accounted for in the COAPT study. Certainly, this rigor in terms of dosage and drug optimization implemented in the COAPT study does not reflect the daily clinical practice.

Success in Reducing MR: At the end of 12 months, 83% of MITRA-FR patients had MR ≤ +2 (moderate) compared with 95% of COAPT patients. Consequently, 17% of MITRA-FR patients had MR ≥ +3 (moderate/severe) in 12 months compared with 5% of COAPT patients. The COAPT study had a more aggressive strategy in terms of implanted clips when compared with MITRA-FR (use of one clip in 36% of cases for COAPT vs. 46% for MITRA-FR; two clips in 55% of COAPT cases vs. 46% for MITRA-FR; three clips in 55% of COAPT cases vs. 9% of MITRA-FR; four clips in 0.3% of COAPT patients vs. 0% for MITRA-FR). The higher success rate in reducing MR may be associated with favorable results.

Pathophysiology: Divergences in terms of pathophysiology have been elegantly demonstrated by Packer and Grayburn et al.,[23] who presented the concept of proportionate MR versus disproportionate MR based on the combination of ERO and end-diastolic volume (EDV) – ERO/EDV ratio. Assuming a LVEF of 30% and a regurgitant fraction of 50% (profile of patients

in the trials), the authors graphically showed that an ERO of 30 mm² and a higher EDV (between 220-240 mL) could result in a regurgitant fraction of 50%, and a 20 mm² ERO and normal EDV could result in a 50% regurgitant fraction.[23] The authors suggest that percutaneous treatment of the mitral valve by MitraClip® is more beneficial for patients with disproportionate MR as for the size of the LV, i.e., when the MR is greater than expected for an dilated LV, treatment with MitraClip® may have a more favorable result (larger ERO and lower LV). In contrast, proportionate MR would represent sicker patients, with larger ventricles and a lower grade of MR. In other words, patients with late-stage cardiomyopathy selected for interventional treatment.

Nevertheless, Gaasch and Meyer et al.[24] suggested that the severity of MR between the two trials is actually quite similar. The authors argue that the pathophysiology of MR is better described by RV (or the regurgitant fraction) than by ERO. RV is determined by ERO and the magnitude and duration of the systolic pressure gradient through the regurgitant valve, i.e., ERO is only one of the determining variables of RV. In fact, RV affects the LV size at a given LVEF, and has a direct relationship with the EDV. Thus, they graphically proposed that the association between severity of MR and LV size should be based on the ratio between RV and EDV – RV/EDV ratio –, with its quotient being uniformly corrected, making it a dimensionless index. Assuming a 50% regurgitant fraction in the COAPT study (assumption based on LVEF and echocardiographic data) and a 53% regurgitant fraction provided in MITRA-FR, the RV/EDV ratio was 0.18 and 0.15, respectively. These coefficients of proportionality are relatively low (both < 0.20) and similar to the values reported in previous studies on secondary MR, reflecting a proportionally small contribution of RV to a large EDV. Thus, there is a disproportionate increase in the LV in the patients' profile of the two trials typically observed in patients with secondary MR (disproportionate MR) compared with patients with primary MR (EDV proportional to RV).

Underestimated volumes: In the COAPT study, patients had a mean ERO of 41 ± 15 mm², which corresponds to a RV of at least 45-60 mL. The total stroke volume of the LV in the COAPT study was 57 mL (LV end-diastolic volume subtracted from the end-systolic volume), which is totally incompatible to maintain a satisfactory cardiac output. Assuming a 57-mL total stroke volume of the LV, RV is hence the total stroke volume of the LV subtracted from the stroke volume in the outlet (i.e., the total stroke volume of the LV is equal to the mitral RV plus the stroke volume in the left ventricular outflow tract, the forward stroke volume ranges from 0 to 15 mL, which would be incompatible with life. It is clear that EDV in the COAPT study is underestimated. If we assume a 41-mm² ERO and a 60-mL RV (similar to the COAPT study), EDV should be greater than 300 mL (assuming a 50% regurgitant fraction and 31% LVEF as reported in the study). Nevertheless, the LV diastolic diameter was smaller in the COAPT study (mean of 69 mm in MITRA-FR versus 62 mm in COAPT), confirming smaller LVs.

In fact, the quantification of secondary MR using two-dimensional echocardiography is challenging due to the numerous limitations of the method itself, in addition to the complex pathophysiology of MR. In patients with functional MR, ERO and RV, according to the PISA method, are mostly underestimated with values of cardiac resonance[25] and three-dimensional echocardiography.[26] The non-circular orifice and the dynamic behavior of MR significantly contribute to these differences. Perhaps the regurgitant fraction can overcome these limitations and corroborate as an essential variable of severity, in addition to its important prognostic role.[12] The regurgitant fraction is calculated by the ratio between RV and total stroke volume (RV/total stroke volume) – which, despite being variables dependent on LV loading conditions, size, and function, its quotient is uniformly corrected by these parameters, thus being a more robust indicator.[27]

Other factors: It is worth noting that unlike primary MR, in which severity is purely quantified based on the MR grade, secondary MR is complex, heterogeneous, and influenced by several factors: age, underlying disease, comorbidities, LV remodeling, extent of infarction, hemodynamic disorders, among others.[28] In the COAPT study, the combined outcome mortality or hospitalization for heart failure in the group that was treated with MitraClip® was relatively significant (46%). This shows that, regardless of valve repair, these patients continue to have a poor prognosis, considering that most part of the risk is related to these factors.

Likewise, Cavalvante et al.[29] demonstrated that the regurgitant fraction and the infarction size measured in patients with ischemic heart disease consist in important risk stratifications that go beyond the size of the LV and other clinical variables. The authors also reported that the prognosis of these patients is worse as the infarction size and the grade of MR increase. Noteworthily, the extent of fibrosis was not measured in MITRA-FR and COAPT studies, but the authors of the present article believe that it certainly had a clinical impact on the outcome of these studies. Perhaps patients with larger hearts and a larger area of infarction cannot benefit from MitraClip®. Likewise, it is possible to speculate that patients in the MITRA-FR study had a larger area of fibrosis and, therefore, less benefit from the MitraClip® therapy. New studies correlating clinical outcomes in patients treated with MitraClip® and the extent of fibrosis would be interesting.

Implications for Clinical Practice

Both studies evaluated the same clinical entity: functional or secondary MR. In the COAPT study, patients were symptomatic despite rigorous optimized clinical therapy, had more severe MR, smaller LV, and better systolic function compared with MITRA-FR. In the MITRA-FR study, patients had less severe MR, larger LV, and worse systolic function, in a more advanced stage of cardiomyopathy. Ventricular dysfunction was the main cause of HF and clinical outcomes and, therefore, therapy with MitraClip® may not be considerably beneficial.[30]

The early identification of secondary MR before LV is over-dilated is crucial. Although being considered a successful procedure a residual MR ≤ +2 (moderate), the goal of the procedure should be MR ≤ +1 (mild), and the implantation of additional clips should be taken into account in order to achieve this goal. Considering the findings of COAPT and MITRA-FR studies, the authors of the present article believe that both studies are complementary. It is expected for the randomized study RESHAPE-HF (*A Randomized Study of the MitraClip Device in Heart Failure Patients With Clinically Significant Functional Mitral Regurgitation*),[31] still in the recruitment step and with the

same inclusion criteria as COAPT, to provide an even greater understanding of the pathophysiology of secondary MR, especially after conflicting data.

Moreover, the authors are currently in the process of defining the ideal candidate for the treatment of secondary mitral regurgitation by MitraClip®. The size of infarction and/or fibrosis may also assist in better selecting these patients.[31,32] In addition, the severity of MR must be confirmed as being purely due to the severity of MR and not to other risk and confounding factors. The COAPT study emphasizes the important role of MR in the pathophysiology of systolic HF and, with appropriate patient selection, excluding those with larger LV, sicker, with larger area of fibrosis, and moderate MR, and selecting patients with very severe MR in such a way it contributes to the severity of the disease itself, percutaneous treatment of secondary MR by MitraClip® can be beneficial as long as it meets the following criteria (Figure 1):

To ensure that the severity of MR is purely attributable to the severity of MR and not to other factors that influence MR (age, comorbidities, other heart diseases, degree of ventricular dysfunction, extent of fibrosis, extent of remodeling).

Assessment of the severity of MR by integrating multiple parameters in addition to ERO: RV, regurgitant fraction, and possible quantification of the extent of the fibrosis area.

MR ≥ +3 (moderate to severe), defined as ERO ≥ 30 mm^2 and/or 45 mL RV per beat.

LVEF of 20-50% and LV systolic diameter < 70 mm.

Symptoms of HF despite optimized clinical therapy (maximum tolerated dose), including cardiac resynchronization therapy and myocardial revascularization, if appropriate.

Experienced interventionist group, with technical success in reducing MR ≥ +2 greater than 95%.

The presence of a multidisciplinary team (heart team) for the management, treatment, and optimization of HF.

After intervention, close monitoring of medications and volume status.

Early identification of secondary MR and referral to a multidisciplinary team (heart team) before over-dilation of the ventricle or the patient is hospitalized, requiring intensive care or inotropic support.

Author Contributions

Conception and design of the research: Barros-Gomes S; Writing of the manuscript: Barros-Gomes S, Lemos PA, Fischer CH, Vieira MLC; Critical revision of the manuscript for intellectual contente: Barros-Gomes S, Tarasoutchi F, Rodrigues ACT, Nhola LF, Lemos PA, Morhy SS.

Potential Conflict of Interest

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

Sources of Funding

There were no external funding sources for this study.

Study Association

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

Ethics approval and consent to participate

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

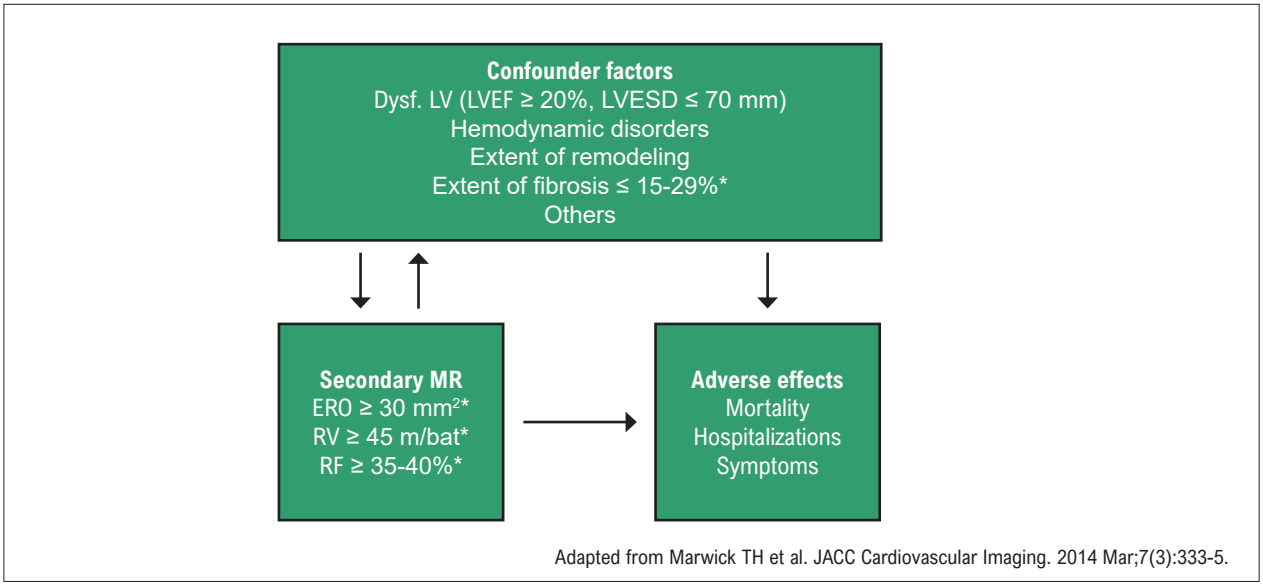

Figure 1 – *The complexity of functional mitral regurgitation and the selection of the ideal candidate* for the MitraClip® implant. Dysf.: dysfunction; LVESD: left ventricular end-systolic diameter; ERO: effective regurgitant orifice area; LVEF: left ventricular ejection fraction; RF: regurgitant fraction; RV: regurgitant volume.*

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Heart Failure with Supra-normal Left Ventricular Ejection Fraction – State of the Art

Ziyin Huang,[1*] *Yufeng Jiang,*[1*] *Yafeng Zhou*[1,2]

First Affiliated Hospital of Soochow University,[1] *Jiangsu Province – China*

Dushu Lake Hospital Affiliated to Soochow University,[2] *Jiangsu Province – China*

** The authors also contributed to this article.*

Abstract

In 2019, an article published in the European Heart Journal recognized for the first time heart failure (HF) with left ventricular ejection fraction (LVEF)≥ 65% as a new HF phenotype, heart failure with supra-normal left ventricular ejection fraction (HFsnEF), with the main purpose of promoting research on this new category. They analyzed mortality in people with HF and found that there was a u-shaped relationship between mortality and LVEF. Accordingly, HFsnEF patients had a higher all-cause mortality compared with other patients diagnosed with HF with preserved ejection fraction (HFpEF). This article describes the current situation of HFsnEF and discusses future perspectives based on the preliminary results of our group. To better treat patients with HFsnEF, it is fundamental that cardiologists and physicians understand the differences and similarities of this new phenotype.

Introduction

It is estimated that more than 100 million people suffer from heart failure (HF) worldwide.[1] In the DIGITALIS trial performed in Brazil, 64.2% of these patients were diagnosed with HF with preserved ejection fraction (HFpEF). Recently, a new type of HF, called HF with mid-range ejection fraction (HFmrEF) has been described. According to unpublished data from the DIGITALIS database, the prevalence of HF with reduced ejection fraction (HFrEF) was 19%, HFmrEF was 22% and HFpEF was 59%. It shows that HFpEF accounts for a large proportion of HF.[2-4]

In an article published in the European Heart Journal, which investigated the relationship between clinically assessed left ventricular ejection fraction (LVEF) and mortality in a large clinical cohort, a u-shaped relationship between mortality and LVEF was found, suggesting that it may be inappropriate to pool all patients with HFpEF into a single group.[5] These results may herald the recognition of a new phenotype of HF with LVEF ≥ 65%, which is characterized by a higher all-cause mortality.[6]

Heart failure with supra-normal ejection fraction (HFsnEF) has shown to have special clinical manifestations, treatment and prognosis. More research needs to be carried out to explore the characteristics and treatment of this new HF category. The HFsnEF phenotype might be recognized as a clinically relevant classification by national and international guidelines.

Pathophysiology and Pathology of HFsnEF

Optimal left ventricular (LV) performance depends on two conditions: a compliant LV, which allows it to fill from low left atrial pressure during diastole and a firm LV in systole, which ejects the stroke volume at arterial pressure. The echocardiogram is the most commonly used imaging technique to evaluate diastolic and systolic function, and the LVEF is the most widely used index. Patients diagnosed with HFpEF often have a normal LVEF (LVEF≥50%) and that is characterized by diastolic dysfunction.

As a special type of HFpEF, HFsnEF is also characterized by diastolic dysfunction. In a recently published study, it was concluded that patients with higher LVEF have a poorer prognosis.[5] The possible reason is that people with hypertrophic hearts (and very high LVEF) may pump more volume of blood with each beat and be particularly susceptible to oxygen supply–mediated ischemia.[7] Neurohormonal activation may be another reason for poor prognosis in HFsnEF. Higher LVEF may be due to higher activation of the adrenergic and renin–angiotensin–aldosterone system (RAAS) and higher activation of these systems may contribute to progressive heart remodeling and contractile dysfunction.[8] Patients with a remodeled heart were more likely to suffer from cardiac arrest or ventricular fibrillation, when compared with the normal EF group.[9] The reasons described above might explain the increased mortality of the HFsnEF patients (Figure 1).

Diagnostic approach

According to the latest ESC Guidelines for acute and chronic HF, the diagnosis of HF is based on the combination of symptoms, signs, natriuretic peptides and results of the echocardiogram.[1] In a recent analysis of a large dataset, researchers started defining patients with LVEF≥65% as a new type of HF, called HFsnEF. As a special type of diastolic HF, the diagnosis of HFsnEF may require the presence of signs or symptoms of HF, elevated BNP levels, evidence of normal systolic LV function and evidence of diastolic dysfunction or surrogate markers that include LV hypertrophy,

Keywords

Heart Failure; Stroke Volume; Heart Failure Diastolic; Mortality; Cardiomegaly; Echocardiography/methods; Prognosis.

Mailing Address: Yafeng Zhou •
First Affiliated Hospital of Soochow University - Suzhou City, Jiangsu Province, P. R. China. Suzhou 215006 – China
E-mail: zhouyafeng73@126.com

Manuscript received November 26, 2019, revised manuscript February 27, 2020, accepted March 16, 2020

DOI: https://doi.org/10.36660/abc.20190835

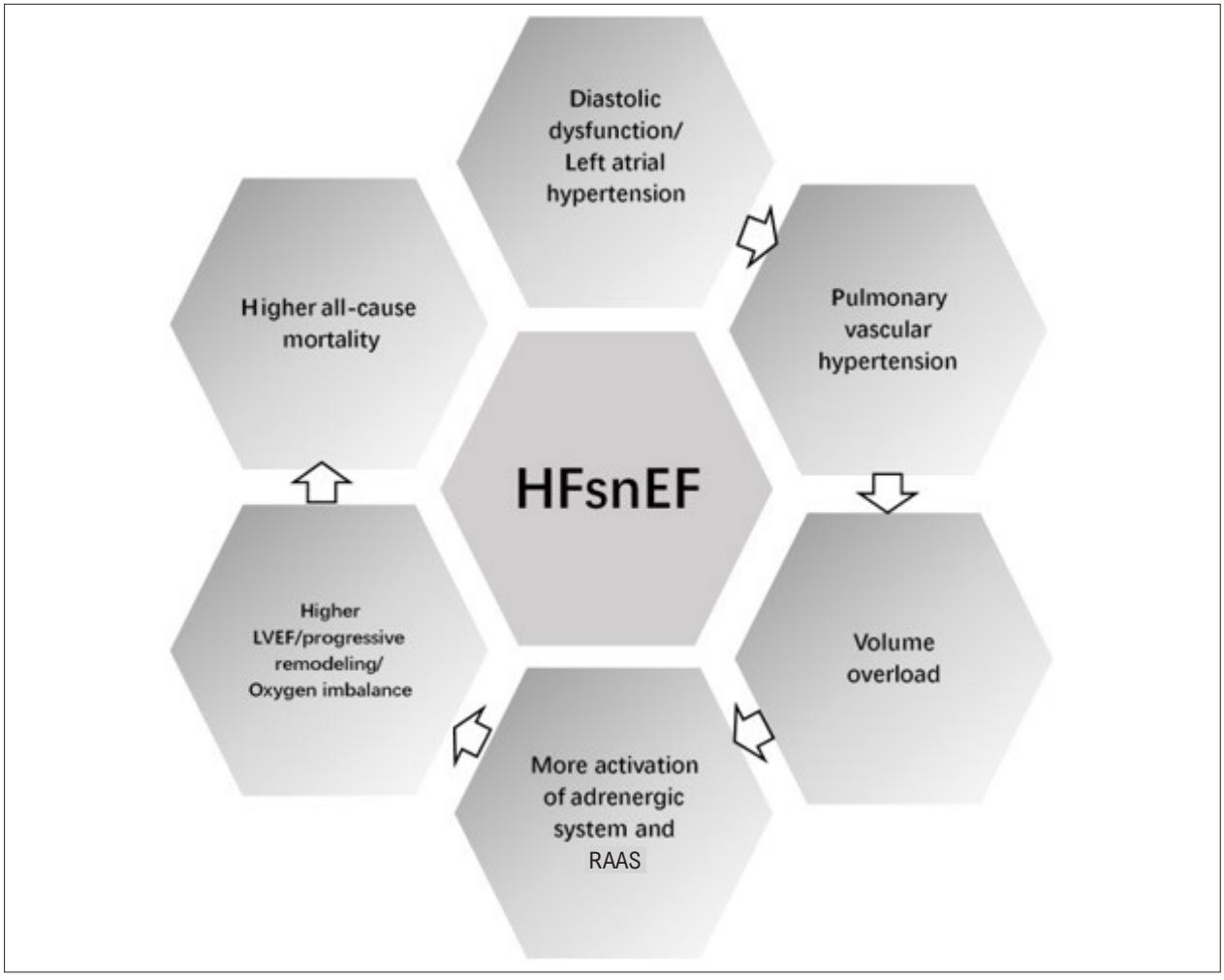

Figure 1 – *HFsnEF mechanisms. HFsnEF: heart failure with supra-normal left ventricular ejection fraction; LVEF: left ventricular ejection fraction; RAAS: Renin-angiotensin-aldosterone system.*

Table 1 – Clinical criteria in the investigation of HFsnEF

Categories	Criteria
Symptoms and/or signs of HF	Breathlessness, Paroxysmal nocturnal dyspnea, Reduced exercise tolerance, Fatigue, tiredness, increased time to recover after exercise, Ankle swelling
	Elevated jugular venous pressure, Hepatojugular reflux, Third heart sound (gallop rhythm), Laterally displaced apical impulse
LVEF	LVEF ≥65%
Elevated levels of NPs	BNP>35 pg/mL and/or NT-proBNP>125 pg/mL
Objective evidence of other cardiac functional and structural alterations underlying HF	Left atrial volume index (LAVI), left ventricular mass index (LVMI), E/e', mean e' septal and lateral wall, longitudinal strain or tricuspid regurgitation velocity (TRV)
A stress test or invasively measured elevated LV filling pressure	A diastolic stress test performed with echocardiography, pulmonary capillary wedge pressure (PCWP), left ventricular end diastolic pressure (LVEDP)

HF: heart failure; LVEF: left ventricular ejection fraction.

LA enlargement, and atrial fibrillation.[10] At the same time, LVEF ≥65% measured by the echocardiogram is one of the essential conditions for the diagnosis of HFsnEF. The detailed clinical criteria for the diagnosis of HFsnEF are shown in table 1.

Treatment of HFsnEF

Although there is already a rudimentary classification of HF used for precision treatment in HF, a true Precision Medicine approach to HF is currently still in its infancy, and the treatment of HFpEF and HFrEF patients is also based on a "one-size-fits-all" approach.

Based on the pathology and pathophysiology of HFsnEF, one can deduce that patients with HFsnEF may be sensitive to several traditional drugs that are beneficial for other kinds of HF. But no drugs have shown any experimentally confirmed benefits. For example, β-blockers may be useful for the treatment of HFsnEF, as its negative chronotropic effect (decreased heart rate) increases the diastolic filling period and oxygen supply to the myocardium. ACEIs, ARBs and spironolactone may also have an effect on HFsnEF by decreasing progressive remodeling. But all of the drugs need prospective studies and clinical trials to identify their effects.

Exercise training in patients with HFsnEF may benefit patients by improving exercise tolerance and managing obesity. But the right amount of exercise for HFsnEF requires clinical trials to confirm it. In a recently published article , researchers assessed the topic of Precision Medicine in HFpEF. Precision Medicine provides a new concept for the treatment of HF and it may also have an effect on HFsnEF.[11]

Future perspectives

Our recent study has calculated the adjusted hazard ratios (HRs) for mortality with a nadir at LVEF of 60–64% and found that LVEF deviation from 60% to 64% was associated with poorer survival (Figure 2). HFsnEF patients had a risk of death that was almost 2-times higher than that of patients with LVEF between 60%-64%. We also divided HFsnEF patients into two groups by treating them with ACEIs/ARBs or not. Preliminary data showed a favorable effect on patient survival. ACEIs/ARBs may be attractive therapeutic agents to treat patients with HFsnEF. More prospective studies and randomized clinical trials are essential for the establishment of therapies with solid evidence-based recommendations.

After this new HF category has been proposed, there will be increasingly more research on this type of HF, contributing to a better understanding of this new phenotype, and whether an increase in mortality for LVEF ≥65% applies to people with hypertension and obesity remains a significant question that deserves further studies.

Conclusions

Based on the existing research, we conclude that patients diagnosed with HFsnEF (LVEF≥65%) have a special clinical manifestation, which is characterized by a higher all-cause mortality compared with other HFpEF patients.

Author contributions

Conception and design of the research: Huang Z, Zhou Y; Data acquisition, Analysis and interpretation of the data, Statistical analysis and Writing of the manuscript: Huang Z, Jiang Y; Obtaining financing: Zhou Y; Critical revision of the manuscript for intellectual content: Jiang Y, Zhou Y.

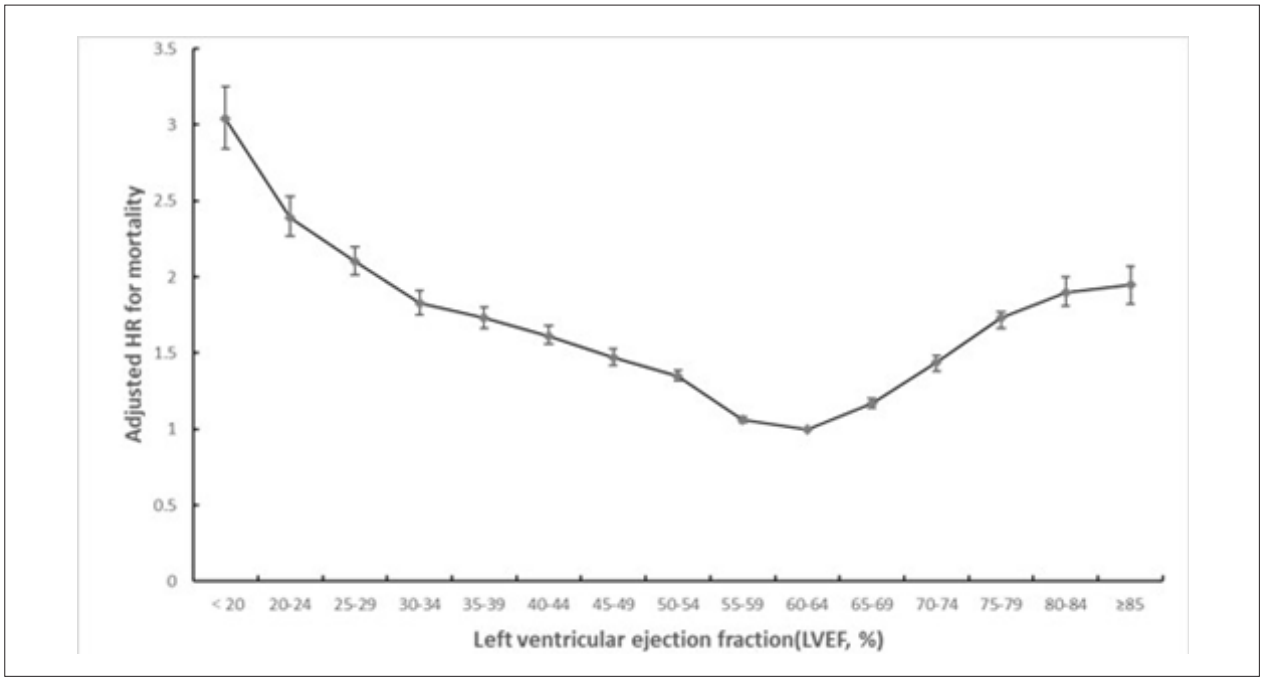

Figure 2 – *Adjusted Hazard Ratio for mortality according to LVEF.*

Potential Conflict of Interest

The authors report no conflict of interest concerning the materials and methods used in this study or the findings specified in this paper.

Sources of Funding

This study was funded by National Natural Science Foundation of China (81873484) e Natural Scientific Foundation of Jiangsu Province (BK20161226).

This study was partially funded by Jiangsu Province´s Key Provincial Talents Program (ZDRCA2016043) and Jiangsu Province´s 333 High-Level Talents Project (BRA2017539).

Study Association

This study is not associated with any thesis or dissertation.

Ethics approval and consent to participate

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

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Prosthetic Aortic Valve Endocarditis by *Neisseria Elongata* after Bentall Procedure: When Multimodality Imaging is Key to Diagnosis

Mariana Brandão,[1] *Pedro Gonçalves-Teixeira,*[1] *Pedro Ribeiro Queirós,*[1] *Nuno Dias Ferreira,*[1] *Marco Oliveira*[1]

Centro Hospitalar de Vila Nova de Gaia Espinho EPE,[1] *Vila Nova de Gaia – Portugal*

A diabetic 65-year-old male with previous Bentall procedure and mechanical aortic valve prosthesis presented with fever and abdominal pain, along with systolic murmur (III/VI) and elevated inflammatory markers. Abdominal computed tomography (CT) revealed splenic infarction. Transesophageal echocardiogram (TEE) was negative for vegetations. Given the persistent suspicion of infective endocarditis (IE) with peripheral embolism, empirical antimicrobial therapy was initiated. The patient subsequently presented with complete atrioventricular block, requiring temporary transvenous pacing. An epicardial pacemaker was later implanted.

At the time, cardiac CT revealed an irregular-shaped hypoattenuating mass attached to the ventricular side of the prosthetic suture ring, consistent with vegetation (Figure 1A), interfering with the normal opening of one of the prosthesis discs (Video 1). Repeat TEE also showed a small highly mobile vegetation and an annular abscess in the prosthetic aortic valve (Figure 2). Blood cultures were positive for *Neisseria elongata*, confirming the diagnosis of prosthetic valve endocarditis (PVE); antimicrobial therapy was tailored. Despite early improvement, the patient later presented with de novo ataxia and brain CT revealed infarction in the right vertebrobasilar territory. New sets of cultures remained negative and coagulation levels were within therapeutic range. A small vegetation persisted on cardiac CT and TEE, and inflammatory infiltrate was apparent at the mitro-aortic curtain.

The patient was refused for surgery due to the prohibitively high risk of re-operation, and a conservative strategy was pursued after Heart Team discussion. Following eight weeks of antimicrobial therapy, clinical and laboratory remission were achieved. CT scan disclosed a normally functioning prosthesis (Video 2) and the previously observed pathological findings were absent (Figure 1B). Vegetations were no longer evident on TEE (Figure 3).

The patient remained asymptomatic at 1-year follow-up, without echocardiographic or laboratory signs of recurrence.

Keywords

Infective endocarditis; Neisseria elongata; Bentall procedure; Prosthetic valve; Multimodality imaging

Mailing Address: Mariana Brandão •
Centro Hospitalar de Vila Nova de Gaia Espinho EPE - Rua Conceição Fernandes S/N Vila Nova de Gaia 4400-129 – Portugal
E-mail: mariana_brandao@msn.com
Manuscript received June 25, 2020, revised manuscript September 05, 2020, accepted November 09, 2020

DOI: https://doi.org/10.36660/abc.20200706

This is, to our knowledge, the first case report of PVE in a patient with previous Bentall procedure due to *Neisseria elongata*. We highlight the importance of multimodality imaging, particularly when diagnosis remains uncertain after inconclusive echocardiographic evaluation. The diagnosis ultimately relied on CT findings, included as a major diagnostic criterion in the latest endocarditis guidelines.[1] CT has excellent spatial resolution and enables detailed visualization of paravalvular anatomy and complications, with less artifact and shadowing from the prosthesis.[2]

Despite the obvious surgical indications, the patient was successfully treated with a conservative (controversial) strategy. Although removal and replacement of prosthetic material was traditionally considered mandatory, if intervention is not feasible, patients should be treated with prolonged antibiotic therapy.[3] Multiple series, including the ESC-EORP EURO-ENDO registry,[4] have stated the discrepancy between guideline-directed surgical indications and actual practice, largely explained by evermore complex patients, with more co-morbidities and previous interventions with intracardiac prosthetic material. This case is illustrative of the current challenges involved in the diagnosis and management of PVE, where conservative treatment may sometimes prove successful and the only acceptable option.

Author Contributions

Acquisition of data: Ferreira ND; Writing of the manuscript: Brandão M, Gonçalves-Teixeira P; Critical revision of the manuscript for intellectual content: Gonçalves-Teixeira P, Queirós PR, Ferreira ND, Oliveira M.

Potential Conflict of Interest

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

Sources of Funding

There were no external funding sources for this study.

Study Association

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

Ethics Approval and Consent to Participate

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

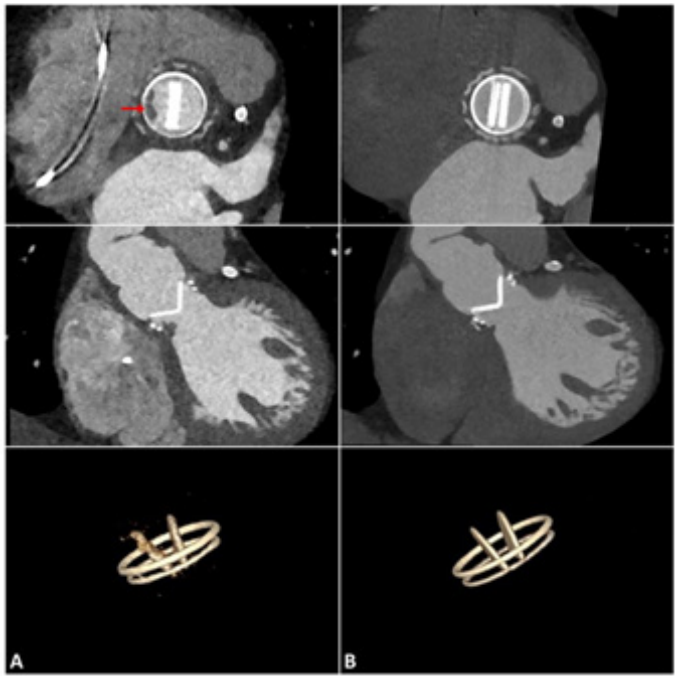
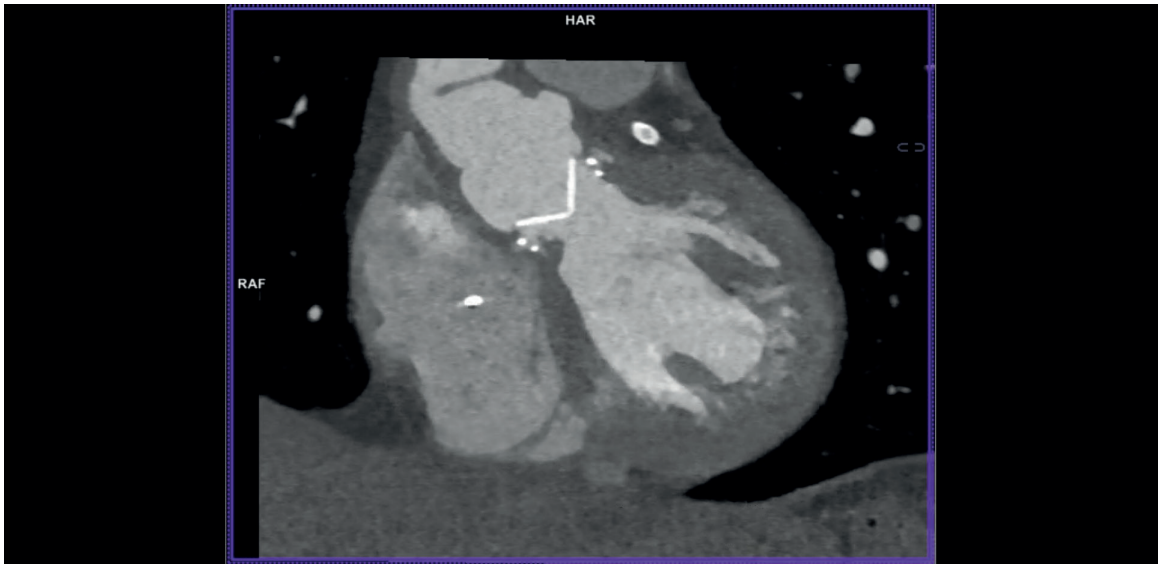


Figure 1 – *1A) Cardiac CT scan at admission showing vegetation in the aortic valve and inflammatory changes in the intervalvular fibrosa and inter-atrial septal spaces. 1B) Cardiac CT scan at discharge with residual inflammatory tissue.*



Video 1 – *URL: http://abccardiol.org/supplementary-material/2021/11605/2020-0706-video1.mp4*

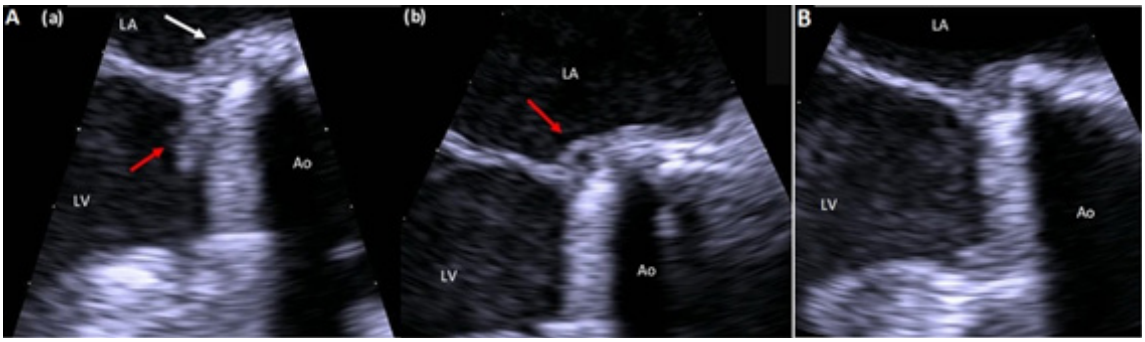
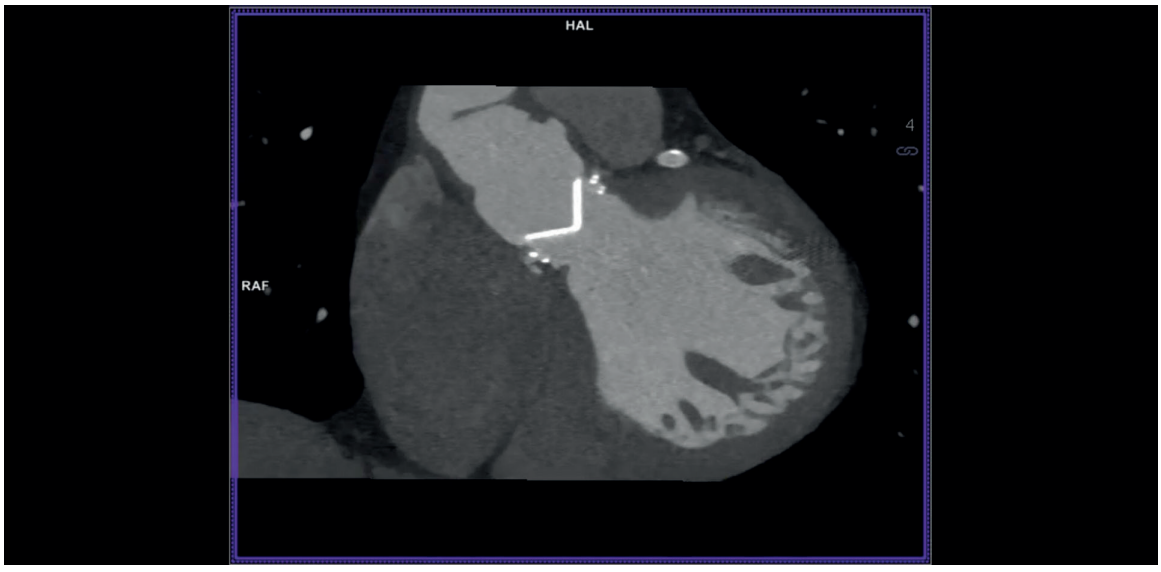


Figure 2 – *2A) Transesophageal echocardiogram, midesophageal long-axis aortic valve plane. (a) Vegetation (red arrow) and inflammatory infiltrate (white arrow). (b) Annular abscess (red arrow). Ao: ascending aorta; LA: left atrium; LV: left ventricle. 2B) Transesophageal echocardiogram at discharge, midesophageal long-axis aortic valve plane. No vegetation or abscess visible. Ao: ascending aorta; LA: left atrium; LV: left ventricle.*



Video 2 – *URL: http://abccardiol.org/supplementary-material/2021/11605/2020-0706-video2.mp4*

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